Abstract Publication
More than 4,400 abstracts are published in this supplement. Abstracts are arranged by the abstract type**, then by presentation date*, and then by chronological publication number. Abstracts with a “PUB” number will not be presented at the ASN Annual Meeting.

* TH = Thursday, FR = Friday, SA = Saturday
** OR = Oral, PO = Poster, PUB = Publication Only

The presenting author’s name is underlined. For the poster sessions, the publication numbers and poster board numbers are the same.

Abstract Author Index
The Author Index lists all abstract authors in alphabetical order. To locate an abstract, first reference the abstract type (OR, PO, or PUB) and then the presentation day (TH, FR, or SA), and then the chronological publication number.

Abstract Keyword Index
The Keyword Index lists major keywords from each abstract in alphabetical order. To locate an abstract, first reference the abstract type (OR, PO, or PUB) and then the presentation day (TH, FR, or SA), and then the chronological publication number.

Abstract Reference Format
To cite abstracts in this publication, please use the following format: Author Names: Abstract Title [Abstract]. J Am Soc Nephrol 28, 2017: Page(s).

Abstract Experts
Abstract submissions were rigorously reviewed and graded by multiple experts. ASN thanks the abstract category chairs and reviewers for assistance with the abstract process. The ASN website lists all abstract experts.

Abstract Disclaimer and Copyright
The Abstract Issue of JASN® contains proprietary information belonging to the American Society of Nephrology (ASN). It is published as a service for the personal, noncommercial, and informational use only of its members and Kidney Week participants. Any commercial use is strictly prohibited. ASN’s program materials and publications facilitate scientific discourse for educational purposes. ASN accepts no responsibility for any products, presentations, opinions, statements, or positions expressed, and inclusion of such material within Kidney Week and other ASN publications, or online postings does not constitute an endorsement by ASN.

ASN General Information
Kidney Week Program and Presentations
The Kidney Week 2017 program, which can be found on the ASN website and in the Kidney Week mobile app, includes:

- Plenary Sessions
- Basic/Clinical Science Sessions
- Clinical Practice Sessions
- Translational Sessions
- Special Sessions
- Educational Symposia
- Oral Abstract Sessions
- Poster Sessions

Disclosure Statement
ASN requires all individuals in a position to control content for Kidney Week 2017 to complete a disclosure form. Responses are listed on the ASN website.

Trademark
The American Society of Nephrology®, ASN®, Kidney Week®, CJASN®, JASN®, NephSAP®, and ASN Kidney News® are registered trademarks of ASN.

Contact ASN
American Society of Nephrology
1510 H Street, NW, Suite 800
Washington, DC 20005
Phone 202-640-4660, Fax 202-637-9793
e-mail@asn-online.org, www.asn-online.org
TH-OR001

Comorbid Disease Trends in Hemodialysis and Peritoneal Dialysis Patients


Tufts University School of Medicine, Boston, MA; University of Michigan, Ann Arbor, MI; University of Chicago, Chicago, IL.

Background: The US Renal Data System has collected comorbid conditions data on incident hemodialysis (HD) and peritoneal dialysis (PD) patients since 1995. We evaluated the prevalence of several comorbid conditions over 20 years, and compared trends in both groups.

Methods: All first-time HD and PD patients 1996-2015 were included, and analyzed by year of initiation. Diabetes (DM) and cardiovascular disease (CVD) were condensed into single variables, to align data obtained from the 1995 and 2005 Medical Evidence forms. The proportions of co-morbid conditions were evaluated with logistic regression, treating year of initiation as a continuous variable, stratifying by dialysis type, and adjusting for age, sex, and race. Five year prevalence trends were expressed as odds ratios (OR) and 95% confidence intervals, with OR>1 representing increasing prevalence.

Results: Among 1,864,386 HD and 137,395 PD patients, the mean age increased by 3 years; PD patients were consistently 5-6 years younger than HD patients. CVD decreased in PD but remained flat in HD. In HD patients, hypertension (HTN), DM and lung disease (COPD) increased and peripheral vascular disease (PVD) decreased. PD patients had a smaller increase in DM, and COPD and PVD decreased, but HTN increased. Stroke and cancer did not change significantly over time. Five-year OR’s are shown below.

Conclusions: While HD and PD patients in the United States are both becoming older, with decreases in acute and diabetic, the comorbid disease burdens have been diverging over the past 20 years, resulting in PD patients having less DM, CVD, and COPD than their counterparts receiving HD.

Funding: NIDDK Support

TH-OR002

Racial Disparities in Coronary Artery Bypass Graft Surgery in Maintenance Dialysis Patients

Robert Nee, Keith C. Norris, Christina M. Yuan, Lawrence Agodoa, Kevin C. Abbott.

NIDDK, National Institutes of Health, Bethesda, MD; Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA; Nephrology, Walter Reed National Military Medical Center, Bethesda, MD.

Background: Racial disparities in invasive cardiac procedures such as coronary artery bypass graft (CABG) in the general population are well documented. However, contemporary national-level data on such disparities in the end-stage renal disease (ESRD) population are lacking. Herein we assessed racial differences in the receipt of CABG between Blacks and Whites with ESRD, after the start of maintenance dialysis.

Methods: Using the US Renal Data System database, we identified 281,464 Medicare primary patients initiated on maintenance dialysis from 1 January 2009 through 1 January 2013, and followed until 31 December 2013. We abstracted Medicare hospital claims for CABG among patients who had primary diagnoses of either native coronary atherosclerosis (NCA) or acute myocardial infarction (AMI). We conducted logistic regression analyses, adjusted for demographic characteristics, Hispanic ethnicity, cause of ESRD, comorbidities, socioeconomic factors (insurance type to include Medicare-Medicaid dual eligibility as a proxy measure of individual-level poverty, employment status, and ZIP code-level median household income [MHI] obtained from the 2010 US Census).

Results: 8,004 patients underwent CABG surgery during the study period, of whom 19.4% were Blacks and 74.6% were Whites. Fully adjusted models demonstrated that, among patients with hypertension diagnoses of NCA or AMI, Blacks were significantly less likely to undergo CABG compared to Whites (odds ratio [OR] 0.76, 95% CI 0.64-0.90; p=0.002). The odds were similar in non-Hispanic Blacks vs. non-Hispanic Whites (OR 0.74, 95% CI 0.62-0.88; p=0.001). There were no significant interactions between race and ZIP code-level MHI (p=0.31), or dialysis status (p=0.60).

Conclusions: Similar to the general population, there exists a racial gap among incident dialysis patients undergoing CABG surgery despite having comprehensive coverage with Medicare. These findings persisted despite accounting for demographic, clinical and socioeconomic factors. Disclaimer: The views expressed in this abstract are those of the authors and do not reflect the official policy of the Department of the Army/ Navy/Air Force, the Department of Defense; National Institutes of Health, or the United States government.

Funding: commercial support - non-NIH

TH-OR003

Clinical Effects of Molecular Hydrogen (H2) Delivery during Hemodialysis in Chronic Dialysis Patients: Five Years Prospective Observational Study

Masaaki Nakayama, Wan-Jun Zhu, Tae Yamamoto, Mariko Miyazaki, Sadayoshi Ito, Tohoku Graduate School of Medicine, Sendai Miyagi, Japan; Tohoku University, Sendai, Japan; Tohoku University Hospital, Sendai, Japan; Tohoku University Hospital, Sendai City, Japan.

Background: Enhanced oxidative stress and inflammation are supposed to play a crucial role for poor clinical outcomes in patients on chronic hemodialysis (HD) treatment. Recent studies have revealed unique biological characteristics of molecular hydrogen (H2) as an anti-inflammatory agent. Thus, we developed a novel hemodialysis system which delivers H2 (30 to 80 ppb)-enriched dialysis solution by water electrolysis technique, and conducted a prospective study to study the clinical impact of H2 delivery as compared to the conventional HD (C-HD) system.

Methods: Provenant HD patients (n=309, mean HD vintage, 7.8 years; age, 66 years old; male, 57%; history of cardio- and cerebro-vascular disease (CVD), 29%) were registered from 7 HD centers in Japan (from Mar 2011 to Dec 2012), and allocated to either E-HD (n= 161, 60.2%) or C-HD (n=148). They had been treated by the respective HD treatment during the study. Primary end-point was composite of all-cause of mortality, and development of non-letal CVDs (apoplexy, cardiac diseases, and peripheral artery disease).

Results: During the five-year observation periods (end of Oct 2016), no differences were observed in dialysis parameters between the two groups. However, there were unique changes in clinical profiles in patients on E-HD, i.e. significant reduction in post-HD systolic BP in those who had remained hypertensive state after HD at baseline, which was accompanied by significant reductions of prescriptions of anti-hypertensive agents. There were 91 events in the mean observation periods of 3.28 years. The number of primary events were 50 cases in C-HD (17 in death and 29 in CVD: Event Rate; 107.1 /1000 patients-year:95%CI:81.2-141.1), and 41 cases in E-HD (20 in death and 20 in CVD: Event Rate;75.4:55.6-102.2), respectively. Multivariate analysis of Cox proportional hazard model revealed that E-HD was an independent significant factor for the primary event (HR 0.59, 95%CI:0.38-0.92) after adjusting for confounding factors (age, history of CVD, serum albumin, and CRP).

Conclusions: The data indicates E-HD could improve prognosis of chronic HD patients, through the unique BP control effect during HD treatment.

Funding: Commercial Support - Nikon Trim. Co, Government Support - Non-U.S.

TH-OR004

Increased Risk of Premature Cerebral Small Vessel Diseases in Dialysis Patients: A Cross-Sectional Controlled Study


Peking Union Medical College Hospital, Beijing, China.

Background: Growing evidence suggests a higher prevalence of cerebrovascular diseases in patients with end-stage renal disease and undergoing dialysis. As an important cause of stroke, dementia or disability, cerebral small vessel disease (CSVD) has been associated with chronic kidney disease (CKD) and its complications. However, there are few studies focused on the controlled assessment of CSVD in a dialysis cohort of large sample size.

Methods: In this cross-sectional controlled study, we enrolled a total of 179 dialysis patients (116 in hemodialysis (HD) and 63 in peritoneal dialysis (PD)) and 351 matched non-chronic kidney disease (CKD) controls. We collected detailed clinical characteristics and all participants underwent brain MRI. We assessed and compared the prevalence and location of CSVD in the dialysis patients and controls, including lacunes, microbleeds, and white matter hyperintensities (WMH). We used univariable and multivariable logistic regression to investigate the risk factors.

Results: Prevalence of the CSVD lesions were significantly higher in the dialysis patients compared with non-CKD controls (OR: 1.86 (95% CI 1.23–2.81) in lacunes; 3.61 (95% CI 2.32-5.61) in microbleeds; 1.92 (95% CI 1.31–2.82) in WMH). In dialysis patients, the majority of lacunes were detected in the subcortical white matter and basal ganglia, while the majority of the microbleeds were found in the lobes and basal ganglia. After adjusting age, dialysis vintage, hypertension, diabetes mellitus (DM), hyperlipidemia, smoking and drinking habits, significantly increased risk was observed in the dialysis patients for microbleeds (OR 2.83, 95% CI 1.70-4.65) and WMH with total Fazekas larger than two (OR 2.04,95% CI 1.25-3.34). Finally, the age of lesion detection was significantly smaller in dialysis patients (p<0.017, 0.004 and 0.020 for lacunes, microbleeds and WMH). In our dialysis cohort, these was no significant differences in all three categories of CSVD lesions between HD and PD modalities. The age of lesion detection was significantly smaller in dialysis patients (p<0.017, 0.004 and 0.020 for lacunes, microbleeds and WMH).

Conclusions: Patients on dialysis were associated with significantly increased risk of CSVD comparing with controls, they also demonstrated a trend toward increased CVD. CSVD:

Funding: Government Support - Non-U.S.
TH-OR005
Intradialytic Hypertension Frequency and Short-Term Clinical Outcomes among Hemodialysis Patients
Magdalene M Assimon, Jennifer E. Flythe. University of North Carolina, Chapel Hill, NC.

Background: Intradialytic hypertension (ID-HTN) occurs in 5-20% of hemodialysis treatments. Observational data support an association between ID-HTN and increased long-term mortality. However, the short-term cardiovascular (CV) consequences of recurrent ID-HTN are unknown.

Methods: Data were taken from a cohort of prevalent hemodialysis patients receiving treatment at a large U.S. dialysis organization on 01/01/2010. Using a retrospective cohort design with a 180-day baseline, 30-day exposure assessment and 30-day follow-up period, we estimated the association between ID-HTN frequency and: 1) 30-day mortality and 2) 30-day hospitalizations. We defined ID-HTN frequency during the 30-day exposure period as the proportion of hemodialysis treatments with a pre-to-post-dialysis systolic blood pressure (BP) rise ≥10 mmHg. Multivariable Cox proportional hazards models, adjusting for numerous clinical, laboratory and dialysis treatment covariates, were used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: Of 37,094 study patients, 5,242 (14%), 17,965 (48%), 10,821 (29%), 3,066 (8%) had ID-HTN in 0%, 1-32%, 33-66% and ≥67% of exposure period treatments, respectively. More frequent ID-HTN was associated with incremental increases in 30-day mortality and volume overload hospitalizations (Figure). Patients with ID-HTN in ≥67% (vs. 0%) of exposure period treatments had the highest risk of all-cause death, adjusted HR [95% CI]: 2.6 [1.7-3.9]; CV death, 3.7 [1.9-7.1]; and volume overload hospitalizations, 2.3 [1.3-4.2]. Analogous incremental associations were observed for all-cause and CV hospitalizations. In sensitivity analyses, use of alternative BP thresholds (≥5 or ≥10 mmHg) to define ID-HTN yielded similar results (data not shown).

Conclusions: Among prevalent hemodialysis patients, ID-HTN frequency is incrementally associated with short-term morbidity and mortality. Randomized trials are needed to determine if ID-HTN frequency mitigation improves patient outcomes.

Funding: NIDDK Support

TH-OR006
Pre ESRD Coronary Artery Revascularization and Post ESRD Mortality
Abduzhappar Gainov,1 Miklos Z. Molnar,4 Praveen Kumar Potukuchi,1 Keichi Sumida,2 Robert B. Canada,4 Oguz Akbilgic,4 Kairat Kabulbayev,1 Kamyar Kalantar-Zadeh,3 Csaba P. Kovacsdy,4 1Kazakh national medical university, Almaty, Kazakhstan; 2Nephrology Center, Toranomon Hospital Kajigaya, Kawasaki, Japan; 3University of California - Santa Barbara, Santa Barbara, CA; 4University of Tennessee Health Science Center, Memphis, TN.

Background: Coronary artery bypass grafting (CABG) is associated with better survival than percutaneous coronary intervention (PCI) in patients with mild-to-moderate CKD and ESRD. However, the optimal strategy for coronary artery revascularization in advanced CKD patients who transition to ESRD is unclear.

Methods: We examined a contemporary national cohort of 815 US veterans with incident ESRD, who underwent first CABG or PCI up to 5 years prior to dialysis initiation. We examined the association of CABG versus PCI with all-cause mortality following transition to dialysis, using Cox proportional hazards models adjusted for time to dialysis start, sociodemographics, comorbidities and medications.

Results: 596 patients underwent CABG and 219 patients underwent PCI. The mean age was 66±8 years, 99% of patients were male, 78% were white, 20% were African Americans, and 84% were diabetic. The all-cause post-dialysis mortality rates after CABG and PCI were 301/1000 patient-years (PY) [95% CI=271–333] and 436/1000PY [95% CI=371–512], respectively. Mortality was lower after CABG (Figure). The multivariable adjusted hazard ratio of all-cause mortality in patients who underwent CABG compared to PCI was 0.72 [95% CI=0.58–0.89, p=0.003].

Conclusions: In patients with advanced CKD CABG is associated with lower risk of post-ESRD death compared to PCI.

Funding: NIDDK Support

TH-OR007
Association of Peridialytic Systolic Blood Pressure Change and Pre-Dialysis Systolic Blood Pressures on Mortality among Hemodialysis Patients
Hanjie Zhang,1 Priscilla Preciado,2 Yuedong Wang,2 Anna Meyring-Wosten,2 Alice Topping,2 Jochen G. Raimann,3 Jeroen Kooman,4 Frank van der Sande,5 Len A. Uyyat,3 Dugan Maddux,1 Franklin W. Maddux,1 Peter Kotanko,6 Fresenius Medical Care, Waltham, MA; 2University of California - Santa Barbara, Santa Barbara, CA; 3Fresenius Medical Care North America, Melrose, MA; 4Maastricht University Medical Centre, Maastricht, Netherlands; 5Maastricht University Medical Centre, Maastricht, Netherlands; 6Renal Research Institute, New York, NY; 7Renal Research Institute, New York, NY.

Background: Pre-dialysis systolic blood pressure (pre-SBP) and peridialytic SBP change (ASBP) had been associated with mortality in former studies, but the nature of this interaction is still not fully explained.

Methods: Pre-SBP and ASBP (post-HD – pre-HD) were analyzed by 1/2001 and 12/2012 in HD patients treated in Fresenius Medical Care (FMC) facilities. Baseline was defined as months 4-6 in the first year of HD, the primary outcome was all-cause mortality. Censoring events were renal transplantation, modality change, or study end. Only patients who survived the baseline and had no missing covariates were included. We fitted Cox proportional hazard model with a bivariate spline for the primary predictors, pre-SBP and ASBP, with adjustment for age, gender, race, diabetes, access-type, relative interdialytic weight gain (IDWG), body mass index (BMI) and albumin, ePCR, and ultrafiltration rate (≥13 or <13 mL/kg body weight/hour).

Results: A total of 191 491 patients were included. We found that a peridialytic SBP increase in the presence of high pre-SBP was associated with an increased mortality, while in patients with low pre-SBP a peridialytic SBP increase was associated with better survival (Fig. 1).

Conclusions: We showed association of pre-SBP and peridialytic SBP changes with all-cause mortality in a large and diverse HD population. Patients with low pre-SBP may benefit from an increase in peridialytic SBP, while an increase in SBP may be detrimental in patients with a high pre-SBP.

Funding: Commercial Support - Fresenius Medical Care

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

Alexander Bullen, CA

Individualized Cool Dialysate as an Effective Therapy for Intradialytic Hypotension

Background: Intradialytic hypotension (IDH) is the most common dialytic complication identified in 15-20% of all dialysis encounters. Cool dialysate by promoting peripheral vasodilation leads to decreased IDH and may be an effective approach to reduce IDH. However, only small studies have been done to date using a cool dialysate and they have not typically used an individualized cool dialysate temperature. Therefore, we designed a study to determine if cool dialysate would decrease the number of episodes of IDH in a high-comorbidity dialysis population served within our hospital.

Methods: We conducted a single center study at the UCSD dialysis unit. Baseline characteristics were obtained from the electronic medical record including age, race, and co-morbidities. The study consisted of baseline and intervention phases, and each patient served as their own control. In the first phase, core baseline temperature (CBT) was determined as an average of oral temperature prior to three HD sessions. During this phase hemodynamic parameters during dialysis were recorded for 6 HD sessions. In the second phase, the CBT was then decreased by 0.5 degrees Celsius and hemodynamic parameters were then collected again for 6 more HD sessions. Parameters during the control phase and cool phase were compared.

Results: 93 participants with mean age was 56.7±15.3 years were included. 53% were women, and 53.8% were Hispanic. The average years on HD were 4.7±0.5 years. The number of IDH episodes during the control phase was 3.27±0.29 per patient to 1.96±0.42 per patient (P<0.001). The lowest recorded intradialytic MAP increased from 78.22±7.18 mmHg to 85.60±5.80 mmHg, the mean increase was 1.60±1.20 mmHg to 78.22±7.18 mmHg (P<0.001). No correlation was found between a change in UF and a change in MAP. No correlation was found between a change in UF and a change in SBP.

Conclusions: Individualized cool dialysate is an effective and easy to implement method to decrease intradialytic hypotension and it may ameliorate clinical symptoms and ease nursing burden in patients with frequent IDH.

TH-OR009

Ratio of Early Mitral Inflow Velocity to Global Diastolic Strain Rate and Global Left Ventricular Longitudinal Systolic Strain Predicts Overall Mortality and Cardiovascular Events in Hemodialysis

Background: The associations between the ratio of early mitral inflow velocity (E) to global diastolic strain rate (E’sr) and global left ventricular longitudinal strain (GLS) obtained from two-dimensional speckle-tracking echocardiography with cardiovascular (CV) outcomes remain unclear in patients undergoing hemodialysis (HD). This study aimed to examine the ability of E/E’sr ratio and GLS to predict overall mortality and CV events in maintenance HD patients.

Methods: Cardiopulmonary exercise testing was performed in 190 HD patients. E’ and GLS were measured from three standard apical views using the index beat method. CV events were defined as CV death, non-fatal stroke, coronary artery disease, peripheral arterial disease and heart failure.

Results: During the mean follow-up period of 2.7 years, 28 patients died and 28 CV events were recorded. After multivariate adjustment, the E/E’sr ratio (hazard ratio [HR]: 1.561; 95% confidence interval [CI], 1.221–1.995) and GLS (HR: 1.229; 95% CI, 1.061–1.423) were associated with overall mortality. Furthermore, the E/E’sr ratio (HR: 1.233; 95% CI, 1.001–1.518) and GLS (HR: 1.299; 95% CI, 1.104–1.529) were both associated with CV events in multivariate analysis. The E/E’sr ratio and GLS had a better predictive ability of overall mortality and CV events than the ratio of E to early diastolic mitral annular velocity (E’) and left ventricular ejection fraction (LVEF). Moreover, adding the E/E’sr ratio and GLS to a clinical model with conventional echocardiographic parameters improved the prediction of both mortality (p = 0.002) and CV events (p < 0.001).

Conclusions: The E/E’sr ratio and GLS are stronger than the E/E’ ratio and LVEF in predicting unfavorable outcomes, and may provide additional prognostic value to conventional clinical and echocardiographic parameters in maintenance HD patients.

Predictive values of echocardiographic parameters in relation to overall and cardiovascular events

| Parameters | Overall mortality | Cardiovascular events | p | p
| --- | --- | --- | --- | --- |
| | Difference in Hazard ratio | p | difference in Hazard ratio | p
| Ratio model + BMI + UA, spMVC, CTR, AoAC | 0.000 | 0.138 | 0.000 | 0.000 |
| Basic model + BMI + UA, spMVC, CTR, AoAC | 0.000 | 0.138 | 0.000 | 0.000 |
| Basic model + BMI + UA, spMVC, CTR, AoAC + LVMI, LVEF, E/E’sr | 0.000 | 0.138 | 0.000 | 0.000 |
| Ratio model + BMI + UA, spMVC, CTR, AoAC | 0.000 | 0.138 | 0.000 | 0.000 |

Terms p value was based on the incremental value compared with the basic model which was adjusted for demographic, clinical, and biochemical risk factors.

TH-OR010


Background: The transition to hemodialysis (HD) is associated with a decline of cognitive function and an increased incidence of cerebrovascular accidents and white matter lesions. It has been hypothesized that the repetitive circulatory stress of dialysis may contribute to this decline. However, the specific role of HD in altering cerebral blood flow is controversial.

Methods: We performed [15O]H2O-PET-CT scans in 10 healthy elderly individuals prior to and at the end of hemodialysis (4.5 ± 0.5 h, 4.2 ± 0.5 h, respectively) and in 10 control subjects (4.5 ± 0.5 h each). The scans were performed in the supine position using a 64-slice PET/CT scanner. The cerebral blood flow was quantified using the index beat method.

Results: The cerebral blood flow (CBF) significantly decreased from 56 ± 11 mL/100 g/min at baseline to 49 ± 10 mL/100 g/min after HD (p < 0.001). The decrease was more pronounced in the frontal and parietal lobes (15% and 17%, respectively) than in other brain regions.

Conclusions: These results suggest that HD induces a significant reduction in cerebral blood flow in elderly patients, which may contribute to cognitive decline.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
ID induces ischemic injury to the brain, but the mechanism is unclear. Despite the significant difference between WT and CD47 mice, rTEC from CD47− mice displayed basal upregulation of autophagy genes that was preserved under exogenous stress (hypoxia, Fio2, 1%, or treatment with TSP1, 2.2 mM for 24 h), and this correlated with enhanced viability when compared to WT cells. Treatment of WT rTEC with an oligomeric TSP1−CD47 signifying increased autophagy. Human rTEC similarly demonstrated downregulated autophagy in response to exogenous TSP1, which was mitigated in conjunction with a CD47-blocking antibody. Finally, in a syngeneic mouse kidney transplantation model, treatment with a CD47-blocking antibody improved renal function and histologic damage compared to control mice, and this was associated with increased autophagy.

Conclusions: These data suggest activated CD47 is a proximate promoter of renal IRI through inhibition of autophagy and cell viability, and point to CD47 as a target to restore renal function following injury.

Funding: Government Support - Non-U.S.

TH-OR013

JNK1 Promotes Renal Ischemia-Reperfusion Injury
Kerry Grynberg,1 Elyce Ozols,1 William R. Mullins, Karen Blase,2 David J. Nikolic-Paterson,3 Frank Y. Ma.2 1Department of Nephrology, Monash Medical Centre, Monash, Victoria, Australia; 2Celgene, San Diego, CA.

Background: Tubular activation of the e-Jun amino-terminal kinase (JNK) pathway is prominent in most forms of acute and progressive tubulointerstitial damage, including renal ischemia/reperfusion (IR) injury. Both Jnk1 and Jnk2 genes are expressed in most cells of the kidney resulting in considerable redundancy. Combined blockade of Jnk1/2 is protective in renal I/R injury; however, the relative contribution of each isoform is unknown. The aim of this study is to determine the relative contribution of Jnk1 versus Jnk2 in renal I/R injury.

Methods: Preferential pharmacological inhibition of Jnk1 (CC90001) was compared to mice with global deletion of jnk1 or jnk2 and mice with combined global deletion of both jnk1 and jnk2. Bilateral warm renal ischemia injury was induced with vascular clamps and animals killed 24h after reperfusion. Controls were sham operated. Sprague-Dawley rats (n=8-10/group) were treated with CC-90001 (10mg/kg) or vehicle starting 1 hour prior to surgery. Renal I/R injury studies were also performed in Jnk1−/− (n=10), Jnk2−/− (n=8), Jnk PT (n=8) and wild type (WT) mice (n=10).

Results: Treatment with CC-90001 provided significant protection in rat I/R injury (8.0±0.5 vs 20±2 fold increase in serum creatinine (sCr), drug versus vehicle, respectively; p<0.0001). In a separate study, Jnk1−/− mice also showed significant protection from I/R injury compared to WT mice (4.0±0.5 vs 8±1 fold increase in sCr respectively; p=0.01); however, this was not replicated in Jnk2−/− mice (16±0.5 vs 15±2 fold increase in sCr, Jnk2−/− versus WT, respectively; p>0.05). Jnk−PT mice exposed to renal I/R injury showed significant protection from injury compared to WT mice (5.5±0.7 vs 15±2 fold increase in sCr respectively; p<0.01). CC-90001 treatment reduced tubular damage and macrophage infiltration. This protection was replicated in Jnk1−/− and Jnk−PT mice.

Conclusions: Using complementary approaches, we have established that JNK1 in the proximal tubule is crucial for renal I/R injury. Prophylactic JNK1 inhibition may have clinical utility in anticipated renal I/R injury.

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

TH-OR014

A Snapshot of RNA Expression in a Single Segment of the Kidney Reveals Stimulus Specific Responses
Katherine Xu,3 Jacob Stauber,4 Jonathan M. Barasch,1 1Columbia Presbyterian, New York, NY; 2Columbia University, New York, NY; 3None, East Elmhurst, NY.

Background: The identification of acute kidney disease at the time of patient encounter remains a central problem in clinical medicine. A single analyte, the serum creatinine (sCr) is currently in use as a surrogate for tubular, vascular, or interstitial cellular damage. Nonetheless, the sCr test is not specific to kidney injury, but rather might reflect physiological responses to a primary disease in a distant organ. In addition, while cellular events occur over minutes or hours, sCr requires 24 hours or more to reach a worrisome clinical threshold or demonstrate further deterioration of tissue function and predict the need to start renal replacement therapy.

Methods: To examine the cell and stimulus specific responses, we have adapted the method of Gay et al. (2013) to allow cell specific labelling of RNA at the time of our choosing after injury. The technique involves cre driven, cell specific expression of a transgenic fluorescent labelled nascent RNA. We used this technique with Atp6b1v1-Cre and Hoxb7-Cre to perform transcriptional profiling of the newly newly synthesized RNA in the cell types in mouse models of AKI (intrisic-AKI) and vAKI (volume-depleted-AKI).

Results: We found hundreds of genes responding in each cell specific and stimulus specific RNA pool. There was almost no overlap between vAKI and iAKI, although they both raise sCr, and limited overlap between Atp6b1v1-Cre and Hoxb7-Cre RNA pools. To validate this technique, we show that collecting duct marker genes are enriched and genes from other segments of the kidney are enriched in the tagged RNA. In addition, we validated the technique by independently using a GFP-Hoxb7 mouse and FAC-sorting out the collecting duct cells for gene expression.

Conclusions: Hence, a snapshot of newly synthesized RNA reveals the complexity of renal injury and points to new approaches that might allow for better early diagnosis of different types of injury.
points after the onset of injury. These data will replace our current diagnostic strategies with Precision Medicine approach to AKI.
Funding: NIDDK Support

TH-OR015
Parabiosis Reveals Renal Resident Leukocytes in Quiescence and AKI Jeremie M. Lever,1 Ravindra Boddla,1 Oreloluwa O. Adeyoeni, Zhengqin Yang,1 Lingling Guo,1 Amie Traylor,1 Roy Joseph,2 James F. George,1 Anupam Agarwal.1,2 1University of Alabama at Birmingham, Birmingham, AL; 2VA Medical Center, Birmingham, AL.

Background: Inflammation drives damage and promotes tissue regeneration in AKI, but the origin of inflammatory cells found in renal tissue (infiltrative versus resident) has remained elusive. In this study, we developed a novel model of AKI in parabiotic chimeras to study exchange of inflammatory cells with the circulation. Our goal was to discern which renal leukocyte populations are tissue-resident and how this may change in the setting of injury-induced inflammation.

Methods: Parabiosis was established between C57BL/6J adult congeneric mice with differing CD45 allotypes, allowing identification of cells from each individual. After 28d, chimeras were subject to 28h of renal ischemia-reperfusion injury (IRI) or sham surgery and harvested at 24 and 72h. Kidney, peripheral blood, and spleen were analyzed by multicolor flow cytometry.

Results: After 28d of parabiosis, chimerism for intrarenal neutrophils was 24.2% (95% CI, 14.2 to 34.2). In contrast, F4/80+CD11b++CX3CR1++CD16c– macrophages, CD3+CD4+CD8+ T lymphocytes, and NK1.1+ CD3+ NKT cells in the kidneys demonstrated low chimerism with the blood, with chimerism equal to 2.4% (95% CI, 1.0 to 3.8%; p = 0.002 compared with blood), 2.3% (95% CI, 0.6 to 4.1%; p = 0.02), and 2.3% (95% CI, 0.7 to 3.9%; p = 0.002), respectively in uninjured kidneys. In injured kidneys, a trend toward chimeric CD45.1+ leukocyte infiltration was observed relative to sham control (6.6 ± 1.1 × 10^4 vs 1.8 ± 10^4 ± 8.4 × 10^4 cells/g tissue, p = 0.10, n = 3 pairs, 24h after injury). However, absolute numbers of chimeric F4/80+CD11b++CX3CR1++CD16c– macrophages were not different, indicating bone marrow progenitors from the peripheral blood do not supplement this population, even in the setting of acute inflammation.

Conclusions: Certain renal leukocyte populations exhibit low or no exchange with the peripheral blood, indicating they are long-lived or undergo self-renewal in situ. Kidneyresident macrophages do not appear to be supplemented by infiltrating cells during acute inflammation. These findings may be important in targeting inflammation after AKI with small molecule drugs or development of cell-based therapeutics.
Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support

TH-OR016
Endothelial Marker Expressing Stromal Cells Are Important Regulators of Recovery from AKI Katherine V. Marvin,1 Elna Mukherjee,2 Sunner Sims-Lucas,1 1Children’s Hospital of Pittsburgh, Pittsburgh, PA; 2Pittsburgh, PA; Pediatric Nephrology, University of Pittsburgh, Pittsburgh, PA.

Background: Acute Kidney Injury (AKI) is characterized by an abrupt decrease in renal function that can lead to renal failure, contributing to morbidity and mortality. We have identified a subset of endothelial marker expressing stromal (EMES) cells that contribute to peritubular capillary endothelium. The peritubular capillaries are the primary sites of damage during AKI. We have previously shown that EMES cells are important during the injury phase of AKI. Subsequently, we hypothesized that EMES cells are important contributors to recovery after AKI.

Methods: To determine the importance of EMES following ischemia reperfusion injury (IRI) we utilized lineage tracing, using a TDFgene reporter (labeling all EMES cells) and interrogated the percentage of EMES cells present in IRI and contralateral kidneys. We then interrogated re-expression of stromal genes using RT-PCR. Furthermore, we generated mice with a conditional deletion of Flk1 (Vegfr2, essential for vascular development) in Foxd1+ positive renal stroma (Flk+/Cre+), and evaluated tissue after blood flow dependent AKI, utilizing, and blood flow independent/nephrotic AKI utilizing cispalatin and focused on the recovery phase (7, or 28 days) post injury.

Results: We determined that EMES cells were upregulated 7 days after IRI contributing to vascular recovery. We next determined following both AKI models that development of stromal gene expression was re-expressed, suggestive of stromal de-differentiation, which may drive EMES proliferation. To interrogate the importance of EMES cells after AKI, we used Flk1+ animals subjected to IRI or cispalatin, and found mutants had less perfusion and increased HIF1α expression at 7 days in IRI models while cispalatin treatment increased perfusion but increased HIF1α. In both models, prevalent proximal tubule de-differentiation was observed in mutants. Furthermore, 28 days after IRI injury mutants contained significant fibrosis, and damage compared to controls.

Conclusions: Following AKI the renal stroma requires de-differentiation and re-expression of development stromal genes prior to proliferation and re-differentiation. This coupled with EMES cell proliferation, reestablishes normal oxygen concentrations and regulates HIF signaling to modulate repair and recovery from AKI.
Funding: NIDDK Support

TH-OR017
Kidney PANX1 Releases ATP to Mediate Ischemia-Reperfusion Injury Jakub Jankowski,1 Heather M. Perry,1 Liping Huang,1 Diane L. Rosin,2 Christopher B. Medina,3 Brant Isaksen,4 Kodi S. Ravichandran,5 Mark D. Okusa.1 1Department of Medicine, University of Virginia, Charlottesville, VA; 2Department of Pharmacology, University of Virginia, Charlottesville, VA; 3Department of Microbiology, Immunology, and Cancer Biology, Center for Cell Clearance, University of Virginia, Charlottesville, VA; 4Robert M. Berne Cardiovascular Research Center, Department of Molecular Physiology and Biological Physics, University of Virginia, Charlottesville, VA.

Background: Extracelluar ATP, a DAMP molecule, is deleterious in a number of kidney disease models. There is little data on its source and impact in AKI. We hypothesize that ATP is released from injured kidney cells by transmembrane panxemkn (PANX1) channels and mediates ischemia-reperfusion injury (IRI). Earlier we reported that global PANX1 KO mice are protected against kidney IRI. We hypothesize that PANX1 expression on specific cell types in the kidney can contribute to injury by different mechanisms.

Methods: Proximal tubule (PT) and endothelial cell (EC) specific PANX1 KO mice (PepckCrePannx1−/− and VECAcadCrePannx1−/−, n = 7 and 9 respectively) and appropriate controls were subjected to 26m bilateral kidney IRI or sham operation and 24h of reperfusion. To generate bone marrow chimeras global PANX1 KO and control mice (n = 18 and 20) were lethally irradiated and 1×10^6 donor bone marrow cells were administered i.v. and after 9 weeks mice were subjected to IRI. Kidney function and injury were assessed by plasma creatinine (Pcr) and stereological quantification of acute tubular necrosis (ATN). Markers of kidney injury were quantified by real-time PCR of whole kidney lysates. Marime proximal tubule cell line (TKPTS) was transfected using CRISPR/Cas9 to create stable PANX1 deficiency. Injury after in vitro hypoxia/reoxygenation (H/R) was assessed by fluorescent ATP release assay and qPCR.

Results: PANX1 KO mice receiving PANX1 KO bone marrow (KO→KO) had lower Pcr levels compared to WT→WT group after injury (0.57 vs 1.67; p<0.0001). KO→WT and WT→KO chimeras had increased levels of plasma creatinine compared to WT→WT (1.67 vs 0.38; p<0.0001), suggesting importance of parenchymal PANX1 deficiency in mediating tissue protection. The increase in Pcr in WT mice subjected to IRI was attenuated in both PT (1.75 vs 0.28; p<0.0001) and EC specific PANX1KO (1.3 vs 0.16; p<0.0001). Histological injury scores were also lower in both PT (28.7% vs 87.8%; p<0.001) and EC PANX1KO (22.5% vs. 89.3%; p<0.001) compared to their respective controls. In TKPTS cells subjected to H/R medium ATP content and TNFα expression correlated positively with Pannx1 expression.

Conclusions: These results show that loss of PANX1 from both PT and endothelium protects mice kidneys from IRI. Targeting parenchymal PANX1 may lead to new therapeutic agents in the treatment of AKI.
Funding: NIDDK Support

TH-OR018
Towards Single Cell RNA-sequencing of Tubular Epithelium in AKI Haojia Wu,1 Erin L. Donnelly,1 Samantha A. Morris,2 Benjamin D. Humphreys.3 1Division of Nephrology, Washington University in St. Louis, Saint Louis, MO; 2Department of Developmental Biology, Washington University in St. Louis, Saint Louis, MO.

Background: A complete transcriptional atlas of epithelial states and dynamics during acute kidney injury is a goal of the Kidney Precision Medicine Project. Here, we apply DropSeq, a microfluidic single cell RNA sequencing (scRNA-seq) technique, to characterize kidney tubule single cell transcriptional signatures. We additionally asked if MeOH fixation allows storage of single cells for subsequent scRNA-seq.
Methods: Mouse kidney was dissociated with Liberase TL and DNase I. Single cells were fixed by methanol and stored in -80°C for 4 days. Rehydrated cells were purified by FACs and Dropseq performed according to Macosko et al. Unsupervised clustering was performed to group the kidney cells into separate clusters based on the biological variation in gene expression. Cell types were annotated with known markers or by comparing to a published tubular cell transcriptional profiling dataset.

Results: High quality DropSeq cDNA libraries (average insert size of 1284bp) was generated from MeOH fixed kidney cells. We sequenced 3103 fixed cells at a depth of 7795 reads/cell, detecting an average of 2283 transcripts and 961 genes per cell. Unbiased clustering revealed 12 separate cell types in kidney. This included six tubular cell types, including proximal tubule (PT), Loop of Henle (LOH), distal tubule, connecting tubule and collecting duct. A majority of the cells (67.7%) expressed proximal tubular markers (Slc34a1 and Lp2), highlighting the preference of PT cell type dissociation with the use of Liberase TL. Reclustering analysis of Slc34a1 expressing cells further revealed 5 separate subtypes within the PT cluster. These included three distinct PT subtypes that correspond to s1, s2 and s3 segments. Interestingly, we identified two distinct PT subtypes co-expressing LOH markers (e.g. Wdca2 and Ptfl). Differences between s1 and s2 were statistically significant as assessed by Wilcoxon rank-sum test.

Conclusions: DropSeq can be performed on MeOH fixed mouse kidney cells. This will facilitate future analysis of human kidney, whose availability is unpredictable, and allow generation of biobanks for downstream scRNA-seq analysis. Our approach enriches for tubular cell types, including s1, s2 and s3 segments of the proximal tubule, making it well suited for analysis of acute tubular injury and repair at cellular resolution.
Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
TH-OR019

Inhibition of Endothelial PHD2 Protects against Ischemic Kidney Injury through HIF-1 Dependent Suppression of Neutrophilic Inflammation
Ganeshkumar Rajendra,1 Michael P. Schonfeld,2 Rafael Torsosyan,3 Fineopli P. Kapitsinou.1 KANSAS UNIVERSITY MEDICAL CENTER, KANSAS CITY, KS; 2KUMC - University of Kansas Medical Center; Kansas City, KS; 3University of Kansas Medical Center, Kansas City, KS.

Background: Peritubular endothelial cells (ECs) are major determinants in renal ischemia reperfusion injury (IRI) but the molecular mechanisms remain undefined. Key regulators of hypoxic vascular responses are Hypoxia-Inducible-Factors (HIF) 1 and 2, transcription factors whose activity is inhibited by prolyl-hydroxylase domain proteins 1 to 3 (PHD1 to PHD3). PHD2 being the main oxygen sensor. We previously reported that deficiency of endothelial PHD2 exacerbated renal IRI, while inactivation of endothelial PHD2 provided renoprotection. Here, we investigated the contribution of HIF1/HIF2 in renoprotection induced by endothelial PHD2 loss.

Methods: EC-specific HIF activation was achieved by crossing Vecadherin (Cdh5)-Cre transgenic mice with HIF-1 deficient and/or PHD2 deficient mice. Double PHD2 deficient mice were cross-bred with HIF-1α deficient mice. Immunohistochemistry, TUNEL analysis, cell apoptosis and capillary density were measured.

Results: Deletion of HIF-1 in endothelial PHD2 deficient background completely reversed the renoprotection conferred by endothelial PHD2 loss as indicated by histological injury scores and Ki67 mRNA levels in kidney homogenates (Day 3 post IRI, n=8 mice). In contrast, double ePHD2HIF2 mutants had attenuated kidney injury with ~1.7 fold down-regulation in Ki67 transcript levels compared to controls. CD45 staining showed comparable inflammatory cell infiltration in ePHD2HIF1 injured kidneys with C57, while ePHD2HIF2 kidneys had significantly less CD45+ area than their corresponding controls. Consistently, FACS analysis indicated significant reduction in neutrophils in ePHD2HIF2 kidneys while no difference was detected in ePHD2HIF1 in ECs. IRI was induced by unilateral renal artery clamping.

Conclusions: These results suggest that miR-709 plays an important role in mediating the effects generated by endothelial PHD2 deficiency through suppression of leukocyte recruitment and adhesion to endothelium.

Funding: Other NIH Support - NIH/NIGMS/PO2GM104936, Private Foundation Support

TH-OR020

MicroRNA-709 Mediates Acute Tubular Injury by Negatively Regulating the TFAM/Mitochondria Axis
Songming Huang,1 Zhanjun Chang,1 Liping Zhu,1,2,3 Xiaobo Zhou,1,2,3 Xiaoyan Guo,2 Yue Zhang,1 Songming Huang,1,2,3 Zhanjun Jia1 1Nephrology Department, Children’s Hospital of Nanjing Medical University, Nanjing, China; 2Nanjing Medical University, Nanjing, China.

Background: Mitochondrial dysfunction (MtD) plays important roles in the pathogenesis of acute kidney injury (AKI), whereas therapeutic approaches to improve mitochondrial function are still limited. In the present study, we investigated the pathogenic role of miR-709 in mediating mitochondrial impairment and tubular cell death in AKI.

Methods: We used cisplatin-induced AKI mouse model and renal tubular cells to investigate the role of miR-709 in AKI, as well as the mechanisms. The mitochondrial function was determined by the examination of mitochondrial DNA copy number, mitochondrial membrane potential, mitochondrial ROS production, oxygen consumption, and the expressions of mitochondrial proteins.

Results: In cisplatin-treated mice, renal miR-709 was significantly upregulated by more than 2 folds. In proximal tubular cells (PTCs), cisplatin led to 6-fold increase of miR-709. Depletion of miR-709 in mouse PTCs significantly induced MtD and cell apoptosis (50%), whereas inhibition of miR-709 ameliorated cisplatin-induced MtD and cell apoptosis (about 50%). Further analyses showed that TFAM (mitochondrial transcriptional factor A) is a target gene of miR-709 and that genetic restoration of TFAM blocked the MtD and cell injury induced by cisplatin or miR-709 overexpression.

More importantly, miR-709 antagonism with a miR-709 antagonim dramatically attenuated cisplatin-induced kidney injury and MtD in mice. Finally, we verified the overexpression of miR-709 in renal PTCs of 21 patients with AKI of various etiologies (ischemia, nephrotoxins et al), and found a close correlation between the expression of miR-709 and the severity of kidney injury.

Conclusions: These results suggest that miR-709 plays an important role in mediating cisplatin-induced AKI via negative regulation of TFAM and subsequent MtD.

TH-OR021

DNAJ Homolog Subfamily B Member 9 Is a Putative Autoantigen in Fibrillary Glomerulonephritis
Nicole K. Andeen,1 Han-Yin Yang,1 Daf-Dai,1 Michael Maccoss, Kelly D. Smith. University of Washington, Seattle, WA.

Background: Fibrillary glomerulonephritis (FGN) is a rare form of glomerulonephritis of uncertain pathogenesis, which is characterized by the glomerular accumulations of non-branched, randomly arranged fibrils composed of immunoglobulin and complement proteins. In this study, we utilized mass spectrometry to comprehensively define the glomerular proteome in FGN compared to controls and non-FGN renal diseases.

Methods: Glomeruli from formalin-fixed and paraffin-embedded biopsies were isolated using laser capture microdissection (LCM) and analyzed with liquid chromatography and data-dependent tandem mass spectrometry (LC MS/MS). Findings were correlated with immunohistochemistry (IHC).

Results: These studies identified DNAJ homolog subfamily B member 9 (DNAJB9) as a frequently sampled protein by mass spectrometry in FGN cases that was not detected in other samples. The glomerular proteome of FGN cases also contained IgG1 as the dominant immunoglobulin and proteins of the classical complement pathway. Immunostaining with anti-DNAJB9 demonstrated strong and specific staining of the glomerular tufts in a distribution that mimicked the immune deposits of FGN cases.

Conclusions: Our results identify DNAJB9 as a putative autoantigen in FGN and IgG1 effector pathways as likely mediators for the destructive glomerular injury in FGN.

Funding: Other NIH Support - This work was supported by NIH grants: R21 CA192983, P41 GM103533, and P30 AG013280 (MM), and the University of Washington Department of Pathology (KS, NA).

TH-OR022

Antibody Guided Therapy with Cyclophosphamide and Prednisone in Patients with Membranous Nephropathy
Anne-Els van Logt1, Coralien Vink- van Setten,2 Julia M. Hofstra,2 Jack F. Wetzels.2 Hospital Gelderse Vallei, Ede, Netherlands; 1Radboud University Medical Center, Nijmegen, Netherlands.

Background: The discovery of anti-PLA2R antibodies provides options for individualized therapy in patients with membranous nephropathy (MN). We previously showed that monitoring of anti-PLA2R allowed shortening of the overall duration of cyclophosphamide (Cyc) treatment (van de Logt, Kidney week 2015). Here we present longer-term follow-up data.

Methods: Cyc therapy (combined with steroids) is started in patients with aPLA2R positive MN and high risk of progression. In our antibody guided cohort aPLA2R are repeatedly monitored (IFT test) at 8, 16, and 24 weeks after start of treatment. If
remission beyond two years after start of therapy (Figure 1). The relapse rate however is increased. Still, 70% of patients remain in remission at 12 months after onset of remission was 21% and after 24 months 30% in our cohort. Disappearance of aPLA2R was on average short (median 2.1 month), however ranged from 1.4 to 14.6 months. Cumulative remission rates (PCR <3.0 g/l 10 mmol) were 52% and 76% respectively and 6 and 12 months after start of therapy, not significantly different from historical controls (40% and 60%). The cumulative incidence of relapses at 12 months after onset of remission was 21% and after 24 months 30% in our cohort (respectively 16% at 24 months in historical controls, van der Brand JASN 2014).

Conclusions: Overall, this strategy shortens the duration of Cyc therapy, maintaining remission rates. The relapse rate however is increased. Still, 70% of patients remain in remission beyond two years after start of therapy (Figure 1).

Funding: Government Support - Non-U.S.

TH-OR024

Presence of Cellular or Fibrocellular Crescent Is Important for a Long-Term Renal Prognosis in Patients with IgA Nephropathy Followed for 10 Years or Longer on Average

Takayuki Fujii, Satoshi Suzuki, Noriko Terasaki, Kaiji Saito, Mizuki Shinozaki, Mayu Morimoto, Tanaka Hiroaki. Seirei Sakura Citizen Hospital, Sakura-shi Chiba, Japan.

Background: Regarding the prognosis of patients with IgA nephropathy, the addition of the crescent score: C0 (no crescent), C1 (crescents in more than zero but less than one fourth of glomeruli), and C2 (crescents in one fourth or more of glomeruli), to the conventional factors of the Oxford classification: M, E, S, T score has been proposed (J Am Soc Nephrol 2017). However, the observation period in the above study was relatively short (mean: 4.7 years) and it is unclear whether the C score, which may be modified by treatment, serves as a factor associated with the long-term prognosis of patients followed for more than 10 years on average. We investigated the influence of the C score on the long-term prognosis.

Methods: The subjects were 658 patients with biopsy-proven IgA nephropathy who could be followed up for one year or longer, or reached end stage kidney disease and required renal replacement therapy within one year. A single-center retrospective cohort study was performed involving these patients. Setting the outcome at 50% reduction of eGFR, the influence of the C score on the prognosis was investigated using the Kaplan-Meier method and Cox proportional hazard model. Model A was adjusted with the clinicopathological data including time average proteinuria (TAMAP) and time average mean blood pressure (TAMP) during the course, and the M, E, S, and T scores, and model B was adjusted with model A + treatment with or without steroid and RAS inhibitors for analysis.

Results: The mean observation period was 10.9±8.8 years, eGFR at the time of kidney biopsy was 75.8±26.4 mL/min/1.73 m², TAMAP was 8.8±1.2 g/day, and C1 and C2 accounted for 18.2% and 1.5%, respectively, and the outcome was reached in 18.0%. On analysis using the Kaplan-Meier method, the outcome was significantly more favorable in the order of C0, C1, and C2 (log-rank p<0.0001). Regarding C0 as the reference, HR of C1 was 1.68 (95% CI: 1.04-2.64) in model A and 1.81 (95% CI: 1.11-2.87) in model B, showing that the score was applicable as a prognostic predictor in addition to the Oxford T score, TAMAP, and eGFR at the time of kidney biopsy.

Conclusions: The C score was important for a long-term renal prognosis even when treatment was included in the analysis.

TH-OR023

Immunological Remission in PLA2R-Associated Antibody-Associated Membranous Nephropathy (MN): Cyclophosphamide versus Rituximab

Anne Els Ronco,2 Karine Dahan,3 Alexandra Roussseau,1 Hanna Debiec,5 Pierre M. Ronco,2 Jack F. Wetzels,4 AP-HP, Paris, France; Hospital Tenon, Paris, France; INSERM UMR S702, Paris, France; Radboud University Medical Center, Nijmegen, Netherlands.

Background: Rituximab (cumulative dose 750 mg/m2) induces remissions in patients with MN (Kahan JASN2017). However, efficacy is limited in patients with high anti-PLA2R (aPLA2R) levels. Rituximab therapy is effective independent of anti-PLA2R levels (van de Logt SA-PO 631, kidneyweek 2016). aPLA2R disappeared in all patients with MN (Kahan JASN2017). However, efficacy is limited in patients with high anti-PLA2R (aPLA2R) levels. Cyclophosphamide therapy is effective independent of aPLA2R levels (van de Logt SA-PO 631, kidneyweek 2016). Incidence of partial remissions was higher with Cyclophosphamide vs Rituximab (van de Brand JASN2017). Rituximab. The response was associated with baseline titers (table 1). Rituximab did not significantly improve the relapse rate, but one patient treated with Cyclophosphamide, and in 13 of 27 patients treated with Rituximab in a dose of 750mg/m² is less effective than with Cyclophosphamide (1.5mg/kg/day, duration 8-24 weeks; Nijmegen cohort) and Rituximab (cumulative dose 375 mg/m² at day 1 and 8).

Methods: We included 30 anti-PLA2R positive patients treated with Cyclophosphamide and 27 patients treated with Rituximab. In stored samples (baseline, and at the end of therapy or after 6 months) aPLA2R were measured with ELISA (Euroimmun®).

Results: In the Cyclophosphamide cohort 19 patients were male, mean age was 56 ± 13 years, median serum creatinine level was 1.3 g/dl (IQR 1.1-1.6) and median protein creatinine ratio 7.7 g/g (IQR 5.5-11.3). In the Rituximab cohort, 21 patients were male, mean age was 51 ± 14 years, median serum creatinine level was 1.1 g/dl (IQR 0.93-1.3) and median protein creatinine ratio 8.4 g/g (IQR 4.4-11.0). aPLA2R disappeared in all but one patient treated with Cyclophosphamide, and in 13 of 27 patients treated with Rituximab. The response was associated with baseline titers (table 1). Rituximab did not induce immunological remission in patients in the highest tertile of aPLA2R levels.

Conclusions: Rituximab in a dose of 750mg/m2 is less effective than Cyclophosphamide in inducing an immunological remission in patients with MN and high antibody levels. This multi-center cohort study compared the clinico-pathological parameters at diagnosis, initial therapies and outcomes between 106 adult (age 19 - 64 years), and 46 elderly (age 65 years) patients with biopsy proven MN who were registered in the J-RBR between 2007 and 2012. The primary end-points comprised a 50% increase in serum creatinine (C) values or end-stage kidney disease. Factors affecting a decrease in renal function were assessed using a Cox proportional hazards model.

Results: The rates of hypertension, impaired renal function, hypalbuminemia, and crescentic glomerulonephritides were significantly higher among the elderly, compared with the adult patients. About 80% and 80% of the patients in both groups were respectively treated with corticosteroid and renin-angiotensin system (RAS) inhibitors. Both groups had favorable renal survival rates for nine years (93.6% and 91.4% of the adult and elderly patients, respectively). Significantly more elderly than adult patients developed a 50% increase in C during a mean observation period of 3.9 years (21.7% vs. 4.7%, p = 0.012). In addition, significantly fewer elderly than adult patients achieved clinical remission (24% vs. 46%, p = 0.016). Multivariate analysis revealed that advanced age (≥ 65 years) was an independent prognostic factor for a decline in renal function (HR, 6.08; p = 0.018).

Conclusions: The renal prognosis of adult and elderly patients with Henoch-Schönlein purpura nephritis has not been investigated in detail. We therefore surveyed the features and outcomes of HSPN based on nationwide data from the Japan Renal Biopsy Registry (J-RBR). This multi-center cohort study compared the clinico-pathological parameters at diagnosis, initial therapies and outcomes between 106 adult (age 19 - 64 years), and 46 elderly (age 65 years) patients with biopsy proven MN who were registered in the J-RBR between 2007 and 2012. The primary end-points comprised a 50% increase in serum creatinine (C) values or end-stage kidney disease. Factors affecting a decrease in renal function were assessed using a Cox proportional hazards model.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
TH-OR026

Renal Complications during Pregnancy Before and After Glomerulonephropathy Diagnosis
Andrea L. Oliverio,1,2 Monica L. Reynolds,1,2 Laura H. Mariani,1,2 Michelle M. O’Shaughnessy,1,2 Jarcy Zec,1,2 Michelle A. Hladunewich,1,6 1Arbor Research Collaborative for Health, Ann Arbor, MI; 2Stanford University Medical Center, Palo Alto, CA; 3University of Michigan, Ann Arbor, MI; 4University of Toronto, Toronto, ON, Canada; 5University of North Carolina, Chapel Hill, NC; 6CureGN Women’s Health Working Group, Bethesda, MD.

Background: Pregnancy studies in women with glomerulonephropathy (GN) are limited to single centers and small samples. Delinquent pregnancy-associated risks would better inform counseling and determine safe management strategies.

Methods: CureGN is an ongoing 64-center prospective cohort study of children and adults with biopsy-proven MCD, FSGS, MN, or IgAN/IgA. Patient-reported pregnancy outcomes and maternal/fetal complications are collected at each study visit. Descriptive statistics were used to assess complications of pregnancies before and after GN diagnosis. Among pregnancies prior to diagnosis, a generalized estimating equation model was fit to compare time to diagnosis for those with and without pregnancy complications.

Results: As of May 2017, 273 out of 427 adult women enrolled in CureGN reported 585 pregnancies prior to GN diagnosis and 30 after diagnosis, excluding elective terminations. Of pregnancies after GN diagnosis, 9.0% were with MCD, 42.0% with FSGS, 13.3% with MN, and 33.3% with IgAN. Of those with pregnancies prior to GN diagnosis, 12.5% reported increasing proteinuria, 5.8% worsening kidney function, and 5.8% worsening blood pressure and 88.5% full term delivery compared to 48.1%, 35.7%, 25.9%, and 57.1%, respectively among pregnancies after diagnosis. Women with pregnancy complications prior to diagnosis had a significantly shorter time between pregnancy and subsequent GN diagnosis than those with uncomplicated pregnancies (Figure).

Conclusions: Pregnancies in women with GN diagnosis had high rates of maternal/fetal complications, necessitating high-risk care. Decreased latency between complicated pregnancies and subsequent GN diagnosis suggests that diagnosis may have been missed during pregnancy or that the physiologic stress of pregnancy may have unmasked a smoldering glomerular disease. While currently at 73% of target enrollment, CureGN is projected to be the largest multi-center international cohort study to pose study pregnancy outcomes in women with GN.

Funding: NIDDK Support

TH-OR027

Similarities between THSD7A and PLA2R Antigens in Autoimmune Membranous Nephropathy (AMN) (AMN) Samuel Rhoden,1 Maryline Fresquet,2 Thomas A. Jowitt,1 Jennet O. Gummadova,1 Ian Roberts,1 Rachel Lennon,1 Paul E. Brenchley,1,7 John Radcliffe Hospital, Headington, United Kingdom; 2Manchester Royal Infirmary, Manchester, United Kingdom; 3University of Manchester, Manchester, United Kingdom.

Background: Patients with AMN either have autoantibodies against PLA2R (75%) or THSD7A (2%). PLA2R and THSD7A proteins share similar structural and biochemical properties. Both proteins are large transmembrane receptors expressed on podocytes with multiple disulfide-bonded and N-glycosylated extracellular domains. We previously described the major epitope within PLA2R but the dominant epitope in THSD7A is still unknown. Hypothesis: The major epitope in THSD7A may share shape homology with PLA2R.

Methods: Recombinant full length extracellular domains of THSD7A (FL 180kDa) and a fragment (NT 120kDa) were expressed, purified and used to screen 1400 AMN sera by ELISA for anti-THSD7A. Clinical phenotype on 10 cases was collected. Biopsies were stained for THSD7A and PLA2R. Sera were characterised by western blotting, ELISA and slot blotting on various THSD7A fragments and peptides. The homology model of the PLA2R CyR domain was used to thread the THSD7A epitope peptide.

Results: 22 cases negative for anti-PLA2R were found anti-THSD7A positive (2%). We selected the 10 highest titre sera from the MN group (6F/4M mean age = 64yr). All 10 sera could be inhibited by the THSD7A NT fragment indicating an epitope(s) within this region. Interestingly a short sequence within the NT fragment shares homology with the PLA2R epitope. This short sequence peptide bound antibodies by slot blotting and inhibited binding to the antibodies by ELISA in all patients’ sera suggesting a potential epitope in THSD7A. Homology modelling of these two epitopes in PLA2R and THSD7A revealed two regions important for antibody binding.

Conclusions: We describe the first ELISA for anti-THSD7A and report an incidence of 2% positivity in a large cohort of anti-PLA2R negative AMN patients. We identified a specific region on THSD7A with structural homology to the major epitope in PLA2R and show this sequence to be a potential epitope in THSD7A. These results suggest a pathological epitope structure common to autoantigens involved in MN.

Funding: Private Foundation Support

TH-OR028

The Microbiota Is a Central Determinant in IgA Nephropathy as Its Modulation Prevents Disease Development
Jonathan M. Chemouny,1,2,6 Patricia Lepage,1,3 Patrick J. Glesson,1,2 Lilia Abbad,4 Agnes Jamin,5 Eric Daugas,2,4,6 Francois Vtvosniki,5,6 Sanae Ben mkaddem,7 Laurethel Berthelot,1,8 Marion Leclerc,1 Renato C. Monteiro,1,9 INSERM U1149 & ERL8252 CNRS, Paris, France; 1AP-HP, Hospital Bichat, Paris, France; 2INRA, Jouy-en-Josas, France.

Background: IgA nephropathy (IgAN) is associated with microbiota dysbiosis when compared to healthy individuals (De Angelis et al. PLos One 2014). Here, we studied the composition of fecal microbiota of IgAN patients compared with non-IgAN glomerular disease (non-IgAN-GD). An IgAN mouse model (e1KI1-CD89f) was used to study the effect of gut microbiota modulation in disease development.

Methods: We collected feces from patients with IgAN and non-IgAN-GD. Fecal microbiota compositions were studied through 16S rDNA pyrosequencing. For the experimental part of the study, 31 four-week old male e1KI1-CD89fTg mice were fed an antibiotic mix (ATB) or vehicle twice a week for 8 weeks. Urine samples were collected before the first administration. At the end of experiments, urine, blood samples and kidneys were collected. Proteins and creatinine were measured.

Results: IgAN and non-IgAN-GN patients showed significant differences in proportions of the main phylum Firmicutes (p=0.020) and in Lentispherae (p=0.019). As the data suggest an IgAN-linked dysbiosis, we targeted the gut microbiota in a mouse model of IgAN to modulate disease expression. As expected total bacterial load was significantly lesser in the ATB group (p=0.001). Protein/creatinine ratio (PCR) did not rise over the course of 12 weeks in the ATB group (p=0.436) whereas there was a significant increase (p=0.001) in the PCR in the vehicle control group. Markedly less mesangial IgA1 deposits was seen in the ATB group. While no differences were seen in serum human IgA1 levels in the mice, there were significantly fewer lymphoid follicles in Peyer’s patches (p) among ATB treated as compared to vehicle group.

Conclusions: Our data suggest the gut dysbiosis in IgAN patients may be independent of the effect of KD. Moreover, gut commensal bacteria may have a pathogenic role in IgAN as gut microbiota modulation through the administration of antibiotics prevented disease development in mice. Finally, nephrotic IgA1 may originates from the gut mucosa, as despite the presence of PP alterations in ATB group, serum IgA1 levels remained unaffected.

Funding: Government Support - Non-U.S.

TH-OR029

Ubiquitin Carboxyl-Terminal Hydrodase L1 Is a Podocyte Target of IgG Antibodies in Idiopathic Nephrotic Syndrome (INS) Georges Deschênes,1 Agnes Jamin,1 Laureline Berthelot,4 Renato C. Monteiro,1 Bichat Medical School, Paris, France; 2Hospital Robert Debre, Paris, France; 3INSERM U1149 & ERL8252 CNRS, 75018 Paris, France; 4INSERM U699, Paris, France.

Background: The efficiency of B cell-depleting treatments highlights the involvement of B cells in INS. This study searched for identifying antibodies (Abs) directed against podocytes in patients with INS.

Methods: The study was performed using a biobank including 86 patients sampled at various stages of INS and 76 controls. Fractions of plasma obtained by size exclusion chromatography and tested on cultured podocyte adhesion; specificities of IgG Abs contained in the plasma fraction of interest were studied through immunoprecipitation of a podocyte lysate then identification of cognate antigens by liquid chromatography-mass spectrometry.

Results: Cultured podocyte detachment was observed with one specific plasma fraction in 16/34 INS relapsing patients, 1/11 INS patients in remission and 0/25 controls. IgG were isolated from this specific plasma fraction in 3 INS relapsing patients (all detaching cultured podocytes), 3 from the same INS patients in remission (all not detaching cultured podocytes) and in 3 controls, then used to immunoprecipitate a podocyte lysate. Comparative proteomic analysis allowed selecting 5 proteins according to statistical and biological criteria. Specific Abs were tested and only anti-Ubiquitin Carboxyl-Terminal Hydrodase L1 (UCHL1) IgG led to podocyte detachment. Precipitation of either anti-UCHL1 IgG Abs or plasma fractions with recombinant UCHL1 prevented podocyte detachment. Plasma levels of anti-UCHL1 IgG Abs were increased in 18/34 INS patients compared to the highest level of 38 ± 20 µg of total IgG (0.15-0.29 range; 0.07-0.85). For those 18 patients, the level of anti-UCHL1 IgG Abs in 43 samples available at various stage of INS was confirmed to be significantly higher in relapse (n=23;median=1.22±0.45 of total IgG; IQ 0.92-1.90) compared to remission (n=20;median=0.51±0.3; 0.33–0.77; p=0.001). In those 18 INS patients, proteinuria correlated with anti-UCHL1 IgG Abs level (n=43; r=0.57; p<0.001).

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Circulating Serum miR-148b and let-7b Are Inherited in IgA Nephropathy (IgAN) 

TH-OR030

Circling Serum miR-148b and let-7b Are Inherited in IgA Nephropathy (IgAN)

Trios Grazia Serino, Sharon N. Cox, Massimiliano Copetti, Luigi Bisceglia, Gianluigi Zaza, Isabella Squarzon, Martina Ferarese, Luigi Biancone, Francesco P. Schena, Azienda Ospedaliero Universitaria Integrata Verona, Verona, Italy; ‘Department of Medical Science, Turin, Italy; ‘IRCCS, San Giovanni Rotondo, Italy; ‘Nephrology, Dialysis and Transplantation, Turin, Italy; ‘University of Bar, Bar, Italy; ‘University of Verona, Verona, Italy; ‘IRCCS ‘S. de Bella’, Castellana Grotte (BA), Italy; ‘IRCCS Casa Solltivo della Sofferenza, San Giovanni Rotondo (FG), Italy; ‘Schena Foundation, Valenzano (BA), Italy.

Background: IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis worldwide characterized by aberrant O-glycosylation in the hinge region of IgA1. Our recent work demonstrates that serum levels of the combined miRNA biomarker, let-7b and miR-148b, appears to be a novel, reliable, and non-invasive test to predict the probability of having IgAN (Kidney International, 88, 683-692; 2016). In this study our aim was to evaluate if the serum levels of the combined biomarker are heritable.

Methods: Serum miRNA was extracted using QIAzol Lysis Reagent and miRNAeasy Mini Kit (Qiagen) according to the manufacturer’s protocol. Using quantitative real-time PCR, we evaluated the expression of circulating miRNAs (let-7b and miR-148b) in 90 trios that consists of one IgAN patient and their two parents. Heritability was estimated using the approach proposed in Rabe-Hesketh et al. (Biometrics, 64, 280-288, 2008) implemented in R package “gap”.

Results: We found that serum levels of the combined biomarker (let-7b and miR-148b) were elevated in the first-degree relatives of IgAN patients compared with healthy blood donors (IgA0.3±0.23; IgAN relatives 0.29±0.18; HBD -1.04±0.09). In addition, serum level of the combined biomarker did not differ between IgAN patients and their relatives (p=0.93). The estimated heritability (h2) of the serum biomarkers was 37.54% (95%CI: 13.57%-61.51%; p=0.001) in crude (unadjusted) model. Age- and gender-adjusted heritability improved at 52.94% (95%CI=22.28%-83.59%, p=0.00035).

Conclusions: These results suggest that serum levels of the combined biomarker are, in part, genetically determined and may constitute a helpful tool for screening of relatives at risk for IgAN development.

Funding: Government Support - Non-U.S.

TH-OR031

EXPEDITION-4: Efficacy and Safety of Glecaprevir/Pibrentasvir in Patients with Chronic Hepatitis C Genotype 1b Infection by Dialysis Status

Csaba P. Kovessy, Emily Dumas, Alexander Thompson, Yves Horsmans, Hendrik Reynaert, Peter Ghiili, Laurent Alric, Dominique Larrey, Giuliano Rizzardini, Caroline Park, Yang Lei, David Pugatch, Federico Menua, Magdy Elkhishab, Meghan E. Sise, University of Texas Health Science Center, Memphis, TN; ‘V.S. Vincent’s Hospital Melbourne and the University of Melbourne, Fitzroy, NSW, Australia; ‘Université Catholique De Louvain, Louvain-la-Neuve, Brussels, Belgium; ‘University Hospital UZBrussel, Brussels, Belgium; ‘McGill University, Montreal, QC, Canada; ‘CHU Toulouse, Toulouse, France; ‘Hôpital Saint Eloi CHR Montpellier, Montpellier, France; ‘Ospedale Luigi Sacco, Milan, Italy; ‘AbbVie, Chicago, IL; ‘University of Michigan, Ann Arbor, MI, ‘Tororo Liver Centre, Toronto, ON, Canada.

Background: Hepatitis C (HCV)-infected patients with late-stage kidney disease have limited treatment options. The ribavirin-free regimens of glecaprevir/pibrentasvir (coformulated as G/P; glecaprevir identified by AbbVie and Enanta) has a renal excretion of <1% and has yielded sustained virologic response (SVR) >97% in clinical trials. Here we report efficacy and safety by dialysis status from a Phase 3 study of G/P in HCV genotype 1b (GT) 1-6-infected patients.

Methods: HCV GT1-6 patients with an eGFR <30 mL/min/1.73 m², without cirrhosis or with compensated cirrhosis, received G/P (300 mg/120 mg) once daily for 12 weeks. Patients with compensated cirrhosis, received G/P (300 mg/120 mg) once daily for 12 weeks. Outcomes were analyzed by predialysis (CKD stages 4-5) and dialysis status.

Results: The trial enrolled 104 patients (predialysis, 19; dialysis, 85): 76% were HCV GT1-6 patients with an eGFR <30 mL/min/1.73 m². Median baseline (IQR) age was 58 (50-64) years; 63% were male; 74% were white; and 48% had a BMI ≤30. The mean (SD) baseline HCV viral load was 6.23 ± 0.35 log10 IU/mL. The median (IQR) serum creatinine was 10.6 (8.2-14.9) mg/dL. G/P was generally well tolerated. The most common treatment-emergent adverse events were fatigue (21%), nausea (20%), and headache (19%). The most common adverse events were headache (19%), nausea (20%), and fatigue (21%). All adverse events were related to G/P. The treatment-related adverse events included fatigue (12%), nausea (11%), and headache (10%). The treatment-related adverse events included fatigue (12%), nausea (11%), and headache (10%).

Conclusions: G/P is an all-oral pangenotypic anti-HCV treatment with high efficacy and a favorable safety profile, regardless of patients’ dialysis status.


TH-OR032

Intensive Systolic Blood Pressure (SBP) Control and Incident CKD in Persons with and without Diabetes Mellitus (DM)

Srinidhi Beddhu, Alfred K. Cheung, Glenn M. Chertow, Paul K. Whelton, Guo Wei, Paul L. Kimmel, William C. Cushman, Tom Greene. ‘Univ of Utah, SLC, UT; ‘Stanford Univ, Palo Alto, CA; ‘Tel Aviv Univ, New Orleans, LA; ‘NIDDK, Bethesda, MD; ‘YAMC, Memphis, TN.

Background: In Systolic Blood Pressure Intervention Trial (SPRINT), higher incidence of CKD with intensive SBP control in persons without DM was reported. It is unclear whether intensive SBP control has similar effects in DM.

Methods: SPRINT tested the effects of SBP goal <120 vs. <140 mm Hg on CV outcomes in persons without DM whereas Action to Control Cardiovascular Risk in Diabetes (Atherosclerotic Risk in Diabetes [CARD] or ORBIT) BP trial tested the same in type 2 DM. In separate Cox models, we related the interventions to incident CKD (defined as a >30% decrease in eGFR to a value <60 mL/min/1.73 m²) in participants without CKD at baseline (N = 6677 in SPRINT; N = 4305 in ACCORD).

Results: Baseline characteristics are summarized in (table). The absolute risks of incident CKD estimated by Kaplan Meier (KM) curves at 3 years of follow-up in standard vs. intensive arms were 1.0 vs. 3.5% in SPRINT and 4.6 vs. 11.5% in ACCORD with an absolute risk increase % (95% CI) at 3-years of 2.5 (1.8 to 3.2) in SPRINT and 6.9 (5.2 to 8.5) in ACCORD. KM failure curves and hazard ratios are presented in the figure.

Conclusions: Intensive SBP control increased the risk of incident CKD in persons with and without DM, however, absolute risk increase is higher in DM. The long-term implications of these findings need to be established.

Funding: NIDDK Support, Other NIH Support - NHLBI

Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>SPRINT</th>
<th>ACCORD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66.1±19</td>
<td>66.2±19</td>
</tr>
<tr>
<td>Serum Cr (mg/dL)</td>
<td>7.8±7.4</td>
<td>7.5±7.2</td>
</tr>
<tr>
<td>Serum Urea (mg/dL)</td>
<td>35±24</td>
<td>34±26</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>1.0±1.1</td>
<td>1.0±1.0</td>
</tr>
</tbody>
</table>

KM failure curves for incident CKD by treatment arm in SPRINT and ACCORD BP

TH-OR033

Autologous Hematopoietic Stem Cell Transplantation for Refractory Lupus Nephritis

Xiang-hua Huang, Wencui Chen, Weixin Hu, Zhi-Hong Liu, National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China, Nanjing, China.

Background: To evaluate the efficacy and safety of the treatment of autologous hematopoietic stem cell transplantation (ASCT) for patients with refractory lupus nephritis (LN).

Methods: From Jul 2011 to Jan 2015,a total of twenty-two patients with refractory LN and no response to standard immunosuppressive therapies were enrolled in this study. Peripheral blood stem cells were mobilized with cyclophosphamide (CTX) and granulocyte colony-stimulating factor (G-CSF),and reinused after treatment with CTX and antithymocyte globulin(ATG). The primary end point was remission rate,and the secondary end points included the survival and relapse rate, changes in proteinuria, renal function and serology immunologic test. All the complications were recorded for safety access.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Results: Twenty-two patients were enrolled and underwent stem cell mobilization. There were 9 males and 13 females with a median LN duration of 45.5 (33-71) months. The mean number of CD34+ cells was (7.3 ± 3.8) × 10^6/kg. All patients had successful engraftment, and the median time of granulocyte and platelet engraftment was 8 and 9 days, respectively. The major complications of ASCT were fever and symptoms of gastrointestinal tract. The treatment-related mortality was 4.5% (1/22). After a median follow-up of 53 months, eighteen patients (81.8%) achieved complete remission, one patient (4.5%) achieved partial remission, and one had no response and received peritoneal dialysis at 12 years after ASCT. One patient died for sepsis at 5 months after ASCT. The median time of renal response was 3 months. The 5-years overall survival was 90%. The probability of disease-free survival at 5 years following ASCT was 52.9%. Six patients had relapse during the follow-up and the relapse rate was 27.3%.

Conclusions: Our preliminary data shows that ASCT is a safe and effective treatment of refractory LN, the completed response rate was high and the complications was manageable. Infection is still an important cause of treatment failure, the long-term efficacy still need further observation.

**TH-OR034**

**Influence of Baseline Diastolic Blood Pressure (DBP) Level on the Effects of Intensive Blood Pressure Lowering on Incident CKD in SPRINT**

Srini Beddu,1 Glenn M. Chertow,2 Alfred K. Cheung,3 Mahboob Rahman,3 Tom Greene,1 Guo Wei,1 William E. Haley,4 William C. Cushman,5 Mahboob Rahman,3 Paul K. Whelton,7

1Univ Utah, SLC, UT; 2Stanford, Palo Alto, CA; 3CWRU, Cleveland, OH; 4Mayo Clinic, Jacksonville, FL; 5Memorial VA Medical Center, Memphis, TN; 6Tulane Univ, New Orleans, LA. Group: Team, For SPRINT Research Group.

Background: Lowering systolic blood pressure (SBP) in persons with low DBP might affect kidney perfusion and thereby, ↑ risk for incident CKD.

Methods: SPRINT tested the effects of SBP goal <120 vs. ≤140 mm Hg on CV outcomes. We tested for effect modification by baseline DBP of the intervention on incident CKD (defined as a >30% decrease in eGFR to a value <60 ml/min/1.73 m²) in participants without CKD at baseline (N = 6677).

Results: Participants with lower baseline DBP were older, had ↑ prevalence of CV disease and ↓ eGFR (table). There was a U-shaped relation between baseline DBP and incident CKD (Fig Panel A). Within each baseline DBP quintile, participants randomized to the intensive arm had a higher hazard ratio of incident CKD (Fig Panel B). P-value for comparison of hazard ratios in the lowest quintile to the upper 4 quintiles was non-significant (p = 0.58). P-value for the linear treatment by baseline DBP interaction was also non-significant (p = 0.94).

Conclusions: Lower baseline DBP was associated with ↑ risk of incident CKD, but there was no evidence that the effects of intensive SBP lowering on incident CKD differed by baseline DBP.

Funding: NIDDK Support, Other NIH Support - NHLBI

Baseline characteristics by baseline quintiles of DBP in non-CKD subgroup in SPRINT (N = 6677)

<table>
<thead>
<tr>
<th>Variable name</th>
<th>1st quintile (N = 1334)</th>
<th>2nd quintile (N = 1260)</th>
<th>3rd quintile (N = 1169)</th>
<th>4th quintile (N = 1259)</th>
<th>5th quintile (N = 1245)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td>84.5 ± 11.5</td>
<td>88.1 ± 11.2</td>
<td>90.7 ± 10.2</td>
<td>91.6 ± 10.1</td>
<td>91.6 ± 10.1</td>
</tr>
<tr>
<td>Age (year)</td>
<td>72.3 ± 9.1</td>
<td>67.2 ± 8.2</td>
<td>65.9 ± 8.5</td>
<td>63.8 ± 7.3</td>
<td>60.1 ± 7.6</td>
</tr>
<tr>
<td>Female (%)</td>
<td>37.5</td>
<td>32.7</td>
<td>34.1</td>
<td>34.9</td>
<td>34.9</td>
</tr>
<tr>
<td>Black race (%)</td>
<td>28.7</td>
<td>29.6</td>
<td>32.4</td>
<td>31.0</td>
<td>31.0</td>
</tr>
<tr>
<td>History of cardiovascular disease (%)</td>
<td>26.0</td>
<td>18.9</td>
<td>14.2</td>
<td>15.2</td>
<td>15.8</td>
</tr>
<tr>
<td>Never smokers</td>
<td>43.5</td>
<td>42.7</td>
<td>44.5</td>
<td>45.3</td>
<td>46.2 (0.28)</td>
</tr>
<tr>
<td>Nephrotic range of proteinuria (%)</td>
<td>5.3 (16)</td>
<td>15.8 (13)</td>
<td>15.7 (10)</td>
<td>15.1 (15)</td>
<td>15.5 (16)</td>
</tr>
<tr>
<td>SLE (n=7)</td>
<td>1 (14.3)</td>
<td>5 (11.8)</td>
<td>9 (7.7)</td>
<td>7 (5.6)</td>
<td>8 (6.4)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.5 (5.3)</td>
<td>28.5 (5.8)</td>
<td>30.2 (5.8)</td>
<td>30.5 (5.7)</td>
<td>30.6 (6.0)</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td>79.1 ± 15</td>
<td>84.1 ± 15</td>
<td>81.1 ± 16</td>
<td>82.2 ± 16</td>
<td>83.1 ± 17</td>
</tr>
<tr>
<td>creatinine (mg/dL)</td>
<td>0.67 (0.7)</td>
<td>0.65 (0.8)</td>
<td>0.64 (0.7)</td>
<td>0.65 (0.8)</td>
<td>0.66 (0.9)</td>
</tr>
</tbody>
</table>

**TH-OR035**

Empagliflozin (EMPA) and Incidence of Rapid Decline in eGFR in Patients with Type 2 Diabetes (T2D) and Established Cardiovascular Disease (CVD): An Exploratory Analysis from the EMPA-REG OUTCOME Trial

Samy Hadad,1 Merlin C. Thomas,2 Mark E. Cooper,3 Audrey Kotika-Weber,3 Stefan Hantel,3 Maximilian von Eynatten,1 Christoph Wanner,1 1University Hospital Centre Potters, France; 2Department of Diabetes, Monash University, Melbourne, VIC, Australia; 3Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; 3Boehringer Ingelheim Pharma GmbH & Co. KG, Ingeheim, Germany; 4Dept of Medicine, Würzburg Univ Clinic, Würzburg, Germany.

Background: The eGFR progressively declines in most patients with T2D. In some patients a more rapid decline in eGFR is observed, putting them at risk for the consequences of uremia and ultimately end-stage renal disease. In the EMPA-REG OUTCOME trial, EMPA was associated with slower progression of kidney disease. In this post-hoc analysis, we evaluated the effect of EMPA on the incidence of patients experiencing a more rapid decline in eGFR.

Methods: 7620 patients with T2D and established CVD were randomized (1:1:1) to EMPA 10 mg, 25 mg or placebo (PBO) in addition to standard of care. Change in eGFR decline over the study period (from baseline to follow-up) was calculated by utilizing linear regression models. A rapid decline in eGFR was defined by an annual decline in eGFR ≥5 ml/min/1.73m². Logistic regression analysis was used to investigate differences between EMPA vs PBO groups.

Results: At baseline, mean (SD) eGFR was 74.0 (21.4) ml/min/1.73m². Over the study period, 354 participants (5.1%) experienced a rapid decline in eGFR, including 8.9% in the PBO group and 3.2% in participants receiving EMPA. After adjusting for other covariates, this equated to two-thirds reduction in risk (Figure, odds ratio 0.33 [95% CI 0.26, 0.41], p<0.0001) among participants receiving EMPA. A similar reduction among EMPA-treated participants in the incidence of patients experiencing a rapid decline in eGFR was also observed using a lower threshold (Figure).

Conclusions: Patients treated with EMPA were significantly less likely to experience a rapid decline in eGFR over approximately 3 years of treatment. This finding suggests that EMPA may have the potential to reduce the incidence of chronic renal failure in T2D in the long term.

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

**TH-OR036**

Diffusion MRI for Assessment of Kidney Fibrosis

Lena Berchtold,2 Jost M. Hantel,1 Karine Hadaya,1 Pierre-Yves F. Martin,2 Jean-Paul Seigneux,3 Sophie M. De Seigneux,1 1Hospital Universitaire de Geneve, Geneva City, Switzerland; 2Hôpitaux Universitaire de Genève, Geneva, Switzerland; 3University Hospital of Geneva, Geneva, Switzerland.

Background: Renal interstitial fibrosis (IF) is a process common to all kidney diseases and is predictive of renal prognosis. If can currently only be assessed by biopsy, an invasive procedure associated with complications and focial sampling. There is currently no clinically available noninvasive method to assess IF. Diffusion Magnetic Resonance Imaging (MRI) is emerging as a promising tool to evaluate kidney fibrosis non invasively. The aim of this study was to validate in a mixed CKD population a novel renal MRI diffusion sequence that we recently developed and to create a new non-invasive score for assessment of IF.

Methods: In this prospective study, we included 124 CKD patients having undergone a kidney biopsy (native or transplant). Optimized Diffusion-Weighted Imaging (DWI) and T1 sequences were compared to histological assessment of IF. Differences between cortical and medullary Apparent Diffusion Coefficient (ADC) and T1(ΔT1) values were assessed and compared to gold standard histopathology. Then we combined routinely measured serum markers and ΔADC to create a new score for assessment of IF.

Results: In CKD patients, ΔADC correlated well with IF (r=0.55, p<0.001). This good correlation was observed in both CKD and transplant patients. AADC showed a better discrimination to IF than cortical ADC values, T1 values and ΔT1. To optimize fibrosis prediction, we combined AADC values to routinely obtained markers.
known to correlate to fibrosis (phosphate, hemoglobin, eGFR) to obtain a score of predictive ability. A strong correlation between our score and histological IF(r=0.8, p<0.001). We further built receiver operating characteristic curves and reported area under the curve (AUC) to discriminate between patients with high levels of fibrosis (≥40%). Analysis revealed that the new score was predictive of fibrosis ≥40% with an AUC of 0.79. The sensitivity and specificity to detect IF of more than 75% were 72.6% and 100% respectively, implying that our scoring system is able to identify patients with more than 40% without false positive.

Conclusions: In summary, we validated the use of the AADC to predict IF non invasively. A and kidney transplant patients are at higher risk for their scoring system from AADC and commonly obtained laboratory values and showed a high specificity to identify non-invasively patient harboring extensive fibrosis (≥40%).

Funding: Commercial Support - Keryx Biopharmaceuticals

TH-OR037
A Pilot Pragmatic Randomized Trial of CKD Screening to Improve Care Among Hypertensive Veterans Carmen A. Peralta,1 Martin J. Frigaard,1 Anna Rubinsky,1 Leticia Rolon,1 Lowell J. Lo,2 Santhi Voora,3 Delphine S. Tuot,4 Neil R. Powe,5 Michael Shlipak,4 Kidney Health Research Collaborative, Oakland, CA; 2None, San Francisco, CA; 3Priscilla Chan and Mark Zuckerberg San Francisco General Hospital & University of California San Francisco, San Francisco, CA; 4UC San Francisco, San Francisco, CA; 5University of California San Francisco/SFVAMC, San Francisco, CA; 6University of California, San Francisco, San Francisco, CA.

Background: It is uncertain whether screening for chronic kidney disease (CKD) can improve care of persons at high risk for complications.

Methods: We conducted a 3-arm randomized controlled trial within an integrated primary care clinic at the San Francisco VA (SFVA). The electronic health record (EHR) was used to identify eligible participants (from administrative codes), deliver interventions and ascertain outcomes. Non-diabetic hypertensive veterans without known CKD who receive primary care at SFVA were enrolled and cluster-randomized (41 clusters by provider) to Usual Care (UC), CKD Screening with patient-provider Education (SE) or CKD Screen-Educate plus clinical Pharmacist management (SEP). CKD screening was included creatinine, cystatin C and albuminuria and CKD was defined as eGFR < 60 ml/min/1.73m2 or albumin to creatinine ratio ≥30mg/g. Consent was written for providers and opt-out by mail for veterans.

Results: We mailed 2,012 consent letters and 133 veterans opted out. After exclusions, we randomized 1,819 veterans. Of 1,142 veterans randomized to intervention, 525 were identified with an upcoming appointment and had CKD screening ordered, among whom 371 (71%) completed testing. The yield of new CKD cases was 73% (205/278), CKD 16-29% (132/278) and CKD ≥30% (43/278) in participants who initiated ACE/ARB by electronic prescribing. Proportions who initiated diuretics were 7.3% (SE) and 9.4% (SEP). Differences were not statistically significant (p>0.2). No adverse events were reported by providers.

Conclusions: We successfully implemented an EHR-based pragmatic trial of CKD screening with high rates of participation, and a 20% yield of undetected CKD among those screened. A larger study is required to test whether CKD screening would impact process of care and clinical outcomes.

Funding: NIDDK Support

TH-OR038
Ferric Citrate Reduced FGF23 in Patients with Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD) and Iron Deficiency Anemia (IDA) Irrespective of the Change in Serum Phosphate (P) Geoffrey A. Block,1 Pablo E. Pergola,2 Katrin Ulhig,1 John F. Neylan,3 Steven Fishbane,1 Glenn M. Chertow,1 Keryx Biopharmaceuticals, Boston, MA; 2Renal Associates PA, San Antonio, TX; 3Denver Nephrology, Denver, CO; 4Hofstra Northwell Health, Commack, NY; 5Stanford University School of Medicine, Palo Alto, CA.

Background: Ferric citrate (FC), an oral iron-based P binder approved for control of serum P in patients (pts) with CKD on dialysis, has also been shown to improve hemoglobin (Hb) and iron parameters in pts with NDD-CKD with IDA. FGF23 is a key phosphate-regulating hormone and known to be elevated in patients with iron deficiency. Here, in a post hoc analysis of a phase 3 study, we examine effects of FC on FGF23 in pts stratified by baseline (BL) P and transferrin saturation (TSAT).

Methods: 233 pts with NDD-CKD and IDA were randomized in 1:1:1 to receive FC (n=117) or placebo (n=116) for 16 wks. FC was initiated at 3 1-g tablets/day and titrated to study target levels (≤1.6, ≤2.3, ≤2.5 mg/dl). Pts were stratified by BL P and FC treatment group. ΔP was defined as the difference between post-treatment and baseline P levels.

Results: BL levels of iFGF23 and cFGF23 were positively related to BL P. After 16 wks of FC treatment, iFGF23 concentrations significantly decreased in both TSAT strata and across all strata of BL P except in pts with BL P ≤3.5 mg/dL. cFGF23 significantly decreased in both TSAT strata, and in all BL P strata except the highest (≥5.5 mg/dL). Changes in FGF23 did not consistently track with P changes [Table].

Conclusions: In pts with NDD-CKD and IDA, 16 wks of treatment with FC significantly reduced serum iFGF23 in all strata except in pts with BL P < 1.9 mg/dL. FC decreased serum cFGF23 significantly reduced except in the highest BL P. iFGF23 and cFGF23 reductions occurred irrespective of BL TSAT. BL P and P change. These data suggest that FC reduces FGF23 via several potential pathways in pts with NDD-CKD and IDA.

Funding: Commercial Support - Keryx Biopharmaceuticals

TH-OR039
Subcutaneous Corona Artery Calcification Predicts Future Risk of Acute Coronary Syndrome Among Non-Dialysis CKD: A 5-Year Prospective Analysis Angela Y. Wang,1 Henry H. Wu,1 Sharon Yui Ling Cheung,1 Sharon S. Wong,1 Yat Y. Yau,1 Sharbat Ryskalieva,2 Medicine, University of Hong Kong. Queen Mary Hospital, HONG KONG, China; 2Radiology, Biomedical Imaging Center, Hong Kong, Hong Kong.

Background: Vascular calcification is highly prevalent in chronic kidney disease (CKD) and is considered to be atherothrombotic. Ferric Citrate (FC) is a mineral acid chelator that has been shown to alter the mineral metabolism as a result of impaired kidney function. This is in contrast to studies in the general population suggesting that vascular calcification is a marker of atherosclerotic burden. The current study aims to determine if subclinical coronary artery calcification may predict future risk of acute coronary syndrome (ACS) in non-dialysis CKD.

Methods: Two hundred and seventy-two asymptomatic CKD 3-5 subjects with no known history of coronary artery disease (age: 60 ± 10 years, 56% men) were recruited using University Teaching Hospital. All subjects were followed up prospectively for a median duration of 10 years, 56% men) were recruited using University Teaching Hospital. All subjects were followed up prospectively for a median duration of 10 years, 56% men) were recruited from a University Teaching Hospital. All subjects underwent plain multi-slice computed tomography to estimate coronary artery calcium score (CACS) and blood collection.

Results: All subjects were followed up prospectively for a median duration of 69 months, during which 18% of subjects developed ACS or died from other causes. Having a CACS ≥ 400 was independently associated with an increased risk of ACS and mortality [adjusted hazard ratio (HR), 4.66, 95% confidence intervals (CI), 1.37 - 15.83] controlling for Framingham risk factors. Further adjusting for eGFR, proteinuria, hemoglobin, serum albumin, phosphate, low density lipoprotein-cholesterol, and C-reactive protein did not alter the independent association between CACS ≥ 400 and ACS and death [adjusted HR, 4.31, 95% CI, 1.22 - 15.27]. The area under the receiver-operator characteristic curve for estimating a single outcome and mortality was 0.74 (95% CI, 0.67 - 0.82). Having a CACS ≥ 400 showed a specificity of 86% in predicting a future risk of ACS and mortality.

Conclusions: This study for the first time demonstrates the importance of subclinical coronary artery calcification in predicting future risk of ACS and mortality among asymptomatic non-dialysis CKD subjects. These novel findings suggest that coronary artery calcification reflects atherosclerotic disease burden; it is a marker for 'late identify CKD subjects at future risk of ACS warrant further large scale evaluation.

Funding: Commercial Support - Sanofi Renal Co.

TH-OR040
Comparative Performance of Longitudinal Measures of Change in Kidney Function in Predicting ESRD and Death Benjamin C. Bow,3 Yan Yan,1,2 Yan Xie,3 Hong Xian,1 Tingting Li,2 Ziyad Al-Al,2 Department of Biostatistics, Saint Louis University College for Public Health & Social Justice, St. Louis, MO; 2Department of Epidemiology Center, Research, and Development Service, Veterans Affairs St Louis Healthcare System, St. Louis, MO; 3Department of Medicine, Washington University School of Medicine, St. Louis, MO.

Background: Four different methods are commonly used in the evaluation of longitudinal changes of eGFR: ordinary least square (OLS), annualized change (AC), group-based trajectory models (GBT), and empirical Bayes slopes (EBS). Their comparative predictive performance for ESRD and death is unknown.

Methods: We built a development (N=274,277) and five validation cohorts (N=54,857 each) of US Veterans with stage 3a CKD and aimed to comparatively evaluate risk discrimination and reclassification of Cox proportional hazard regression models using these different longitudinal measurement methods.

Results: For the outcome of death, when eGFR change was captured over a 5-year period, risk discrimination improved gradually from baseline model, OLS, AC, GBT, and EBS with a corresponding c-statistic of 0.698 (0.696-0.700), 0.702 (0.700-0.704), 0.703 (0.702-0.705), 0.706 (0.704-0.708), and 0.708 (0.705-0.711), respectively.

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

11
TH-OR041

NPHP1 Gene Deletions Cause ESRD in 0.9% of Adult-Onset Cases
Rozemarijn Snoek,1 Jessica Van setten,2 Bert Van der zwaag,2 Brendan Keating,3 Nina V. Knoors,2 Martin H. De Borst,1 Albertien M. van Eerde.2
1University Medical Center Groningen, Groningen, Netherlands; 2University Medical Center Utrecht, Utrecht, Netherlands; 3University of Pennsylvania, Philadelphia, PA. Group/Team: International Genetics & Translational Research in Transplantation Network.

Background: Nephronophthisis (NPH) is the most prevalent (15%) genetic cause for end-stage renal disease (ESRD) in children. ~16% is caused by homozygous full gene deletions of the autosomal recessive NPHP1 gene. However, little is known about the prevalence of these mutations in adult-onset ESRD. With data generated to perform genome sequencing in adult-onset ESRD patients, we aimed to determine the prevalence of homozygous NPHP1 full gene deletions.

Methods: Renal transplant recipients were genotyped using the Affymetrix Axiom Tx GWAS Array, containing ~780,000 markers across the genome with probes to cover a priori candidate and strong association regions. CNVs were identified and validated based on median log2 ratios and allele-frequency patterns. All findings were independently validated. In this abstract we report on 1272 cases, all Caucasian, from the renal transplant population from a single center (27%).

Results: We identified 1252 cases in the TransplantLines-Geneicohets cohort met the age criteria, of whom 11 (0.9%) showed a homozygous deletion of the NPHP1 gene. Median age at start of RRT was 35 years (range 18-42), with eight cases aged ≥30. Notably only three out of 11 had NPH, with the other 8 being having NPH1 mutations. The other cases (9:1:1, 73%) were characterized as chronic kidney disease with unknown etiology (n=5), glomerulonephritis (n=1), sporadic primary reflux nephropathy (n=1) and autosomal dominant polycystic kidney disease (n=1).

Conclusions: NPH1 is a classical pediatric kidney disease. However, we show that homozygous NPHP1 full gene deletions alone cause 0.9% of all adult-onset ESRD in our dataset, with the majority of NPH1 cases ≥30 years of age. Considering that other types of mutations in NPHP1 were not analyzed, and the other 19 known NPH genes were not even investigated, NPH is a relatively frequent cause of adult-onset ESRD. As only 27% of NPHP1 cases were registered clinically as NPH, these results warrant widespread application of genetic testing in adult-onset ESRD.

TH-OR042

Mutations of DNAJB11 Cause Autosomal Dominant Polycystic Kidney Disease
Emilie Cornic-Le Gall,1,2 Vladimir Gainullin,1 Binu Porath,1 Christinna M. Heyer,1 Marie-Florence Audrezet,1 Yannick Le Meur,3 Francois Jouret,1 Dominique A. Joly,4 Claude Ferec;5 Alan S. Yu;6 Vicente E. Torres;6 Peter C. Harris.1,2
1University of Washington, Seattle, WA; 2University Health Network and Toronto University of Toronto, Toronto, ON, Canada

Background: Polycystic kidney disease (PKD) is a life-threatening disorder in which tubular epithelia form fluid-filled cysts, disrupting organ architecture. A major barrier to understanding the pathophysiology of PKD is the absence of human cellular models that accurately and efficiently recapitulate cystogenesis. Previously, a genetic model of PKD has been generated using human pluripotent stem cells (hPSCs) and derived kidney organoids. Here we show that systematic substitution of physical components in this system can be used to dramatically increase or decrease cyst formation, unveiling a critical role for microenvironment in PKD.

Methods: Genome-modified PKD1−/−, PKD2−/−, or inorganic control hPSCs were differentiated into vitro into kidney organoids and subjected to conditions predicted to influence cystogenesis (e.g., exclusion of extracellular matrix and/or mechanical forces). To directly test the effect of PKD mutations on the microenvironment, individual organoids were embedded into larger collagen droplets. Structure and composition of organoids were analyzed by immunofluorescence, microarray and immunoblot, and compared histologically to disease tissue from PKD patients.

Results: Removal of adherent cues increased cystogenesis 10-fold, producing cysts that phenotypically resembled human PKD cysts and expanded massively to formcystic pseudocysts. Cysts derived from hyperproliferative kidney tubular epithelial cells and showed upregulation of known PKD signaling pathways. Removal of stroma enabled proliferation and outgrowth of PKD cell lines, which revealed PC1 deficiency as a common molecular endpoint. Collagen droplets implanted with organoids furthermore contracted dramatically over a period of 2 weeks in a PKD-dependent manner.

Conclusions: Culture conditions have a significant impact on rates of cystogenesis in PKD organoids, enabling us to establish a highly efficient model of PKD cystogenesis. Collagen contraction could not be explained by differences in proliferation alone. Our findings directly implicate the microenvironment as a critical component at the earliest stages of PKD, with PKD likely functioning as an adhesion or signaling molecule to control tissue contractility.

Funding: NIDDK Support, Government Support - Non-U.S. (unrestricted gift), Private Foundation Support

TH-OR043

Highly Efficient Organoid Cystogenesis Reveals a Critical Role for Physical Microenvironment in Human Polycystic Kidney Disease
Nelly M. Cruz,1 Xuewen Song,2 York P. Pei,1 Benjamin S. Freedman.1
1University of Washington, Seattle, WA; 2University Health Network and Toronto University of Toronto, Ontario, Canada

Background: Polycystic kidney disease (PKD) is a life-threatening disorder in which tubular epithelia form fluid-filled cysts, disrupting organ architecture. A major barrier to understanding the pathophysiology of PKD is the absence of human cellular models that accurately and efficiently recapitulate cystogenesis. Previously, a genetic model of PKD has been generated using human pluripotent stem cells (hPSCs) and derived kidney organoids. Here we show that systematic substitution of physical components in this system can be used to dramatically increase or decrease cyst formation, unveiling a critical role for microenvironment in PKD.

Methods: Genome-modified PKD1−/−, PKD2−/−, or inorganic control hPSCs were differentiated into vitro into kidney organoids and subjected to conditions predicted to influence cystogenesis (e.g., exclusion of extracellular matrix and/or mechanical forces). To directly test the effect of PKD mutations on the microenvironment, individual organoids were embedded into larger collagen droplets. Structure and composition of organoids were analyzed by immunofluorescence, microarray and immunoblot, and compared histologically to disease tissue from PKD patients.

Results: Removal of adherent cues increased cystogenesis 10-fold, producing cysts that phenotypically resembled human PKD cysts and expanded massively to formcystic pseudocysts. Cysts derived from hyperproliferative kidney tubular epithelial cells and showed upregulation of known PKD signaling pathways. Removal of stroma enabled proliferation and outgrowth of PKD cell lines, which revealed PC1 deficiency as a common molecular endpoint. Collagen droplets implanted with organoids furthermore contracted dramatically over a period of 2 weeks in a PKD-dependent manner.

Conclusions: Culture conditions have a significant impact on rates of cystogenesis in PKD organoids, enabling us to establish a highly efficient model of PKD cystogenesis. Collagen contraction could not be explained by differences in proliferation alone. Our findings directly implicate the microenvironment as a critical component at the earliest stages of PKD, with PKD likely functioning as an adhesion or signaling molecule to control tissue contractility.

Funding: NIDDK Support, Government Support - Non-U.S. (unrestricted gift), Private Foundation Support

TH-OR044

Loss of Cep120 Disrupts Centriole Maturation and Ciliary Assembly and Function and Causes Cystic Kidney Disease
Ewelineta Betleja, Tao Cheng, Moe Mahjoub, Washington University, St Louis, MO.

Background: Jeune asphyxiating thoracic dystrophy (JATD) is a skeletal dysplasia characterized by a small thoracic cage, shortened bone length and polydactyly. Infants develop difficulties with breathing due to abnormal development of their thoracic cage, but may survive into early childhood following surgery to correct these defects. However, these children develop life-threatening renal abnormalities, namely cystic kidney diseases. Whole-exome sequencing of JATD patients recently identified mutations in CEP120, which we previously showed to be important for centriole duplication. What remains unknown is the functional role of CEP120 in kidney development.

Methods: To determine the function of CEP120 in kidney development, and adult kidney homeostasis, two complementary approaches were used to characterize the loss-of-function of Cep120. First, siRNA-mediated depletion of Cep120 was performed in mouse embryonic fibroblasts and epithelia to analyze its role in vitro. Next, we utilized a transgenic mouse model harboring a conditional allele (Cep120f/f) to delete Cep120 in PKD organoids, enabling us to establish a highly efficient model of PKD cystogenesis.

Results: Cep120 knockdown did not form cysts. Cysts derived from hyperproliferative kidney tubular epithelial cells and showed upregulation of known PKD signaling pathways. Removal of stroma enabled proliferation and outgrowth of PKD cell lines, which revealed PC1 deficiency as a common molecular endpoint. Collagen droplets implanted with organoids furthermore contracted dramatically over a period of 2 weeks in a PKD-dependent manner.

Conclusions: Culture conditions have a significant impact on rates of cystogenesis in PKD organoids, enabling us to establish a highly efficient model of PKD cystogenesis. Collagen contraction could not be explained by differences in proliferation alone. Our findings directly implicate the microenvironment as a critical component at the earliest stages of PKD, with PKD likely functioning as an adhesion or signaling molecule to control tissue contractility.

Funding: NIDDK Support, Government Support - Non-U.S. (unrestricted gift), Private Foundation Support

TH-OR045

Conclusions: Our findings extend the spectrum of genetic causes of ADPKD. DNAJB11 differs from typical ADPKD, with no renal enlargement but progressive renal atrophy. In addition to inhibiting PC1 maturation and leading to cystogenesis, mutations of DNAJB11 may inhibit responding appropriately to ER stress in the kidney. Recognizing this further genetic heterogeneity is important since these patients may not benefit from the same therapeutic strategies.

Funding: NIDDK Support, Government Support - Non-U.S.
characterization of the role of Cep120 (and potentially other daughter centriolar proteins) in the cystogenesis of patients with JATD.

Funding: NIDDK Support

TH-OR045

Defective Mitochondrial Structure and Function Might Explain the Metabolic Derangement in Polycystic Kidney Disease

Laura Cassina, Marco Chiaraavalli, Christine Podrini, Isaline Rowe, Gianfranco Distefano, Alessandra Boletta. San Raffaele Scientific Institute, Milan, Italy. Group: Team: Molecular basis of Polycystic Kidney Disease Unit.

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a common genetic disorder characterized by bilateral renal cyst formation. By metabolic profiling, we showed that Pkd1 mutations result in enhanced glycolysis in cells and murine models of PKD. Moreover, inhibition of mitochondrial ATP synthase only mildly decreased ATP content in Pkd1−/− cells, indicating a mitochondrial contribution to the overall ATP production (Rowe et al, Nat Med 2013). Interestingly a recent study implicated a role for the Polycystins in mitochondrial function (Padovano et al, Mol Cell Biol 2017).

We are investigating the role of mitochondria in the metabolic alterations in PKD.

Methods: Mitochondrial size, shape, and structural organization were analyzed by transmission electron microscopy (TEM). Mitochondrial oxygen consumption rate (OCR) was measured using Seahorse XF96 Analyzer, and mitochondrial network morphology by confocal microscopy.

Results: TEM images of the cystic epithelium showed evidence of grossly altered mitochondrial structure in kidneys of Pkd1−/− -Kap-Cre mice at P4, as compared to control littermates. We also observed mitochondria with altered cristae and decreased matrix electron density scattered among apparently normal mitochondria. Morphometric analysis of TEM images from Pkd1−/− -Kap-Cre indicated decreased mitochondrial area and length. Time course analysis of mitochondrial shaping-proteins with western blot showed that the structural alterations seem to precede the biochemical ones. In parallel, we are assessing mitochondrial morphology in Pkd1−/− MEFS and CRISPR/Cas9-mediated Pkd1 knockout IMCD cells and preliminary findings indicate that the absence of PC-1 affects mitochondrial network morphology. In line with this, functional analyses indicated that both basal and maximal OCRs are severely affected in cells lacking Pkd1.

Conclusions: Our data indicate that alteration in mitochondrial structure might explain the severe metabolic alterations in PKD models. Alternatively, the mitochondrial structural impairment might be secondary to metabolic defects. Our investigations along with ongoing genetic interaction studies will clarify whether mitochondria are players or modifiers in the pathophysiology of ADPKD.

TH-OR046

The Noncoding RNA Hoxb3os Is Dysregulated in Autosomal Dominant Polycystic Kidney Disease and Regulates mTOR Signaling

Karam S. Aboudehen,1 Mohammed S. Kanchwala,2 Shayan A. Farahani,3 Sophia M. Vrba,4 Shi Chiu Chan,5 Svetlana Avdulov,1 Alan Mickelson,1 Vishal Patel,1 Chao Xing,6 Peter Igarashi.1 University of Minnesota, Minneapolis, MN; 1University of Texas Southwest Medical Center, Dallas, TX; 2UT Southwestern Medical Center, Dallas, TX.

Background: Polycystic kidney disease (PKD) is a debilitating disease that is characterized by the accumulation of numerous fluid-filled cysts in the kidney. Autosomal dominant polycystic kidney disease (ADPKD), is primarily caused by mutations in two genes, PKD1 and PKD2. The pathophysiology of PKD is incompletely understood, and no FDA-approved treatment currently exists. Long noncoding RNAs (IncRNAs) are single-stranded RNA molecules that are ~200 nucleotides in length, lack a long open-reading-frame, and have recently emerged as epigenetic regulators of development and disease; however, their involvement in PKD has not been explored previously.

Methods:

Results: Here, we performed deep RNA sequencing to identify IncRNAs that are deregulated in two orthologous mouse models of ADPKD (kidney-specific Pkd1 and Pkd2 mutant mice). We identified a kidney-specific and highly conserved IncRNA, called Hoxb3os, that was down-regulated in cystic kidneys from Pkd1 and Pkd2 mutant mice as well as in a Pkd2 mutant renal cell line. Its human ortholog HOXB3-AS was down-regulated in kidneys from PKD patients. Hoxb3os was normally highly expressed in renal tubules in wild-type mice, whereas its expression was lost in the cyst epithelium of mutant mice. To investigate the function of Hoxb3os, we performed RNA-seq analysis on Hoxb3os knockdown mIMCD3 cells. Knockdown of Hoxb3os resulted in ~2-fold dysregulation of ~77 genes, 40 of which were similarly dysregulated in PKD mouse models. Pathway analysis suggested that Hoxb3os activated mTOR signaling, a pathway that has been implicated in PKD. Consistent with this result, ablation of Hoxb3os in mIMCD3 cells with CRISPR/Cas9 resulted in hyperactivation of mTOR signaling, as evidenced on mutant mice). We identified a kidney-specific and highly conserved lncRNA, called HOXB3-AS (Hoxb3os).

Results: Here, we studied a newly generated standardized ADPKD mouse model for Pkd2 (C57-Cre,Pkd2+/−) (Li et al. J Cell Mol Med 2017) with Cmb1−/− mice to generate a mouse model that recapitulates the cystogenesis of Cmb1 knockout (C57-Cre,Pkd2+/−,Cmb1−/−). In addition, we also explored the effects of canonical Wnt signaling inhibitors (XAV939 and LGK974) on amelioration of disease phenotypes. XAV939-treated group and its soluble DMSO control group (ns) were intraperitoneally treated with 50 mg/kg/d and the same amount of DMSO from postnatal days 10 (P10) to 60 (P60); while LGK974-treated group and its soluble control group were intragastrically treated with 3mg/kg/d from postnatal days 30 (P30) to 90 (P90). The XAV939 and LGK974 treated animals were sacrificed at P65 and P95, respectively.

Results: C57-Cre,Pkd2+/− mice with Cmb1−/− allele and the mice treated with XAV939 or LGK974 exhibit significantly prolonged lifespan, decreased cyst index, kidney/body ratio and improved renal function (BUN and Cr). All treated mice showed significantly decreased proliferation, but no change for apoptosis, in renal cyst-lining cells. Canonical Wnt signaling targeted genes, including Axin2, Ctnnb1, and e-cMyc, were also significantly downregulated in the treated ADPKD mouse kidney.

Conclusions: Our study provides clear evidence for the importance of β-catenin signaling in Pkd2-associated ADPKD phenotypes and develops new Wnt inhibitors XAV939 and LGK974, which affects at different targets of Wnt signaling, as a potential therapeutic modality for ADPKD that currently lacks effective therapy.

Funding: Government Support - Non-U.S.

TH-OR049

A Novel Strategy to Identify an Effective Treatment for Juvenile Nephronophthisis

Hugo Garcia,1 Flora Silbermann,1 Esther Poroc,1 Clementine Mahaut,2 Berangere M. Deleglise,2 Pamela C. Rodriguez,2 Soraya Sin-Monnot,2 Luis Briseno-Roa,2 Jean-Philippe M. Annerue,2 Corinne Antignac,1 Remi Salomon,3 Marion H. Delous,1 Sophie Sauvaint.1 Imagine Inst, INSERM UMR1163, Paris, France; 2Alexion R&D France, Paris, France; 3Pediatric Nephrology, Necker Hospital, Paris, France.

Background: Nephronophthisis (NPH) is an autosomal recessive tubulointerstitial nephropathy and the most common cause of hereditary end-stage renal disease in children and young adults. No specific treatment is currently available. Almost all the 21 identified NPHP genes encode proteins localized in the primary cilium.

Methods: We designed an in vitro high-throughput drug-screen strategy based on the Prestwick Chemical Library that includes more than 1120 compounds (mostly FDA-approved). We first evaluated migration and cilogenesis in mammalian renal epithelial cells invalidated for either Nphp1 or Nphp4, the two main genes involved in juvenile NPH, and identified 78 modulating drugs in these models. Then we selected 30 molecules...
based on pharmacodynamics and assessed their effect on ciliogenesis of immortalized renal tubular cells derived from urine samples of NPHP1-deficient patients (UERCs).

Results: We validated the positive effects of one compound (ARDF006) that increases the percentage of ciliated cell from and normalizes cilia length distribution. A similar rescue was observed when using specific agonists and antagonists targeting ARDF006 receptors. These G protein-coupled receptors partially localize at primary cilia. We could confirm in vivo effects of ARDF006 and a structural analog by using the npfl4-ATG morphant zebrafish model, which present a classical ciliopathy-related phenotype: body curvature and pronephric cysts. By using semi-automated imaging and analysis tools, we observed that ARDF006 treatment of morphant embryos does not have a significative impact on body curvature; however, it leads to a 27% relative reduction of pronephric cysts formation and an increase of ciliated cells percentage and cilia length in the distal part of the pronephros.

Conclusions: UERCs and zebrafish represent useful and fast models to recapitulate patients’ ciliogenesis defects and implement a pharmacologic approach for genetic deletion-related disease such as NPH.

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

TH-OR050
Fenofibrate, a PPARA Agonist, Enhances Mitochondrial Metabolism and Slows Kidney and Liver Cyst Progression in a 6 Month Pre-Clinical Trial
Ronak Lakhia, Maniela Yeshkel, Andrea N. Flaten, Ezekiel Quittner-Storm, Vishal Patel. University of Texas Southwestern Medical Center, Dallas, TX.

Background: Impaired fatty acid oxidation (FAO) and oxidative phosphorylation (OXPHOS) are thought to underlie ADPKD pathogenesis. Peroxisome proliferator-activated receptor alpha (PPARα) is a key regulator of FAO and OXPHOS. PPARα is downregulated in mouse and human ADPKD kidney cysts. We recently showed that deletion of Ppara aggravates cyst formation in an ADPKD model. The goal of this study was to determine if augmentation of FAO using the PPAR agonist fenofibrate can slow cyst growth.

Methods: Q-PCR, Western blot, and immunofluorescence staining confirmed downregulation of Ppara and its FAO-related targets in 200-day-old Pkd1RC/RC mice. Sixteen 50-day-old Pkd1RC/RC mice were randomized to receive either standard chow diet or standard chow diet supplemented with fenofibrate. All mice underwent MRI to determine total kidney volume and total cyst volume at 180 days of age and were subsequently sacrificed at 200 days of age for molecular and histological analysis. An additional cohort of mice underwent serial body mass assessment by 13HOO-PB (a tool to follow changes in body composition) for 60 days.

Results: Fenofibrate treatment upregulated PPARA and enhanced FAO and OXPHOS in the kidneys of Pkd1RC/RC mice as evidenced by upregulation of FAO/OXPHOS genes, improved mitochondrial biogenesis, and increased oxidation of 13HOO-PB. MRI-assessed total kidney volume and total cyst volume was reduced by 30% and 60%, respectively, in fenofibrate-treated Pkd1RC/RC mice compared to Pkd1RC/RC mice on control diet. Moreover, kidney-weight-to-body-weight ratio, cyst index and serum creatinine were also reduced in the fenofibrate-treated Pkd1RC/RC mice. Fenofibrate treatment was associated with reduced kidney cyst proliferation and M2-like macrophages infiltration in Pkd1RC/RC mice treated with fenofibrate compared to Pkd1RC/RC mice on control diet. Fenofibrate treatment also reduced liver cyst burden, cyst proliferation, and liver inflammation and fibrosis.

Conclusions: PPARα augmentation Ppara expression, improves FAO, and slows kidney and liver cyst growth. Our findings indicate that targeting Ppara activity may be a useful therapeutic strategy for ADPKD.

Funding: NIDDK Support

TH-OR051
The Use of Four or More Drugs for Intensive Control of Blood Pressure Is Associated with Deterrential Renal Effects in the SPRINT Indranil Dasgupta,1,2 Linsay McCallum,3 Alan G. Jardine,3 Sandra Padmanaban,4 Renal Medicine, Heartlands Hospital, Birmingham, United Kingdom; 1University of Birmingham, Birmingham, United Kingdom; 2University of Glasgow, Glasgow, United Kingdom; 3University of Glasgow, Glasgow, United Kingdom.

Background: In the SPRINT trial, a Randomized Trial of Intensive versus Standard Blood Pressure Control, achievement of target SBP in the intensive arm required a higher number of drugs. Intensive treatment was associated with lower CV events and death but an increased incidence of adverse events. In this analysis, we assessed the relationship between number of antihypertensive drugs classes used to achieve blood pressure target and renal adverse events.

Methods: Number of drug classes prescribed at randomisation and at 1.2, 3.6, 9,12 months were used to identify distinct trajectory groups in the standard and intensive arm using Latent Class Mixed Modelling, in 8,449 participants. Cox-PH models, adjusted for age, sex, SBP (AUC 0-12 months), prevalent CVD, prevalent CKD and number of drug classes at randomisation, were used to assess the association between drug class trajectories and renal adverse events.

Results: The 6 groups based on the trajectories of drug classes prescribed over the first year are shown in the panel A with corresponding SBP by drug class groups in panel B. Cox-PH model (reference category: Int-4, SBP<125 on 2.5 drug classes) showed that in those without CKD at baseline, in Int-5 (125 on 4 drug classes) there was a higher risk of 30% reduction in eGFR (HR 4.25 [2.57-7.02]; p <0.0005) whilst those in Std-1 (SBP 133 on 1.5 drugs) had a lower risk (HR 0.17[10.29]; p <0.0005) (panel C). Those in Int-5 had a higher risk of hyperkalaemia (HR 1.64 [1.03-2.61]; p<0.05) with trend towards significance compared to Std-1 (p=0.09).

Conclusions: Within the intensive arm of the SPRINT, treatment with ≥4 antihypertensive drug classes was associated with adverse renal events, independent of BP achieved in the first year.

Funding: Commercial Support - Alexion Pharmaceuticals, Private Foundation Support, Government Support - Non-U.S.
MAP did not change in shamDNX but returned to pre-diet levels cryoDNX fructose-fed HS rats (P < 0.05). Blood glucose (BG) was 100 ± 9 mg/dL in C rats vs 131 ± 8 mg/dL in conscious fructose-fed rats (P < 0.02). Glucose-insulin ratio in shamDNX rats was lower (47 ± 8) than in cryoDNX rats (105 ± 18; P < 0.05) regardless of sodium intake, consistent with improved insulin sensitivity in the cryoDNX rats.

Results: We conclude that bilateral renal denervation normalizes MAP in prediabetic fructose-fed rats on high salt diet and also improves insulin sensitivity in fructose-fed rats regardless of sodium intake. Further studies are needed to identify whether different inputs from or efferent sympathetic inputs to the kidney are involved. Thus, the renal nerves likely play important role in glucose disposal.

Funding: Veterans Affairs Support

TH-OR054

In Two-Kidney One-Clip Hypertensive Sheep Cardiac and Contralateral Renal Sympathetic Nerve Activity Are Differentially Controlled

Tycho R. Tromp,1,2 Jaap A. Joles,2 Rohit Ramchandra,1 The University of Auckland, Auckland, New Zealand; 1University Medical Center Utrecht, Utrecht, Netherlands.

Background: Hypertension is often initiated and maintained by elevated sympathetic tone. We investigated changes in directly recorded sympathetic nerve activity (SNA) to the heart and nonclipped kidney in two-kidney one-clip (2K-1C) hypertensive sheep.

Methods: Adult ewes either underwent unilateral renal artery clipping (n=12) or sham surgery (n=15). Two weeks later, the carotid artery was cannulated and electrodes were placed in the (nonclipped) renal and/or cardiac nerve. Blood pressure (BP), heart rate (HR) and baseline and baroreflex control of SNA were recorded in the conscious sheep one week later.

Results: Unilateral renal artery clipping induced hypertension (systolic blood pressure 130±3 vs 114±4 mmHg in shams, p<0.001) after 2.5 days, and shifted the heart rate baroreflex curve rightwards (BP120±12 vs 140±16 mmHg, p<0.01). HR was unchanged. The renal SNA (RSNA) baroreflex curve was also shifted rightwards (BP93±3 vs 85±2, p<0.01) and showed increased gain (p<0.05). In the hypertensive group, cardiac SNA (CSNA) burst incidence was increased (39±14 vs 25±9 in normotensives, p<0.05), whereas RSNA burst incidence was decreased (69±20 vs 93±8 in normotensives, p<0.01).

Conclusions: In this ovine model of 2K-1C renovascular hypertension we show that cardiac and contralateral renal sympathetic nerve activity were differentially controlled three weeks after clipping; baseline CSNA was increased whilst RSA to the nonclipped kidney was decreased. We speculate that the observed contralateral RSNA decrease is a homeostatic response to increased blood pressure and the sodium avid state of the clipped kidney.

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

Differential control of contralateral renal and cardiac sympathetic nerve activity (SNA). Baseline contralateral renal SNA was decreased whereas cardiac SNA was increased (A). Baroreflex control of contralateral renal (B) and cardiac SNA (C) was differentially regulated.

TH-OR055

Sodium-Sensitive Blood Pressure Response in Type 1 Diabetes Is Accompanied by Impaired Skin Lymphangiogenesis

Elanie F. Wenslødt1, Nienke M. Rorije, Rik H. Olde Engberink, Bert-Jan Van den Born, Jan Aten, Liffert Vogt. Academic Medical Center, Amsterdam, Netherlands.

Background: Studies showed that sodium can be non-osmotically stored within the skin. In response to high sodium diet (HSD), skin sodium content increases and macrophages are attracted, inducing lymphangiogenesis. Disruption of this system has been shown to lead to sodium-sensitive hypertension. This study investigates the effects of HSD on skin lymphatic and blood capillaries as well as blood pressure (BP) in type 1 diabetic patients (DM1).

Methods: We performed a randomized crossover study in males with DM1 and healthy controls. All subjects pursued an 8-day low sodium diet (LSD: <50 mmol Na daily) and HSD (>200 mmol Na daily). Diet order was randomized and time in-between diets was 1-2 weeks. After each diet, BP measurements and skin biopsies were obtained. Macrophages (CD68), vascular endothelium (CD31) and lymphatic endothelium (D2-40) were identified through immunohistochemistry.

Results: This study included 8 patients with DM1 and 12 controls who were similar regarding age, BMI and eGFR. In DM1 patients, mean arterial pressure was higher after HSD as compared to LSD (mean (SE) 85(2) vs. 80(1) mmHg, p=0.03) whereas in controls no differences were observed (78(1) vs. 78(2) mmHg, p=0.66). HSD increased lymphatic cross sectional surface area in controls (p<0.01) but not in DM1 patients (fig 1a). Less CD68 macrophages were present in DM1 patients compared to controls (p<0.001) (fig 1b). In both groups, there was a strong association between lymphatic capillary density and macrophage density (DM1 r=0.57 p=0.02; controls r=0.71 p<0.02).

Conclusions: The sodium-sensitive BP increase in DM1 patients is accompanied by impaired skin lymphangiogenesis and reduced skin macrophage content. Lymphangiogenesis may help to prevent sodium-sensitive hypertension.

Funding: NHF/NOFOD

TH-OR056

Renal Medullary Interstitial Cell COX-2 Protects against Salt-Sensitive Hypertension and Papillary Necrosis

Ming-Zhi Zhang,1 Aolei Niu,2 Yinquang Wang,2 Suwan Wong,2 Chuang-Ming Hao,2 Raymond C. Harris,2 Huashan Hosp., Shanghai, China; Vanderbilt University Medical Center, Nashville, TN.

Background: Cyclooxygenase 2 (COX-2)-derived prostaglandins regulate renal hemodynamics and salt and water homeostasis. COX-2 is highly expressed in renal medullary interstitial cell (RMICs). COX-2 inhibition causes blood pressure elevation and papillary necrosis and COX-2 sustains RMIC survival in response to hypertonicity in vitro. However, the role or COX-2 in vivo is in response to stimuli has not yet been definitively studied. We investigated the effect of COX-2 deletion in RMICs on blood pressure and papillary integrity in response to high salt intake.

Methods: We used inducible COX-2 deletion in RMICs in adult mice to avoid any potential developmental abnormalities of the inner medulla/papilla. Male COX-2(-/-) (WT) and Tet-on-CreER2;COX-2(-/-) mice were fed a high salt diet, and blood pressure was monitored with tail cuff plethysmography. Mice were sacrificed at 2, 4, 9 weeks. For acute salt loading, mice were IP injected with isotonic saline equivalent to 120 mOsm/kg H2O. For chronic high salt intake, mice were fed a diet equivalent to 2% NaCl for 4 weeks. For acute salt loading, mice were IP injected with isotonic saline equivalent to 120 mOsm/kg H2O and then progressively increased. In addition, RMIC COX-2(-/-) mice had impaired pressure natriuresis one week after high salt diet (% of sodium excretion: 69.6±8.9 vs. 97±2, n=7).

Results: Tamoxifen efficiently induced COX-2 deletion in inner medulla/papilla of the Tet-on-CreER2;COX-2(-/-) mice. Blood pressure was similar between RMIC COX-2(-/-) and WT mice on a normal salt diet. Although blood pressure was not altered in WT mice on a high salt diet, it increased gradually in RMIC COX-2(-/-) mice, peaked at 4-5 weeks (131±5 vs. 121±4 mmHg, P<0.05, n=7), and then progressively decreased to levels significantly lower than corresponding WT. After return to a normal salt diet for 3 weeks, RMIC COX-2(-/-) mice still had lower blood pressure (101±4 vs. 116±3 mmHg, P<0.05, n=4) and a urine concentrating defect (2535±97 vs. 3080±120 mOsm/kg H2O of WT, P<0.01, n=6), in association with stripping loss of papillae. Increased apoptotic cells in papillae of high salt treated RMIC COX-2(-/-) mice were seen 2 weeks after high salt intake. In addition, RMIC COX-2(-/-) mice had impaired pressure natriuresis one week after high salt diet (% of sodium excretion: 69.6±8.9 vs. 97±2, n=4).

Conclusions: These studies indicate that RMIC COX-2 plays an important role in salt and water homeostasis and provides cytoprotection for papillary structures in response to chronic high salt intake.

Funding: NIDDK Support

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

Underline represents presenting author.
TH-OR057
Loss of Salt Sensing Kinase, SGK1, in T Cells Abrogates Memory Cell Formation, Hypertension, and End-Organ Damage
Hana A. Imani, Arvind K. Pandey, David G. Harrison. Clinical Pharmacology, Vanderbilt University Medical Center, Nashville, TN.

Background: Accumulating evidence indicates that NaCl can be concentrated in tissues with high salt-intake, age and in the setting of hypertension. Elevated NaCl has been shown to promote T cell formation in an SGK1-dependent manner. We have previously shown that engagement of T cells plays a major role in the genesis of hypertension. These long-lived cells remain responsive to repetitive hypertension stimuli, such as salt feeding, and can be mobilized to enter the kidney where they release cytokines that promote renal dysfunction. To examine mechanisms by which T cells sense salt and contribute to salt-sensitivity, we tested the hypothesis that SGK1 in T cells is necessary for formation of memory T cells and their activation in salt-sensitive hypertension.

Methods: To study the role of SGK1 in hypertension, we produced mice with T cell specific deletion of SGK1, SGK1fl/fl x Tg[CD4+] mice and used SGK1+/- mice as controls. To impose repeated episodes of hypertension, we treated these mice with L-NAMe (0.5mg/ml) in drinking water for two weeks, allowed a two-week normotensive interval and then fed high salt (4% NaCl) for three weeks.

Results: L-NAME followed by high salt increased memory T cells in the kidney, aorta and bone marrow of SGK1+/- control mice but not in SGK1fl/fl x Tg[CD4+] mice, as identified by the surface marker CD44. To assess markers of renal injury, we measured albumin in 24-hour urine samples collected at the end of the L-NAME/high salt, L-NAME/high salt caused striking albuminuria in SGK1fl/fl mice and was absent in SGK1+/- x Tg[CD4+] mice. In additional studies, we found that loss of SGK1 in T cells abolishes renal and vascular inflammation and protects against hypertensive renal and vascular injury in the L-NAME/high salt model.

Conclusions: Thus, our data provide a potential mechanism by which SGK1 in T cells promotes their development of salt sensitivity and their mediation of renal and vascular dysfunction in hypertension.

TH-OR058
Angiotensin II Type 2 Receptor Contributes to Hypertension in Elastin Insufficiency
Carmen M. Halabi. Washington University School of Medicine, Saint Louis, MO.

Background: Hypertension and vascular stiffness are major consequences of elastin insufficiency, as seen in patients with Williams syndrome and animals models of elastin insufficiency. Altered reactivity of resistance vessels was recently proposed to contribute to hypertension in elastin insufficiency. Specifically, mesenteric arteries of elastin insufficient mice were shown to be hypercontractile to AngII (AngII) ex vivo. Interestingly, this hypercontractile response to AngII was partially mediated by AngII type 2 receptors (AT2R) as blockade of AT2R by PD123319 abrogated the hypercontractile response to AngII. The purpose of this study was to determine whether AT2R contributes to the hypertension seen with elastin insufficiency in vivo.

Methods: Elastin haploinsufficient (Eln) mice were bred to AT2R knock-out (Agtr22/2) mice. Arterial pressure measurement and large artery compliance studies were performed on three month-old male littersmate pregnant with the following genotypes (Agtr22/2/Eln+, Agtr22/2/Eln−, Agtr22/2/Elnhetero+, and Agtr22/2/Elnhetero−). Structural examination of ascending aorta and mesenteric arteries was done via Alexa-633 hydrazide staining and transmission electron microscopy, respectively.

Results: As expected, compared to wild type (WT) mice, loss of AT2R had no effect on blood pressure or large vessel compliance in the presence of WT elastin (Agtr22/2/Eln+), while elastin insufficiency resulted in elevated systolic blood pressure, pulse pressure, and reduced large vessel compliance in the presence of AT2R (Agtr22/2/Elnhetero). Loss of AT2R in elastin insufficient mice (Agtr22/2/Elnhetero) resulted in significant reduction of systolic and diastolic blood pressures, but no change in pulse pressure or large artery compliance. There were no structural changes in either the ascending aorta or mesenteric arteries of Agtr22/2/Elnhetero compared to Agtr22/2/Elnhetero.

Conclusions: These results provide in vivo evidence for a role of AT2R in mediating elastin insufficiency-associated hypertension. Furthermore, these data suggest distinct mechanisms for the development of hypertension and vascular stiffness in elastin insufficiency, as loss of AT2R reduced blood pressure, but had no effect on large artery stiffness in this mouse model. Studies are underway to determine the effect of AT2R loss on resistance artery reactivity.

Funding: Other NIH Support - Child Health Research Career Development Award (K12)

TH-OR059
Interference with COP9 Signalosome Mimics FHH Effects on WNK4: Loss of BP Lowering with Captopril
Leon D. Guzman,1 Ester Marasi,1 Thu H. Le,1 Juan-Jae Chung,1 Jasmine Goldstein,2,4 Paul Le,3 Andrey K. Pandey,4 Hiroshi Arai,3 Carmen M. Halabi. Washington University School of Medicine, St. Louis, MO.

Background: COP9 signalosome (CSN) is a large ubiquitin specific protease complex that regulates cullin-RING ligases. The mouse glomeruli were obtained using the droplet-based 10x Genomics Chromium single cell technology which distinguishes the three major cell types in the glomerulus (podocytes, mesangial cells, and endothelial cells). Analyses of gene expression of the identified novel candidates for mesangial cell markers. After induction of anti-GM1 ganglioside, we observed

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
accumulation of immune cells and significant changes in the gene expression patterns ofglomerular cells. After resolution of the heterologous phase, global gene expression pattern of podocytes largely reverted back to its original state, whereas the transcriptome profile of mesangial cells and endothelial cells remained altered. We observed heterogeneous expression of CCL2 in the mesangium of a CCL2-reporter mouse, which was increased after induction of glomerulonephritis. CCL2 expression was enriched in mesangial cells that had higher levels of immediate early genes, suggesting these cells may act as sentinels during glomerular injury. Comparing the transcriptomes of each cell type from healthy and nephritic glomeruli reveal candidate genes for further functional studies.


TH-OR062
Human iPS-C-Derived Glomeruli Facilitate Accurate Modeling of Podocyteopathy Lorna J. Hale,1 Sara E. Howden,2 Belinda Phipson,2 Irene Gholbri,2 Pei Xuan Er,3 Santhosh V Kumar,1 Alicia Oshlack,2 Melissa H. Little,2 1Murdoch Children’s Research Institute, Parkville, NSW, Australia; 2Murdoch Children’s Research Institute, MELBOURNE, NSW, Australia; 3Murdoch childrens research institute, Melbourne, NSW, Australia.

Background: Numerous kidney diseases leading to proteinuria result from alterations to the podocyte which leads to foot process effacement and loss of slit diaphragms. Immortalised cell lines have been the gold standard in podocyte biology, however, this model has inherent limitations. Consequently, validation of novel disease-associated mutations is most often performed in animal models which may not replicate the human condition. The advent of iPSC organoids now provides a new avenue for the study of human podocyte disease ex utero.

Methods: Sieved glomeruli isolated from human iPSC kidney organoids were characterised and compared to conditionally immortalised human podocytes by RNA-sequencing. The capacity of organoid-derived glomeruli to recapitulate podocyteopathy through podocyte injury and clinically relevant mutations into iPSC was assessed using CRISPR-Cas9 technology.

Results: Organoid-derived glomeruli showed superior podocyte-specific gene expression when compared to conditionally immortalised podocytes, with an upregulation of 2187 genes. In vitro injury associated with slit diaphragm development, and podocyte epithelial cell differentiation and development were significantly enriched. Glomeruli isolated from homozygous MAFB mutant organoids accurately recapitulated anticipated disease related transcriptional changes.

Conclusions: We provide the first evidence that human iPSC kidney organoids can readily generate such an accurate model of the human glomerulus from iPSC. This model will provide valuable tools for assessing podocyte response to injury, including disease associated mutations, and facilitate the understanding of podocyteopathy.

Funding: Government Support - Non-U.S.

TH-OR063
Calcium/Calmodulin-Dependent Kinase IV Compromises Podocyte Function in Autoimmune and Non-Autoimmune Kidney Diseases Kayavo Maeda,1 Kotaro Otomo,1 Nobuya Yoshida,1 Sean D. Bicketon,2 Tarek Fahmy,3 Maria Tsokos,4 George C. Tsokos,4 Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, 1Harvard Medical School, Boston, MA; 2Kio University School of Medicine, Tokyo, Japan; 3Yale School of Medicine, New Haven, CT.

Background: Podocyte dysfunction is a common feature of renal injury in autoimmune and non-autoimmune renal diseases and the good target of proteinuric kidney diseases. We previously reported that calcium/calmodulin-dependent kinase IV (CaMK4) was upregulated as a result of exposure to IgG from the patients with lupus nephritis (LN). Since podocytes from patients and mice with lupus have increased levels of CaMK4 linked to decreased nephrin expression, we considered that targeted delivery of a CaMK4 inhibitor (KN93) to podocytes should preserve podocyte function.

Methods: We treated lupus-prone MRL-lpr mice starting at 8 weeks age, mice injected lipopolysaccharide (LPS) or adriamycin with anti-podocin or nephrin tagged nanoparticles (nlg) loaded with KN93 intraperitoneally (i.p.). We also used immortalized differentiated human podocytes to examine the actin structure and function under LPS of lupus IgG treatment.

Results: Podocytes from lupus-prone or LPS or adriamycin-treated mice and patients with LN or focal segmental glomerulosclerosis (FSGS) displayed increased expression of CaMK4. Targeted delivery of KN93 to podocytes suppressed proteinuria, immune complex deposition and crescent formation in lupus-prone mice and proteinuria in mice with LPS or adriamycin-induced podocyte injury by preserving podocyte structure, nephrin and synaptopodin, associated with slit diaphragm development, and podocyte specific delivery of KN93 prevented and reversed renal disease. Similarly, CaMK4 deficiency also protected from those podocyte injuries. Inhibition or silencing of CaMK4 protected from LPS-induced the actin cytoskeleton injury and synaptopodin degradation in human podocytes. Anti-CaMK4 interacted with 14-3-3-d and disrupted the binding of synaptopodin with 14-3-3 leading to actin cytoskeleton rearrangement of podocytes.

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

Conclusions: We conclude that inhibition of CaMK4 preserves podocyte structure and function and targeted delivery of a CaMK4 inhibitor to podocytes should have therapeutic value in lupus nephritis and podocyteopathies including FSGS.

Funding: NIDDK Support

TH-OR064
Ex Vivo Induced Neutrophil Extracellular Traps Are Intrinsically Different in ANCA-Associated Vasculitis- and Systemic Lupus Erythematosus Laura S. van Dan,1 Tineke Kraaij,2 Sylvia Kamerling,1 Hans Ulrich Scherer,1 Charles D. Pusey,3 Ton J. Rabelink,1 Gisela Tieg,1 Yoe Kie Onno Teng,1 1LUMC, Leiden, Netherlands; 2Imperial College London, London, United Kingdom.

Background: Neutrophil extracellular traps (NETs) are immunogenic, extracellular DNA structures that harness important autoantigens to be recognized by the adaptive immune system. NETs are thought to play a pivotal role in the pathogenesis of AAV and SLE. However it is still unclear how and if NETs act as a common pathway in the pathophysiology of these clinically divergent autoimmune diseases. The aim of the present study is to characterize AAV- and SLE-induced NETs.

Methods: Healthy neutrophils were stimulated with 10% serum of AAV (n=101) and SLE (n=59) patients to induce NETs. Ex vivo NET induction by serum and IgG-depleted serum was measured by a novel, highly-sensitive NET quantification assay using 3D-confocal microscopy. Qualitative characteristics of NETs were studied by immunofluorescence to detect NET-related auto-antigens. Additionally, the morphology and kinetics of AAV- and SLE-induced NETs were visualized by live cell imaging and electron microscopy.

Results: Ex vivo NET induction by AAV sera was 20.74 [9.56 – 74.14], (median [Q1 - Q3]) fold higher than sera of healthy controls (n=10) and also significantly higher than NET induction by SLE sera 5.02 [1.88 – 14.33]. Depletion of IgG from serum did not reduce NET induction in AAV, whereas it was significantly decreased in SLE.

Conclusions: We demonstrate distinct features of ex vivo AAV- and SLE-induced NETs, indicating that NET formation in AAV and SLE is based on different mechanisms. Future studies should be directed at unravelling how different NETs are involved in causing SLE- or AAV-associated glomerulonephritis.

TH-OR065
The Co-Inhibitory Molecule PD-L1 Contributes to Regulatory T Cell-Mediated Protection in Murine Crescentic Glomerulonephritis Katrin Neumann,1 Annett Ostmann,2 Philippe C. Breda,3 Hans-Joachim Paust,1 Ulf Panzer,4 Gina Tieg,1 University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

Background: Glomerular diseases such as crescentic glomerulonephritis (cGN) are mediated by inappropriate cellular and humoral immune responses towards autoantigens subsequently leading to end-stage renal failure. Previously, we demonstrated a crucial role for regulatory T cells (Tregs) in suppressing pro-inflammatory Th1 and Th2 cell-mediated immune responses during nephrotic nephritis (NTN), the murine model of cGN. However, mechanisms of immune regulation in cGN are insufficiently understood. Here, we aim at investigating the role of the co-inhibitory molecule PD-L1 in Treg-mediated protection from NTN.

Methods: NTN was induced in PD-L1−/− mice by injection of the nephritic serum. Disease severity was investigated at day 8 after NTN induction and compared to C57BL/6 wild type (WT) mice. Kidney damage was quantified by crescent formation in PAS-stained tissue sections and determination of albumin-to-creatinine ratio by ELISA. PD-L1 was blocked in WT mice by injection of an anti-PD-L1 antibody. To neutralize IFNγ, PD-L1−/− mice were treated with an anti-IFNγ antibody. Tregs from nephritic PD-L1−/− or WT mice were adoptively transferred into Rag1−/− mice one day before NTN induction. Gene and protein expression analysis was done by quantitative RT-PCR and flow cytometry.

Results: PD-L1−/− mice developed more severe NTN compared to WT mice. Histological analysis revealed increased numbers of T cells, macrophages/DCs but also Foxp3+ Tregs in the kidneys of nephritic PD-L1−/− mice. Moreover, renal and systemic IFNγ-mediated Th1 immune response as well as systemic humoral immune response were strongly enhanced in nephritic PD-L1−/− mice. Blockage of PD-L1 in WT mice amplified renal Th1 response and aggravated disease pathogenesis. Furthermore, neutralization of IFNγ ameliorated NTN in PD-L1−/− mice. In co-culture, renal DCs from nephritic PD-L1−/− mice suppressed expression of IFNγ in CD4+ T cells. Interestingly, PD-L1−/− Tregs were not able to suppress activation and proliferation of responder CD4+ T cells in vitro and they also failed to protect from NTN in vivo.

Conclusions: PD-L1 displays a protective role in NTN, which is related to Treg- and DC-dependent suppression of the Th1 immune response. Thus, targeting PD-L1 may represent a novel therapeutic option in cGN.
TH-OR066
DNA-Aptamer Raised against RAGE Improves the Development of Lupus Nephritis in MRL/lpr Mice
Kizuna Nakanishi,1,2 Akito Maeshima,2 Shio-ichi Yamagishi,3 Yusuke Nakayama,4 Yusuke Kaida,4 Yuichiro Higashimoto,1 Craig R. Brooks,1 Kei Fukami.1 Division of Nephrology, Department of Medicine, Kurume University, Kurume, Japan; 2Gunma University Graduate School of Medicine, Maebashi, Japan; 3Kurume University, Kurume, Japan; 4Kurume University School of Medicine, Kurume, Japan; 1Yanderbilt University Medical Center, Nashville, TN.

Background: Lupus nephritis (LN) affects 60% of patients with systemic lupus erythematosus (SLE). Although immunosuppressive drugs are used as a first-line therapy, LN still negatively impacts the survival and quality of life in SLE patients. The Receptor for advanced glycation endproducts (RAGE), which belongs to the immunoglobulin superfamily, is strongly associated with innate immune responses. In this study, we examined whether RAGE could be involved in LN development in lupus prone MRL/lpr mice.

Methods: A DNA-aptamer raised against RAGE (RAGE-apt) or Control-apt (Ctrl-apt) was subcutaneously administered to MRL/lpr mice for 10 weeks. Histological and serological analyses were performed.

Results: A RAGE levels, but not proteinuria excretion, were significantly increased in 8-week-old MRL/lpr mice compared with control MRL/MpJ mice. In addition, glomerular RAGE expression was markedly increased starting at 12 weeks and was associated with the increased glomerular extracellular matrix accumulation and cellular crescents. RAGE expression was dramatically increased in endothelium and infiltrating macrophages of the glomeruli. Administration of RAGE-apt significantly ameliorated mesangial expansion, wing-like and crescent formation, and macrophage infiltration into the glomeruli in MRL/lpr mice. In addition, RAGE-apt, but not Ctrl-apt, significantly reduced the levels of urinary NGAL (AUC; 0.769, 95% CI: 0.603-0.935) outperformed conventional biomarkers (serum creatinine, urine protein, and GFR) in differentiating complete and partial responders. Administration of RAGE-apt significantly increased in 8-week-old MRL/lpr mice compared with control MRL/lpr mice. In addition, glomerular RAGE expression was markedly increased starting at 12 weeks and was associated with the increased glomerular extracellular matrix accumulation and cellular crescents. RAGE expression was dramatically increased in endothelium and infiltrating macrophages of the glomeruli. Administration of RAGE-apt significantly ameliorated mesangial expansion, wing-like and crescent formation, and macrophage infiltration into the glomeruli in MRL/lpr mice. In addition, RAGE-apt, but not Ctrl-apt, significantly reduced the levels of urinary NGAL (AUC; 0.769, 95% CI: 0.603-0.935) outperformed conventional biomarkers (serum creatinine, urine protein, and GFR) in differentiating complete and partial responders. Administration of RAGE-apt significantly increased urinary NGAL (AUC; 0.769, 95% CI: 0.603-0.935) outperformed conventional biomarkers (serum creatinine, urine protein, and GFR) in differentiating complete and partial responders.

Conclusions: RAGE at baseline performed better than conventional markers in predicting a clinical response to treatment of active LN except serum complement C3 level. It may have the potential to predict poor response after induction therapy.

Funding: Other NIH Support - This study was supported by a grant from the National Science and Technology Development Agency (NSTD4, P-13-00505), Bangkok, Thailand.

TH-OR068
Molecular Profiling of Renal Compartments from Serial Lupus Nephritis Kidney Biopsies to Identify Markers of Response
Samir V. Parikh,4 Ana Malvar,1 Huijuan Song,1 John P. Shapiro,4 Valeria G. Alberton,1 Juan M. Mejia-Villegas,1 Isabelle Ayoub,1 Anjali A. Satoskar,1 Jianying Zhang,1 Limbo Yu,2 Paolo Fadda,3 Michael T. Eadon,2 Danielle J. Eadon,2 Christian Kaida,1 Hyoung Won Ahn2マンション, Hiroshi Inoue,3 Kurume University, Kurume, Japan; 2Gunma University Graduate School of Medicine, Maebashi, Japan; 3Kurume University, Kurume, Japan; 4Kurume University School of Medicine, Kurume, Japan; 1Yanderbilt University Medical Center, Nashville, TN.

Background: Lupus nephritis (LN) affects 60% of patients with systemic lupus erythematosus (SLE). Although immunosuppressive drugs are used as a first-line therapy, LN still negatively impacts the survival and quality of life in SLE patients. The Receptor for advanced glycation endproducts (RAGE), which belongs to the immunoglobulin superfamily, is strongly associated with innate immune responses. In this study, we examined whether RAGE could be involved in LN development in lupus prone MRL/lpr mice.

Methods: A DNA-aptamer raised against RAGE (RAGE-apt) or Control-apt (Ctrl-apt) was subcutaneously administered to MRL/lpr mice for 10 weeks. Histological and serological analyses were performed.

Results: A RAGE levels, but not proteinuria excretion, were significantly increased in 8-week-old MRL/lpr mice compared with control MRL/MpJ mice. In addition, glomerular RAGE expression was markedly increased starting at 12 weeks and was associated with the increased glomerular extracellular matrix accumulation and cellular crescents. RAGE expression was dramatically increased in endothelium and infiltrating macrophages of the glomeruli. Administration of RAGE-apt significantly ameliorated mesangial expansion, wing-like and crescent formation, and macrophage infiltration into the glomeruli in MRL/lpr mice. In addition, RAGE-apt, but not Ctrl-apt, significantly reduced the levels of urinary NGAL (AUC; 0.769, 95% CI: 0.603-0.935) outperformed conventional biomarkers (serum creatinine, urine protein, and GFR) in differentiating complete and partial responders. Administration of RAGE-apt significantly increased urinary NGAL (AUC; 0.769, 95% CI: 0.603-0.935) outperformed conventional biomarkers (serum creatinine, urine protein, and GFR) in differentiating complete and partial responders. Administration of RAGE-apt significantly increased urinary NGAL (AUC; 0.769, 95% CI: 0.603-0.935) outperformed conventional biomarkers (serum creatinine, urine protein, and GFR) in differentiating complete and partial responders.

Conclusions: RAGE at baseline performed better than conventional markers in predicting a clinical response to treatment of active LN except serum complement C3 level. It may have the potential to predict poor response after induction therapy.

Funding: Other NIH Support - This study was supported by a grant from the National Science and Technology Development Agency (NSTD4, P-13-00505), Bangkok, Thailand.

TH-OR069
Effects of Blisibimod, a Selective Inhibitor of B-Cell Activating Factor, on Urinary Protein:Creatinine Ratio (UPCR) in Subjects with Renal Manifestations of Systemic Lupus Erythematosus (SLE) Joan T. Merrill,1 Renee Martin,2 William Shanahan,3 Kenneth Kalunian,4 David Wofsky,4 1Oklahoma Medical Research Foundation, Oklahoma City, OK; 2Anthera Pharmaceuticals, Inc., Hayward, CA; 3UCSD, La Jolla, CA; 4University of California, San Francisco, CA.

Background: The CHABLIS-SC1 trial (NCT01395745) was a Phase 3 trial of blisibimod in 442 patients with active systemic lupus, 135 of whom had UPCR≥0.5 mg/mg at study entry.

Methods: Subjects in the CHABLIS-SC1 trial were randomized to receive weekly subcutaneous blisibimod (200 mg) or placebo. All subjects had anti-nuclear antibody or anti-dsDNA antibodies and SLEDAI score ≥10 on standard of care medications. Patients with renal manifestations were eligible unless proteinuria exceeded 6 g/24 hour or disease severity was likely to require escalation of immunosuppressive therapy. This report evaluates the effects of blisibimod in the subgroup of subjects with baseline UPCR≥0.5 mg/mg.

Results: In the renal subgroup, greater decreases in UPCR from baseline were observed in the blisibimod arm (Figure). Significantly more subjects who received blisibimod achieved ≥50% reduction in UPCR from baseline (59.7% vs 30.8%, p<0.006). A higher proportion also achieved UPCR<0.5 (53.2% and 30.8%, p=0.021). No treatment effects were noted on eGFR and serum creatinine, which typically were within normal ranges throughout the trial. Across all 442 enrolled subjects, adverse events were balanced between treatment arms excepting mild or moderate injection site erythema and injection site reaction which occurred more frequently with blisibimod.

Conclusions: The reduction in proteinuria in SLE subjects with clinical evidence of nephritis suggests that blisibimod may have therapeutic potential in lupus nephritis and, perhaps, other B-cell-associated renal diseases.

Funding: Commercial Support - Anthera Pharmaceuticals
Treatment Effects on UPCR

**TH-OR070**

**Treatment and Outcomes of the ANCA-Associated Vasculitides in the Very Elderly – A Single Centre Experience**

Taneem Noura S. Chagger, Epnom and St Holler NHS Trust, London, United Kingdom.

Background: ANCA-associated vasculitides has a peak incidence between 65-74 years of age, and not uncommon to present in the very elderly (>80yrs). Decisions regarding immunosuppression in the very elderly can be challenging, given likely co-morbidities and general frailty, and on treatment and outcomes in this age group is lacking.

Methods: Patients were identified retrospectively from the local renal database. A total of 23 patients presented with ANCA associated vasculitis between 2006 and 2017. Data from patients >= 80 years during the study period were collected. Follow-up was until May 2017. The collected data were analysed with respect to age, sex, renal function at diagnosis, patient and renal survival, induction and maintenance treatment and disease relapse.

Results: We identified 32 patients from this cohort, mean age of 83.5 yrs (range 80-90 years), mean follow-up period of 35.5 months (range 0.2 – 106). Of these, 14 were PR-3 positive and 18 were MPO positive. Overall survival to completion of induction therapy at 3 months was 91% (29/32) and 1 year survival was 90% (29/32). Mean creatinine at presentation was 406 mmol/L and 38% (12/32) required replacement therapy (RRT) within 72 hours of presentation. Induction of remission was achieved using corticosteroids with either cyclophosphamide (25/32), MMF (1/32) or rituximab (1/32).

In two patients azathioprine was used with corticosteroids as first line therapy. N=6 had Plasma Exchange in addition to RRT. Of these, 4 were RRT independent at 3 months. Renal survival was 79% (23/29) at 3 months and 85% (22/26) at 1 year. No patients progressed to ESRD after 3 months. Disease relapse occurred in 2 patients, with a mean time to relapse of 21.5 months.

Conclusions: AAV is a disease with substantial mortality and morbidity among elderly patients. The results of this retrospective study showed that very elderly patients can benefit from immunosuppressive therapy with good outcomes to 3 months and 1 year survival. Relapse rates are low. Dialysis independence can be achieved in those patients requiring RRT on admission and this treatment ensures that patients are maintained off RRT up to a median of 35.5 months follow-up.

**TH-OR079**

**Single-Cell RNA-Seq Reveals Distribution of Na, K, and Cl Transporters among the Major Cell Types of the Collecting Duct**

Lihe Chen,1 Chun-Ling Chou,2 Maurice B. Burg,3 Jill W. Verlander,3 Susan M. Wall,3 Mark A. Kneppe,3 Emory University School of Medicine, Atlanta, GA; 1University of Florida, Gainesville, FL; 2National Heart Lung and Blood Institute, Bethesda, MD.

Background: Fine control of water, ion, and acid-base homeostasis is maintained by transport processes in the collecting duct. Collecting ducts are made up of at least 5 cell types: type A intercalated cells (A-ICs), type B intercalated cells (B-ICs) and principal cells (PCs). To identify transporters for A-ICs, B-ICs and PCs, it is necessary to carry out RNA-Seq at a single-cell level.

Methods: We used cell-surface markers for A-ICs (c-KIT), B-ICs (PNA) and PCs (DBA), allowing these cell types to be enriched from kidney cell suspensions from untreated mice using fluorescence-activated cell sorting (FACS). The enriched fractions were used for microfluidic-based single-cell RNA-Seq. We performed a t-distributed stochastic neighbor embedding (t-SNE) analysis and resolved cell clusters. Based on the gene expression patterns, three major clusters are identified as A-ICs, B-ICs and PCs.

Results: In the table below, we present transcript abundances in TPM values for major Na, K, and Cl transporters and associated regulators in the three major cell types of the collecting duct (largest value in bold). Our data confirm the selective expression of Hflu1b2, Scnn1b and Scnn1g, and major potassium channels (Kcnj1, Kcnel, Kcngl0, Kcnj16) in PCs. We also found A1f4 (Slc4a9) and pendrin (Slc26a4) are mutually exclusive in A-IC and B-IC, respectively. Interestingly, we found that ENaC alpha (Scnn1a) and Na-K-ATPase (Atpal) transcripts are more abundant in B-ICs than in PCs or A-ICs.

In addition expression patterns, three major clusters are identified as A-ICs, B-ICs and PCs. Glucose cotransporter is expressed in all three cell types. AEA (Slc4a4) was expressed in both IC cell types (confirmed by immunohistochemistry).

Conclusions: In conclusion, the single-cell RNA-Seq profiling results revealed a distinct Na+ transport pattern in transporters and their regulators in A-ICs, B-ICs and PCs. The identification of transcripts related to Na+ transport and its regulation in B-ICs is consistent with a direct role of B-ICs in regulated Na+ reabsorption.

**Funding:** Other NIH Support - NHLBI

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
induced a rapid increase in Na+ current. This latter effect was blocked by SGK1 or mTOR inhibitors. Similarly, in mice pretreated to patch clamp, ENaC currents were significantly greater in the presence of 5 mM (330 +/- 25, Na-, N-5) than in the presence of 1 mM (250 +/- 20, Na-, N-5) (K+ (p < 0.05).

Conclusions: Changes in extracellular [K+] rapidly modulate mTORC2-dependent SGK1 activation in intercalated cells of CCD, which support an altered Na+-transport. Our findings complement recent evidence of Na-Ci cotransporter (NCC) phosphorylation and activity are regulated in distal convoluted cells directly by extracellular fluid [K+]i, these data support a new model of coordinated regulation of Na+-transport between distal convoluted tubule and CCD, which is directly modulated by local renal [K+]i.

Funding: NIDDK Support

TH-OR074

Aldosterone Is Essential for Angiotensin II-Induced Upregulation of Pendrin in Mouse Interrenal Tissues

Nobutada Dajia,1 Nobuhisa Hideyama,1 Naohiro Akiyama,1 Kohhei Ueda,1 Mitsuhiro Nishimoto,1 Wakako Kawarazaki,1 Atsushi Watanabe,1,2 Tatsuo Shimosawa,3 Takeshi Marumo,1 Shigeru Shibata,1,4 Toshio Fujita,5 Research Center for Advanced Science and Technology, The University of Tokyo, Tokyo, Japan; 2Department of Nephrology, Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan; 1Division of Clinical Laboratory, School of Medicine, International University of Health and Welfare, Narita, Chiba, Japan; 4Division of Nephrology, Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan.

Background: The renin-angiotensin-aldosterone system (RAAS) is known to play an important role in the control of fluid homeostasis and blood pressure during volume depletion. Dietary salt restriction elevates circulating angiotensin II (AngII) and aldosterone, which increases levels of C1/HCO3-, exchange (pendrin) in β-intercalated cells and Na–Cl cotransporter (NCC) in distal convoluted tubules; however, the role of these transporters in aldosterone responsive levels remains unclear.

Methods: In both C57BL/6 mice receiving a low-salt diet or AngII infusion and adenalec-tomized mice receiving either AngII or co-administration of AngII and aldosterone, we evaluated membrane-protein abundance of pendrin, NCC and mineralocorticoid receptor (MR) phosphorylation, which selectively inhibits aldosterone binding in intercalated cells. We also measured blood pressure (BP) by radiotelemetry in pendrin-deficient mice. The Cystic Fibrosis Transmembrane Regulator (CFTR) and the Na+/H+ Exchanger NHE-2 Play Important Roles in Compensatory Salt Absorption in Kidneys of Na-CI Cotransporter (NCC) Deficient Mice

Manocheer Soleimanian,1,2 Sharon L. Barone,1,3 Jie Xu,1 Marybeth Brooks,1 Kamary A. Zahedi,1,2 University of Cincinnati, Cincinnati, OH; 3Research Services, Veterans Administration, Cincinnati, OH.

Background: The ablation of the Na-Ci cotransporter NCC (Slc12a3) does not cause any significant salt wasting in mice, in part due to activation of the Cl-/HCO3- exchanger and the epithelial sodium channel ENaC. However, whether other transporters/channels contribute to compensatory salt absorption in NCC null mice remains speculative.

Methods: To better identify the compensatory salt absorptive mechanisms in NCC deficient mice, RNA-seq analysis was performed on kidney cortices of wild type, NCC KO and pendrin KO mice. Results were verified by expression studies in kidneys and complemented by functional studies in live animals.

Results: One notable transporter/channel, which was significantly upregulated in NCC KO but downregulated in pendrin KO mice was CFTR. Another transporter which was upregulated in NCC KO mice was NHE2. Northern hybridizations verified enhanced expression of CFTR and NHE2 in the kidney cortex of NCC KO mice and immunofluorescence labeling studies indicated the upregulation of CFTR and NHE2 in the CCD and DCT, respectively. To ascertain the role of CFTR in compensatory salt absorption in NCC KO mice, WT and NCC KO mice were placed in metabolic cages and injected twice/day with the CFTR inhibitor GlyH-101 for 4 days. Urine volume increased by ~60% and urine sodium increased by ~35% vs. baseline in response to GlyH-101 treatment (p<0.05 for both parameters). Wild type mice showed no significant increase in urine output or sodium excretion in response to GlyH. NCC KO, but not WT mice showed enhanced salt excretion in response to amiloride injection which was likely resulting from combined inhibition of NHE2 and ENaC.

Conclusions: CFTR is critical in the distal nephron and plays an important role in compensatory salt absorption in NCC deficient mice. In addition, NHE-2 is activated in the distal nephron and facilitates the activity of the Cl/HCO3- exchanger pendrin and ENaC in intercalated cells and principal cells, respectively, leading to enhanced salt absorption in NCC KO mice. We further propose that NHE-2 is activated and works in tandem with pendrin to facilitate the electroneutral absorption of sodium and chloride.

Funding: Veterans Affairs Support, Private Foundation Support

TH-OR075

Role of CIC-K and Barttin in Low-Potassium Induced Sodium-Chloride Cotransporter Activation and Hypertension in Mouse Kidney

Naohiro Nomura,1 Wakana Shoda, Younglong Wang, Daiei Takahashi, Moko Zeniya, Eisei Sohara, Tatemitsu Rai, Shinichi Uchida. Tokyo Medical and Dental University, Tokyo, Japan.

Background: The sodium-chloride cotransporter (NCC) was identified as a key molecule regulating potassium balance. The mechanisms of NCC regulation during low extracellular potassium concentrations have been investigated in vitro showing that the hyperpolarization induced by low potassium concentrations increased chloride efflux through the CIC-K chloride channels, leading to the activation of chloride-sensitive WKNa kinases and their downstream molecules including SPAK and NCC. However, this mechanism was not investigated in vivo.

Methods: We used the barttin hypomorphic mouse (Bsndneo/neo mice), expressing very low levels of barttin and CIC-K channels since barttin is an essential β-subunit of CIC-K. Mice were fed a normal diet or a low-potassium diet in vivo. Kidney slices were incubated in different potassium concentration buffer ex vivo. Then, SPAK and NCC phosphorylation was evaluated by Western blotting.

Results: In contrast to Bsnd−/− mice, Bsndneo/neo mice survived to adulthood, which enabled us to investigate the role of CIC-K in NCC activation. When mice were fed a normal diet or a low potassium diet, there was no significant difference in total and phosphorylated NCC levels between wild-type mice and Bsndneo/neo mice. In Bsnd−/− mice, SPAK and NCC activation (phosphorylation) after consuming a high-salt and low-potassium (HSKL) diet was clearly impaired compared to that in wild-type mice. In ex vivo kidney slice experiment, the increase in potassium phosphorylated NCC in low-potassium medium was also blunted in Bsndneo/neo mice. Furthermore, the increase in blood pressure was observed in wild-type mice fed a HS KL diet, which was not evident in the Bsndneo/neo mice.

Conclusions: Our study provides in vivo evidence that CIC-K and barttin play important roles in the activation of the WKNa4-SPA4-NCC cascade and the blood pressure regulation, in response to a low-potassium diet.

Funding: Government Support - Non-U.S.

TH-OR077

Paracervical Properties of the Cystic Collecting Duct

Nina Himmerkus,2 Julian Isermann,2 Lieske Jarck,2 Yongfeng Gong,1 Susanne Milatz,1 Zhanghui Hou,1 Markus Bleich.1 1Washington University School of Medicine, Saint Louis, MO; 2Christian-Albrechts-University Kiel, Kiel, Germany.

Background: Collecting duct salt and water transport is involved in the regulation of extracellular volume and blood pressure. Ions are transported either transcellularly or through the paracellular pathway following electrochemical driving forces. Claudins are the major determinants of tight junction permeability. They form the paracellular pathway and claudin-4 and -8 have been discussed to be involved in paracellular chloride transport.

Methods: Cortical collecting ducts (CCD) from principal cell-specific claudin-4 knockout animals (KO) and their respective controls (Ctrl) were investigated under normal diet and low salt diet. CCD were isolated by manual dissection, perfused in vitro and investigated for their basic trans- and paracellular transport properties. Transepithelial voltage (Vte), transepithelial resistance (Rte) and equivalent short circuit current (Isc) were measured before and after luminal application of 50 μM amiloride and 100 μM hydrochlorothiazide to inhibit transcellular ion transport. A diffusion potential was generated by changing the basolateral solution from 145 to 30 mM NaCl (isotonic) to test for paracellular ion selectivity and the permeability ratio Pcl/Pna was calculated. Immunofluorescence was used to localize and quantify claudin-4 expression along the membranous and particularly in the collecting duct.

Results: Under normal diet CCDs of Ctrl as well as of KO showed similar transcellular amiloride dependent luminal negative Vte. Under inhibition of transcellular transport, however, Rte was lower in KO CCD (114±8 cm2) vs. Ctrl CCD (155±11 cm2). Similarly, Pcl/Pna values showed chloride selectivity in Ctrl CCD (1.36±0.08) but hardly any selectivity in KO CCD (1.07±0.03). Low salt diet increased amiloride dependent Vte in both genotypes to a similar extend, however, with increased Rte in KO CCD (192±16 cm2) vs. in Ctrl CCD (147±11 cm2), under inhibition of transcellular transport, respectively. Pcl/Pna values did not change in Ctrl CCD (1.24±0.05) nor in KO CCD (1.04±0.03). Immunofluorescence confirmed claudin-4 knockout with residual low expression of claudin-4 in intercalated cells.

Conclusions: In summary, claudin-4 is expressed in both, principal and intercalated cells of CCD and claudin-4 deficiency leads to the loss of Cl- selectivity.

Funding: Other NIH Support - R01DK084059

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
**TH-OR078**

HIF Regulation of Nephron Progenitor Metabolic State Mediates Cell Fate Decisions

Anjali Murali, Kasey Cargill, Elina Mukherjee, Zubaida R. Saifudeen, Sunder Sims-Lucas. Children’s Hospital of Pittsburgh, Pittsburgh, PA; Tulane University School of Medicine, New Orleans, LA; University of Pittsburgh, Pittsburgh, PA.

**Background:** Hypoxia inducible factors (HIFs) are transcription factors involved in the differentiation of nephron progenitors (NP) into functional nephrons. Alterations in nephron differentiation lead to renal abnormalities. As renal oxygen increases, von Hippel-Lindau (VHL) marks HIF-1α for degradation and facilitates normal nephron differentiation. Alternatively, pathological hypoxia results in HIF-1α accumulation and initiation of processes including cellular survival and metabolism. Previous in vitro studies have also linked HIF-1α stabilization to mitochondrial pathologies suggesting that HIF-1α plays a role in cellular and mitochondrial respiration. Therefore, we hypothesize that HIF-1α alters mitochondrial function, mediating a metabolic switch to determine NP fate.

**Methods:** To determine the role of HIFs in the NPs we utilized VHL floxed mice bred with the Six2-ZFGEFPere line, to generate Six2cre.VHLflx/flx mutant mice. RNA sequencing was conducted on E14 whole kidneys to look at differential gene expression, and validated via RT-PCR. We also performed a metabolic assessment using seahorse extracellular flux analysis, and coupled this with immunofluorescence (IF) and western blot analysis to analyze metabolic markers.

**Results:** RNA sequencing of Six2cre.VHLflx/flx mutant mice revealed metabolic gene dysregulation. Furthermore, seahorse extracellular flux analysis suggested that mutants with HIF-1α stabilization in the NPs remained in a glycolytic state, and were subsequently unable to switch to oxidative phosphorylation, which drives NP differentiation. IF staining and western blot analysis supported these results revealing fewer mature nephron structures and decreased mitochondrial content in mutant kidneys.

**Conclusions:** HIFs are critical in determining the metabolic state of the NPs. In the absence of VHL, HIF-1α is stabilized. This stabilization maintains NPs in a state of glycolysis and in turn blocks the switch to oxidative phosphorylation causing NP differentiation defects and kidney malformations.

**Funding:** NIDDK Support

---

**TH-OR080**

Single-Cell Analysis of Progenitor Cell Dynamics and Lineage Specification of the Human Fetal Kidney

Kristina Cebrisan Ligero, Rajasree Menon, Edgar A. Otto, A. Austin Kokoruda, Jann Zhao, Zidong Zhang, Olga Troyanska, Jason R. Spence, Matthias Kretzler. University of Michigan Medical School, Ann Arbor, MI; Princeton University, Princeton, NJ.

**Background:** The study of animal models has identified a plethora of genes and pathways driving the repetitive and reciprocal interactions between the Ureteric Bud (UB) and the Metanephric Mesenchyme (MM) that give rise to the collecting system and the nephron pool. However, these expression patterns and how they drive differentiation have not been systematically characterized in the human kidney. We have used single-cell transcriptomics to study individual cell dynamics and characterize the expression profile of the human kidney.

**Methods:** Fetal kidneys (105 to 115 days of gestation) were dissociated to single cells and processed for DropSeq workflow as described by the McCarroll lab. Individual isolated cells were sequenced by barcoding, and subsequently tagged with Unique Molecular Identifiers. Paired-end RNASeq was performed on a HiSeq2500 platform. Bioinformatics analysis employed the Picard tools developed by the Broad Institute and unsupervised clustering algorithms were executed with the R package toolkit “Seurat”. RNA profiles were mapped into trajectories derived using a nonparametric ridge estimation statistical framework. Gene expression was confirmed by immunofluorescence on fetal kidneys.

**Results:** Single cell transcriptome analyses of 3,865 cells (fig.A) enabled the distinction of UB-4 and MM-1 progenitors as well as their intermediate and differentiated lineages including the mature collecting ducts-18, the renal vesicle and comma- and s-shaped bodies-9, immature-9 and mature podocytes-13, proximal tubules-6, Henle’s loop and distal tubules-8, as well as mesangium-5 and cortical-5 and medullary interstitium-10. Importantly, known as well as novel markers for these cell types were revealed in the analysis.

**Conclusions:** We have generated an accurate map of gene expression and lineage relationships (fig.B) in the human fetal kidney. These results confirm the expression of genes identified by studying animal models. New gene-expression patterns have also been identified that may help understand human renal development.

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

---

**TH-OR079**

Caderhin-11 Is Induced by BMP7 and Stimulates Cap Mesenchyme Formation

Midori Ayawaz, Michio Nagata, Mariko Hida. Keio University School of Medicine, Tokyo, Japan; Keio Institute of Radiology, Tokyo, Japan.

**Background:** Caderhin-11 (CDH11) is an adhesion molecule specific to mesenchymal cells, which has been shown to promote cell migration and compaction and be involved in the differentiation of progenitor cells. In the developing kidney, CDH11 is expressed in cap mesenchyme and the interstitium. We investigated the role of CDH11 in kidney development and its relationship to BMP7, a growth factor necessary for maintaining and priming nephron progenitors.

**Methods:** Mice embryonic day 12 (E12) and E13 kidneys were transfected with two different siRNA against CDH11 (a or b) or irrelevant siRNA and cultured. Ureteric bud and cap bud were stained with pancytokeratin and Six2, respectively. An immortalized metanephric mesenchymal cell line MS7 was generated from the metanephiros of E11.5 homozygous mouse transgenic for H-2Kb-ta (J Am Soc Nephrol 12:964, 2001). The effect of different concentrations of BMP7 (0.25, 1, and 10 nM) on CDH11 expression in MS7 was assessed by quantitative real-time PCR and immunoblot.

**Results:** Cap mesenchyme, marked by Six2, was well observed around ureteric tips in control metanephiros and those transfected with irrelevant siRNA. In metanephiros transfected with siRNA a or b, on the other hand, Six2-positive cells were diffusely distributed and condensation around the ureteric tips was faint. CDH11 expression, assessed by whole mount staining, was distinctly observed in cap mesenchyme in controls, but was diffuse and reduced in metanephiros transfected with siRNAs. Ureteric bud tip number was significantly reduced by siRNAs (a 6.3±1.5, b 5.8±0.2) compared with controls (7.3±2.4 kidney).

**Conclusions:** Caderhin-11 is induced by BMP7 via ERK and p38, and stimulates cap mesenchyme formation.

**Funding:** Government Support - Non-U.S.
TH-OR082
Polycomb Repressive Complex-2 (PRC2) Fine-Tunes Timing of the Final Wave of Nephrogenesis

Samar S. El-Dahar, Zubaida R. Saifudeen, Hongbing Liu. Tulane, New Orleans, LA; Tulane University School of Medicine, New Orleans, LA.

Background: The mechanisms that control cessation of nephrogenesis are not well understood. Heterochromatin transcription and epigenome profiling suggest that old nephron progenitor cells (NPC) are poised for differentiation limiting their lifespan. In contrast, enhanced recruitment of Ezh1 and Ezh2, the catalytic components of PRC2, mediate H3K27 methylation to maintain lineage-specific genes in a silent yet poised state. We hypothesized that PRC2 activity restrains NPC aging and is essential for timely cessation of nephrogenesis.

Methods: We generated conditional Six2fl/fl; Rosa26m819Cre and compound Six2fl/fl; Rosa26m819Cre; Ezh1+/-; Ezh2+/-; Rosa26m819 Cre mice. Molecular and phenotypic analyses were accomplished by section IF and ISH at E15.5, E17.5, and P0, and transcriptome profiling of Six2-GFP+ of E17.5. Results were integrated with genome-wide maps of accessible chromatin, Six2 and histone mark occupancy, and scRNA-seq databases.

Results: Six2fl/fl and germline Ezh1/- NPCs are morphologically normal. In contrast, E17.5 Six2fl/fl; Ezh1+/- and Six2fl/fl; Ezh1+/- NPC fail to form the cap mesenchyme and display a unique gene expression signature consisting of the cell cycle inhibitor Cdk2a/p16, Lin28B (inhibitor of Let-7 mRNA upregulated in Wilm’s tumor), Six1 (normally expressed in early metanephric mesenchyme but absent in mouse cap mesenchyme), Hox13 and Wnt5A/10A genes. In wild-type NPCs, these aberrantly expressed genes are silent and heavily methylated on H3K27, yet display small peaks of accessible chromatin suggesting a state of epigenetic poising.

Conclusions: We conclude that H3K27 methylation fine-tunes the last wave of nephrogenesis by restraining Cdk2a/p16 and unscheduled activation of canonical Wnts in NPC. Ectopic induction of Lin28B, Hox and Six1 in mutant progenitors suggests a state of arrested differentiation of metanephric mesenchyme. Interventions targeting PRC2 function may be beneficial for nephron progenitor maintenance and regeneration.

Funding: NIDDK Support

TH-OR083
DNA Methylation Changes in Human Kidney Development and Disease Revealed by Whole Genome Bisulfite Sequencing of Tissue Samples

Jennifer Dame, Notre Dame, IN; 2Tulane, New Orleans, LA; 3Tulane University School of Medicine, New Orleans, LA.

Background: Numerous epidemiologic studies have confirmed the associations between “fetal programming” and development of chronic kidney disease (CKD) and hypertension. The epigenetic system is not only heritable but also under the influence of “fetal programming” and development of chronic kidney disease (CKD) and hypertension. The epigenetic system is not only heritable but also under the influence of “fetal programming” and development of chronic kidney disease (CKD) and hypertension.

Methods: Here, we generated base pair resolution methylome maps of early (11.5 weeks) and late (18.5 weeks) human fetal kidneys and microdissected tubules from healthy and CKD adult subjects (n=12). Our whole genome bisulfite sequencing (WGBS) analysis and PCA. Functional regions were mapped using histone modification ChIP-Seq analysis and PCA. Regional deletion of Six2fl/fl; Rosa26m819Cre; Ezh1+/-; Ezh2+/-; Rosa26m819 Cre mice. Molecular and phenotypic analyses were accomplished by section IF and ISH at E15.5, E17.5, and P0, and transcriptome profiling of Six2-GFP+ of E17.5. Results were integrated with genome-wide maps of accessible chromatin, Six2 and histone mark occupancy, and scRNA-seq databases.

Results: Results: Six2fl/fl and germline Ezh1/- NPCs are morphologically normal. In contrast, E17.5 Six2fl/fl; Ezh1+/- and Six2fl/fl; Ezh1+/- NPC fail to form the cap mesenchyme and display a unique gene expression signature consisting of the cell cycle inhibitor Cdk2a/p16, Lin28B (inhibitor of Let-7 mRNA upregulated in Wilm’s tumor), Six1 (normally expressed in early metanephric mesenchyme but absent in mouse cap mesenchyme), Hox13 and Wnt5A/10A genes. In wild-type NPCs, these aberrantly expressed genes are silent and heavily methylated on H3K27, yet display small peaks of accessible chromatin suggesting a state of epigenetic poising.

Conclusions: We conclude that H3K27 methylation fine-tunes the last wave of nephrogenesis by restraining Cdk2a/p16 and unscheduled activation of canonical Wnts in NPC. Ectopic induction of Lin28B, Hox and Six1 in mutant progenitors suggests a state of arrested differentiation of metanephric mesenchyme. Interventions targeting PRC2 function may be beneficial for nephron progenitor maintenance and regeneration.

Funding: NIDDK Support

TH-OR084
TFC21 is a Novel Regulator of Renal Progenitor Fate during Kidney Ontogeny

Brooke A. Chambers, Rebecca A. Wingert, University of Notre Dame, Notre Dame, IN.

Background: Occurring in 1 in 500 births, Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) are the primary cause of pediatric end-stage renal disease. The central etiology of these conditions involves aberrant development of nephrons, which are the functional units of the kidney.

Methods: Zebrabfish have emerged as a powerful genetic system to study the molecular coordination of cell fate decisions during vertebrate nephron formation. Here, through a forward ENU screen, we isolated a nephron mutant with abrogated distal tubules. Whole genome sequencing revealed a lesion that disrupts splicing of transcription factor AP-2 alpha (tpfa2a), thereby truncating essential transcriptional activation and DNA binding domains. Until now, tpfa2a has been known as essential for neural crest and epidermis differentiation but was not appreciated to act during renal ontogeny.

Results: We found that tpfa2a was dynamically expressed in zebrabfish renal progenitors, eventually restricting to the distal tubules. During mouse embryogenesis, tpfa2a expression was abundant within the developing urogenital tract encompassing structures such as the ureteric tip and distal tubules. Human tpfa2a mutations result in branchio-oculo-facial syndrome (BOFS), which primarily affects craniofacial tissue, though case reports have linked tpfa2a lesions to multicystic dysplastic kidney. Complementation tests between our mutant line and tpfa2a+/null, which encodes a nonsense allele, as well as knockdown studies similarly abolished the distal tubule. Conversely, overexpression of tpfa2a caused a striking expansion of distal cells. Through a subsequent suite of functional studies, we have determined that tpfa2a acts upstream of several key lineage factors necessary for distal tubule formation, like the T-box transcription factor tbx2b. In addition, our data suggests tpfa2a interplays with Iroquois homeobox genes irx1b/2a, which in turn promote a distinct cell fate, namely the cystic cell line.

Conclusions: Taken together, our studies have revealed novel mechanisms by which tpfa2a directs cell fate during nephrogenesis. Examining the molecular activities of this conserved transcription factor in renal progenitors will shed light on the regulatory role of the mammalian homologue, AP-2α, in congenital diseases.

Funding: NIDDK Support

TH-OR085
Transcription Factor 21 (TFC21) Controls Branching Morphogenesis via GDNF Signaling and Has Pleiotropic Roles in Kidney Development

Gail Finger, Shirato Ide, Tomokazu Souna, Minghao Ye, Jing Jin, Yoshio Maezawa, Susan E. Quaggan, Chiba University Graduate School of Medicine, Chiba, Japan; None, Chicago, IL; Northwestern University, Chicago, IL; Kidney Diseases, Northwestern University, Ann & Robert H. Lurie Children’s Hospital of Chicago, Chicago, IL.

Background: Congenital anomalies of the kidney and urinary tract (CAKUT) are the leading cause of chronic kidney disease in children. Although the pathogenesis of CAKUT is incompletely understood and heterogeneous, many cases arise from alterations in genes critical for kidney development. We previously showed that absence of TcF21 causes CAKUT in the mouse but the mechanisms remain obscure.

Methods: We utilized systemic and conditional TcF21 knockout mouse models and employed immunohistochemistry, in-situ hybridization, RT qPCR and kidney explant studies.

Results: Global deletion of TcF21 showed abnormal UB branching and arrested mesenchymal to epithelial transition with resultant severe renal dysplasia. These kidneys had markedly reduced expression of Gdnf, Wnt11 and Ret mRNA to 16%, 29% and 52% of control mRNA levels respectively. When TcF21 was selectively deleted from the cap mesenchyme and its progenitors (TcF21fl/fl;Six2-Cre), mutant kidneys showed abnormal UB branching at early developmental stages (E11.5-13.5) but normal appearing collecting ducts subsequently. Importantly however, when TcF21 was selectively deleted from kidney stromal cells (TcF21fl/fl;FoxD1-Cre) the developing diabetes insipidus-like phenotype suggestive of functional defect in the collecting ducts. This was also supported by findings of severe defect in UB branching at early stages of kidney development and by the absence of collecting ducts at P0 in TcF21fl/fl;FoxD1-Cre mice. Mechanistically, deletion of TcF21 from renal stromal cells was again associated with down-regulation of Gdnf and Wnt11 supporting impaired branching signaling. Moreover, the stromal factor BMP4, a known inhibitor of GDNF, was up-regulated in TcF21 null kidneys both at the mRNA and protein levels. This suggested that TcF21 controls UB branching by regulating BMP4.

Conclusions: Taken together, these results suggest that TCF21 is essential for normal branching morphogenesis via regulation of Gdnf/Wnt11-Ret axis, likely via control of BMP4 in the renal stroma. Further study is required to identify direct gene targets for TCF21.

Funding: Private Foundation Support
Identification of GREB1L as a Novel Causative Gene for Bilateral Kidney Agenesis

Lara Jelena
Joëlle Christelle
Robert Jean

From the University of Michigan, Ann Arbor, MI; \(1\)University of California Davis, El Dorado Hills, CA; \(2\)University of Minnesota, Minneapolis, MN.

Background: Renal hypoplasia (RH) is a heterogeneous condition encompassing a spectrum of developmental kidney defects, i.e. renal agenesis, hypoplasia, and cystic and non-cystic dysplasia. Many studies have identified gene involvement in kidney development. Heterozygous mutations in several of these genes have been shown to lead to various forms of RH. However, the pathophysiological mechanisms leading to bilateral renal agenesis (BRA) remain largely elusive.

Methods: In a family with non-obstructive bilateral nephronophthisis, we used whole exome-sequenced targeted exome sequencing and assessed familial and rare variants in the RH17 gene. BRA was confirmed by light-sheet imaging of cleared kidneys.

Results: Whole genome sequencing identified heterozygous loss-of-function variants in GREB1L (Growth Regulation By Estrogen In Breast Cancer 1-Like) in two families with BRA fetuses. Targeted exome sequencing revealed GREB1L variations in 14 additional families, including 10 with BRA fetuses. Altogether, two exons, one frameshift, one splice and twelve damaging missense variants were identified. All these variants were absent from the ExAC database. GREB1L encodes an uncharacterized target of retinoic acid, never yet associated with kidney abnormalities. Embryonic lethality was observed in GREB1L knockout mice in the homozygous state. Analysis of E13.5 embryos expressing all GREB1L alleles showed smaller transfer with exencephaly and lack of kidneys. Light-sheet imaging of cleared kidneys did not reveal any differences in size or branching in GREB1L embryonic kidneys compared to wild-type. We also showed that the fetal kidney was the major site of GREB1L expression. Analyses in two families with prenatally identified kidney involvement show branching failure and a decreased expression level of GREB1L in the kidneys. In parallel, we generated GREB1L KO IMCD3 cells that are currently being used to analyse the role of GREB1L in epithelialization and branching. These cells will also be used to validate the pathogenicity of the missense variants.

Conclusions: These data demonstrate that GREB1L represents a novel RH gene with a crucial role in kidney development.

Funding: Government Support - Non-U.S.

Survival and Kidney Transplant Incidence on Home versus In-Center Hemodialysis, Following Peritoneal Dialysis Technique Failure

Thursday, 23

Peritoneal Dialysis Outcomes and Practice Patterns Study Group (PDOPPS) \(1,2\)Ruchika F. Lin, \(3\)Tao Zhang, \(4\)Demetrios B. Argyropoulos, \(5\)Brian Bieber, \(6\)Yu Li, \(7\)Ronald L. Pisoni, \(8\)Bruce M. Robinson, \(9\)David W. Johnson, \(10\)Hideki Kawanishi, \(11\)Simon J. Davies, \(12\)Martin J. Schreiber, \(13\)Jeffrey Perl, \(14\)University of Michigan Health Center, Ann Arbor, MI; \(15\)Arbor Research Collaborative for Health, Ann Arbor, MI; \(16\)University of Michigan, Ann Arbor, MI; \(17\)Princess Alexandra Hospital, Brisbane, QLD, Australia; \(18\)Tsuichiya General Hospital, Hiroshima, Japan; \(19\)University Hospital of North Midlands, Stoke-on-Trent, United Kingdom; \(20\)DaVita HealthCare Partners Inc., Denver, CO; \(21\)St. Michael's Hospital, Toronto, ON, Canada.

Background: Gaps in knowledge exist regarding anemia management among peritoneal dialysis (PD) patients. We sought to understand international variation in anemia management among patients receiving PD.

Methods: PDOPPS is an international prospective cohort study based on randomly selected national samples of PD patients. Hemoglobin (Hgb), TSAT, and ferritin levels, as well as iron (iron (Fe), ESA and iron, ferritin) use, between countries. PD patients at study enrolment. Results were analysed by country: Australia and New Zealand (A/NZ), Canada, Japan, United Kingdom (UK), and United States (US).

Results: Mean Hgb ranged from 10.9-11.2 g/dL across countries (table). ESA use was higher in Japan (93%) vs. 65-71% elsewhere, with ESA type varying by country. Median epoetin dose ranged from 2500-7250 units/week. In US and Japan, 87-88% of patients had a TSAT<20%, compared to 75-76% of patients in other countries. Ferritin <50 ng/mL was most common in Japan, and >7-35% in other countries. IV iron use was higher in US (53%) than elsewhere (5-18%).

Conclusions: In the largest international study to date of anemia and iron management in PD patients, we have demonstrated comparable Hgb levels across countries, significant variations in TSAT and iron adequacy, and ESA and iron use. Notably, US PD patients have higher ferritin levels, iron saturation and IV iron use than other countries. Future analyses will investigate whether these differences persist after patient- and facility-level adjustments, and will evaluate associations between anemia management practices and clinical outcomes.

Funding: Commercial Support - Agena, AstraZeneica, Baxter Healthcare, Kyowa Hakko Kirin, Hexal AG, Janssen, Kryex, Proteon, Relypsa, Roche, Vifor Fresenius
Patients’ characteristics & peritonitis details

Methods: Intraperitoneal (IP) cefazolin/ceftazidime were the empirical treatment for PD peritonitis. Severe cases were defined as persistent symptoms with PD effluent (PDE) leukocyte count >109/mm³ on day 3. We excluded patients with concurrent exit site infection (ESI), or known fungal/mycobacterial growth from the PDE. Recruited patients with severe peritonitis were randomized into the lavage or control group. While both groups involved empirical antibiotics escalation (vancomycin/gentamicin) before IPD, we added a regimen of ESI (n=1), fungal (n=3) or mycobacterial growth (n=1) from the PDE. The peritonitis episodes were not recruited mostly because of their mild severity or treatment initiated in other units. Among the recruited patients, 5 were excluded due to later development of ESI (n=1), fungal (n=3) or mycobacterial growth (n=1) from the PDE. The peritonitis details and outcome are shown in the Table.

Results: During a 6-year observational period, 142 out of 421 PD patients developed AUFF, and 49 (34.5%) in AUFF of them were diagnosed as RPL by MR peritonography. None of RPL patients had hernia, pleural fistula or PD tube exit fistula, while one patient had scrotal fistula. Twenty-one (42.9%) of the RPL cases occurred in the first 3 months, while 16 (32.7%) occurred after 2 years’ PD therapy. The percentage of male patients was significantly higher in the RPL group than in the controls (75% vs. 51%, P=0.003). RPL patients were younger than non-RPL patients (48.4±6.4 vs. 55.86±16.99, P<0.001). No child bearing history was a risk factor for RPL in female PD patients (3/12 vs. 10/119, P=0.002). While multi-variants analysis showed that only younger age was a risk factor (P=0.017). After 8 weeks’ intermittent peritoneal dialysis (IPD) or hemodialysis, four patients turned to hemodialysis permanently because of severe and persistent leakage, while others improved remarkably confirmed by MR peritonography and renal CAPD.

Conclusions: RPL is common in PD patients and an important cause of AUFF. MR peritonography is an ideal diagnostic method to detect RPL. Risk factors for RPL include younger age and probably no child-bearing experience in females. RPL is reversible after transitional therapy of IPD or hemodialysis.

Funding: Government Support - Non-U.S.

TH-OR092

Bio Impedance Measurements Taken Over a Period of Time May Be Better Predictors of Survival Than Baseline Measurements in Peritoneal Dialysis Patients

Hari Dukka,1 Mark Lambic,1 Simon J. Davies,2 Keele University, Crewe, United Kingdom; 3University Hospital of North Midlands, Stoke-on-Trent, United Kingdom; 4Nephrology, University Hospital North Midlands, Stoke on Trent, United Kingdom.

Background: Numerous recent studies have shown that a single measure of body composition estimated from bioimpedance (BI) in dialysis patients is predictive of survival. However, 12-month survival varies with time and it is not known whether repeated measures improve predictions when compared to a single measure.

Methods: We analysed the long-term predictive value of baseline and longitudinal (5 measures over 12 months) BI measurements obtained from 289 patients enrolled into the UK and Shanghai BI trial (4 centres, 2009-2010).Patients were followed up until a censor date of 30 April 2016 and events such as death, haemodialysis and transplantation were recorded. Analysis was performed using Cox model stratified for centre.

Results: On univariate analysis, increased extracellular water to total body water ratio (ECW/TBW) and low phase angle (PA) predicted worse survival with HR’s of 1.063 (95% CI 1.030-1.097) and 0.792 (95% CI 0.671-0.933) respectively. In a multivariate adjusted model for age, comorbid score, albumin and urine volume, baseline values of both ECW/TBW and PA provided estimated hazard ratios closer to 1 (HR 1.023, 95% CI 0.984-1.063, and HR 0.913, 95% CI 0.761-1.095 respectively). When time varying rather than baseline values were used in the same adjusted analysis, the goodness of fit statistics improved significantly (ECW/TBW Δ2LL 7.7, PA Δ2LL 6.2) and estimated HR’s were further from 1 (ECW/TBW HR 1.063, 95%CI 1.023-1.106, PA HR 0.726, 95% CI 0.577-0.913). Our analysis demonstrated that repeated BI measurements over a period of time increases the predictive value compared to baseline measurements.

Conclusions: Survival analysis of longitudinal ECW/TBW measures.

TH-OR093

Effects of Long-Term Treatment with Low GDP, pH Neutral Solution on the Peritoneal Functions and Morphological Changes in PD Patients

Mitsuhito Tawada,1,2 Yasuhiko Ito,1,2 Chiie Hoaka,1,2 Mitsuhiro Mizuno,1,2 Yasuhiro Tawada,1,2 Masashi Mizuno,1 Yusuhito Suzuki,1 Fumiko Sakata,1 Shoichi Maruyama,1 Kouyakai Kasugai Hospital, Kasugai, Japan; 2Nagoya University Graduate School of Medicine, Nagoya, Japan; 1Aichi Medical University, Nagakute, Japan; 2Nagoya University, Tokyo, Japan.

Background: Effects of long-term treatment with acidic solution on the peritoneal membrane are well known. However, the peritoneal membrane damage induced by long-term peritoneal dialysis low GDP, pH neutral solution (neutral solution) has not been studied sufficiently.

Methods: Oral Abstract/Thursday

Underline represents presenting author.

TH-OR090

Randomized Trial on Adjunctive Lavage for Severe Peritonitis

Steve Sin-Man Wong,1 Yuk L. Cheng,1 Alex W. Yu,2 Alice Ho Ming Lui Netherton Hospital, N.T., Hong Kong; 2Hong Kong Baptist Hospital, Kowloon, Hong Kong.

Background: No adjunctive therapy has been shown to improve the antibiotic response in peritoneal dialysis (PD)-related peritonitis. This study was conducted to assess if adjunctive lavage is useful for severe cases, as it may enhance the removal of bacteria and inflammatory cells from the peritoneal cavity.

Methods: Patients with severe peritonitis were randomized into the lavage or control group. While both groups involved empirical antibiotics escalation (vancomycin/gentamicin) before IPD, we added a regimen of ESI (n=1), fungal (n=3) or mycobacterial growth (n=1) from the PDE. The peritonitis episodes were not recruited mostly because of their mild severity or treatment initiated in other units. Among the recruited patients, 5 were excluded due to later development of ESI (n=1), fungal (n=3) or mycobacterial growth (n=1) from the PDE. The peritonitis details and outcome are shown in the Table.

Conclusions: Adjunctive lavage did not bring additional merit. Yet, the high treatment success rates in both groups indicated that an early antibiotic escalation could be beneficial in severe PD peritonitis with poor clinical response.

TH-OR091

Retroperitoneal Leakage as an Important Cause of Acute Ultrafiltration Failure in Peritoneal Dialysis Patients

Min Zhang,1 Qionghong Xie,1 Da Shang,1 Chuan-Ming Hao,1 Tongying Zhu.1 Division of Nephrology, Huashan Hospital, Fudan University, Shanghai, China; 2Huashan Hospital, Fudan University, Shanghai, China; 3Huashan Hospital, Fudan University, Shanghai, China; 4Juntendo University, Tokyo, Japan.

Background: Acute ultrafiltration failure (AUFF), characterized by a sudden reduction in ultrafiltration, is one of the causes of technique failure in peritoneal dialysis (PD). AUFF can lead to fluid overload, which is a high risk factor for mortality in PD patients. Retroperitoneal leakage (RPL) is one of the causes of AUFF. In this study, we aimed to analyze the risk factors of RPL in PD patients and observe the outcomes.

Methods: RPL was determined by magnetic resonance (MR) peritonography in the patients with AUFF. Non-AUFF patients were chosen as controls. Demographic and PD-related characteristics were analyzed between these two groups and treatment outcome was observed in RPL patients.

Results: During a 6-year observational period, 142 out of 421 PD patients developed AUFF, and 49 (34.5%) in AUFF of them were diagnosed as RPL by MR peritonography. None of RPL patients had hernia, pleural fistula or PD tube exit fistula, while one patient had scrotal fistula. Twenty-one (42.9%) of the RPL cases occurred in the first 3 months, while 16 (32.7%) occurred after 2 years’ PD therapy. The percentage of male patients was significantly higher in the RPL group than in the controls (75% vs. 51%, P=0.003). RPL patients were younger than non-RPL patients (48.4±6.4 vs. 55.86±16.99, P<0.001). No child bearing history was a risk factor for RPL in female PD patients (3/12 vs. 10/119, P=0.002). While multi-variants analysis showed that only younger age was a risk factor (P=0.017). After 8 weeks’ intermittent peritoneal dialysis (IPD) or hemodialysis, four patients turned to hemodialysis permanently because of severe and persistent leakage, while others improved remarkably confirmed by MR peritonography and renal CAPD.

Conclusions: RPL is common in PD patients and an important cause of AUFF. MR peritonography is an ideal diagnostic method to detect RPL. Risk factors for RPL include younger age and probably no child-bearing experience in females. RPL is reversible after transitional therapy of IPD or hemodialysis.

Funding: Government Support - Non-U.S.
reported in detail. The aim of this study was to investigate the effects of neutral solutions on peritoneal functions and morphological changes.

*Methods:* This study used pathological and immunopathological techniques to assess peritoneal membrane biopsy samples from peritoneal dialysis patients treated with acidic solution or neutral solution. We analyzed the D/P Cr changes by long-term neutral solution treatment.

*Results:* The morphological changes were compared between the acidic solution group (n=54) and neutral solution group (n=67). According to the analyses, the ratio of lumen diameter to vessel diameter (L/V ratio) was significantly smaller (p<0.01), peritoneal membrane was thicker (p<0.01) and accumulation of advanced glycation end-products (AGEs) was higher in the acidic solution group than the neutral solution group (p<0.01). In addition, acidic solution group (n=33) and neutral solution group (n=31) who were treated for 4 to 10 years were compared. In this study, the L/V ratio was significantly smaller (p<0.01) and peritoneal membrane was thicker (p<0.034), and there were no significant differences in number of CD31 positive vessels and CD68 positive cells between the two groups. Furthermore, the L/V ratio in the acidic solution group significantly decreased over time (p<0.01), no such change was seen in the neutral solution group. According to the results of peritoneal equilibration tests for long term neutral solution treatments, D/P Cr also did not change over time.

*Conclusions:* These findings suggest that neutral peritoneal dialysis solutions prevents morphological changes and keep peritoneal functions with no changes in D/P Cr after long term PD treatment.

**TH-OR094**

**Socioeconomic Factors and Racial/Ethnic Disparities in PD Initiation**

**Jenny L. Shen,**1 Holly Wilhamle,2 Sitaram Vangala,3 Anjali B. Saxena,2 Keith C. Norris,2 1LaBiomed at Harbor-UCLA, Torrance, CA; 2Stanford University / Santa Clara Valley Med Ctr, Los Altos, CA; 3UCLA, Los Angeles, CA.

*Background:* Peritoneal dialysis (PD) has been underutilized in the US. The discrepancy is most pronounced in black and Hispanic patients who, despite having a higher prevalence of chronic kidney disease than non-Hispanic White and Asian patients, are less likely to use PD. We investigated the association of socioeconomic factors with racial and ethnic disparities in the initiation of dialysis with PD in the US.

*Methods:* We identified from the USRDS all adult patients who initiated dialysis on Day 1 with either hemodialysis (HD) or PD from 2005-13 and categorized them as either non-Hispanic White, Hispanic White, non-Hispanic Black, or non-Hispanic Asian. We then used logistic regression to estimate the odds ratio (OR) of initiating dialysis with PD vs. HD for each of the minority groups compared to non-Hispanic White patients.

*Results:* Of 522,767 patients, 55% were non-Hispanic White, 28% black, 13% Hispanic white, and 4% Asian; 8% started dialysis on PD. In unadjusted analyses, Blacks and Hispanics were 30% and 21% less likely and Asians were 32% more likely to start on PD than White patients (Table). The gap for Blacks and Hispanics widened and for Asians lessened when adjusted for age, sex, and calendar year of dialysis initiation. However, the disparities narrowed when adjusted for individual and neighborhood level socioeconomic factors.

*Conclusions:* Black and Hispanic patients are less likely to start on PD than White patients, especially given their age, sex, and era of dialysis initiation. This disparity is reduced, but still statistically significant when adjusted for socioeconomic factors. More research is needed to determine whether these variables are associated with potentially modifiable factors such as race or patient bias against starting PD in patients of a certain socioeconomic background.

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

**OR** (95%CI) of starting dialysis on PD (vs. non-Hispanic Whites)

<table>
<thead>
<tr>
<th></th>
<th>Blacks</th>
<th>Hispanic White</th>
<th>Asian</th>
</tr>
</thead>
<tbody>
<tr>
<td>unadjusted</td>
<td>0.69 (0.68;0.71)</td>
<td>0.81 (0.78;0.84)</td>
<td>1.32 (1.26;1.38)</td>
</tr>
<tr>
<td>1: adjusted for age, sex, and race*</td>
<td>0.56 (0.53;0.59)</td>
<td>0.66 (0.64;0.69)</td>
<td>1.37 (1.22;1.53)</td>
</tr>
<tr>
<td>2: added for education &lt; high school, or ≤ $15,000/year</td>
<td>0.66 (0.64;0.69)</td>
<td>0.69 (0.65;0.73)</td>
<td>1.30 (1.09;1.50)</td>
</tr>
<tr>
<td>3: adjusted for 2+ socioeconomic factors*</td>
<td>0.70 (0.64;0.76)</td>
<td>0.90 (0.87;0.94)</td>
<td>1.00 (0.96;1.05)</td>
</tr>
</tbody>
</table>

*SES factors: early referral, insurance, employment, neighborhood poverty, neighborhood education, neighborhood % black/Hispanic, neighborhood linguistic isolation, rural/urban, % of nephrologists & large PD units/population, census division

**TH-OR095**

**Quasi-Continuous Monitoring of intraperitoneal Volume Using Segmental Bioimpedance in Peritoneal Dialysis Patients**

**Fansan Zhu,**1 Samer R. Abbas,2 Roxana M. Bologa,2 Nathan W. Levin,1 Peter Kotanko.2

1Renal Research Institute, New York, NY; 2The Rogosin Institute, New York, NY; 3Ichan School of Medicine at Mount Sinai, New York, NY.

*Background:* Ultrafiltration failure (UFF) is a frequent complication in peritoneal dialysis (PD) patients. The peritoneal equilibration test (PET) is the standard method for assessing peritoneal transport characteristics. However, dynamic changes in intraperitoneal volume (IPV) during the dwell cannot be determined by PET. Therefore, in this pilot study we explored the feasibility of segmental bioimpedance analysis (SBIAs) to quasi-continuously monitor IPV during dwell periods.

*Methods:* 10 PD patients (7 females, age 59±8.8 years, weight 71±12 kg) with standard 4 house محلات dialysis using 2L of 2.5% dextrose PD solution were studied. Eight paired electrodes were placed as shown in Figure 1. A 15 kHz resistance (R, Ohm) was measured from each pair of electrodes minute-by-minute with the Hydra 4200 device. During the

PET IPV was calculated from the average R, of the left and right sides of the abdomen (Zhu et al., Am Kidney Dis. 42:167-172, 2003). This increased allowed us to follow the IPV time course and determine the maximum IPV from visual inspection of the recordings.

*Results:* In 9 patients the IPV measurements were technically successful; in 1 patient signal quality was poor. Figure 2 shows a typical IPV measurement. Average (SD) drain IPV was 0.5±0.3 L by SBIAs compared to weight loss (AW) of 0.5±0.27 kg. Maximum IPV indicated by SBIAs was 1.0±0.4 L. The difference between maximal IPV and drain volume was 0.5±0.4 L (95% confidence interval: 0.2 to 1.2; P<0.01 in a paired t-test). Maximal IPV was reached after a dwell time of 157±57 minutes (range 113 to 200 min).

*Conclusions:* This pilot study demonstrates the feasibility of segmental bioimpedance to quasi-continuously monitor IPV and to identify the time point of maximum IPV. These insights may help to optimize individual PD treatments and improve ultrafiltration efficiency. While these results are encouraging, additional validation studies, to automatically detect maximum IPV, and efforts to improve measurement convenience are required.
**TH-OR097**

New Overhydration Definition and Mortality Risk Assessment in Automated Peritoneal Dialysis Mexican Patients

Javier Ponce,1 Ruben Arriaga,2 Gabriela Leal,3 Bernardo Moguel,1 Instituto Nacional de Cardiología, Mexico City, Mexico; 2Instituto Nacional de Cardiología Ignacio Chavez, Tlalpan, Mexico, Mexico; 3Instituto Nacional de Cardiología, México, Mexico

**Background:** CKD prevalence in Mexico is about 33% and peritoneal dialysis (PD) represents 66% of renal replacement therapy. Overhydration assessment with bioimpedance in APD patients may be a key point predictor for mortality.

**Methods:** We analyze an APD cohort of 64 Mexican patients. Anthropometric, blood and nutritional profiles, time in APD, dialysis prescription, use of medication and for mortality were \( p=0.05 \) between groups \( p<0.05 \).

**Results:** Among the 121,158 included patients, 17,481 (14.4%) developed KDIGO stage 2 AKI, with 60% of the data used for derivation and 40% for validation. Area under the curve (AUC) was calculated in the validation cohort, and subgroup analyses were conducted across admission SCR, AKI severity, and hospital location.

**Outcomes:** Results were compared to SCR-based KDIGO stage 2 AKI, with 60% of the data used for derivation and 40% for validation. Area under the curve (AUC) was calculated in the validation cohort, and subgroup analyses were conducted across admission SCR, AKI severity, and hospital location.

**Conclusions:** Results were compared to SCR-based KDIGO stage 2 AKI, with 60% of the data used for derivation and 40% for validation. Area under the curve (AUC) was calculated in the validation cohort, and subgroup analyses were conducted across admission SCR, AKI severity, and hospital location.

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

**TH-OR098**

Development of an AKI Prediction Model Using Machine Learning

Jay L. Kovner, Kyle Carey, Matthew M. Cherupk. University of Chicago, Chicago, IL.

**Background:** Early identification of hospitalized patients at risk for the development of AKI prior to changes in serum creatinine (Scr) may improve patient outcomes. We aimed to develop an AKI risk prediction algorithm using electronic health record (EHR) data across ward and ICU patients.

**Methods:** All hospitalized patients at the University of Chicago who had Scr measured from 11/2008 to 1/2016 were eligible. With a first Scr>3.0mg/dl, those who had an ICD9 code for CKD Stage 4 or higher, or received renal replacement therapy (RRT) within 48 hours (hrs) of admission were excluded. Demographics, vital signs, lab results, interventions, medications, blood transfusion & diagnostic testing were utilized in a gradient boosted machine learning algorithm to predict Scr-based KDIGO stage 2 AKI, with 60% of the data used for derivation and 40% for validation. Area under the curve (AUC) was calculated in the validation cohort, and subgroup analyses were conducted across admission SCR, AKI severity, and hospital location.

**Results:** Among the 121,158 included patients, 17,481 (14.4%) developed KDIGO stage 2 AKI, with 60% of the data used for derivation and 40% for validation. Area under the curve (AUC) was calculated in the validation cohort, and subgroup analyses were conducted across admission SCR, AKI severity, and hospital location.

**Conclusions:** Results were compared to SCR-based KDIGO stage 2 AKI, with 60% of the data used for derivation and 40% for validation. Area under the curve (AUC) was calculated in the validation cohort, and subgroup analyses were conducted across admission SCR, AKI severity, and hospital location.

**Funding:** Government Support - Non-U.S.
of uMMP-7 and other injury biomarkers were analyzed during the perioperative period. Severe AKI was defined as Kidney Disease Improving Global Outcomes stage 2 or 3.

Results: uMMP-7 peaked within 6 hours after surgery in patients who subsequently developed severe AKI. After multivariate adjustment, the highest quintile of uMMP-7 was associated with increased risk of composite events (severe AKI, acute dialysis, and in-hospital death) and longer stay in intensive care unit and hospital. For predicting severe AKI, uMMP-7 had an area under the receiver-operating characteristic curve (AUC) of 0.81 (in children) and 0.76 (in adults). Urine transforming growth factor beta-1, urinary angiotensinogen, urinary neutrophil gelatinase-associated lipocalin, urinary albumin to creatinine ratio, urinary tissue inhibitor metalloproteinase-2 (TIMP2) and uGF-1β, and the clinical model. uMMP-7 significantly improved risk reclassification over the clinical model alone as measured by net reclassification improvement and integrated discrimination improvement.

Conclusions: uMMP-7 is a promising predictor for severe AKI and poor in-hospital outcomes in patients after cardiac surgery.

Funding: Government Support - Non-U.S.

TH-OR101

Urinary Insulin-like Growth Factor Binding Protein 1 (IGFBP1): Novel Prognostic Biomarker in AKI

Background: Serum creatinine (Cr) is a poor prognostic marker in early AKI. Prognostic urinary biomarkers could be valuable tools to help identify high risk patients in early AKI. We identified urinary IGFBP1 as a potential biomarker using discovery proteomics and validated it in a larger cohort.

Methods: We performed liquid chromatography/tandem mass spectrometry on urine from patients who developed stage 1 AKI within 48 hours after cardiac surgery. 10 patients with acquired renal replacement therapy within 7 days after surgery were matched to 20 patients with similar comorbidities, baseline Cr, surgical type, bypass status and change in Cr at urine collection. The biomarker concentration was subsequently measured in 213 patients by ELISA to validate the prognostic ability. The primary outcome in the validation study was the composite of death, renal replacement therapy (RRT) and KDIGO stage 3.

Results: In the discovery phase we identified 2065 high confidence proteins of which 126 had p-values of less than 0.01 between groups. IGFBP1 had the largest fold increase in RRT and KDIGO stage 3. Median urinary IGFBP1 in controls was 0% (range 0 -1.5%) and 26% (0-38%) in RRT. Based on these data, we performed validation with ELISA in a larger cohort. Of the 213 patients included in the validation set, 27 met the primary outcome. The median time to urine collection from cardiac surgery was 22 hours (range 19-43). There were no significant differences between the outcome groups with respect to demographics, underlying medical conditions, type of surgery or pre-op Cr. The median concentration of IGFBP1 was significantly higher in the primary outcome group at 40 (95% CI:10-244) vs 3 (1-11) ng/ml; p<0.05. Median concentration of IGFBP1 was significantly higher in those that met secondary outcomes of mortality (40,95% CI: 10-333 vs 3: 1-16 ng/ml; p<0.05) and RRT (81: 13-335 vs 4: 1.7 ng/ml; p<0.05) compared those who did not meet these outcomes. Urine IGFBP1 levels were highly discriminative for identifying the primary outcome (ROC AUC: 0.85) and the secondary outcomes death (0.81), and kidney dysfunction (0.82). These results did not significantly change when urine IGFBP1 concentrations were normalized to Cr.

Conclusions: Urinary IGFBP1 is a prognostic biomarker of AKI after cardiac surgery and can predict adverse outcomes early in the course of disease.

Funding: NIDDK Support, Veterans Affairs Support, Clinical Revenue Support

TH-OR102

Polymyxin-B Induces Fas-Mediated Apoptosis in a Human Kidney Proximal Tubule Microphysiological System (Organ-on-a-Chip)

Background: In response to the emergence of multi-drug resistant gram negative infections, polymyxin-B (PM) use has increased despite the clinical observations of severe nephrotoxicity. Our lab is modeling PMB-induced nephrotoxicity in 2D proximal tubule epithelial cells (PTECs) and in a 3D microphysiological system (MPS) to identify biological pathways in the development of renal epithelial cell injury.

Methods: PTECs were treated in 2D with escalating doses of PMB (0 μM to 800 μM). Cellular viability (cell cytotoxicity assay) and caspase 3, 7 activation (fluorescent caspase detection) were measured. The minimal concentration that led to cell death in 2D cultured PTECs was used in the MPS. The MPS system was treated with 50 μM for 48 hours and cell viability was measured at 24 hours and analyzed for caspase cleaved cytokeratin 18 (CK-18). Additionally, transcriptional response was analyzed via RNA-sequencing (RNA-seq) of PMB treated MPS.

Results: In two separate donors, PMB-induced toxicity was observed in 2D in a concentration-dependent manner with decreasing toxicity with increasing PMB concentrations. The EC50 for PMB was 130 μM (SD +/- 12.3) and the minimal concentration that led to cell death was 50 μM. Additionally, we observed increased caspase activation with decreasing cellular viability (one way ANOVA p-value <0.0015). In the 3D MPS, PMB significantly increased CK-18 effluent levels (control 70 +/- 11 U/l versus PMB 207 +/- 24 U/l, p < 0.0001). RNA-seq demonstrated increased transcription of Fas/Fasl, related genes including Fas cell surface receptor (FAS), Fas associated death domain (CARD) and Fas ligand (FASL) gene response was distinct compared to MPS treated with cadmium, another known nephrotoxic.

Conclusions: We have demonstrated that in 2D and in 3D, PMB induced injury is mediated through apoptosis. Furthermore, transcriptional response data demonstrates regulation of Fas pathways in human PTECs after PMB exposure. This study supports a continued study of apoptosis and the Fas-pathway to potentially develop therapies that ameliorate PMB induced nephrotoxicity. Clinically, CK-18 may be useful as a biomarker of PMB induced-AKI. This research was supported by an unrestricted gift from the Kidney Research Council, The Kidney Center to the Kidney Research Institute, F32DK112532, UHTR000504.

Funding: NIDDK Support, Private Foundation Support

TH-OR103

Precision Medicine in Renal Failure: Role of Lanthanol Synthase Gene and Endogenous Ouabain in AKI

Background: A key question in renal failure concerns the mechanism(s) that underlie the decline in renal function. Endogenous Ouabain (EO) has been proposed as a predictive biomarker for acute kidney injury (AKI), and effecter of glomerular damage in experimental models of acute AKI. EO is a key enzyme in the EO biosynthesis. This study explores the association of LSS genotypes and kidney EO with renal damage and its progression.

Methods: Three different conditions were investigated: 1. Renal EO: we analyzed EO content of the cortex and medulla of healthy kidneys derived from non-symptomatic patients genotyped for LSS genetic variants. 2. Essential Hypertension: 338 naïve patients (f 162, m 176, age 44.5±10.42 years) were enrolled for a prospective follow-up study, in which BP was maintained in similar range and changes in renal function were followed. 3. AKI: 1097 individuals undergoing elective cardiovascular surgery were enrolled for a prospective, observational study, to identify the clinical prediction to AKI.

Results: Among LSS genotypes, individuals with LSS AA variant had higher renal EO content than their LSS GG counterparts. The follow-up study revealed a genotype-dependent decline in renal function over time. LSS AA individuals showed greatly reduced time in normal Cr (CC 22±4 vs CC 2.24±4.76 ml/1.73m2y; p=0.027), despite similar blood pressure values. Likewise, the incidence of AKI following cardiovascular surgery was greater among LSS AA individuals, and proportional to the number of A alleles (AA 30.7% vs AC 26.0% vs CC 17.4%; p=0.001).

Conclusions: Our findings support the view that LSS drives a common mechanism of renal damage in Hypertension and AKI and this appears to be mediated in part by LSS-based risk stratification can be used for the timely preoperative recognition and improved management of acute kidney failure.

TH-OR104

Cell-Cycle Arrest Biomarkers TIMP2*IGFBP7 Predict Worse Outcomes in Septic Patients without Clinical Evidence of AKI

Background: Acute kidney injury (AKI) is associated with both short and long-term adverse outcomes in patients with sepsis. Standard criteria for AKI, like serum creatinine (sCr) and urine output (UO), are poor, late and non-specific diagnostic tools. The purpose of this study is to analyze the performance of several biomarkers in addition to standard criteria for early prediction of sepsis-associated AKI.

Methods: We analyzed data from 1243 patients with septic shock enrolled in a prospective trial of early goal-directed therapy, for which biomarkers at admission were available. TIMP2*IGFBP7, uNGAL and uKIM1 at the time of admission were compared to baseline in septic patients without clinical evidence of AKI. We randomly divided the cohort into two groups: 657 individuals for model selection (80% of the cohort) and 586 individuals for model validation (20% of the cohort). The optimal cutoff was derived in the training set by receiver operating characteristic curve analysis and the best cutoff from the validation set was considered. The area under the ROC curve was calculated for each biomarker. The combined group was compared to the single biomarkers using the LR model. A logistic regression model was built using the selected biomarkers and clinical parameters to identify independent risk factors. The receiver operating characteristic curve was calculated for the model on the validation set. The area under the ROC curve was calculated for each patient group. The performance of the model was assessed with the Hosmer-Lemeshow test and the concordance index (cindex).

Conclusions: These results suggest that TIMP2*IGFBP7 may be a promising biomarker for early prediction of AKI in septic patients without clinical evidence of AKI. Further studies are needed to validate these findings in an independent cohort.
AKI Severity and Risk of Adverse Pregnancy Outcomes in Women with Recovered AKI

Elizabeth

AKI severity demonstrated a dose-response relationship with many adverse pregnancy outcomes. Longer duration between AKI episode and pregnancy was associated with decreased risk for preeclampsia (OR 0.7 95% CI 0.6-0.9). Patients subsequently reported to be alive a90 days without continued dialysis treatments or kidney transplant were considered missed AKI-D and not true ESRD cases. We used linear regression and interrupted time-series (ITS) regression to estimate temporal trends in AKI-D misclassification, with particular attention to mid-2012 when the Centers for Medicare & Medicaid Services (CMS) changed reimbursement policy to forbid ESRR facilities from providing dialysis to AKI-D outpatients.

Results: The overall AKI-D misclassification rate was 6.2%, but with a distinct temporal trend (Figure). AKI-D misclassification increased on average 0.36% (95% CI 0.33-0.38%) per year from 2000 to 2010. It then abruptly changed in July 2012, when our universe ITS model estimated that misclassification incidence decreased 2.14% (1.11-3.18%).

Conclusions: Approximately 1 in every 16 patients in the ESRD registry is actually misclassified AKI-D, a much higher proportion than reported previously. The incidence of misclassification increased throughout the first decade of the 21st century but subsequently decreased around the time of a key Medicare reimbursement policy change.

Funding: NIDDK Support

Mitochondria Homing Drug MA-5 Protects against Contrast Induced AKI

Methods: Human proximal tubular cell line HK-2 cells were cultured to 80% confluence and MA-5 at 10μM final concentration for 24hr without serum and then added radiocontrasts sodium ditrizoate, Iopamidol and iohexol at 75mg iodine/ml for another 1hr. Cell viability and cytotoxicity were assessed by WST-8 assay and LDH assay respectively. Male CD-1 and C57/BL6 mice, 10-12 week old were left-nephrectomized (Nx) and MA-5 was administrated, at 50mg/kg body weight by gavage, to mice 2hr before they injected with an inhibitor of prostaglandin synthesis (indomethacin, 10 mg/kg) intraperitoneally and MA-5 was administrated, at 50mg/kg body weight by gavage, to mice 2hr before they injected with an inhibitor of prostaglandin synthesis (indomethacin, 10 mg/kg) intraperitoneally and iohexol (300 mg iodine/ml, 2 g iodine/kg) intravenously. 24hr before injection, mice were sacrificed, serum creatinine (Cr), urine Neutrophil gelatinase-associated lipocalin (NGAL) and renal pathology were examined.

Results: MA-5 improved cell viabilities and reduced injected cell derived LDH activity in culture medium in Sodium ditrizoate, Iopamidol and iohexol treated HK2 cell culture. Serum Cr at 24hr after isohexol injection showed tendency to improve but not significant in MA-5 treated mice compared to control group. Urinary NGAL was significantly decreased in MA-5 treated animals compared to vehicle gavaged mice.

Conclusions: MA-5 exhibited improved viability in contrast medium treated HK-2 cells as well as decreased renal injury marker NGAL in CI-AKI model mice. MA-5 might have the therapeutic potency on CI-AKI.

Funding: Government Support - Non-U.S.
TH-OR108

ADAM17 Induces Sustained Pro-Fibrotic EGFR Activation via a Positive Feedback Loop Involving YAP1-Dependent Transcription of Pro-AREG

Firnke Kefalogiannia, Andreas Herrlich. Washington University in St. Louis, St. Louis, MO.

Background: We recently showed that the cell-surface metalloprotease ADAM17 and its substrates, including in particular the epidermal growth factor receptor (EGFR) ligand pro-angiopoietin (pro-AREG) are highly upregulated after kidney injury and that inducible proximal tubule (PT)-specific knockout of ADAM17 confers protection against fibrosis in ischemic and obstructive kidney injury mouse models. To clarify the role and function of ADAM17 and its substrate AREG in PT cells in vivo, we have now genetically labeled (tdTomato) PT cells in ADAM17 wt or ADAM17 PT-KO mice and studied them after kidney ischemia-reperfusion injury (IRI). We have also examined the transcriptional regulation and function of pro-AREG in PT cells in vitro. Finally, we investigated the activation of these pathways in acute kidney injury (AKI) and chronic kidney disease (CKD) in human samples.

Methods: We used SLC34a1-Cre-ER2;R26tdTomato;ADAM17fl/fl (PT-KO) and respective littermates and subjected them to unilateral IRI. tdTomato positive cells were isolated from FACS. ADAM17 and downstream pathways were studied in human and mouse PT cells in vitro and in human AKI and CKD samples.

Results: IRI induces the transcriptional upregulation of ADAM17 and pro-AREG in PT cells (tdTomato+ cells). This upregulation is diminished in PT cells lacking ADAM17, suggesting that a positive feedback loop exists in which ADAM17 activity drives not only the release of soluble active AREG but also the upregulation of pro-AREG. This positive feedback is also observed in vivo, soluble AREG causes sustained (pro-fibrotic) activation of EGFR that requires Yap1-dependent upregulation of pro-AREG expression, followed by ADAM17-mediated release of soluble AREG. AREG is unique among other EGFR ligands in inducing a panel of proinflammatory and profibrotic cytokines in vitro. PT cells isolated from injured mice and lacking ADAM17 show diminished production of these factors as compared to controls. Finally, levels of urinary and serum soluble AREG are upregulated in human AKI and CKD samples, suggesting that this pathway is also active in human kidney disease.

Conclusions: Injury-induced ADAM17-dependent release of soluble AREG drives a profibrotic positive feedback loop of further AREG release via Yap1-dependent transcriptional upregulation of pro-AREG.

Funding: NIDDK Support

TH-OR109

Macrophage Mitophagy Modulates Pro-Fibrotic Response in Renal Fibrosis

Divya Bhattacharya, Mary E. Choi, Division of Nephrology and Hypertension, Weill Cornell Medicine, New York, NY.

Background: Kidney injury involves infiltration of pro-inflammatory macrophages and oxidative stress induced mitochondrial dysfunction, and pro-fibrotic macrophages drive progression of renal fibrosis. Mitophagy, the selective autophagy of dysfunctional mitochondria, is important for cellular homeostasis. We examined the role of PTEN-induced kinase1 (PINK1), major mediator of mitophagy, in regulating macrophage derived fibrotic response.

Methods: Wild type (WT) and PINK1-KO mice, subjected to unilateral ureteral obstruction (UUO), a model of progressive renal fibrosis, were sacrificed at day 3. Peritoeonal and bone marrow-derived macrophages were isolated. The expression levels of CD11b, Ly6C, F4/80, CD206 and Cx3cr1 were detected by flow cytometry. Arginase1 (Arg1), TGFβ1 type 1 receptor (TGFβR1), fibronectin and α-smooth muscle actin (αSMA) expression was determined by western blot. Mitosox staining was used to assess mitochondrial derived superoxide production. Mitophagy was suppressed in RAW264.7 cells through transfection of PINK1 small interfering RNA (siRNA).

Results: UUO-induced increase in the expression of circulating Ly6C++ CD11b+ pro-inflammatory monocytes was higher in PINK1-KO mice compared to WT. PINK1-KO mice displayed higher expression of F4/80+ CD206+ pro-fibrotic macrophages and chemokine receptor Cx3cr1 in obstructed kidneys compared to WT and contralateral kidneys. Flow cytometric data revealed increase in the Ly6C++ pro-inflammatory cells in kidney post-UUO at day 3. However, their expression was comparable in kidneys from KO and WT mice. The expression of Arg1 and fibronectin was higher in kidneys of KO mice after UUO. Furthermore, PINK1 deficient macrophages (both primary PINK1-KO and siRNA knockdown RAW264.7) exhibited enhanced polarization towards pro-fibrotic phenotype. Primary PINK1-KO macrophages also showed higher expression of Arg1, TGFβRI, fibronectin and α-SMA. The expression levels of Arg1, fibronectin and α-SMA were further increased after stimulation with TGFβ3. In addition, PINK1 deficient macrophages displayed higher mitochondrial superoxide levels upon TGFβ3 stimulation compared to WT.

Conclusions: PINK1-mediated mitophagy deficiency results in increased oxidative stress and enhanced pro-fibrotic response by macrophages. Macrophage mitochondrial superoxide production may play a critical role in activation of their pro-fibrotic phenotype and progression of renal fibrosis.

Funding: NIDDK Support

TH-OR110

Therapeutic Angiogenesis in CKD

Alejandro R. Chade, Gene L. Bidwell. University of Mississippi, Jackson, MS.

Background: Renal microvascular (MV) loss in CKD correlates with progressive loss of renal function. However, whether this is an association or a cause-effect relation is unclear. We developed a drug-delivery construct of an elastin-like polypeptide (ELP) fused to VEGF-A and showed that intra-renal infusion of ELP-VEGF in CKD improved renal function. We tested the hypothesis that ELP-VEGF therapy may induce long-term recovery in CKD by stimulation of MV proliferation and repair.

Methods: CKD was induced in 8 pigs by bilateral renal artery stenosis and diet-induced dyslipidemia. Blood pressure was continuously measured (telemetry). Bilateral RBF and GFR were quantified in vivo using multi-detector CT after 6 weeks of CKD, and then pigs randomly treated with a single intra-renal administration of ELP-VEGF (100 µg/kg) or placebo (n=4 each). In vivo studies were repeated 4 and 8 weeks after treatment, pigs were then euthanized, and ex vivo studies performed to quantify renal MV density (micro-CT), MV remodeling, and angiogenic signaling.

Results: RBF and GFR were reduced in CKD, accompanied by hypertension, cortical and medullary MV remodeling and loss, and blunted expression of VEGF, HGF, specific VEGF/HGF receptors, and markers of cell progenitors (Oct-4 and CD-34). However, 4 weeks ELP-VEGF pigs showed 28% and 53% improvement in RBF and GFR 4 weeks after treatment, and 46% and 74% recovery after 8 weeks, respectively (compared to pre-treatment), followed by increased expression of angiogenic and progenitor cell markers, reduced MV loss and remodeling [Figure]

Conclusions: Therapeutic angiogenesis via single-dose ELP-VEGF therapy stimulates renal neovascularization and MV repair, which likely drove recovery of renal function and improved CKD stage from 2 to 1. CKD recovery was progressive, and our data imply that underlying mechanisms of the long-term effects may involve sustained stimulation of cell progeny and remodelling of the kidney.

Funding: Other NIH Support - AHA and NHLBI

TH-OR111

The Impact of a Young Circulation on Renal Injury and Fibrosis in Aged Mice

David A. Ferchenbach,1,2 Cuiyan Xin,1 Julia Willifingseder,1 Jeremy Hughes,2 Joseph V. Bonventre,1 1Brigham and Women’s Hospital, Boston, MA; 2MRC Centre for Inflammation Research, University of Edinburgh, Edinburgh, United Kingdom

Background: Aging is associated with an increased risk of acute kidney injury (AKI) and higher rates of subsequent fibrotic chronic kidney disease (CKD). The mechanisms accounting for these changes in injury and fibrosis susceptibility remain poorly understood. We used heterochronic parabiosis to test whether the young circulation can influence injury imposed on an older mouse.

Methods: Parabiotic pairs were established between young (Y, 8 weeks old) and old (O, 14 months old) female C57BL6 mice to generate YY, OO, OY and YO pairings, and a sham parabiosis was also performed. Animals were followed for 28 days. Baseline and post-injury renal characteristics were assessed by immunofluorescence, western blotting, microarray analysis and Somascan measurement of circulating protein levels. AKI was induced via 20 minutes bilateral renal ischaemia/reperfusion injury (IRI), and chronic fibrosis via unilateral ureteric obstruction. Animals were followed for 4 hours for peak IRI severity, and up to 14 days for UUO-induced fibrosis

Results: Baseline renal function was equivalent in all groups. At d28 of parabiosis, old animals in both OY and OO pairs had increased levels of baseline fibrosis (p<0.05) compared to the young in YO and YY pairs. In the acute injury model on the Old mice, OY animals demonstrated significantly lower 24 hr serum creatinine compared with OO animals (p<0.05). In the UUO model of chronic renal fibrosis, Old animals in OY pairs showed reduced scarring, macrophage infiltration and inflammatory gene transcription compared to Old paired with Old mice (OO) (all p<0.05). Microarrays revealed multiple transcriptional processes which alter with aging and injury and revert to 'young' patterns after OY pairing. Bulk proteomics on >1000 circulating proteins identified 11 compounds which track with the protected phenotype.
Catalyze the production of LTB4 and cysteinyl leukotrienes, respectively. We hypothesized that 5-lipoxygenase promotes renal interstitial injury and fibrosis. Background: Although macrophages promote renal fibrosis, the mechanism is incompletely understood. Macrophages may exert tissue damage through activation of 5-lipoxygenase (5-LO). 5-LO and 5-LO associated protein (FLAP) initiate leukotriene synthesis; the downstream enzymes LTA4H, LTA4H (Lta4h) and LTC4 synthase (Ltc4s) catalyze the formation of LTB4 and cysteinyl leukotrienes, respectively. We hypothesized that leukotriene eicosanoids would decrease renal fibrosis after unilateral ureteral obstruction (UUO). Methods: C57Bl/6 mice undergoing UUO were treated with zileuton (5-LO antagonist) or vehicle. UUO was also done in wild type, Flap knock out (ko), Lta4h ko and Ltc4s ko mice. Renal fibrosis was measured using both a biochemical assay (hydroxyproline) and microscopy to detect second harmonic generation (SHG) signal from collagen. To measure metabolic changes in renal tubular epithelial cells, fluorescent lifetime imaging microscopy (FLIM) was performed to determine alterations in free and bound NADH levels. Results: We found a large induction in 5-LO expressing interstitial leukocytes in kidneys of UUO mice. Treatment of mice with zileuton before UUO significantly decreased hydroxyproline content at 7 days (37% reduction vs. vehicle). SHG microscopy also confirmed a significant decrease in renal fibrosis in zileuton-treated mice (40% reduction). Compared to littermate controls, Flap ko mice had less interstitial fibrosis as measured by hydroxyproline assay (33% reduction). Lta4h ko mice, but not Ltc4s ko mice, were significantly protected from UUO-induced fibrosis (44% reduction in hydroxyproline content and 11% reduction in fibrotic area by SHG). We then performed FLIM for NADH to determine if 5-LO inhibition led to metabolic changes in renal tubular epithelial cells. We found that there was significant shift to glycolytic metabolism after UUO in control mice; this was partially abrogated in zileuton-treated mice. To validate these findings, we tested whether 5-LO is induced in other models of chronic kidney disease and found increased numbers of 5-LO expressing leukocytes in mice with polycystic kidney disease. Conclusions: 5-LO expression and LTC4 synthase play potentiocidal effects of leukotrienes may be partially mediated through changes in renal tubular epithelial metabolism.

MicroRNA-214 Confers the Pathogenesis of CKD by Disrupting the Mitochondrial OXPHOS. Aihua Zhang, Bai, Yue Zhang, Songming Huang, Zhanjun Jia. Nephrology Department, Children’s Hospital of Nanjing Medical University, Nanjing, China.

Background: Mitochondria are critical in determining the energy homeostasis and cell fate. Mitochondrial dysfunction (MiD) presenting with aberrant mitochondrial oxidative phosphorylation (OXPHOS) and other abnormalities is involved in the chronic kidney disease (CKD). Here we investigated the role of miR-214 in mediating the MiD and kidney injury in CKD.

Methods: The CKD patients’ renal biopsy tissues, three CKD animal models (UOU, albumin-overload, and post-AKI), and tubular cells challenged with several insults were used to define the role of miR-214 in CKD, as well as the potential mechanisms.

Results: In CKD patients, the tubulointerstitial presented more abundant miR-214 expression compared with the healthy controls, which was accompanied by a positive correlation with the severity of proteinuria and renal fibrosis. Meanwhile, several lines of CKD animal model of UOU, albumin-overload, and post-AKI and renal tubular cell models induced by IL-1β, hypoxia, albumin, or TGF-β displayed similar enhancement of miR-214. Importantly, systemic inhibition or specific tubular deletion of miR-214 strikingly attenuated CKD pathology in line with the ameliorated responses of apoptosis, inflammation, and fibrosis in CKD models mentioned above. In contrast, overexpressing miR-214 induced tubular cell apoptosis. Moreover, in the mechanistic study, we proved that cytoplasm miR-214 could be translocated into the mitochondria to target mitochondrial gene ND4L and ND6 to disrupt mitochondrial OXPHOS, leading to mitochondrial dysfunction and subsequent tubular injury and fibrosis in CKD.

Conclusions: These results not only demonstrated a pathogenic role of miR-214 in CKDs by targeting mitochondrial gene ND4L and ND6 to disrupt mitochondrial OXPHOS, but also suggested the potential of this microRNA as the therapeutic target and diagnostic biomarker of CKDs.

Biopsy Transcriptome Expression Identifies Loss of FRMD3 as a Mediator of Declining Renal Function in CKD. Eoin P. Brennan,1 Caitriona M. McEvoy,2 Oisín Gough,2 Susan M. McAnallen,2 Mohd R. Rodclan Akb,1 Anthony M. Dorman,1,3 Peter J. Conlon,1 Denise M. Sadler,1,4 Catherine Godson.1 Department of Nephrology and Pathology, Beaumont Hospital, Dublin, Ireland; 2Diabetes Complications Research, Conway Institute & School of Medicine UCD, University College Dublin, Dublin, Ireland; 3Royal College of Surgeons Ireland, Dublin, Ireland; 4Mater Misericordiae University Hospital, Dublin, Ireland.

Background: We have generated global transcriptome profiles of renal biopsies from patients with chronic kidney disease (CKD). Here, we investigated the relationship between renal gene expression and clinical parameters of kidney function, and identify an association between loss of a gene domain-containing protein 3 (FRMD3) and a decline in renal function. Methods: We performed RNA-Seq gene expression profiling on material obtained from patients undergoing clinically indicated biopsy (n=44). Using this phenotypically homogeneous cohort of patients, the association of gene expression with clinical parameters (tubulo-interstitial fibrosis (TIF), score, cGFR, serum creatinine, glomerular basement membrane thickness) was investigated. Follow-up clinical data (serum creatinine measurements 3-6 years post-biopsy) was used to identify gene expression profiles predictive of disease progression. Subsets of genes were identified that were significantly associated (FDR P<0.05) with these parameters of kidney disease.

Results: Pathway analyses identified enrichment for pro-inflammatory signalling (e.g. T-cell infiltration, TNF-α, NF-κB, IFN-γ, CD3) in patients with severe CKD. 1,590 genes were significantly associated with renal decline in these patients during a 3-6 year follow-up period (FDR P<0.05), including loss of FRMD3 expression (FDR P=0.006). Interestingly, large scale genome-wide association studies have recently implicated FRMD3 as a genetic candidate in kidney disease. Using functional studies we investigated genetic variants in FRMD3 in renal cells using in vitro models of renal fibrosis. Here, FRMD3 knockout caused exaggerated fibrotic responses to TGf-β1 in renal tubule epithelial cells. Finally, mass spectrometry analysis of FRMD3 binding partners indicated interactions with mitochondrial respiratory chain components (complex I, III and V).

Conclusions: Taken together, these data implicate FRMD3 as a novel regulator of renal function in CKD.

Rescue of Renal-Protective BMP7 by Low-Dose Hydralazine Protects Functional Parenchyma with Restoration of Solute and Solvent Transporters. Bijorn Tampe, Desiree Tampe, Gerhard A. Mueller, Michael Zeisberg. University Medical Center Goettingen, Goettingen, Germany.

Background: CKD progression remains an unsolved problem in clinical Nephrology since approaches to reverse or repair chronic renal injury are not yet available. BMP7 and its agonists are among leading compounds currently under clinical testing and widely accepted as a suitable agent for the treatment of the injured kidney, ultimately associated with attenuation of disease progression. The impact of restoring intrarenal BMP7 with regard of renal excretory function on a molecular level remains elusive.

Methods: In multiple mouse models of acute (moderate IRI), acute-on-chronic (severe IRI) and chronic kidney disease (UOU, 5/6 Nx, FAN, NTN), dynamic regulation of BMP7 and signaling (pSmad1/5/8) were analyzed by qRT-PCR, Western blotting and immunostaining. Furthermore, BMP7 promoter methylation was assessed by MeDIP in cohorts of mice treated with low-dose Hydralazine and corresponding cell culture models of EMT program in TECs. Finally, impact on expression of solute and solvent transporters was analyzed by qRT-PCR, immunostaining and functional monitoring of transporter function.

Results: Based on a genome-wide transcriptional expression dataset for bioactive small molecules, transcriptional induction of BMP7 was among top induced candidate genes in response to Hydralazine. Low-dose Hydralazine mediates TET3-dependent normalization of BMP7 promoter methylation in multiple rodent CKD models and human cell lines. On a mechanistic level, transcriptional induction of renoprotective BMP7 attenuates intracellular EMT program commonly observed during CKD progression, ultimately associated with protection from G2/M arrest of TECs and attenuation of renal fibrogenesis. We provide evidence that protection of functional parenchyma restores solute and solvent transporter function, including AQP1, AQP3 and Na+/K+-ATPase, supporting a protective role also for renal excretory function on a molecular level. Based on existing transcriptional profiling datasets, decline of renal excretory function is commonly associated with loss of intrarenal BMP7 expression, suggesting that renoprotection mediated by Hydralazine may also have promise among CKD patients.

Conclusions: In summary, low-dose Hydralazine induces renoprotective BMP7 and protects functional parenchyma with restoration of solute and solvent transporters.
TH-OR116

SIRT6-Knockout Mice Exhibit Marked Type IV Collagen Deposition, Causing Phenotypes Similar to Those of Diabetic Tubulopathy Hirokazu Muroa, Kazuhiro Hasegawa, Shu Wakino, Hiroshi Itoh. Keio University, Tokyo, Japan.

Background: The class of NAD-dependent deacetylase and longevity genes called sirtuins comprises seven isoforms (SIRT1 to SIRT7). Here we investigated the role of SIRT6 in the kidneys.

Methods: Results: We investigated the intrarenal distribution of SIRT6 expression in different physiological conditions using wild-type mice and human renal biopsy specimens. High SIRT6 levels were detected in the nucleus of proximal tubules (PTs), whereas low levels were observed in glomeruli and other tubules. To assess the temporal changes in SIRT6 expression in different physiological conditions, we modeled several kidney injuries. Among these, diabetic nephropathy models displayed marked alterations. We next evaluated the temporal changes in SIRT6 expression every 8 weeks (4W, 16W, 24W, and 32W) in STZ and db/db models. At 8W and 16W, SIRT6 expression exhibited no difference. However, SIRT6 expression was conspicuously downregulated at 24W and was further augmented at 32W in both STZ and db/db models. To delineate the endogenous role of SIRT6 in the kidneys, we newly created PT-specific SIRT6 conditional knockout (CKO) mice by crossing SIRT6 flox/flox[Editor1] mice with g-CT Cre mice. PT-SIRT6 CKO mice exhibited marked proximal tubular basement membrane (TBM) thickening and widespread peri-proximal tubular fibrosis. We next tested the molecular mechanisms underlying tubulopathy augmentation caused by SIRT6 knockdown. By performing DNA microarray and confirmatory real-time PCR analyses after microdissecting PT-injured regions together with immunostaining and immunogold electron microscopy, we could demonstrate that tissue inhibitor metalloproteinase 1 (TIMP-1) mRNA levels were elevated, leading to decreased MMP-9 activity and upregulated type IV collagen protein levels. These changes were consistent with the phenotypes of PT-SIRT6-CKO mice. Lastly, we analyzed in detail the mechanisms whereby SIRT6 knockdown directly elevated TIMP-1 mRNA levels and revealed that SIRT6 deficiency in PTs directly hyperacetylated histone H3 lysine K9 and RELA at these target regions within the TIMP-1 promoter.

Conclusions: PT Sirt6 is suggested to be involved in type IV collagen-related TBM thickening and peri-tubular fibrosis, which directly regulates TIMP-1 expression and plays a crucial role in tissue fibrosis, especially in diabetic nephropathy.

TH-OR117

Aging Phenotype(s) in KIdneys of Diabetic Mice Are p66ShcA Dependent Himanshu Vashishta, Alyson E. Bradley, 1 Bronwyn Leblanc, 1 Frank C. Abbascato, 2 Ashwani Malhotra, 2 Pravin C. Singhal, 2 Leonard G. Meggs. 1 Ochsner Health System, New Orleans, LA, 2 Feinstein Inst.Med research and NSLIJ, Manhasset, NY.

Background: Hyperglycemia constitutively activates the p66ShcA protein, which controls cellular responses to oxidative stress, aging and apoptosis. Here, we test the hypothesis aging phenotype(s) in kidneys of diabetic mice, that are commonly associated with the broad category of chronic kidney disease (glomerulosclerosis, interstitial fibrosis, tubular atrophy), are linked to the p66ShcA locus.

Methods: Stem cell antigen-1 (Sca-1)-mesenchymal stem cells (MSCs) were isolated from kidneys of WT and p66 KO mouse, and plated in media containing normal or high glucose. Parameters evaluated were ROS metabolism, apoptosis, cellular and molecular markers of senescence and DNA microarray gene profiles. p66 KO diabetic mice, were generated by crossing Akita (Ins2+) with p66 KO mouse. Kidneys were examined at 12 mo of age by light microscopy and deconvolution microscopy.

Results: WT-MSCs exhibit an exponential increase in ROS metabolism, upregulation of senescence associated proteins (p21; p16a**, p53) and enter apoptotic or senescent phenotypes. DNA microarray detected downregulation of Wnt regulatory genes, implicated in self renewal and differentiation. By contrast, p66KO-MSCs are resistant to H2O2-stress, apoptosis/cell senescence and express increased levels of intracellular b-catenin, mimicking canonical Wnt signaling. Small clusters of Sca-1-MSCs in kidneys of p66 KO Akita were captured by deconvolution microscopy scattered in the interstitium adjacent to tubules, but were only rarely seen in kidneys of WT and Akita. Furthermore, the senescent biomarker p16** was upregulated in proximal tubular epithelial cells of Akita, whereas expression levels did not differ between p66 KO-Akita and WT (non-diabetic); indicative p66ShcA participates in activation of p16** in diabetic kidneys. Histologic markers of injury were prominent in Akita kidneys, whereas these aging phenotypes were barely detectable in kidneys of p66 KO-Akita. Taken together, p66 ShcA is necessary and sufficient for the expression of aging phenotypes in kidneys of diabetic mice.

Conclusions: Our results establish a genetic link between diabetes, constitutive p66ShcA expression and accelerated aging phenotype(s) in the kidney, that may serve as precursors to diabetic nephropathy.

Funding: Private Foundation Support

TH-OR118

Kidney Allografts with High Risk APOL1 Genotypes Have Worse Outcomes: Association with Decreased Podocyte Density Hiroshi O. Tan, 1 Dinhui P. Chen, 2 Ziad S. Zaky, 1 Jesse D. Schold, 1 Leal C. Herlitz, 1 Rasha El-Rifai, 1 Paul E. Drawz, 1 Leslie A. Braggeman, 1 John R. Sedor, 1 Emilio D. Poggio, 1 John F. O’Toole, 1 1Cleveland Clinic, Cleveland, OH; 2MetroHealth Medical Center, Cleveland, OH; 1NONE, Cleveland, OH; 3University of Minnesota, Minneapolis, MN; 4Case Western Reserve University, Cleveland, OH.

Background: Variants in APOL1 gene (G1 or G2), which encodes apolipoprotein Li(1)APOL1, associate with non-diabetic kidney diseases in African Americans (AA) but the mechanisms driving this association remain unclear. Kidney diseases only develop in a subset of individuals with high risk APOL1 genotypes, consistent with a need for a “second hit” or stress to initiate disease. Mice transgenic for G2 have a podocyte depletion phenotype compared to wild-type mice or mice expressing the reference allele (GO). We hypothesized that variant APOL1 generates subclinical, prodomal podocyte injury that is a “first hit.”

Methods: A cohort of 107 AA kidney donors, living (LD) and deceased (DD), with available implant biopsy tissue and DNA were genotyped for APOL1 risk variants and evaluated for baseline kidney phenotypes, histology, and podocyte density in implant biopsies. Recipients were genotyped for APOL1 and outcomes collected, including graft loss and rate of eGFR decline.

Results: Donor demographic data and clinical phenotypes at graft implant were similar between high risk (HR, 2 risk variants, n=16) and low risk groups (LR, <2 risk variants, n=91). Glomerular volume was lower in HR group (2.58 um^3/X10 vs. 3.13 um^3/X10, p=0.03) of implant biopsies. Podocyte density was significantly less in HR compared to LR (108 ± 26 vs. 127±40 podocytes/10um^2; p=0.03). Similarly, podocyte coverage of glomerular area was reduced in HR vs. LR donors (30% vs. 39%, p=0.05). Recipients were 64% AA and 36% White or not specified;38% of AA recipients had HR APOL1. Recipients were followed for 48 months, and increased graft loss of HR donor was confirmed via a multivariable model (Hazard Ratio = 2.7; 95% CI (0.7, 8.3) and Kaplan Meier graft survival (HR 61% vs. LR 91%, log rank p-value=0.049). eGFR decline was also greater in recipients of HR APOL1 allografts with slope of overall decline statistically significantly different (p<0.001), eGFR/mL/min at 60 months was 27 in HR vs. 51 in LR.

Conclusions: In living and deceased donors, outcomes of APOL1 variant patients were significantly worse. Importantly, variant APOL1 generates subclinical, prodomal podocyte depletion, which only becomes clinically evident when subsequent stress supervenes and initiates progressive CKD in African Americans with APOL1 HR.

Funding: Other NIH Support - T32

TH-OR119

Interaction of SHROOM3 with FYN Impacts Phosphorylation of Nephrin Causing Proteinuria with Foot Process Effacement Megan C. Meen, 1 Nimrod Philippe, 2 Chengguo Wei, 1 Ruijie Liu, 1 Jennyong Wong, 1 Zhengzi Yu, 1 Weijia Zhang, 3 John C. He, 4 Barbara T. Murphy, 1 1Icahn School of Medicine at Mount Sinai, New York, NY; 2Mount Sinai Hospital, New York, NY; 3Mount Sinai Medical School, New York, NY; 4Mount Sinai School of Medicine, Forest Hills, NY.

Background: In the GoCAR study, we identified that a CKD-associated SHROOM3-SNP, and tubular Shroom3 expression correlated with the development of renal fibrosis post-transplant. We showed that SHROOM3 facilitated TGF-B signaling suggesting its potential role as a therapeutic target. However, recent data suggest a protective role for SHROOM3 in glomerular development.

Methods: To study the role of SHROOM3 in adult glomeruli, we used doxycycline-inducible (DOX), shRNA-mediated SHROOM3 knockdown, Podocin- and tubular-specific (PAK8)-RTTA mice, comparing these to non-transgenic DOX-fed littermates.

Results: Adult Podo-RTTA mice, but not PAX8-RTTA, developed significant albuminuria compared to littermates with DOX. Albuminuria was reversible on DOX-withdrawal, and reappeared on re-IMATION. EM revealed diffuse foot process effacement (Figu1). Glomerular RNA-seq identified downregulated intracellular signaling/ actin-cytoskeleton among Gene-ontology terms in knockdown mice. We performed mass spectrometry on protein lysates of 293-T cells overexpressing SHROOM3 immunoprecipitated (IP) with either anti-V5, -SHROOM3 or IgG. Among 491 unique interactions, we identified FYN – a src-kinase – as a top ranking candidate. Podocyte FYN overexpression for NPHS1 phosphorylation, and FYN-deficient mice show a proteinuria phenotype. In human podocytes, we confirmed the interaction of endogenous SHROOM3 and FYN by IP. Glomerular protein extracts of Shroom3-knockdown mice showed decreased phosphorylation of FYN, and NPHS1. In human allografts from GoCAR, we found corresponding reduced albuminuria (~1year post-transplant) associated with homozgyosity of the risk allele in the donor.

Conclusions: In summary, Podocyte-specific SHROOM3 knockdown causes a reversible proteinuria phenotype in adult mice, by interacting with FYN, a mechanism distinct from its effect on renal fibrosis in allografts.
**TH-OR120**

**Polygenic Risk Score as a Determinant of Risk of Non-Melanoma Skin Cancer Post-Transplant Renal Transplantation**

**Caragh P. Stapleton,1 Kelly A. Birdwell,1 Patrick B. Mark,4 M. Lee Sanders,2 Paul J. Phelan,3 Alexander P. Maxwell,4 AJ. McKnight,4 Claire Kennedy,1 Alan G. Jardine,6 Jamie P. Traynor,1 Fiona A. Chapman,1 Brendan Keating,2 Peter J. Conlon,4 Gianpiero Cavallerti,3 Beaumont Hospital, Dublin 9, Dublin, Ireland; 1University of Pennsylvania, Philadelphia, PA; 2NHS Greater Glasgow and Clyde, Glasgow, United Kingdom; 3NHS Scotland, Glasgow, United Kingdom; 4Queen’s University Belfast, Belfast, United Kingdom; 5University of Glasgow, Glasgow, United Kingdom; 6University of Iowa Hospitals and Clinics, Iowa City, IA; 7Vanderbilt University, Nashville, TN; 8Department of Molecular and Cellular Therapeutics, Royal College of Surgeons, Dublin, Ireland; 9Royal Infirmary of Edinburgh, NHS Lothian, Edinburgh, United Kingdom.

**Group/Team:** International Genetics & Translational Research in Transplantation Network.

**Background:** Multiple genetic loci have been identified for non-melanoma skin cancer (NMSC) in the general population. Polygenic risk score (PRS) was defined as the sum of all alleles associated with a trait weighted by the effect size of that allele as determined by a previous genome-wide association study (GWAS). We tested whether PRS, calculated using a GWAS of NMSC in a non-transplant population, can be used to determine risk of developing and time to NMSC post-kidney transplant.

**Methods:** Post-kidney transplant NMSC cases (n=155) and controls (n=442) were collected from Tennessee, Ireland and Scotland. Genetic variants that reached pre-defined levels of significance were chosen from a squamous cell carcinoma (SCC), and a basal cell carcinoma (BCC) GWAS, both conducted in non-transplant populations. Using these GWAS results, BCC and SCC PRSs were calculated at each p-value threshold (pT) for each sample in the renal transplant cohorts. PRSs were normalized so mean = 0 and standard deviation = 1. PRSs were tested as a predictor of case:control status in a logistic regression model and time to NMSC post-transplant in a survival model. Age of recipient at transplant, recruitment centre, azathioprine exposure and the first four principal components were included as covariates in both models.

**Results:** SCC PRS calculated at pT of 1x10^-6 was the most significant predictor of case: control status of NMSC post-transplant (OR per 1 standard deviation increase in PRS = 2.3; corrected P = 0.04). When we subdivided NMSC into SCC and BCC, SCC PRS pT 1x10^-6 was a significant predictor of case:control SCC (OR = 2.5, P = 0.02) and BCC status (OR = 7.6, P = 0.002). SCC PRS pT 1x10^-6 was also a significant predictor of time to post-transplant BCC (P = 0.007, HR = 1.8) and SCC (P = 0.05, HR = 1.4).

**Conclusions:** PRS of non-transplant NMSC can be used to predict case:control status of post-transplant NMSC, SCC and BCC as well as time to developing BCC and SCC post-transplant.

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

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

---

**TH-OR121**

**Effect of Conversion to Belatacept on Tacrolimus-Induced Diabetes Mellitus**

**Chul Woo Yang,1• Sun Woo Lim,2 Kang Luo,2 Yoo-Jin Shin.2 1Department of Internal Medicine, Seoul St. Mary’s Hospital, Seoul, Republic of Korea; 2Transplant Research Center, The Catholic University of Korea, Seoul, Republic of Korea.

**Background:** The effect of belatacept conversion on tacrolimus (TAC)-induced diabetes mellitus (DM) is still undetermined. In the present study, we first tested the dose-dependent effect of belatacept on pancreatic islet function and viability in rats. Second, in an experimental model of TAC-induced DM, TAC was switched to belatacept and parameters of glucose control were measured. In addition, the direct effect of belatacept on TAC-induced pancreatic islet cell injury was evaluated in vitro.

**Methods:** The first study was designed to evaluate whether belatacept has a diabetogenic effect in rats. We tested the dose-dependency of belatacept (0.25, 0.5, 1, 2, and 4 mg/kg) on pancreatic islet function and viability. The second study aimed to evaluate the effect of conversion from TAC to belatacept on pancreatic islet function in established TAC-induced DM. After the establishment of TAC-induced DM (three weeks), TAC was continued, withdrawn, or replaced by belatacept treatment (1 or 2 mg/kg), or vehicle. Rats were treated with vehicle or subcutaneous TAC daily, and belatacept was injected weekly via the tail vein. The effect of belatacept on TAC-induced diabetes was evaluated by assessing pancreatic islet function, histopathology. The protective effect of belatacept was evaluated by measuring markers of oxidative stress, apoptosis, and infiltrating macrophage. Reactive oxygen species production using MitoSOX RED and cell death using Annexin V were also evaluated in INS-1 cells.

**Results:** Pancreatic islet function and islet cell death were not affected by any of the tested doses of belatacept. TAC withdrawal ameliorated pancreatic islet dysfunction compared with that in the group in which TAC treatment was continued, and conversion to belatacept further improved pancreatic islet function compared with that in the TAC withdrawal group. TAC-induced oxidative stress, apoptotic cell death, and infiltration of macrophages decreased with TAC withdrawal, and belatacept conversion further reduced those values. In an in vitro study, belatacept decreased TAC-induced pancreatic islet cell death and reactive oxygen species production.

**Conclusions:** The results of these studies suggest that conversion to belatacept is an effective approach to reduce TAC-induced DM. Moreover, belatacept has a protective effect against TAC-induced pancreatic islet injury.

---

**TH-OR122**

**Tacrolimus Prevents Von Willebrand Factor Exocytosis from Human Neonatal Glomerular Endothelial Cells Treated with Anti-HLA Antibodies**

**Stephanie Beland, Olivier Desy, Patrice Vailin, Sacha A. De Serres. University Health Center (CHU) of Quebec, Laval University, Quebec, QC, Canada.

**Background:** Mechanistic knowledge about the direct effect ofDSA on the endothelium is lacking. Von Willebrand factor (vWF) is a glycoprotein involved in endothelial hemostasis. Previous studies reported that anti-HLA-I antibodies promote vWF exocytosis. It is known that higher CNI levels associates with better outcomes in patients with DSA. We hypothesized that TAC prevents endothelial damage by inhibiting vWF exocytosis from cells exposed to anti-HLA antibodies.

**Methods:** We measured in vitro the vWF expression of human glomerular endothelial cells treated with anti-HLA-I or II, in the presence and absence of TAC. Cell viability was confirmed in all experiments. vWF was quantified by immunofluorescence and ELISA. Platelet adhesion on the endothelial cells was assessed by immunofluorescence. We next measured the association between vWF and TAC blood levels in 71 samples from 69 kidney recipients.

**Results:** Anti-HLAIs antibodies increased surface expression of vWF as well as vWF levels in cell supernatants (anti-HLA-I 3.6±4, anti-HLA-II 40±4 vs. NS 22±4, respectively, p<0.05). vWF release in the supernatant following anti-HLA-I stimulation was higher than with anti-HLA-I (3.4±2.5 vs. 5.6±3.2 ng/mL; p=0.03). Treatment with TAC (5, 10 ng/mL) abrogated the percentage of vWF-positive cells after anti-HLA stimulation (for anti-HLA-I, TACO vs. TAC5 vs. TAC10 : 32±5 vs. 5.3±5.2 respectively; for anti-HLA-II, TACO vs. TAC5 vs. TAC10 : 36±7 vs. 3±2.1 respectively; all p<0.01) and led to a decrease in platelet adhesion (all p<0.01). In an in vivo model, TAC was a significant negative predictor of vWF blood levels (β=-0.22±0.09; 95% CI -0.4 to -0.03; p=0.03). This association was robust to adjustment for clinical and histological predictors.

**Conclusions:** Direct disruption of endothelial hemostasis through vWF exocytosis is a potential mechanism for higher occurrence of transplant glomerulopathy in patients with DSA. Mechanistic studies are underway to better understand these observations, given that TAC is seldom associated with thrombotic microangiopathy.

---

**TH-OR123**

**B Cell Deficiency Inhibits Chronic Antibody Mediated Rejection in a Th1 and IL-10 Dependent Pathway in a Rat Kidney Transplant Model**

**Sarah E. Panzer, Shannon Reese, Nancy A. Wilson, Lucille D. Ptak, Isabelle S. Renteria, Arjang Djamali. University of Wisconsin Madison, Madison, WI.

**Background:** The pathologic role of B cells in chronic antibody mediated rejection (cAMR) remains unclear.

**Methods:** We generated B cell deficient Lewis rats (B+/-) by CRISPTR technology. Kidney transplantation was performed in 4 groups: syngeneic (Lewis to Lewis), allogeneic (Fisher to Lewis), sensitized (Fisher to Lewis 3 weeks following donor-specific blood transfusion), and allogeneic B cell deficient recipients (Fisher to B-/- Lewis). All animals were harvested at 6 months.

**Results:** B cell CAMR was reduced in B-/- recipients compared to allogeneic and sensitized recipients (Lewis: 0.6; P=0.05). Allograft deposition of IgM was significantly reduced in B-/- recipients compared to allogeneic and sensitized recipients (Lewis: 4.6±1.7, B-/-: 1.5±0.6, P=0.001) and C4d staining (allogeneic: 1.5±0.6, B-/-: 0.6±0.6; P=0.001). Allograft deposition of IgG was significantly reduced in B-/- compared to allogeneic recipients (Fig1A). Interstitial macrophages and fibrosis by Picrosirius red stain demonstrated no differences among allogeneic, sensitized, and B-/- recipients (Fig1B). Th1 (IL-2 and IFN-gamma) and IL-10 cytokines by RT PCR were significantly reduced in B-/- compared to allogeneic recipients, but not Th2 (IL-4 and IL-6) or Th17 (Fig1C). Chronicity scores (Banff chronicity score = eg c+ e1 c+ e2)

---
were elevated in allogeneic, sensitized, and B− recipients (3.0±1.7, 4.6±0.5, and 1.5±0.6, respectively).

Conclusions: B cell deficiency inhibits cAMR in a Th1 and IL-10 dependent pathway. Further studies are needed to determine the contributions from non-B cell mediated factors, such as innate immunity, to the development of fibrosis in chronic rejection.

Funding: Other NIH Support - This project was supported by the Clinical and Translational Science Award (CTSA) program, through the NIH National Center for Advancing Translational Sciences (NCATS), grant UL1TR000427, and the KL2 training Award (KL2TR000428).

Figure 1

Figure 1. B cell deficient recipients demonstrated reduced allograft inflammation. (A) Immunofluorescence showed absent antibody deposition in the allografts of B− recipients. (B) Fibrosis, as determined by Picrosirus red stain, was unchanged among allogeneic, sensitized, and B− recipients. (C) RT PCR of allografts demonstrated a reduction in Th1 cytokines (IL-2, IFN-gamma) and IL-10.

TH-OR125

A Proteomic Analysis of Kidneys Subjected to Normothermic Ex-Vivo Kidney Perfusion Demonstrates Metabolism and Energy Production Are Important Determinants of Kidney Function Following Warm Ischemia

Shelby Reid,1 Peter Urbanelli,2 Matyas Hamar,2 Moritz Kath,2 Lisa Robinson,2 Markus Selzner,3 James W. Scholey,4 Ana Konvulinkova,5 1Institute of Medical Science, University of Toronto, Toronto, Canada; 2The Hospital for Sick Children, Toronto, ON, Canada; 3Toronto General Hospital, Toronto, ON, Canada; 4UHN/TGH/SickKids, Toronto, ON, Canada; 5University Health Network, University of Toronto, Toronto, ON, Canada; 6University Hospital Essen, Essen, Germany; 7University of Toronto, Toronto, ON, Canada.

Background: Organ shortage remains a problem for kidney transplantation, leading to an increased use of marginal grafts. These grafts tolerate cold storage poorly, resulting in more patient sensitization and increased ischemia-reperfusion injury (IRI) and a higher risk of delayed graft function (DGF). This has led to the development of alternative preservation techniques that aim to reduce IRI and the rate of DGF. Normothermic ex-vivo kidney perfusion (NEVKP) is a storage method that may result in improved kidney function and limit IRI compared to traditional static-cold-storage (SCS).

Methods: Porcine kidneys were explanted, subjected to 30 minutes of warm ischemia, and stored via NEVKP or SCS for 8 hours, followed by re-implantation. Creatinine and BUN were measured in serum samples daily, until post-operative day (POD) 10. Kidney biopsies were taken at time of explant, 30 minutes following anastomosis and on POD3.

Results: Tissue samples were subjected to proteomic analysis on Q-Exactive mass spectrometer. Cytoscape software was used for enrichment analysis of differentially expressed proteins.

Conclusions: NEVKP leads to improved kidney function compared to traditional SCS. Metabolism, energy production and catabolism represent key biological processes differentiating NEVKP from SCS proteome. Better understanding and manipulation of metabolism in kidney grafts may lead to amelioration of IRI and prevention of DGF.

TH-OR126

Normothermic Ex-Vivo Kidney Perfusion Improves Function of Marginal Renal Grafts That Were Subjected to Prolonged Ischemia prior to Preservation

Peter Urbanelli,1,2 Matyas Hamar,2 Ivan Linares,2 Dagmar Kollmann,3 Sujani Ganesh,3 Paul M. Yip,3 Rohan John,1 Istvan Musci,3 Ana Konvulinkova,2 Darius Bagli,1 David Grant,1 Lisa Robinson,2 Markus Selzner,3 1The Hospital for Sick Children, Toronto, ON, Canada; 2Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada; 3Multi-Organ Transplant Program, University Health Network, Toronto, ON, Canada.

Background: Normothermic ex-vivo kidney perfusion (NEVKP) is an emerging technique for renal graft preservation. We investigated whether NEVKP could promote improved marginal graft function compared to cold storage in a model of donation after cardiac death.

Methods: Kidneys from 30kg Yorkshire pigs were removed following 30, 60, 90, or 120 minutes of warm ischemia (WI). These grafts were then preserved in either cold histidine-tryptophan-ketoglutarate solution (CS) or subjected to pressure-controlled NEVKP for 8 hours prior to heterotopic autotransplantation.

Results: Prolonging WI time prior to kidney retrieval and subsequent storage in CS resulted in grafts that demonstrated incremental posttransplant increases in serum creatinine with grafts subjected to 120min of WI having persistent elevation (POD7: 13.4±5.30mg/dL vs baseline: 1.1±0.3mg/dL, p<0.01, n=4). During NEVKP perfusion, 120min WI grafts cleared lactate from perfusion solution (0hr: 10.4±0.93mM/L vs 7hr: 1.48±0.85mM/L, p<0.01, n=5), had decreasing intra-renal resistance (0hr: 0.93mmol/L vs 7hr: 0.37mmol/L, p<0.01, n=5), and continuous urine production. Posttransplantation, 120min WI grafts with NEVKP, compared to CS, demonstrated significantly decreased serum creatinine peak values (POD4: 12.62±2.34mg/dL vs POD5: 18.95±1.11mg/dL, p<0.001) and higher creatinine clearance (POD4: 6.61±4.03mL/min vs 0.35±0.30mL/min, p<0.02 and POD 26.31±11.54mL/min vs 9.78±4.64mL/min, p<0.03). On POD7, serum creatinine returned to baseline values in the NEVKP group (POD7: 4.85±3.57mg/dL vs baseline: 1.02±0.57mg/dL), but not the CS group (POD7: 13.4±5.30mg/dL vs baseline: 1.1±0.33mg/dL, p<0.01, n=4). Histology from 120min WI NEVKP grafts demonstrated decreased tubular injury scores compared to cold CS grafts (1.8±0.8 vs 3.0±0.3, p<0.001) as assessed by a blinded pathologist.

Conclusions: Kidney grafts subjected to 120min of WI before retrieval showed significant improvement in function following 8hrs of continuous pressure-controlled NEVKP compared to CS. This suggests NEVKP could be utilized to expand the donor pool through the consideration of marginal renal grafts for transplantation.

Funding: Government Support - Non-U.S.
Bioengineering a Kidney in Secondary Lymphoid Tissues: A LTβR Dependent Pathway for Ectopic Organogenesis

Background: Kidney diseases are rising rapidly worldwide. While further work needs to be done before induced pluripotent stem cells (iPSCs) technol, they can be used to generate transplantable kidneys, disease modeling using iPSCs can facilitate the development of targeted therapies benefiting kidney patients. Unfortunately, while organoids expressing markers of kidney cells have been generated in vitro from mouse nephron progenitors and human iPSCs, there is little evidence that these cells exhibit phenotypic and functional aspects in vivo. Paradoxically, orthotopic engraftment of kidney tissue in the adult does not provide an environment conducive to vascularization and functional differentiation. Among potential endogenous bioireactors, the lymph node (LN) stands out, having permissive properties for kidney rudiments. Understanding LN remodeling and adaptation upon tissue transplantation could prove valuable in future endeavors to create a niche for human kidney cells. We hypothesize that LTβR signaling in LN fibroblastic reticular cells (FRCs) drives ectopic organogenesis.

Methods: Human fetal kidneys, mouse nephron progenitor- or human iPSC-derived kidney organoids were transplanted into mouse LN. The maturation of transplanted cells and tissues was investigated through immunofluorescence. Three-dimensional reconstructions and Dextran uptake assay were used to test graft architecture and glomerular filtration, respectively. To investigate the molecular mechanism contributing to ectopic organogenesis, mice bearing grafts were treated with LTβR-Fc fusion protein. LTβR−/− mice were also used to confirm that LTβR ablation negatively affects ectopic kidney organogenesis (as LTβR−/− mice do not have LNs, omentum was used as an alternative secondary lymphoid organ for transplantation).

Results: Our preliminary data show engraftment of human fetal kidneys as well as efficient maturation of mouse nephron progenitor- and iPSC-derived kidney organoids in LN. Importantly, in the absence of an active LTβR pathway grafts exhibited impaired vascularization and structure.

Conclusions: The LN serves as an innovative bioreactor to organize kidney progenitors into vascularized and functional renal structures. Our study has a wide-ranging impact for tissue engineering approaches for the rebuilding of functional kidneys in vivo.

Funding: Other NIH Support - NIH grant R01 DK085711, Private Foundation Support

Single Cell Transcriptome Atlas of the Mouse Kidney Reveals Important Cell Diversity

Background: A revolution in cellular measurement technology is under way: For the first time, we have the ability to monitor global gene regulation in thousands of individual cells in a single experiment. They overcome fundamental limitations inherent in measurements of bulk cell population that have frustrated efforts to resolve precise cellular states. These methods also provide a stunningly high-resolution view of transitions between states. Single-cell transcriptomics will allow us to identify cell type-specific expression changes, discover novel disease associated cell types and trace cell composition changes in complex disease such as diabetic kidney disease (DKD).

Methods: Using droplet-based single-cell barcoding and sequencing methods we catalogued mouse kidney cell types in an unbiased manner. We have developed a novel cell isolation method and individually profiled over 30,000 cells from the kidneys. Computational analysis included normalization, quality control, dimension reduction and clustering followed by identification of cell types using known markers and bulk RNAseq methods using k-means clustering.

Results: Main clustering analysis identified 15 major cell populations in normal mouse kidneys; three distinct ureteric bud- and 7 metanephric mesenchyme-derived epithelial clusters, in addition to endothelial cells, fibroblasts, different immune cell types, and the novel epithelial cell populations that have not been described before. Cell trajectory analysis highlighted cell type conversion in the collecting duct and discovered novel transient cell type. Furthermore we have developed methods for single cell marker based in silico deconvolution of bulk RNAsequencing datasets. We found that most transcript level changes very likely reported in previous studies are actually type proportion changes in kidney samples, such as accumulation of immune cells and fibroblasts and decrease of tubule epithelial cells in disease development. Finally, we identified key transcription factors, mapped GWAS candidates, known drug targets, and nephrotic syndrome genes in the clusters showing their cell type-specific expression patterns.

Conclusions: In conclusion, our first single cell transcriptome of the entire mouse kidney could have a transformative impact to understand transcriptional networks maintaining cell identity and development of DKD.

Funding: NIDDK Support

SH3D21 Disregulation May Cause Disruption of the Actin Cytoskeleton in Diabetic Nephropathy

Background: Diabetes is the most common cause of end-stage renal disease. The onset of albuminuria and podocyte damage is associated with disruption of the actin cytoskeleton. We identified SH3D21 as a potential key regulator of the actin cytoskeleton in podocytes which changes its expression in diabetes.

Methods: Cultured murine and human podocytes under glucose- and VEGF-stimulation were used to mimic diabetic conditions and compared to osmolality controls with mannitol. To model type I diabetes, C57BL/6 mice were treated for 5 days either with intraperitoneal injections of streptozotocin (STZ) or sodium citrate buffer as control while blood glucose levels were determined for 16 weeks. WB analysis of STZ-injected mice and buffer-injected mice was carried out. Immunofluorescence (IF) staining on cryosections of STZ- or buffer-injected mice was performed. IF of SH3D21 was performed on kidney cryosections of STZ- or buffer-injected mice as well as human and murine cultured podocytes. To identify protein interaction partners of SH3D21, we performed co-affinity purification mass spectrometry (MS) of murine whole kidneys as well as human cultured podocytes. Knockdown of sh3d21 was performed in zebrafish and proteinimania was measured using transgenic zebrafish line (Ftg(1)/alp:eGFP-DBP).

Results: Reduction of SH3D21 protein expression was detected in murine kidney and cultured podocytes under diabetic conditions. IF of diabetic murine kidney cryosections showed loss of SH3D21 expression associated with the absence of SH3D21-Nephrin co-expression. In murine and human podocytes we could document a shift from a membrane to a perinuclear or cytosolic speckled expression pattern which paralleled actin disruption under glucose- or VEGF-treatment. In murine and human podocytes SH3D21 primarily co-localizes with actin cytoskeletal proteins. Knockdown of sh3d21 in zebrafish caused proteinimania and foot process effacement.

Conclusions: SH3D21 is a novel interaction partner of nephrin which appears to be an important regulator of the actin cytoskeleton impacting slit diaphragm functions in diabetes.

Funding: Government Support - Non-U.S.

Amelioration of Diabetic Nephropathy in mir-379 Knockout Mice

Background: Diabetes is the most common cause of end-stage renal disease. The onset of albuminuria and podocyte damage is associated with disruption of the actin cytoskeleton. We identified miR-379 as a potential key regulator of the actin cytoskeleton in podocytes which changes its expression in diabetes.

Methods: mir-379KO mice were generated by CRISPR-Cas9 nickase and dual guideRNA strategy. Diabetes was induced with streptozotocin (STZ) in 10 wk old wild type mice and mir379-KO (miR379-KO-STZ) C57BL/6 mice (n=6). Non-diabetic age/match control mice (WT-Str)-KO mice were carried out. Urine albumin excretion and urinary albumin/creatinine ratio (ACR) were measured before euthanization at 24 wks post diabetes induction. Renal glomeruli were isolated for measuring miRNAs, proteomic and mir379 target genes. Cortical sections were stained for histopathology. Expression of TFGB1 and ER stress regulator EDEM3, a target of miR-379, was examined by immunohistochemical staining.

Results: mir-379KO mice did not depict any abnormalities, and developed diabetes to the same extent as WT mice. On the other hand, miR379-KO-STZ mice did not lose body weight like WT-STZ mice. Increased urine albumin and ACR in WT-STZ mice were attenuated in miR379KO-STZ mice. Glomerular hypertrophy, ECM accumulation and fibrosis observed in WT-STZ mice were all significantly reduced in miR379KO-STZ mice. Glomerular hypertrophy and ECM accumulation associated with early DN. Therefore, here we developed miR-379-knockout (KO) mice using CRISPR-Cas9 system to examine the hypothesis that miR-379, the first miRNA in the cluster, has an in vivo role in DN progression.

Methods: mir-379KO mice were generated by CRISPR-Cas9 nickase and dual guideRNA strategy. Diabetes was induced with streptozotocin (STZ) in 10 wk old wild type mice and miR379-KO (miR379-KO-STZ) C57BL/6 mice (n=6). Non-diabetic age/match control mice (WT-Str)-KO mice were carried out. Urine albumin excretion and urinary albumin/creatinine ratio (ACR) were measured before euthanization at 24 wks post diabetes induction. Renal glomeruli were isolated for measuring miRNAs, proteomic and mir379 target genes. Cortical sections were stained for histopathology. Expression of TFGB1 and ER stress regulator EDEM3, a target of miR-379, was examined by immunohistochemical staining.

Results: mir-379KO mice did not depict any abnormalities, and developed diabetes to the same extent as WT mice. On the other hand, miR379-KO-STZ mice did not lose body weight like WT-STZ mice. Increased urine albumin and ACR in WT-STZ mice were attenuated in miR379KO-STZ mice. Glomerular hypertrophy, ECM accumulation and fibrosis observed in WT-STZ mice were all significantly reduced in miR379KO-STZ mice. Glomerular hypertrophy and ECM accumulation associated with early DN. Therefore, here we developed miR-379-knockout (KO) mice using CRISPR-Cas9 system to examine the hypothesis that miR-379, the first miRNA in the cluster, has an in vivo role in DN progression.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Deletion of Adaptor Protein p66Shc Decreases Afferent Arteriolar KATP Channel Activity and Decreases Renal Damage in Diabetic Dahl SS Rats

Andrey Sorokin,1 Bradley S. Miller,1 Shoshana R. Blumenthal,1 John D. Imig,2 Medicine, Medical College of Wisconsin, Milwaukee, WI; Pharmacology & Toxicology, Medical College of Wisconsin, Milwaukee, WI.

Background: Increased expression of adaptor protein p66Shc has been associated with progression of diabetic nephropathy. Afferent arteriolar dilatation and glomerular hypertension in diabetes are due to increased K_{ATP} channel availability and activity.

Methods: This study tested the hypothesis that p66Shc KO Dahl SS rats with STZ-induced diabetes are protected from glomerular injury because afferent arterioles do not exhibit enhanced K_{ATP} channel activity. Afferent arteriolar responses to the K_{ATP} opener pinacidil and the K_{ATP} channel blocker glibenclamide were assessed in Dahl SS, Dahl SS p66Shc KO, Dahl SS with STZ-induced diabetes, and Dahl SS p66Shc KO with STZ-induced diabetes.

Afferent arteriolar diameter responses were determined using the juxtamediulary nephron technique six weeks following induction of diabetes in both diabetic groups. Hyperglycemia, excessive urination, body weight, albuminuria and glomerular injury was evaluated in all rat groups to monitor the progression of diabetic nephropathy.

Results: Afferent arteriolar diameters at 100 mmHg averaged 22.9 ± 0.9 µm (n=8) in Dahl SS rats, 21.1 ± 0.8 µm (n=6) Dahl SS p66Shc KO. Dahl SS with STZ-induced diabetes rats had a significant increase in the afferent arteriolar diameter (24.7 ± 1.3 µm; n=6). Conversely, Dahl SS p66Shc KO with STZ-induced diabetes rats did not have increased afferent arteriolar diameters (22.1 ± 1.2 µm; n=6). Afferent arteriole dilator responses to pinacidil were not different between Dahl SS rats and Dahl SS p66Shc KO. On the other hand, glibenclamide decreased blood pressure in both Dahl SS and Dahl SS p66Shc KO rats but not in Dahl SS with STZ-induced diabetes rats, which had an increased vasodilator response to pinacidil. Likewise, the K_{ATP} channel blocker glibenclamide (30 µM) resulted in a greater decrease in afferent arteriolar diameter in Dahl SS & STZ-induced diabetes (23 ± 4%, n=6) compared to Dahl SS p66Shc KO & STZ-induced diabetes (13 ± 2%, n=6). The glomerular injury was mitigated in Dahl SS p66Shc KO with STZ-induced diabetes.

Conclusions: Taken together, these results indicate that increased afferent arteriolar K_{ATP} channel activity contributes to increased diameters and renal injury in Dahl SS but not in STZ-diabetic diabetes. Moreover, deletion of the adaptor protein p66Shc decreases afferent arteriolar K_{ATP} channel activity and decreases renal damage in diabetic Dahl SS rats.

Funding: NIDDK Support

TH-OR134

Genetic Ablation of Vasohibin-2 Prevents the Progression of Diabetic Nephropathy in an Experimental Mouse Model

Kana Masuda,1 Katsuuyuki Tanabe, Haruyo Ujike, Norikazu Hinamoto, Hiromasa Miyake, Hitoshi Sugiyama, Yohei Maeshima, Jun Wada. Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Science, Okayama, Japan.

Background: Diabetic nephropathy has been reported to be associated with abnormal angiogenesis and increased glomerular VEGF, which could represent potential therapeutic targets. Vasohibin-2 (VASH2) is a novel pro-angiogenic factor and has been shown to be involved in tumor enlargement. In the present study, we investigated whether VASH2 was involved in the progression of diabetic nephropathy in vivo and in vitro experiments.

Methods: Eight to ten weeks old male C57BL/6 wild type (WT) or VASH2-knockout (VASH2−/−) mice received intraperitoneal injections of 50mg/kg STZ or vehicle for five consecutive days. The experimental subgroups included 1) non-diabetic WT, 2) non-diabetic VASH2−/−, 3) diabetic WT and 4) diabetic VASH2−/−. Blood glucose (BG) and urine albumin excretion (UAE) were evaluated every other week, and 16 weeks after the injections, blood pressure (BP) was measured and blood and kidney samples were obtained. Conditionally immortalized human mesangial cells were stimulated by high glucose (25mM) or TGF-β1 (10 ng/ml) under the presence of control or VASH2 siRNA.

Results: There were no differences in BP, BG and serum creatinine between diabetic WT and VASH2−/− group. However, increased UAE and creatinine clearance observed in diabetic WT mice were significantly decreased in diabetic VASH2−/− mice. In addition, increased glomerular CD31 positive area induced by diabetes was also suppressed in VASH2−/− group. VASH2 deficiency did not affect renal level of VEGF but suppressed diabetes-induced elevation of renal VEGFR2 expression. Increased glomerular type IV collagen accumulation and renal TGF-β1 mRNA in diabetic WT mice were prevented in diabetic VASH2−/− mice. Endogenous VASH2 level was increased by diabetes, and the immunostaining suggested that VASH2 was localized in mesangial cells in glomeruli. Knockdown of VASH2 using siRNA suppressed the increased mRNA level of type IV collagen and α-SMA in cultured mesangial cells treated with high glucose or TGF-β1 stimulation.

Conclusions: Deletion of VASH2 had protective effects in diabetic nephropathy through the suppression of excessive VEGF action on endothelial cells and extracellular matrix production in mesangial cells.
TH-OR135

**Soluble Nogo-B Overexpression Ameliorates Diabetic Kidney Disease**

**Ivan Hernandez, Carlo Alberto Ricciardi, Kathryn E. White, Anthea E. Hayward, Xiao Yan Bai, Fan Fan Hou, David A. Long, Luigi Gnuzi, Kings College London, London, United Kingdom; Nanfang Hospital, Southern Medical University, Guangzhou, China; University College London, University of London, United Kingdom.**

**Background:** Diabetic glomerulopathy (DG) is characterized by altered vascular remodelling, increased vascular permeability, Neutrophil Outgrowth Inhibitor (Nogo)-B and its soluble form (sNogo-B) bind to NgR and have been implicated in vascular remodelling. Full-length Nogo-B is expressed in glomerular endothelial cells and podocytes and is downregulated in experimental model of diabetic nephropathy and in patients with diabetic nephropathy (DN). Our aims were to investigate whether overexpression of sNogo-B could ameliorate DG in an experimental animal model of diabetes.

**Methods:** 8-10 weeks-old male DBA/2J mice were made diabetic (streptozotocin) and administered 12-14 week-old an adeno-associated viral vector (AAV) expressing sNogob or GDF (control). Animals were divided into four groups: non-diabetic (ND) and diabetic (D) mice treated with either GDF-AAV or sNogo-B-AAV followed by 12-14 weeks of diabetes. Blood pressure was assessed with tail-cuff methodology, plasma sNogo-B levels by ELISA, full-length Nogo B and AKT phosphorylation with immunoblotting, creatinine by mass spectrometry, albuminuria by fluorescence, and glomerular ultrastructure by electron microscopy.

**Results:** sNogo-B-AAV allowed a sustained expression of sNogo-B in the circulation (p<0.01) and full-length Nogo-B aluminuria (p>0.05) was ameliorated by sNogo-B upregulation (p<0.05). Similar, increase in creatinine clearance was corrected by sNogo-B overexpression to control ND mice levels (p>0.006). Blood pressure was similar in all groups, sNogo-B overexpression ameliorated diabetes-mediated mesangial expansion (p=0.002) with reduced Nogo-B downregulation (p=0.02) and blunted Akt Serine phosphorylation (p<0.01) in diabetic mice in kidney cortex lysate.

**Conclusions:** Overexpression of sNogo-B ameliorates DG via prevention of diabetes-mediated Nogo-B downregulation. Ongoing work is dissecting the major molecular mechanisms involved. sNogo-B could represent a potential novel future treatment for DG.

---

**TH-OR137**

**Increased Podocyte SIRT1 Function Attenuates Diabetic Kidney Injury**

**Quan Hong, Lu Zhang, Bhaskar Das, Guangyan Bai, Xiangmei Chen, John C. He, Kyung Lee, Chinese PLA General Hospital, Bei Jing, China; Connecticut Kidney Center, LLC, Orange, CT; Xiamen University Affiliated The First Hospital, Aoyu, China; Icahn School of Medicine at Mount Sinai, New York, NY.**

**Background:** We previously found that the glomerular expression of Sirtuin-1 (SIRT1) is reduced in human diabetic kidneys and that overexpressed sagaravir albuminuria and worsened kidney disease progression in diabetic mice. SIRT1 encodes an NAD-dependent deacetylase that modifies the activity of key transcriptional regulators affected in diabetic kidneys, including NF-kB and STAT3. Consistent with reduced SIRT1, acetylation of NF-kB and STAT3 was reduced in diabetic kidneys, resulting in their increased activities. In this study we employed genetic and pharmacological means to interrogate whether the increased SIRT1 function is sufficient to attenuate diabetic kidney injury.

**Methods:** For the genetic approach, we generated doxycycline-inducible podocyte-specific overexpression of SIRT1 (Pod-SIRT1) mice, which were further crossed with diabetic OVE26 mice to generate OVE26;Pod-SIRT1 mice. Littermates without SIRT1 transgene (OVE26;WT) and age-matched nondiabetic mice were used as controls. Healthy control, OVE26;WT and OVE26;Pod-SIRT1 mice were given dox-supplemented chow starting at 16 weeks of age, at which time the OVE26 mice exhibit pronounced hyperglycemia and proteinuria. For the pharmacological approach, OVE26 mice at 16 weeks of age were treated with either vehicle or novel SIRT1 inhibitor, BF175 (0.4mg/kg daily). All mice were sacrificed at 22 weeks of age for analysis.

**Results:** 6 weeks of Dox administration led to significant reduction in kidney-to-body weight ratio and urinary albumin excretion in OVE26;Pod-SIRT1 in comparison to OVE26;WT mice. Glomerular hypertrophy, mesangial matrix expansion, and podocyte foot process effacement were also markedly reduced in OVE26;Pod-SIRT1 mice. Administration of SIRT1 agonist BF175 for 6 weeks similarly led to significant reductions in albuminuria, mesangial matrix expansion, and podocyte foot process effacement in OVE26 mice compared to vehicle treatment. Both OVE26;Pod-SIRT1 and OVE26 mice treated with BF175 showed increased podocyte number compared to control OVE26, suggesting that increased SIRT1 function protected against podocyte loss in OVE26 glomeruli.

**Conclusions:** Our data demonstrates that increased podocyte SIRT1 expression is sufficient to significantly mitigate early diabetic injury and that BF175 is a novel SIRT1 agonist that can be further developed as a potential therapy for early DKD.

**Funding:** NIDDK Support

**FR-OR001**

**Mentorship in the Digital Age: Nephrology Social Media Collective Internship – 2 Year Experience Silvi Shah, Matthew A. Sparks, Saeher Leon, Hector M. Madariaga, Kenan D. Jhaveri, Edgar V. Lema, Timothy Yau, Paul J. Phelan, Nikhil A. Shah, Ali Poyan-Mehr, Michelle N. Rheault, Swapnil Hirnath, Joel M. Topf, Associates in Nephrology, Berwyn, IL; Duke University and Durham VA Medical Centers, Durham, NC; University of Michigan, Ann Arbor, MI; Washington University Medical Center, Brookton, MA; Hofstra Northwell School of Medicine-Northwell health system, Great Neck, NY; Detroit, MI; Washington University School of Medicine, Saint Louis, MO; University of Cincinnati, Cincinnati, OH; University of Ottawa, Ottawa, ON, Canada. Group/Team: Nephrology Social Media Collective Internship Group.**

**Background:** Although social media use by healthcare professionals is increasing, formal education is lacking. The Nephrology Social Media Collective (NSMC) internship is a worldwide collaboration among nephrologists to cultivate leaders in the use of social media in medicine by instilling knowledge, competence, and professionalism.

**Methods:** The NSMC internship was established in 2015. The NSMC faculty consists of 2 members who are clinicians, educators, and scientists. The internship is 1 year. Interns are selected on the basis of their curriculum vitae, personal statement, and interest. There is an entrance discussion with each intern to discuss goals followed by quarterly online meetings. Interns are paired with 2 faculty mentors and are expected to contribute 3-4 hours/month. Interns attend NephJC (online nephrology journal club) and participate in NephJC administrative activities (curating a Twitter chat, constructing a visual abstract, writing blog posts or moderating a session). Interns participate in the two required projects - the annual NephMadness contest and the Renal Fellow Network blog. Internship requirement are based on participation in NephJC, timely completion and quality of projects.

**Results:** The initial class of 2015 class enrolled 4 interns. The subsequent class of 2016 included 7 interns. The classes were near gender balanced with 6/1 male. There were 6 fellows, 2 medical students, 1 practising physician and 1 nurse. 8 were from USA, 2 from the United Kingdom and 1 from Canada. NSMC internship increased exposure and opportunities for engagement in other social media activities. Following completion, interns became part of NephJC (33% of interns (N=5) and NephJC/ann (N=2). Interns were invited to join International Society of Nephrology’s Social Media Task force (N=2), Interns in Nephrology’s communications’ committee (N=2) and ASN’s media and communication committee (N=1). The current class of 2017 has enrolled 9 interns.

**Conclusions:** NSMC internship provides modern communication skills and opportunities to improve skills in social media. It resulted in successful recruitment of the generous interns in various nephrology forums. NSMC internship can be included as a part of nephrology fellowship training curriculum.

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

Underline represents presenting author.
Faculty contact and teaching in both electives and core resident areas also contribute to branding of what they are end of the rotation. They actually make their own t-shirts. They kind of have their own Faculty work hard and play hard. This group of faculty always hosts dinners at the national average (42%). Programs with more IM residents choosing nephrology effective in fostering interest. All programs offered renal electives; 33% were mandatory. Research opportunities (56%), and exposure to nephrology fellows (56%) were most centers. Nephrology TPDs noted faculty mentoring (78%), elective experience (72%), directed focus group sessions were conducted. Most programs were in large tertiary program ranking and compared to a previously-reported national survey. Transcripts from project to increase nephrology interest. Residents graduating 2002-2012 were identified with the AMA Masterfile; programs were ranked by number of residents ultimately qualified applicants. Lack of interest in nephrology was the leading factor in respondents’ decision to not pursue the specialty. Innovative ways to expose trainees to the meaningful rewards and worthwhile challenges of kidney care are needed to continue to attract qualified applicants.

Best Practices to Increase Resident Interest in Nephrology: A Mixed Methods Study

Methodology

- 2002-2012 were identified with the AMA Masterfile; programs were ranked by number of residents ultimately qualified applicants.
- Lack of interest in nephrology was the leading factor in respondents’ decision to not pursue the specialty. Innovative ways to expose trainees to the meaningful rewards and worthwhile challenges of kidney care are needed to continue to attract qualified applicants.

Conclusions:

- Lack of interest in nephrology is a leading factor in respondents’ decision to not pursue the specialty. Innovative ways to expose trainees to the meaningful rewards and worthwhile challenges of kidney care are needed to continue to attract qualified applicants.

Renal Fellows’ Point-of-Care Lung Ultrasound Curriculum

Methodology

- The OSCE is being evaluated prospectively at 5 training programs (16 first-year, 10-second-year fellows) over a two-year period. There are 3 faculty per training site. Primary outcome is overall score on the EEC-GRS for each scenario (first vs. second year fellow performance for each scenario, and individual fellow scores between first and second year). Secondary outcomes include score < 3 (Satisfactory for level of training) on any subsection of the mini-CEX and overall score < 3 on the EEC-GRS. Preliminary satisfaction survey data indicate that 100% of faculty (6/6) and fellows (7/7) rated the OSCE as having met objectives, and 86% (6/7) fellows rated the experience as being “good” or better.

Conclusions:

- The Breaking Bad News OSCE, designed for a 2-year fellowship cycle, uses previously validated instruments (EEC-GRS; MimCEx) to assess nephrology-specific ICU and PFT skills. Fellows and faculty report satisfaction with the OSCE, and indicate that it meets objectives. The views expressed are those of the authors and do not reflect the official policy of the Department of the Army, the Department of the Navy, the Department of Defense or the United States Government.

Funding: Other U.S. Government Support
FR-OR006

Point of Care Echocardiography and Ultrasound-Guided Volume Assessment Training for Nephrologists and Trainees to Teach Point of Care ECHO Skills

Tithin Karakala,1,2 Gerren Hobby,1 Kelly W. Bullough,1 Krishna siva sai Kaikera,1 John T. Huggins.1 Medicine, University of Arkansas for Medical Sciences, Little Rock, AR; 2Medicine, Central Arkansas Care ECHO Skills

Background: Intravascular volume assessment is an extremely important in the care of patients with acute kidney injury (AKI), chronic kidney disease, and patients needing intermittent and continuous renal replacement therapy. The current volume assessment tools like, MAP, heart rate, clinical examination are unreliable in assessing intravascular (IV) volume. The accuracy of invasive methods like central venous pressure, and pulmonary artery pressure measurements in assessing responsive to volume have been questioned in recent years. Nephrologists play a pivotal role in volume assessment and management. Point of care (echocardiogram) ECHO is a very valuable non-invasive tool for volume assessment.

Methods: During an intense 8 hour workshop, participants were trained by an experienced intensivist and a trained nephrologist. There were 2 stations which utilized live standardized patients and a preceptor. Station 1 covered basics of ECHO, cardiac para-sternal short and long axis views, and measurement of Inferior VenaCava (IVC) diameter and variability, second station was cardiac apical 4 and 5 chamber views and lung parenchymal exam. The preceptors initially demonstrated the techniques, and then the participants were allowed to practice under supervision. We conducted a 20 multiple choice question (5 basics of ECHO, 9 cardiac ECHO, and 6 IVC and lung parenchymal volume assessment) per and post-test. There were 5 five-scale questions assessing procedural confidence and improvement.

Results: Twenty two participants (5 nephrologists, 16 trainees) attended and completed the test. There was a significant improvement in mean percentage of correct answers for the post compared to pre-test 78% (SD: 17) vs 40% (SD:11); p<0.0001. The improvement during post compared to pre-test was observed in all 3 categories: basics of ECHO (79%, SD-22 vs 53%, SD-21; p<0.0001), cardiac ECHO (77%: 19 vs 40%; 19: p<0.0001) and IVC and lung (77%: 12 vs 46; 28: p<0.0001). After attending the workshop the participants answered that they were either confident or extremely confident in answering questions like, "Do you have a way to assess volume in different portions of the nephron"? The students gave it an average helpfulness of 3.5. To the question "did the nephron help you learn the histology of the nephron"? The students found the poster helpful in understanding renal (nephron) physiology and histology. Once the poster was complete, it was helpful in understanding the pathophysiologic and the pathologic anatomy of the nephron. Coming before the lectures and the IQ cases, it gave them a frame of reference for understanding the function of the nephron and the mechanisms of action of the diuretics.

FR-OR007

Project Nephron: Teaching Medical Students Physiology and Histology

Lena Vaynberg. FAU Charles E Schmidt College of Medicine, Highland Beach, FL, FL.

Background: The objective of PBL in the FAU COM curriculum is to foster self-directed learning, communication skills, and teamwork among the students as well as linking these skills to basic sciences and patient problems. Students have a difficult time with the physiology of the nephron with regard to channels, transporters, pumps and diuretics. Since 2014, at the start of the renal course, each of eight case inquiry groups completed directed learning, communication skills, and teamwork among the students as well as acquiring or interpreting basic images 62% (SD: 17) vas 4% (SD:8) pre workshop.

Conclusions: To the question "did the nephron help you learn the histology of the nephron"? The students gave it an average helpfulness of 3.5. To the question "did you continue to use nephron in subsequent cases?" The students gave it an average helpfulness of 4.1. As for the comments, the students found it useful a learning tool which they reviewed in subsequent IQ cases.

FR-OR008

NephMadness: 5 Years’ Experience Joel M. Topf,1 Anna M. Burgner,2 Timothy Yau,3 Swapnil Hiremath,3 Matthew A. Sparks.3 1‘Duke University and Durham VA Medical Centers, Durham, NC; 2‘University of Ottawa, Ottawa, ON, Canada; 3‘Vanderbilt University Medical Center, Nashville, TN; 4Washington University School of Medicine, Saint Louis, MO; 5Medicine, Oakland University William Beaumont School of Medicine, Rochester, MI.

Background: NephMadness (NM) is an educational game that takes place entirely online through blogs, forums, articles, participatory interactive website, and Twitter-based discussion. NM leverages social media and Free Open Access Medical Education (FOAMed) to highlight advances and neglected issues in nephrology. NM began in 2013 and has completed 5 iterations. NM has evolved as the organizers have experimented with the medium. This review of the evolution of NM provides lessons to organizers of other online educational campaigns.

Methods: The NM curriculum takes the form of an online game that mimics the March Madness basketball tournament. The field consists of 32 nephrology concepts in 8 topics. The concepts and topics change every year. The field initially consisted of 64 concepts but this was reduced to 32 to encourage participation. Each concept is reviewed in a blog post providing the core educational content of the game. Independent content experts help select the concepts and fact check the blog posts. During the 3-week contest, additional commentaries are published from other experts. In 5 years NM has covered 256 nephrology concepts and posted 185 reviews and commentaries.

Results: Participants attempt to predict the winners of all 31 matchups. Initially the winners of each single elimination contest was scripted by the organizers. After significant push back by the users, winners were selected by participant voting. NM included a pool of experts to select the winners. This year the number of programs to participate using a flipped classroom model. In 2017, 32 training programs participated. NM encourages participation from all levels, ranging from lay people, to medical students, to attendings. Prizes are awarded for the most accurate predictions and for programs with the greatest participation. 1481 individuals from 55 countries, two thirds from the US, have played NM in the last 4 years.

Conclusions: NM is a unique forum to present medical education that takes nephrology education out of the classrooms and textbooks and transforms it into a gamified, interactive campaign that populates social media channels. The mixture of free, evidence-based, expert content with twitter and blogs is a novel method of delivering high quality continuing medical education that could serve as a template for future projects.

FR-OR009

GlomCon – International Web-Based Glomerular Disease Case Conferences: Connecting Peers to Enhance Clinical Experience

Nikhil Agrawal,1,2 Rhea Bhargava,3 Roger A. Rodhy,3 Mihran V. Nalayan,1 Kenar D. Jhaveri,2 Stuart H. Locker,2 Johannes S. Schlondorff,1 Meghan E. Sise,1 Timothy Yau,1 Isaac E. Stillman,2 Jessica H. Cabeza Rivera,1 Jorge L. Castaneda,4 Arley F. Diaz,5 Michael J. Germain,6 Francesco Iannuzzella,7 Olufunmiliola A. Olubukola,8 Adam M. Segal,9 Jonathan Slater,10 Joseph Kupferman,11 David J. Friedman,12 John Danziger,13 Jeffrey H. Williams,14 Bradley M. Denker,15 Martin R. Pollak,1 Ali Poyan-Mehr.16 BIDMC, CONCORD, NH; 17Beth Israel Deaconess Medical Center, Boston, MA; 18Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA; 19Hofstra Northwell School of Medicine- Northwell health system, Great Neck, NY; 20Kidney Care and Transplant Associates of New England, Springfield, MA; 21LSUHSC School of Medicine, New Orleans, LA; 22Massachusetts General Hospital, Boston, MA; 23None, Boston, MA; 24Renal and Transplant Assoc of New England, Hampden, MA; 25Rush University Medical Center, Chicago, IL; 26University of Mississippi Medical Center, Ridgeland, MS; 27Washington University School of Medicine, Saint Louis, MO; 28Nephrology, Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA; 29Harvard Medical School, Boston, MA.

Background: Gaining enough exposure to glomerular diseases is a challenge and may lead to uncertainties in the management of these patients. The aim of our Glomerular Disease Case Conferences (GlomCon) is to increase nephrologist/ nephrophathologist’s exposure to patients with glomerular disorders and to create a forum to discuss diagnosis and management of individual cases in detail with colleagues.

Methods: We have created a web-based, secure video platform at Glomcon.org where nephrologists/nephrophathologists can connect worldwide and participate in live “peer-to-peer” clinical exchange. Participants submit challenging cases from their daily practice. Cases are reviewed by a volunteering nephropathologist/nephrologist and clinico-pathological correlation and therapeutic options discussed in bi-monthly live web sessions. All participants were surveyed in April 2017 for feedback.

Results: Since inception in July 2016, the conferences have seen a steady increase in membership participation. As of April 2017, GlomCon includes over 1000 participants from 27 countries. A survey of 113 participants yielded the following results: 54% responded. Of these, 100% were “Very satisfied” or “Satisfied”, 86% noted that participation impacted their care, for 31% knowledge about glomerular kidney disorders improved “extremely” and for 54% “very”. 100% believe that the conferences improve the care of patients with glomerular kidney disease.

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

Underline represents presenting author.
Conclusions: GlomCon is a new platform which enables nephrologists/ nephropathologists to share their experience and solicit peer-to-peer opinion and expertise. The majority of participants feel it has improved their clinical knowledge and with this impacted and improved patient care. Through this inclusive and open-access initiative, new opportunities for raising awareness and enhancing education in glomerular kidney disease has been created.

FR-OR010
The Use of a Medical Application Improves the Identification and Classification of AKI
Rolando Claire-Leal Granado, Maria F. Iturricha caceres, Etienne Maceda, Ravindra L. Mehta. UCSD, San Diego, CA; 2UCSD School of Medicine, San Diego, California, Bolivia; 3Universidad Mayor de San Simon, School of Medicine, Cochabamba, Bolivia; 4Universidad de San Simon, School of Medicine, Cochabamba, Bolivia; 5University of California San Diego Medical Center, San Diego, CA; 6Hospital Obreiro #2 - C.N.S., Cochabamba, Bolivia.

Background: The use of mobile devices by health care professionals (HCPs) has transformed many aspects of clinical practice. Mobile devices and apps provide many benefits for HCPs, perhaps most significantly they increase the access to point-of-care tools, which has been shown to support better clinical decision-making and improved patient outcomes. In this study we tested the hypothesis that the use of an app specifically designed for recognition and management of AKI will help HCPs to better identify and classify AKI.

Methods: We included 20 AKI cases from our center that were part of the 80/25 Global Snapshot study report. Twenty clinical vignettes of these patients (including baseline serum creatinine (sCr) and a second sCr that was measured in a 7 day period) were presented to 50 last year medical students and ask two simple questions: 1) Did the patient develop AKI? and 2) To classify the stage of AKI; before and after providing them with an app that was developed for early identification, classification and management of AKI (IRA SLANH app, Island of the Moon® V1, 2014; Cochabamba-Bolivia). We analyzed if the use of a medical app could improve correct identification and stage classification of AKI.

Results: Before the IRA SLANH app was introduced to the 50 medical students, the mean number of correct answers were 14.7±4.7 with a minimum of 3 correct answers and a maximum of 20 correct answers; and only in 6.7±4.4 of the cases the correct stage of AKI was identified. After the app was presented to the medical students the number of correct answers improved to 20 and in all cases AKI stage was correctly classified. Before the medical app was presented to the medical students, only 22% of them were able to correctly identify all AKI cases, and 0% of them could correctly classify all cases of AKI.

Conclusions: Medical applications are useful tools in the practice of evidence-based medicine at the point of care. The use of a medical application specifically developed for the identification and staging of AKI could play a very important role in early identification and correct classification of AKI potentially allowing earlier intervention with preventive and treatment strategies to reverse kidney injury and improve recovery.

FR-OR011
The Risk of Stroke with Atrial Fibrillation in CKD Patients
1Institute for Clinical Evaluative Sciences, London, ON, Canada; 2London Health Sciences Centre, London, ON, Canada; 3McMaster University, Hamilton, ON, Canada; 4Ottawa Hospital Research Institute, Ottawa, ON, Canada; 5University of Alberta, Edmonton, AB, Canada.

Background: Both atrial fibrillation (AF) and chronic kidney disease (CKD) are known to increase the risk of ischemic and hemorrhagic stroke. However the relative contribution of albuminuria and eGFR level on stroke risk in patients with and without AF remains unknown.

Methods: From a total cohort of 736,666 patients from Ontario, Canada from 2002-2015, 35,024 patients developed incident AF with an ACR and eGFR measure within 12 months prior. AF and stroke were determined by hospital diagnostic codes at admission. We used propensity-score matched Cox proportional and Fine and Grey sub-distribution adjusted proportional hazard models (HR 95% CI) in this cohort (n=30,222). The main endpoint including all three event types (MACE plus), mortality, drop out from the database, or end of study. The association between CKD and CVD was estimated using varying BB use, it was associated with a similar reduction in all-cause mortality across all eGFR categories [eGFR >90: HR 0.67 (0.48-0.94), eGFR 60-90: HR 0.69 (0.58-0.85), eGFR 30-60: HR 0.68 (0.59-0.80), HR <30: 1.19 (0.92-1.53)]. When examining time-varying BB use, it was associated with a similar reduction in all-cause mortality across all eGFR categories [eGFR >90: HR 0.56 (0.39-0.79), eGFR 60-90: HR 0.63 (0.55-0.73), eGFR 30-60: HR 0.59 (0.52-0.66), eGFR <30: HR 0.47 (0.33-0.66), eGFR category X beta-blocker interaction p=0.458].

Conclusions: In elderly patients with CHF, BB use was associated with a similar reduction in mortality across all eGFR categories. Our findings suggest that mortality benefits of BB's observed in CHF patients included in randomized trials could be extended to patients with eGFR <30 not on dialysis.

FR-OR012
The Association of Beta-Blockers and All-Cause Mortality by eGFR in Patients with Heart Failure
Amrit O. Molnar, Amit X. Garg, Manish M. Sood. 1London Health Sciences Centre, London, ON, Canada; 2McMaster University, Hamilton, ON, Canada; 3Ottawa Hospital Research Institute, Ottawa, ON, Canada.

Background: Congestive heart failure (CHF) and CKD are strongly interrelated and when occurring concurrently, are associated with very high mortality, especially in the elderly. Whether the mortality benefit of beta-blockers (BB) extends to patients with CHF and lower levels of eGFR remains unknown.

Methods: A population-level administrative database study using linked datasets in Ontario, Canada. Incident CHF cases aged > 66 years from April 2002 to March 2014 were included. The date of the first prescription for a BB was the date of inclusion (index date). Patients without evidence of a BB prescription were randomly assigned an index date based on the distribution of index dates for those prescribed a BB. Individuals without an eGFR measure within 1 year prior to the index date, or a prior history of kidney or heart transplant or chronic dialysis were excluded. We matched BB users vs non-users (1:1) based on age, sex, eGFR grouping, and a high dimensional propensity score. We examined all-cause mortality using Cox proportional hazards models with BB prescription at baseline and as a time-varying covariate.

Results: Results: After matching, a total of 3,574 pairs were identified. By eGFR category, the number of all-cause mortality events in the BB versus the no beta-blocker (NBB) groups were eGFR > 90: BB 44 (12.7%) vs. NBB 188 (36.8%), eGFR 60-90, BB 357 (14.0%) vs. NBB 1552 (22.2%), eGFR 30-60, BB 274 (19.0%) vs NBB 917 (47.7%), eGFR < 30 BB 47 (20.4%) vs NBB 166 (53%). Examining baseline BB use, there was no mortality benefit with BB usage in lower eGFR categories [eGFR >90: HR 0.67 (0.48-0.94), eGFR 60-90: HR 0.96 (0.85-1.08), eGFR 30-60: HR 0.96 (0.88-1.05), eGFR <30: HR 0.87 (0.68-1.13), eGFR category X BB interaction p=0.225]. When examining time-varying BB use, it was associated with a similar reduction in all-cause mortality across all eGFR categories [eGFR >90: HR 0.56 (0.39-0.79), eGFR 60-90: HR 0.63 (0.55-0.73), eGFR 30-60: HR 0.59 (0.52-0.66), eGFR <30: HR 0.47 (0.33-0.66), eGFR category X beta-blocker interaction p=0.458].

Conclusions: The association of beta-blockers and all-cause mortality by eGFR in patients with heart failure is modified by congestive heart failure, chronic kidney disease, and lower eGFR level.
Continuation of Statin Therapy Initiated in Pre-ESRD Period and All-Cause and Cardiovascular Mortality after Transition to Dialysis

Elvira Goismanova,4 Miklos Z. Molnar,2 Praveen Kumar Potukuchi,3 Elani Streja,3 Keichi Sumida,2 Kamyar Kalantar-Zadeh,3 Csaba P. Kovessy.5
4Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; 5Carnegie Mellon University, Pittsburgh, PA.

Background: De novo statin therapy in ESRD patients failed to demonstrate significant cardiovascular (CV) protection in randomized clinical trials and, therefore, it is not recommended. However, whether continuation of statins from late-stages of non-dialysis dependent CKD to the post-ESRD period is associated with improved all-cause and CV mortality in dialysis patients is unknown.

Methods: We identified 14,939 US veterans transitioning to dialysis between 2007-2011 who were receiving statins during the 1 year prior to dialysis initiation and had adequate adherence, defined as proportion of days covered (PDC) of ≥80%.

Results: All-cause and CV mortality rates were 285 [95% CI 279-291] 1000 patient-years and 116 [95% CI 112-121] 1000 patient-years, respectively, during a mean ± SD 2.01 ± 1.35 years of follow-up. Statin continuation after ESRD onset was associated with lower all-cause and CV mortality in unadjusted and various adjusted analyses (figure).

Conclusions: Extension of statin therapy following dialysis transition was associated with reduced all-cause and CV mortality. This data support experts’ opinion in the current guideline using Cox regressions adjusted for demographics, comorbidities, medications, and laboratory parameters.

Funding: NIDDK Support

FR-OR014

Incident Atrial Fibrillation and Risk of Subsequent Cardiovascular Events and Mortality: The CRIC Study

Nisha Bansal,3 Daiwei Xie,1 Duangchay Scha,1 Lawrence J. Appel,2 Rajat Deo,2 Harold I. Feldman,1 Jiang He,3 Kenneth A. Jammerson,3 John W. Kusek,4 Steven R. Messe,5 Sarah R. Navaneethan,5 Mahboob Rahman,5 Ana C. Ricardo,9 Elseayed Z. Soliman,4 Raymond R. Townsend,11 Alan S. Go,4 Baylor College of Medicine, Houston, TX; 2Case Western Reserve University, Cleveland, OH; 3Johns Hopkins Medical Institutions, Baltimore, MD; 4Kaiser Permanente Northern California, Oakland, CA; 5Kidney Research Institute, Seattle, WA; 6NIDDK, Bethesda, MD; 7Tulane School of Public Health and Tropical Medicine, New Orleans, LA; 8University of Illinois at Chicago, Chicago, Chicago, IL; 9University of Michigan Health System, Ann Arbor, MI; 10University of Pennsylvania, Philadelphia, PA; 11Wake Forest University School of Medicine, Winston Salem, NC.

Background: Atrial fibrillation (AF) is the most sustained arrhythmia in patients with chronic kidney disease (CKD) and may be associated with poor clinical outcomes. We examined the association of incident AF with the risk of subsequent incident cardiovascular (CVD) events and mortality.

Methods: We studied participants enrolled in the prospective Chronic Renal Insufficiency Cohort (CRIC) Study without AF at baseline. Incident AF was identified by ECGs and physician- adjudicated hospitalizations. Outcomes included: incident heart failure (HF), myocardial infarction (MI), stroke and death after diagnosis of AF. Cox regression models (with time-updated AF) and marginal structural models (MSM) to account for time-dependent confounding were used to examine the association of incident AF with outcomes, adjusting for demographics, clinical characteristics and ECG measures.

Results: Among 2,814 participants, 288 (9.2%) developed incident AF. During a mean (SD) follow-up of 7.0 (2.1) years, rates of HF, MI, stroke and death were higher in those who developed AF versus those who did not (Table). Cox and MSM models demonstrated that incident AF was associated with greater than 4-fold increased risk of subsequent incident HF, MI and death. Cox models also showed a significant association of incident AF with stroke (Table). These associations remained robust with additional adjustment for biomarkers of inflammation, cardiac stress and mineral metabolism as well as left ventricular mass, ejection fraction and left atrial diameter.

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

Underline represents presenting author.
Incident Atrial Fibrillation and the Risk of Subsequent Adverse Outcomes in Patients with a Decreased eGFR

David Massicotte-Azarmouch,1 John Paul Kuwornu,2 Juan J. Carrero,1 Ngan Lam,3 Deborah Lynn Zimmerman,4 Megan K. Mcellum,5 Ron Wald,2 Amit X. Garg,2 Manish M. Sood,6 Institute for Clinical Evaluative Sciences, London, ON, Canada; 2Karolinska Institutet, Stockholm, Sweden; 3London Health Sciences Hospital, Toronto, ON, Canada; 7Medicine, University of Ottawa, Ottawa, Canada; 41Institute for Clinical Evaluative Sciences, London, ON, Canada; 5CHU de Bordeaux, Bordeaux, France; 6Université de Bordeaux, Bordeaux, France; 7Saarland University Medical Centre, Homburg/Saar, Germany; 8Escola Paulista De Medicina, Unifesp, Sao Paulo, Brazil; 9Nigata University, Nigata, Japan; 10Ambrose Pare University Hospital and Inserm U1018 Eq5, Boulogne Billancourt/ Paris cedes, France Group/Team: On behalf of CKDopps and CKD REIN investigators.

Background: The effect of atrial fibrillation (AF) among patients with decreases in eGFR and its subsequent effect on adverse outcomes remain unknown. Among 1,422,978 million adult residents with an eGFR measure < 90 ml/min/1.73m² from CKDopps (2013-2017), a multinational cohort study of pts with eGFR <60 ml/min/1.73m² to describe RAASi prescription patterns by category and patient subgroups. Brazil (BR), Germany (GER), and the US are shown; data from France and Japan are forthcoming.

Methods: We used data from CKDopps (2013-2017), a multinational cohort study of pts with eGFR <60 ml/min/1.73m² to describe RAASi prescription patterns by country and patient subgroups. Brazil (BR), Germany (GER), and the US are shown; data from France and Japan are forthcoming.

Results: Among 2,817 pts, ranges by country were: mean age 66-74 years; eGFR <30 69%-74%; HF 17%-19%; diabetes 41-58%; serum potassium ≥ 21-35%; albuminuria 50-69%. RAASi prescription was more common in GER (80%) than BR (66%) and US (54%); less common in CKD stage 5 in all countries; less common with higher serum K in US; and lower with albuminuria in GER and US (Table 1). RAASi use was higher among pts with (vs. without) CHF/diabetes in BR, but only for diabetes in US. Among pts prescribed RAASi, prescriptions of loop or thiazide diuretics were 68-74%; renins were 6% in GER, almost absent in BR and US, and bicarbonate was 6-8%.

Conclusions: RAASi prescription patterns in CKD vary by country, demographic, and clinical characteristics. RAASi may be underused, especially in the US where only half were prescribed a RAASi even among pts with strong class-specific recommendations including albuminuria, diabetes, or heart failure. Antihyperkalemia measures, such as dietary restriction, loop diuretics, bicarbonate and K binders may raise RAASi use. 

Funding: Commercial Support - Amgen, AstraZeneca, Baxter Healthcare, Kyowa Hakko Kirin, Hexal AG, Janssen, Keryx, Relypsa, Roche, Vifor Fresenius Medical Care Renal Pharma, Private Foundation Support

Table 1. Prevalence of RAASi use in patient subgroups

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Brazil</th>
<th>Germany</th>
<th>US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-65</td>
<td>83%</td>
<td>71%</td>
<td>82%</td>
</tr>
<tr>
<td>65+</td>
<td>89%</td>
<td>68%</td>
<td>89%</td>
</tr>
<tr>
<td>CKD stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>70%</td>
<td>55%</td>
<td>60%</td>
</tr>
<tr>
<td>3a</td>
<td>81%</td>
<td>69%</td>
<td>75%</td>
</tr>
<tr>
<td>3</td>
<td>74%</td>
<td>68%</td>
<td>79%</td>
</tr>
<tr>
<td>2</td>
<td>69%</td>
<td>67%</td>
<td>72%</td>
</tr>
<tr>
<td>1</td>
<td>64%</td>
<td>65%</td>
<td>67%</td>
</tr>
<tr>
<td>0</td>
<td>66%</td>
<td>59%</td>
<td>66%</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>65%</td>
<td>55%</td>
<td>65%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>50%</td>
<td>51%</td>
<td>50%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>50%</td>
<td>43%</td>
<td>49%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>50%</td>
<td>40%</td>
<td>43%</td>
</tr>
<tr>
<td>Cancer</td>
<td>50%</td>
<td>38%</td>
<td>42%</td>
</tr>
<tr>
<td>Stroke</td>
<td>50%</td>
<td>40%</td>
<td>43%</td>
</tr>
<tr>
<td>Liver disease</td>
<td>50%</td>
<td>38%</td>
<td>42%</td>
</tr>
<tr>
<td>Infections</td>
<td>50%</td>
<td>38%</td>
<td>42%</td>
</tr>
<tr>
<td>CVD</td>
<td>50%</td>
<td>38%</td>
<td>42%</td>
</tr>
<tr>
<td>RAASi use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-OR019
Electronic Health Records-Based Computable Phenotype for CKD Diagnosis and Staging Ming Shang,1 Paul E. Drawz,2 Robert J. Carroll,3 Adelaide M. Arruda-Olsson,4 Sumit Mohan,1 Juliana Ionia-Laza,5 Ali G. Gharavi,1 Chunhua Weng,1 George Hippsic,5 Krzysztof Krysiuk,6 1Department of Biomedical Informatics, Columbia University, New York, NY; 2Department of Medicine, University of Minnesota, Minneapolis, MN; 3Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN; 4Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN; 5Department of Medicine, Columbia University, New York, NY; 6Department of Biostatistics, Columbia University, New York, NY.

Background: Chronic Kidney Disease (CKD) diagnosis can be made by blood, urine, or imaging tests. This study is to design and evaluate a portable electronic phenotype for automated detection and staging of CKD based on electronic health records (EHR).

Methods: With urine tests data of 68,617 patients from three major health care systems (Columbia, Minnesota, and Vanderbilt), we used machine learning to design a universal albuminuria (A-stage) classifier that accommodates five common methods for quantification of urinary protein excretion, including two urine dipstick panels in combination with urine specific gravity. The performance of the classifier for each type of urine test was assessed by a 10-fold cross-validation procedure against matched UACR data. By integrating our A-stage classification with kidney-related diagnostic codes and serum Cr-based eGFR, a rule-based method, each individual is automatically assigned as CKD case or control. Each CKD case is additionally placed on a “staging grid” of albuminuria (A-stage) by eGFR (G-stage).

Results: The CKD algorithm has been designed, implemented and tested at Columbia University, achieving 100% and 83% PPs for cases and controls respectively by manual chart review. We then performed external validation at Vanderbilt University and Minnesota. In this electronic cohort, the phenotype had PPs of 85% and 99% for cases and controls, respectively. Based on expert review of 265 charts across all three sites, the PPVs to diagnose CKD Stage 1, 2, 3a, 3b, 4, and 5 were 75%, 98%, 95%, 93%, 89%, and 79%, respectively.

Conclusions: Using machine learning and rule-based methods, we developed and validated a portable CKD diagnosis and staging algorithm in a large multi-center effort. The electronic phenotype follows the latest guidelines and can be applied to both pediatric and adult patients. This algorithm can be implemented within any EHR to enable automated detection and staging of CKD, enabling the implementation of stage-specific clinical decision support tools.

Funding: Other NIH Support - National Human Genome Research Institute, National Institutes of Health (Grant U01HG008680)

FR-OR021
Comparison of Estimated versus Measured GFR Decline in CKD-CV Axis: Epidemiology and Outcomes Xiaoming Wang,1 Lu Yin,2 1Department of Medicine, Columbia University, New York, NY; 2Department of Biostatistics, Columbia University, New York, NY.

With urine tests data of 68,617 patients from three major health care systems (Columbia, Minnesota, and Vanderbilt), we used machine learning to design a universal albuminuria (A-stage) classifier that accommodates five common methods for quantification of urinary protein excretion, including two urine dipstick panels in combination with urine specific gravity. The performance of the classifier for each type of urine test was assessed by a 10-fold cross-validation procedure against matched UACR data. By integrating our A-stage classification with kidney-related diagnostic codes and serum Cr-based eGFR, a rule-based method, each individual is automatically assigned as CKD case or control. Each CKD case is additionally placed on a “staging grid” of albuminuria (A-stage) by eGFR (G-stage).

Results: The CKD algorithm has been designed, implemented and tested at Columbia University, achieving 100% and 83% PPs for cases and controls respectively by manual chart review. We then performed external validation at Vanderbilt University and Minnesota. In this electronic cohort, the phenotype had PPs of 85% and 99% for cases and controls, respectively. Based on expert review of 265 charts across all three sites, the PPVs to diagnose CKD Stage 1, 2, 3a, 3b, 4, and 5 were 75%, 98%, 95%, 93%, 89%, and 79%, respectively.

Conclusions: Using machine learning and rule-based methods, we developed and validated a portable CKD diagnosis and staging algorithm in a large multi-center effort. The electronic phenotype follows the latest guidelines and can be applied to both pediatric and adult patients. This algorithm can be implemented within any EHR to enable automated detection and staging of CKD, enabling the implementation of stage-specific clinical decision support tools.

Funding: Other NIH Support - National Human Genome Research Institute, National Institutes of Health (Grant U01HG008680)

FR-OR022
Plasma Zonulin Levels in Childhood Nephrotic Syndrome (NS) Howard Trachtman,1 Debbee S. Gibson,2 Kevin V. Lemley,3 Jonathan P. Troost,4 Christian Paul,2 Debra J. Morrison,1 Suzanne M. Vento,2 Judith D. Goldberg,2 Dong-hyung Ahn.5 1Children’s Hospital Los Angeles, Los Angeles, CA; 2NYU Langone Medical Center, New York, NY; 3NYU Langone Medical Center, New York City, NY; 4NYU Medical Center, New York, NY; 5University School of Medicine, New York, NY; 6The University of Alabama at Birmingham, Birmingham, AL; 7University of Michigan, Ann Arbor, MI.

Background: Case reports suggest that NS is responsive to dietary modifications including a gluten-free diet (GFD). In celiac disease, zonulin is released from enterocytes after exposure to gluten, stimulates protease activated receptor 2 (PAR2), and perturbs the actin cytoskeleton and cell-cell junctions in the gut. PAR2 is present on podocytes and, therefore, zonulin may increase glomerular permeability in NS. We conducted this study to test the hypothesis that plasma zonulin levels are elevated in pediatric patients with NS.

Methods: Plasma samples collected from patients ≥18 yr old with minimal change disease or FSGS enrolled in the NEPTUNE study, were tested. Clinical and laboratory data were retrieved coincident with the visit when the zonulin level was measured. Samples were available for testing from the 4 or 8 month visit. Plasma zonulin levels were measured by ELISA. Results (mean±SD or median (IQR)) were analyzed by t-test, Wilcoxon, Kruskal-Wallis, or linear regression and considered significant if P<0.05.

Results: There were 113 patients, 9.5±4.9 yr, 53% male, 42% white, 40% black and 18% other. Disease classification was infrequent relapser in 27%, frequent relapser/steroid dependent 42% and steroid resistant 30%. The mean Cr, eGFR, and serum albumin were normal. Urine protein:creatinine (UPC) ratio was 3.9±0.9 (g/g). The plasma zonulin level in NS children was 14.2±6.6 vs 10±5.7 g/mL in healthy adults (P<0.001) and -3 standard deviations above the mean in 27%. There was a trend toward lower zonulin levels in children with UPC 2 vs <2, 12.9±7.4 vs 16.7±8.0 (P=0.051). Plasma zonulin levels did not differ by eGFR, disease classification, or BP. Plasma zonulin and albuminuria concentrations were directly correlated, r=0.24, P=0.04.

Conclusions: The plasma zonulin level was significantly elevated in more than a quarter of children with NS and was unrelated to BP or eGFR. We observed a significant relationship between zonulin values and serum albumin but not proteinuria. There was a trend toward lower zonulin levels in children with nephrotic-range proteinuria. Further study is needed to determine the relationship between plasma zonulin levels and proteinuria and to test whether the plasma zonulin level can be used to predict response to a GFD in children with NS.

Funding: NIDDK Support

FR-OR023
Rhinovirus-Induced Defect of CTLA-4 Expression Plays a Critical Role in Relapse of Childhood Idiopathic Nephrotic Syndrome Ching-Yuang Lin,1 Chen-Ying Chen,1 Christian Trachtman,5 Dong-hyun Goldberg,5 J. Michael Perlman,2 1Clinical Glomerular Disorders: Clinical Translational Science-UPMC, INSERM, Villejuif, France; 2Department of Medicine, Columbia University, New York, NY; 3NYU Langone Medical Center, New York, NY; 4The University of Alabama at Birmingham, Birmingham, AL; 5University of Michigan, Ann Arbor, MI.

Background: The onset of minimal change disease (MCD) in idiopathic nephrotic syndrome (NS) is often preceded by an upper respiratory tract infection (URI) such as human rhinoviruses (HRVs). Transient spontaneous remission of nephrotic syndrome after intercurrent measles infection has also been reported. Upregulation of CD80 with an altered podocyte shape has been reported to result in proteinuria. CTLA-4 is the natural inhibitor of CD80, and the suppressive function of Treg is dependent on CTLA-4. The aim of this study was to investigate whether an increase in systemic CD4+ CD80+CD44+CD103+ T cells caused an increase in CD80 and a 6-fold increase in CTLA-4 on CD4+ CD4 T cells. The surface expression of CD80, CD69, CD160, CD69, and CD69 on CD4+ T cells is upregulated in the nephrotic phase and returned to normal during remission.

Methods: Of the 123 URI were proven to be caused by HRV, Thirty-two patients with relapsing NS and biopsy-proven MCD were enrolled. Peripheral blood mononuclear cells (PBMCs) from the NS patients and six age-matched normal controls were exposed to either one infectious unit/cell of HRV or measles virus for 48 h. The surface expressions of CD80, CD69, CD44, CD103 and Treg ratio, thereby leading to altered endogenous podocyte autoregulation of the CD80/ CTLA-4 ratio and the development of proteinuria.

Results: Systemic CD4+ CD80+CD44+CD103+ T cell and Th17/Treg ratios significantly increased during the nephrotic phase and returned to normal during remission. The urinary CD80/CTL4A ratio increased significantly during relapse and remission. Histologically, strongly positive staining of CD80 and weak staining of CD69 on podocytes were observed in the normal controls. It was also upregulated CD80 and down regulated CD69 in the PBMCs of the normal controls. It was also upregulated CD80 and down regulated CD69 in the PBMCs of the normal controls. It was also upregulated CD80 and down regulated CD69 in the PBMCs of the normal controls.

Conclusions: Systemically high levels of the CD4+ CD80+CD44+CD103+ T cells, and Treg cells, thereby leading to altered endogenous podocyte autoregulation of the CD80/ CTLA-4 ratio and the development of proteinuria.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-OR023
Tissue Transcriptomic Profiles Perform Similarly to Clinical and Pathology Features for Nephrotic Syndrome Outcome Prediction
Laura H. Mariani, Huateng Huang, Brad A. Godfrey, Matthias Kretzler, Yuanfang Guan. University of Michigan, Ann Arbor, MI.

Background: Clinical parameters do not accurately predict outcomes in nephrotic syndrome (NS). Traditional statistics are not well equipped to identify predictors from many potential parameters across the genotype-phenotype continuum. Machine learning techniques have been developed to address this, but have not been widely applied to NS.

Methods: NEPTUNE is a cohort study of NS patients enrolled at the time of biopsy. Clinical data, pathologic features and kidney genome wide mRNA expression data are collected. Elastic net regularization was used to build Cox proportional hazards models for time to (1)composite of ESRD/40% eGFR decline and (2)complete remission (UPCR <0.3mg/ml) using different sets of predictors: clinical/pathology data, gene expression modules, all variables. In 200 bootstrap replicates, models were built in training sets and time-dependent area under the curve (AUC) was computed in test sets. Pair t-test of mean AUCs across replicates was used to compare prediction accuracy between models.

Results: 432 patients were in clinical/pathology models [mean age 33(21), eGFR 83(50), UPCR 3.7(5.5), 41% male, 27% black, 18% MN, 31% MCD, 13% IgA, 38% FSGS]. 198 patients in gene expression models had similar characteristics. Elastic net models had higher AUC than simple cox models(Table). Significant predictors are shown(Fig).

Conclusions: Machine learning elastic net models had highest accuracy and identified novel predictors. Tissue mRNA expression modules were more accurate predictors of composite outcome than routine clinical parameters and may better capture the underlying biologic heterogeneity of NS.

Funding: NIDDK Support, Other NIH Support - NCATS, CTSA-KL2

FR-OR025
The Effectiveness of a Short-Term Steroid Regimen for Adult Steroid Sensitive Nephrotic Syndrome
Takahya Ozeki, Takayuki Katsumo, Sawako Kato, Yoshinari Yasuda, Tomoki Kosugi, Naotake Tsuboi, Shoichi Maruyama. Nagoya University Graduate School of Medicine, Nagoya, Japan.

Background: In pediatric patients with steroid sensitive nephrotic syndrome, recent trials have revealed that 2 months short-term steroid regimen (STSR) is not inferior to the extending steroid course. However, the optimal duration of the initial steroid therapy for adult patients remains unclear.

Methods: Adult MCD or FSGS cases (n=35) who had started STSR from Jan. 2015 through Jun. 2016 were included in this study. Control MCD patients (n=140) who were treated with conventional regimen were also enrolled from our retrospective cohort. All patients fulfilled the criteria below: biopsy proven MCD or FSGS, over 20 years old, first time episode of nephrotic syndrome, and complete remission achieved within 4 weeks. The detail of STSR was as below: (1) prednisolone started 0.8-1.0 mg/kg/day as initial dose and continued for 4-6 weeks. (2) reduced to 0.5-0.6 mg/kg/alternative day and continued for 4 weeks. STSR cases were compared with the control patients who were treated with conventional regimen.

Results: Throughout the observation period (median, 469 days), 23 (65.7%) of 35 STSR patients developed at least one relapse. In survival analysis, STSR associated with earlier first relapse (p=0.001, logrank test) but not with frequent relapse (p=0.21, logrank test). Among STSR group, none had symptom of adrenal insufficiency. The cumulative steroid doses during observational period were significantly smaller in patients with STSR than those with conventional regimen (Figure).

Conclusions: Although the timing of the first relapse in STSR group was earlier compared with conventional group, there was no difference in the occurrence of frequent relapse. Furthermore, STSR achieved lower steroid exposure. The present study suggest that STSR could be an effective treatment option for adult steroid sensitive MCD or FSGS.


FR-OR024
Response to Second-Line Immunosuppressive Treatments in Genetically Stratified Steroid-Resistant Nephrotic Syndrome
Ethan S. Sen,1,2 Agnieszka Bierzynska,1 Gavin I. Welsh,3 Moin Saleem.1,2 University of Bristol, Bristol, United Kingdom; 1Bristol Royal Hospital for Children, Bristol, United Kingdom.

Background: Steroid-resistant nephrotic syndrome (SRNS) is a heterogeneous condition with significant numbers of patients progressing to end-stage renal failure. Response to second-line immunosuppression is variable. This study aimed to evaluate effectiveness of second-line treatment according to genetic aetiology and pattern of response to second-line immunosuppression is variable. This study aimed to evaluate effectiveness of second-line treatments in non-genetic patients, there was CR to ciclosporin in 26.4% compared with 43.3% and 21.7% respectively in 119 non-genetic patients (p<0.0001) and PR was 36.4% compared with 31.4% and 25.2% respectively in 119 non-genetic patients (C24 treatments). Within the non-genetic group, among 92 patients with presumed or primary steroid resistance (SR) (178 treatments), overall CR was 27.0% and PR was 26.6% compared with 43.3% and 21.7% respectively in 25 patients with secondary SR (60 treatments). Fifteen patients suffered post-transplant disease recurrence among whom pre-transplant CR and PR were both 5.9% (34 treatments). When considering only first immunosuppressive treatments in non-genetic patients, there was CR to ciclosporin in 36.5% (19/52), to tacrolimus in 33.3% (9/27) and to cyclophosphamide in 11.5% (3/26).

Conclusions: CR occurred most frequently in patients with secondary SR, followed by non-genetic primary SR and then patients with genetic disease. Subjects retrospectively identified as having circulating factor disease based on post-transplant recurrence had a particularly poor response to immunosuppression.

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

FR-OR026
Long-Term Effect of Sparsentan (SPAR), a Dual Angiotensin and Endothelin Receptor Antagonist, on Proteinuria in Patients with Primary FSGS
Howard Trachtenberg,1 Ivan Rycklik,2 Robert M. Haws,2 Carla M. Nester,2 Alessia Fornoni,2 Radka Chloupek1,2

Background: In the ongoing DUET trial, SPAR (200, 400, 800 mg/day) resulted in greater reduction in proteinuria vs. irbesartan (IRB, 300 mg/day) over the 8-week double-blind (DB) period. Generally, SPAR was safe and well tolerated. After DB, patients continued for 4 weeks. STSR cases were compared with the control patients who were treated with conventional regimen.

Methods: In the ongoing DUET trial, SPAR (200, 400, 800 mg/day) resulted in greater reduction in proteinuria vs. irbesartan (IRB, 300 mg/day) over the 8-week double-blind (DB) period. Generally, SPAR was safe and well tolerated. After DB, patients continued for 4 weeks. STSR cases were compared with the control patients who were treated with conventional regimen.

Results: Throughout the observation period (median, 469 days), 23 (65.7%) of 35 STSR patients developed at least one relapse. In survival analysis, STSR associated with earlier first relapse (p=0.001, logrank test) but not with frequent relapse (p=0.21, logrank test). Among STSR group, none had symptom of adrenal insufficiency. The cumulative steroid doses during observational period were significantly smaller in patients with STSR than those with conventional regimen (Figure).

Conclusions: Although the timing of the first relapse in STSR group was earlier compared with conventional group, there was no difference in the occurrence of frequent relapse. Furthermore, STSR achieved lower steroid exposure. The present study suggest that STSR could be an effective treatment option for adult steroid sensitive MCD or FSGS.

were treated in an open-label extension (OLE). We present interim results of OLE for sustainability of the antiproteinuric effect of SPAR.

**Methods:** In the OLE, patients [biopsy-proven FSGS, baseline (BL) urine protein/creatinine ratios (Up/C) >1/5g, age 7-75 y (U.S.), eGFR≥30 ml/min] randomized to SPAR continued (SPAR:SPAR), and those randomized to IRB received SPAR (IRB:SPAR). Up/C, eGFR and blood pressure (BP) were measured every 12 weeks to Week 48 and compared to BL (Week 0 for SPAR:SPAR, Week 8 for IRB:SPAR).

**Results:** Results of patients with available Up/C are below. In SPAR:SPAR, SPAR resulted in rapid reduction of Up/C and BP which remained sustained over 48 weeks, while eGFR remained stable. In IRB:SPAR, group, transition to SPAR resulted in a significant reduction in Up/C (Week 16), which was sustained until the end of follow-up. In contrast to SPAR:SPAR, IRB:SPAR was associated with mild, temporary, but significant reduction in eGFR, while SPAR-induced BP reduction was less apparent.

**Conclusions:** SPAR was well tolerated and achieved a sustained antiproteinuric effect in primary FSGS with early BP reduction and stable eGFR over 48 weeks. Transition to SPAR from IRB led to significant, sustained reduction of proteinuria and a temporary, mild reduction in eGFR without long-term impact on BP.

**Funding:** Commercial Support - Retrophin, Inc.

---

**FR-OR028**

IgM Bound to the Surface of T Cells: A Novel Prognostic Marker of Steroid Dependence in Idiopathic Nephrotic Syndrome

Manuela Colucci, Francesco Emma, Marina Vivarelli. Bambino Gesù Children's Hospital - IRCCS, Rome, Italy.

**Background:** The pathogenesis of non-genetic forms of idiopathic nephrotic syndrome (INS) is unknown, but the therapeutic success of rituximab suggests a role of B cells and possibly immunoglobulins. During the characterization of the T and B cell phenotype of INS patients pre-rituximab, we observed an unexpected presence of IgM on the surface of T lymphocytes of some patients. Therefore, we investigated the role of IgM on the T cell surface of patients with INS.

**Methods:** We evaluated by FACS analysis the presence of IgM on the surface of T lymphocytes (T-cell IgM intensity) in 103 healthy donors (HD, 78 adults and 25 children) and 113 INS pediatric patients at onset (44 patients) or subdivided between steroid-sensitive (SSNS, 28) and steroid-dependent (SDNS, 41) patients, in relapse or in remission. We compared T-cell IgM intensity with other predictive parameters of response to steroid treatment and explored in *vivo* the mechanism responsible for this unexpected finding and its potential pathogenic role.

**Results:** At disease onset (before treatment) 34% patients showed an intense presence of IgM on the surface of T cells as compared to HD, and individuals with higher T-cell IgM intensity showed a significantly increased risk of relapse by Log Rank test (p<0.03). Furthermore, T-cell IgM intensity discriminated between SDNS and SSNS patients by ROC analysis (AUC, 0.85; p<0.001). In vitro, serum IgM from INS patients bound healthy T cells more than serum IgM from HD (p<0.001) and showed a reduced sialylation of their N-linked glycan residues, more evident in the steroid-dependent group. Commercially available desialylated IgM bind to T cell surface and fail to be internalized, causing elevated T-cell IgM intensity. Interestingly, whereas commercially available sialylated IgM inhibit the induction of T-cell activation and proliferation, desialylated IgM fail to exert this immunomodulatory effect, reduce the T-cell response to steroid inhibition and allow production of T-cell-derived podocyte damaging factors.

**Conclusions:** The presence of IgM on T cells may be a prognostic marker of steroid dependence in INS at disease onset. Desialylated IgM in some INS patients may bind to T cell surface and contribute to T cell dysregulation, possibly playing a role in INS pathogenesis.

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

---

**FR-OR027**

Diagnosing Recurrent FSGS Using a Novel Cell-Based Assay

Pankai Srivastava,1 Eshethem Arif,1 Ashish K. Solanki,2 Kenneth Kwon,2 Michael G. Janecz,3 Deepak Nihalani.1 1MEDICAL UNIVERSITY OF SOUTH CAROLINA, CHARLESTON, SC; 2Medical University of South Carolina, Charleston, SC.

**Background:** Here we report a novel human podocyte cell-based assay that will serve as a non-invasive diagnostic clinical tool to detect rFSGS (recurrent focal and segmental glomerulosclerosis), which provides rapid and accurate identification of rFSGS patients. The concepts and approaches demonstrated in this proposal are widely applicable in designing assays for other forms of FSGS (or ESRD) whose diagnosis and treatment options remain inadequate. This assay is aimed at specifically diagnosing rFSGS to avert the ineffective renal transplant in FSGS patients.

**Methods:** As a first step, we identified rFSGS responsive genes by mRNA profiling of human podocytes treated with plasma derived from human rFSGS and control patients, which also induced significant alterations to podocyte actin cytoskeleton partially mimicking the disease processes. Two unique candidate genes (proprietary information) based on profiling data from control, non-FSGS and rFSGS patients were selected. In second step, the promoter regions for these genes were cloned into a promoterless reporter vector and transduced into podocytes to generate two stable podocyte cell lines, where expression of reporter was under the control of these promoters. This assay allowed us to measure plasma-induced increase in luminescence in these cells.

**Results:** Remarkably, both cell lines showed similar results, where only rFSGS patient plasma showed ~2-fold induction, whereas no induction was observed with plasma from other nephropathies including minimal change disease (MCD), membranous glomerulonephritis (MGN) and FSGS (Fig1).

**Conclusions:** Multiple centers within the country including CureGN and NEPTUNE have been solicited to analyze many rFSGS and non-rFSGS patient plasma using this assay and studies are being planned for conducting clinical trials to utilize its full diagnostic potential.

**Funding:** NIDDK Support

---

**FR-OR029**

Development and Validation of an EHR-Based Computable Phenotype to Rapidly Identify Glomerular Disease in Large Populations

Michelle Denburg,1 Charles Bailey,2 Hanieh Razzagh,2 Danielle Soranno,3 Ari Pollack,4 Donna J. Claes,5 Vikas R. Bambhiri,6 William E. Smerary,7 Michael J. Somers,4 Joshua Zaritsky,8 Joseph T. Flynn,9 Mark Mitsnnes,9 Maryjane Benton,2 Laura H. Mariani,10 Christopher B. Forrest,2 Susan L. Furth.2 1The Children's Hospital of Philadelphia, Philadelphia, PA; 2Children's Hospital Colorado, Aurora, CO; 3Seattle Children's Hospital, Seattle, WA; 4Cincinnati Children's Hospital, Cincinnati, OH; 5Washington University School of Medicine, St Louis, MO; 6Nationwide Children's Hospital, Columbus, OH; 7Children's Hospital, Boston, MA; 8Nemours/Alfred I. duPont Hospital for Children, Wilmington, DE; 9University of Michigan, Ann Arbor, MI.

**Background:** The objective of this study was to develop and validate a computable phenotype algorithm to identify all patients with glomerular disease (GD) using Pedsnet, a pediatric clinical research network (CDRN) that aggregates and standardizes electronic health record (EHR) data on >5 million children from multiple pediatric health systems.

**Methods:** A systematic review of EHR data from 231 patients with GD seen at the Children's Hospital of Philadelphia (CHOP) from April-December 2013 was used to develop, iterate, and validate a computerized algorithm comprised of Systematized
Nomenclature of Medicine (SNOMED) diagnosis codes, kidney biopsy and transplant procedures, and pediatric nephrologist encounters. The algorithm identified 6138 cases of GD from 7 PEDSnet institutions. For validation, non-cases were defined as non-cases (n=697) were evaluated at each site using a standardized chart review form, and with the reviewer blinded to case status.

**Results:** When first implemented at CHOP, the computable phenotype identified GD with a sensitivity (SENS) of 100%, specificity (SPEC) of 93%, positive predictive value (PPV) of 92%, and negative predictive value (NPV) of 100%. When implemented across 7 hepatic systems in PEDNet, the performance characteristics were: SENS 97%, SPEC 89%, PPV 76%, and NPV 97%. One SNOMED code contributed considerably to the false positives, and refining the algorithm to exclude it as a qualifying code improved performance: SENS 96%, SPEC 87%, PPV 83%, and NPV 97%. The most common biopy-based diagnoses were focal segmental glomerulosclerosis (18%), minimal change disease (17%), lupus nephritis (16%), and IgA nephropathy (13%). The most common non-biopsy diagnosis was nephrotic syndrome (41%).

**Conclusions:** We developed and validated an EHR-based computerized algorithm that identifies virtually all patients with GD within the PEDSnet CDRN. This method for identifying disease activity and stressors, and treatment adherence monitoring.

**Methods:** This was a prospective trial at CHOP with the software available to all sites, including the blinded reviewers. Parents or children 12 years old participated in daily messages on the results of their urine protein testing and weekly messages on the presence of stressors (infections, allergies, or other). Adherence to NSAID medications was monitored by self-reported medication administration. Parents or children 12 years old participated in daily messages on the results of their urine protein testing and weekly messages on the presence of stressors (infections, allergies, or other). Adherence to NSAID medications was monitored by self-reported medication administration.

**Results:** Adherence was defined as self-reported report of not taking prescribed NS medications in the first week of SMS. Time to remission was described using Kaplan-Meier method, stratified by adherent/non-adherent groups. Strengers were examined for relationship to disease relapses within a 7 day window via Chi-squared test. Among those who remained, 25 (48%) later relapsed, with 47 relapse events. Median time to remission was 7 days among adherent patients and 34 days among non-adherent patients (Figure). The frequency of stressor occurrence in the week prior to relapse did not differ from other weeks while a patient was in remission (6/47 (13%) vs. 171/1,641 (10%) p=0.03).

**Conclusions:** Mobile text messaging was an effective method to monitor disease activity and adherence in childhood NS. Non-adherence to medications was associated with a longer time to remission. Allergies, infections, or other stressors were not found to be associated with disease relapse.

**Funding:** NIDDK Support

---

### FR-OR030

**Title:** Mobile Text Messaging for Disease Activity, Stressors, and Treatment Adherence Monitoring in Pediatric Nephrotic Syndrome: Chia-Ming Wang, Jonathan P. Troost, Larry A. Greenbaum, Tarak Srivastava, Keisha L. Gibson, Howard Trachman, Emily G. Herreshoff, Debbie S. Gibson.

**Background:** There is limited information on the role of medication adherence or infectious/other stressors on the response to corticosteroids (IST) or risk of relapse in childhood nephrotic syndrome (NS). Mobile text messaging (SMS) technology may capture the impact of these factors on childhood NS disease course.

**Methods:** SMS data were collected on incident pediatric NS patients enrolled in the Nephrotic Syndrome Study Network (NEPTUNE) within 30 days of IST initiation. Parents or patients ≥12 years old responded to daily messages on the results of their urine protein testing and weekly messages on the presence of stressors (infections, allergies, or other) and adherence to NSAID medications. Non-adherence was defined as self-reported report of not taking prescribed NS medications in the first week of SMS. Time to remission was described using Kaplan-Meier method, stratified by adherent/non-adherent groups. Stressors were examined for relationship to disease relapses within a 7 day window via Chi-squared test.

**Results:** 69 pediatric NS patients were included in this analysis. Response rate to messages was 95%. Median follow-up was 364 days. 52% (76%) patients reached complete remission during follow-up. Among those who remitted, 25 (48%) later relapsed, with 47 relapse events. Median time to remission was 7 days among adherent patients and 34 days among non-adherent patients (Figure). The frequency of stressor occurrence in the week prior to relapse did not differ from other weeks while a patient was in remission (6/47 (13%) vs. 171/1,641 (10%) p=0.03).

**Conclusions:** Mobile text messaging was an effective method to monitor disease activity and adherence in childhood NS. Non-adherence to medications was associated with a longer time to remission. Allergies, infections, or other stressors were not found to be associated with disease relapse.

**Funding:** NIDDK Support

---

### FR-OR031

**Title:** Conserved Transcriptional Changes in Drosophila and Mouse Models of APOL1 Nephropathy: Zhe Han, Yulong Fu, Peng Zhang, Jun-ji Zhu.

**Background:** We identified diagnostic or likely pathogenic mutations in 28 cases (10.8%; 15.5% of familial 7.0% of sporadic NS): these included variants in WT1, LMV1, and TRPC6. To identify novel susceptibility genes for NS we conducted a rare variant collapsing analysis comparing 259 cases and 6,905 controls. The analysis yielded 25 genes at a p-value <2.5x10^-3

**Results:** We performed whole exome sequencing in 310 patients with idiopathic NS (116 (44%) of these cases were familial and 143 (56%) were sporadic). A case-control exome-wide collapsing analysis for rare functional variants (i.e. burden tests) was performed, comparing 259 index affected by familial or sporadic idiopathic NS with 6,905 controls. The analysis yielded 25 genes at a p-value <2.5x10^-3 with minimal genomic inflation. Among these top-ranking signals, we identified 6 genes implicated in Mendelian forms of NS or structural kidney disease: TRPC5 (rank 3; p=2.0x10^-10; OR 12.1); COL4A3 (rank 7; p=5.3x10^-10; OR 6.98); UMOD (rank 17; p=5.1x10^-10; OR 19.9); ACE (rank 18; p=1.5x10^-10; OR 7.0); LMV1 (rank 19; p=5.1x10^-10; OR 19.9); and WTI (rank 24; p=2.3x10^-10; OR 15.9). Aggregate analysis of 12 known genes involved in adult-onset NS identified qualifying variants in 30 (11.6%) cases and 152 (2.2%) controls (OR 5.8; p=1.6x10^-10).

**Conclusions:** Rare variants collapsing analysis represent a powerful approach to identify known and novel monogenic forms of NS in absence of large pedigrees or segregation data, and holds promises to help dissecting the complex genetic architecture of NS.

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

---

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

*Underline represents presenting author.*
FR-OR033

Connectivity Mapping in Experimental Alport Syndrome Identifies Lysine Deacetylase Inhibition as a Potential Therapy

Vanessa J. Groopman, MD, MSc
University of Michigan, Ann Arbor, MI

Background: Alport syndrome (AS) is a hereditary progressive nephropathy caused by mutations in type IV collagen genes. Currently there are few effective therapies for AS. We applied a drug repurposing strategy based on gene expression to identify a novel treatment.

Methods: Wild-type (WT) and Col4a3–/– (KO) mice on a 129/SvJ background were studied. Global RNA expression profiling was performed on whole kidney cortex at 4 and 7 weeks of age. Differential gene expression was verified with Significance Analysis of Microarrays (SAM). A disease progression signature was generated and then subsequently used to query the Connectivity Map (CMAP). CMAP identified vorinostat, a lysine deacetylase inhibitor, as a potential treatment. KO mice were treated with vorinostat at a dose of 50 mg/kg/day in DMSO by oral gavage from 4 to 7 weeks of age. DMSO-treated KO mice served as the control group. Mice were sacrificed at 7 weeks of age for analysis of kidney structure, function, inflammation, and fibrosis. Separate groups were followed out to 12 weeks of age.

Results: Pilot studies showed that vorinostat increased the acetylation of lysine in the kidney. Vorinostat led to a significant increase in survival (n = 19/group). This effect was associated with a trend toward decreased mean values in serum creatinine and urine protein excretion rates that did not reach statistical significance (n = 6/10/group). There was no effect of vorinostat treatment on glomerulosclerosis scores. mRNA and -SMA expression were reduced in cortical tissue from treated animals (n = 6/group). Western blot analysis showed that vorinostat lowered α-SMA expression in kidney cortex. This was associated with a trend toward decreased urinary excretion rates of TGF-β1. The urinary excretion rate of NGAL, a marker of tubular injury, was significantly reduced by vorinostat treatment.

Conclusions: CMAP can be used to identify new treatments for kidney disease based on expression profiling. Vorinostat was identified by CMAP analysis. We found that it extended the lifespan of kidney disease models but had modest effect on kidney function. It did not impact on glomerular injury but reduced kidney inflammation and excretion of a tubular injury marker. Future studies will provide more insight into the role of lysine acetylation in the progression of AS nephropathy.

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

FR-OR034

Glimeral and Tubulointerstitial eQTLs of Patients with Nephrotic Syndrome

R. Butler, Xiaoyan Chen, M.D., PhD
University of Michigan, Ann Arbor, MI

Background: Using intrarenal mRNA expression as a molecular phenotype in expression quantitative trait loci (eQTL) studies of nephrotic syndrome (NS) can lead to discovery of transcripts under significant genetic control, reveal novel NS-related biology, and identify loci associated with clinically meaningful outcomes. To describe the intrarenal eQTL landscape of NS, we paired whole genome sequencing with glomerular (GLOM) & tubulointerstitial (TI) transcriptomes from patients in the Nephrotic Syndrome Study Network (NEPTUNE).

Methods: NEPTUNE is a prospective, longitudinal study of NS enrolling affected adults and children receiving a clinically indicated biopsy. Rich demographic, clinical, and genomic data is collected and GLOM & TI transcriptomes are derived from a microdissected research biopsy core. We performed a ciseQTL study to identify GLOM & TI transcripts under genetic regulation by SNPs within 1Mb of the gene. We used the Bayesian “Deterministic Approximation of Posteriors” (DAP), which uses linkage disequilibrium and annotation information, to discover & fine-map eQTL signals within each locus while controlling for multiple testing. We included appropriate covariates for each dataset. We utilized MatrixEQTL for the same data to gain insight into direction of effect for these signals.

Results: At genome-wide significance, we discovered 340 independent eQTL signals in 313 unique genes in GLOM and 862 independent signals in 772 unique genes in TI. PLOC2, previously implicated in steroid sensitive NS via burden testing, was one of the strongest GLOM eQTLs. Five of 30 Mendelian NS genes had both a GLOM eQTL and a TI eQTL, previously implicated in steroid sensitive NS via burden testing, was one of the strongest NS candidates, with mostly shared, and a few distinct loci across the two subgroups in relation to kidney function.

Conclusions: We conducted two genome-wide association studies (GWAS) in the Million Veteran Program (MVP) cohort to detect associations with eGFR: in self-reported black and white, non-diabetic veterans (N = 181,315) and diabetic veterans (N = 91,523).

Funding: NIDDK Support

FR-OR035

Clinical Utility of Whole-Exome Sequencing for CKD

Emily Groopman, MD
University of Michigan, Ann Arbor, MI

Background: Whole-exome sequencing (WES) has recently been introduced into clinical diagnostics, but its value for adult constitutional disorders requires further evaluation. We are assessing the diagnostic yield of WES in a large cohort of adults with all-cause CKD or ESRD recruited at Columbia University (N = 1920).

Methods: WES was performed in 1920 patients evaluated at Columbia University for various forms of CKD. To date, the exomes of 765 patients have been analyzed using American College of Medical Genetics (ACMG) guidelines for clinical sequence interpretation.

Results: 97.4% of 765 patients were adults and 51.0% were non-Caucasian; 54% had glomerulopathy, 7% had congenital defects, and 17.5% had CKD of unknown etiology. In total, 82 (10.7%) patients had a diagnostic variant for a genetic form of nephropathy. Among these diagnosed cases, 19.5% had presented with “CKD of unknown origin” and 41.5% noted no family history of nephropathy. In 47.6% of diagnosed cases, the molecular diagnosis confirmed the clinical diagnosis (e.g., Alport syndrome); in 52.4% it clarified the diagnosis (e.g., UMOD mutation in a patient with tubulointerstitial nephropathy) or provided an additional diagnosis (e.g., Dent disease in a case of suspected glomerulopathy). Diagnostic variants were mainly found in genes for glomerulopathies (65.9%), followed by those for cystic disease (11.0%), tubulointerstitial disease (9.8%), other nephropathies (9.8%), and congenital anomalies (3.7%). In addition, 6 patients (0.8%) had a secondary, pathogenic variant in one of the 59 ACMG actionable genes. In the majority of cases, the results impacted clinical decision-making, through aspects such as initiation of targeted surveillance, family counseling, selection of transplant donors, and changes in therapy.

Conclusions: In a large all-cause CKD cohort, WES gave a molecular diagnosis for 21% of patients, and in 52.4% of positive cases pinpointed an etiology not detected using traditional diagnostics, impacting clinical care. The completion of this study will inform the utility of genetic testing for nephropathy across broad demographic subgroups and etiologic subgroups in CKD.

Funding: Veterans Affairs Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
FR-OR037

Analysis of Humans and Mice with DSTYK Mutations Reveals Complex Association with Urinary Tract Malformations and Neurological Phenotypes
Jeremiah Martino,1 Shouhong Xuan,1 Alejandro Perez,2 Katarina Vukovic,2 Qingxue Liu,1 Rik Westland,1 Adele Mitrotti,1 Cathy Mendelsohn,1 David B. Goldstein,1 Ali G. Gharavi,1 Simone Sanna-Cherchi1,2 Columbia University Medical Center, New York, NY; 2Columbia University College of Physicians & Surgeons, New York, NY.

Background: Our previous work has shown that dominant splice-site or premature termination mutations in DSTYK produce urinary tract malformations associated with epilepsy/ataxia in humans.

Methods: We sequenced exome data from large datasets of epilepsy patients and controls. We analyzed DSTyk null mice and human DSTYK null 293T cells generated using CRISPR technology.

Results: We sequenced exome data for 11,081 epilepsy patients, and 36,952 in house controls. The disease-imputed splice variant 654-1G>A is present in ~1 in 3,300 European individuals from ExAC, and in 12/36,952 house controls and 3/11,081 epilepsy patients, suggesting it may be an incompletely penetrant allele. Healthy controls were completely depleted of any DSTYK loss-of-function (LOF) mutations. We also identified a new splice mutation, absent in ExAC and all our controls, in monozygotic twins with bilateral congenital hydrencephrosis, and two premature termination mutations in two epilepsy patients for whom renal history is not yet available. Inactivation of Dtysk in the mouse showed perinatal lethality at P0/P1 and CAKUT. We observed unilateral renal agenesis and hypoplasia, shortened ureters and pelvic kidneys, and bladders diverticuli. Age-dependent obstructive uropathy was observed in ~70% of Dnky embryos. Hydrencephrosis, papillary septation and maldevelopment increased in severity with age. To gain more insight into molecular pathogenesis, we generated two compound heterozygotes in 293T cells. Analysis of RNA-seq data of WT and DSTYK null cells show alterations in cell adhesion and neurogenesis pathways, including altered signaling by BMP, POF, NOTCH, and WNT pathways. Genes associated to monogenic forms of epilepsy (GABRB3, PCDH19, and PRRT2) and CAKUT (GDNF, ITGA8, GPC3) were also downregulated. Finally, DOK5, an adaptor protein that interacts with RET was also downregulated in the DSTYK null cells.

Conclusions: In summary, we identified novel LOF mutations in patients with epilepsy confirming a new potential clinical association, provide evidence for genetic causality of CAKUT based on gene inactivation in the mouse, and identified cellular pathways perturbed by DSTYK inactivation.

Funding: NIDDK Support

FR-OR038

The Multi-Phenotype Derived Nephrotic Syndrome Severity (NS2) Score Empowers Genomic Discovery
C. Gillies,1 K Yasutaka,2 Xiaoan Wen,2 Matt G. Sampson,1 1University of Michigan, Ann Arbor, MI; 2University of Michigan, Ann Arbor, MI, Group/Team: NEPTUNE.

Background: Among patients with nephrotic syndrome (NS), we are interested in discovering genomic factors associated with disease severity over time. This requires creating accurate models of NS biology and a statistical strategy that takes advantage of diverse bioinformatic questions for converging on sample sizes and multiple testing. Thus, we developed a Nephrotic Syndrome Severity (“NS2”) score for patients in the Nephrotic Syndrome Study Network (NEPTUNE).

Methods: NEPTUNE is a prospective, longitudinal study of NS enrolling affected adults and children receiving a clinically indicated biopsy. Rich demographic and clinical data are collected at baseline and over time. Genomic and histologic data are collected at baseline. We used the following parameters to create the multi-phenotype NS2 score: interstitial fibrosis, eGFR, protein/creatinine ratio, eGFR slope, time to conversion/remission, time to a composite endpoint. We modeled the relationships between these variables and meaningful covariates using a Bayesian network (BN). The NS2 score represents a latent factor explaining the correlations in the observed data. The BN’s parameters were inferred from 616 patients NEPTUNE participants using Markov chains Monte Carlo.

Results: Compared to existing multi-phenotype methods, NS2 score increased power for discovery without inflicting Type I error. With regards to known biomarkers of NS severity, a worse NS2 score was significantly associated with the 4POL1 high-risk genotype in black patients (p=2.2 x 10^(-5)) and lower tubulointerstitial expression of EGF (p=5.7 x 10^(-10)). After FDR control, 1,040 glomerular transcripts were significantly associated with NS2 score. These transcripts are enriched for genes involved in kidney function and inflammation, with a high degree of overlap with known renal disease risk factors.

Conclusions: The NS2 score is a robust metric created on utilizing extensive clinical data and NS-specific knowledge. As a robust multi-phenotype method, it improved statistical power for discovery without inflicting false positives and replicates known risk associations. Ultimately, using NS2 score as an outcome measure in analyses ranging from gene expression correlation to GWAS may empower genomic discoveries.

Funding: NIDDK Support

FR-OR039

Novel Loci for Renal Decline in Type I Diabetes (T1D)
Marcus G. Pezzolesi,1,6 Jan Skupien,1,8 Chunyi Wu,7 Adam Smiles,7 Tanveerur S. Ahluwalia,1 Niina Sandholm,1,9 Erika A. Valo,10 Beata Gyorgy,11 Sune Onenugut-Gumuscu,11 Wei-Min Chen,12 Carol Forsblom,13 Joey M. Sibalic,14 Michel Marre,15 Stephen Rich,1 Andrea Galecki,1 Samy Hadjadj,1 Peter Rossing,1 Per- Henrik Groop16,6,17 Andrzej S. Krolevski,18,19 Stono Diabetes Center Copenhagen, Gentofte, Denmark; 1University of Michigan, Ann Arbor, MI; 2University of Virginia School of Medicine, Charlottesville, VA; 3Folkskapiae Institute of Genetics, Folkskapiae Research Center, Helsinki, Finland; 4University of Helsinki and Helsinki University Hospital, Helsinki, Finland; 5Joslin Diabetes Center, Boston, MA; 6INSEMP, Postiers, France; 7Jagellonian University Medical College, Krakow, Poland; 8University of Utah, Salt Lake City, UT; 9Harvard School of Medicine, Boston, MA.

Background: Progressive renal decline is the predominant clinical feature of diabetic kidney disease (DKD) that leads to end-stage renal disease. Although genetic factors are known to contribute to DKD’s susceptibility, despite intense effort, the identification of variants that underlie its risk has proven challenging. To advance this area of research, as part of the JDRF-sponsored Diabetic Nephropathy Collaborative Research Initiative, we have recently performed the first genome-wide association study (GWAS) aimed at identifying variants associated with progressive renal decline in T1D.

Methods: We performed a linear mixed-effects model (LMM) meta-GWAS using sQTL data of estimated glomerular filtration rate (eGFR) to estimate the effects of genetic variants on eGFR slope in 1,614 T1D patients with proteinuria assembled from 4 cohorts of European ancestry (Boston, Finland, Denmark and France). In total, more than 38,000 longitudinal eGFR measures collected over 5-20 years of follow-up were used to establish eGFR slopes in these patients.

Results: Our LMM meta-GWAS identified a number of novel loci that were strongly associated with eGFR decline. Our top finding was a variant in LRIP1 that approached genome-wide significance (P=7.3 x 10^(-10)). In total, 37 variants across 20 distinct loci achieved P<1x10^(-8) including 6 variants with P<1x10^(-6) in genes previously not associated with DKD. In addition to new loci for progressive renal function decline, our LMM meta-GWAS replicated an association at FRMD1, a gene that we initially identified as part of our GWAS in the GoKinD cohort.

Conclusions: Using a LMM meta-GWAS approach and longitudinal measures of renal function, we discovered several novel loci that contribute to progressive renal decline in patients with T1D and, thereby, further our understanding of the biology underlying DKD.

Funding: Private Foundation Support

FR-OR040

GSTM1 Deficiency Exaggerates Hypertension, Oxidative Stress, and Kidney Injury in Experimental Mouse Models of Hypertension and CKD
THU H. Le,1,2 Gabor Bodonyi-Kovacs,3 Phillip Ruiz,4,7 Sylvia Cechova,3,4 1Renal Division, George Washington University, Washington, DC; 2University Of Miami, Miami, FL; 3University of Virginia, Charlottesville, VA; 4,5Medicine, University of Virginia, Charlottesville, VA.

Background: GSTM1 encodes the glutathione S-transferase m-1 (GSTM1) enzyme that belongs to a superfamily of phase II antioxidant enzymes. In humans, a common deletion mutation, the null allele GSTM1(0), results in decreased GSTM1 enzymatic activity and is associated with higher levels of oxidative stress. We reported that GSTM1(0) is associated with accelerated kidney disease progression in the African Americans Study of Kidney Disease (AASK). This has been confirmed in the Atherosclerosis Risk in Communities (ARIC) Study, in which GSTM1(0) is associated with incident kidney failure in both European Americans and African Americans.

Methods: To directly determine the impact of loss of GSTM1 enzyme on kidney disease development, we deleted Gstm1 in the mouse to determine its consequence in the angiotensin II model of hypertension (Ang II-HTN) and the surgical remnant model of chronic kidney disease (Nx-CKD).

Results: Compared to wild-type mice, Gstm1(-/-) mice display higher levels of urinary 8-isoprostane and a modest but significantly higher BP at baseline. In both Ang II-HTN and Nx-CKD models, Gstm1(-/-) mice have exaggerated HTN, increased supersoxide levels and worse kidney injury, independent of activation of Nox2 and Nox4 NADPH oxidases. In AngII-HTN, Gstm1(-/-) mice display increased renal expression of genes involved in inflammation - CXCL-1, MCP-1, IL-1b and IL-6 – and increased renal macrophage infiltration. In the Nx-CKD model, deletion of Gstm1 resulted in early mortality, and significantly higher plasma creatinine and increased albuminuria. Isolated primary podocytes from Gstm1 KO mice also displayed a higher rate of migration in wound-healing assays.

Conclusions: In hypertension and CKD, GSTM1 enzyme may be protective by modulating oxidative stress and inflammation. Therapy directed at GSTM1 pathway in those genetically most susceptible may ameliorate kidney disease progression.

Funding: NIDDK Support
FR-OR041

Early Transcriptional Changes Associated with the Altered Flow Environment and Intimal Hyperplasia Following AVF Creation

Kyle M. Staton, Jared Rozovsky, Qiongyao Hu, Sarah Barbey.
1The University of Florida, Gainesville, FL; 2University of Florida, Gainesville, FL.

Background: While recent clinical studies have provided insights into factors that dictate success or failure in arteriovenous fistulae (AVF) maturation, advances in our understanding of the fundamental biology within the fistula vein wall that controls these events has been limited to animal models. Two-stage basilic vein transposition (BVT) fistula offer the unique opportunity for collection of vein wall sample at initial placement and 4-6 weeks following AVF creation. This study utilizes high-throughput genomics to evaluate the transcriptional changes associated with the independent effects of vein wall pathology versus the altered flow environment on mRNA expression.

Methods: Vein samples were collected from patients at Stage 1 and Stage 2 of BVT creation (n=14). mRNA was isolated and analyzed for 44,699 genes using the HTA 2.0 microarray. BRB ArrayTools and Ingenuity Pathway Analysis was used to identify genome changes, relevant ontologies, and upstream regulators. Histomorphometry was evaluated using Movat’s stain.

Results: Substantial heterogeneity was identified at the time of AVF creation (intimal thickness: range ~42-260 µm; mean = 133 µm). 86% of the Stage 2 samples demonstrated an increase in intimal thickness from baseline, with 50% of these veins exhibiting a greater than 2-fold increase in intima. A linear mixed model demonstrated 150 genes associated with the stage of fistula creation and 51 genes associated with extent of intimal disease (P<0.05; Figure). Genes regulating AVF creation/local flow environment were associated with cell cycle progression, metabolism, and inflammation (with IL1, IL12, and CCL4 as extracellular regulators). Genes related to the extent of intimal disease were related to cell migration, cell cycle progression, and cell death (with ADAMTS1, PGDF, and TGFβ as regulators).

Conclusions: Within the vein wall of patients undergoing AVF creation, independent genomic signatures related to alterations in flow and intimal hyperplasia can be identified. These differences offer the opportunity for development of target interventional strategies to improve AVF maturation and durability. Funding: Other NIH Support – RO1

FR-OR042

A Randomised Controlled Trial of Early Cannulation Grafts (ecAVGs) versus Tunneled Central Venous Catheters in Patients Requiring Urgent Vascular Access for Haemodialysis: One Year Follow-Up

Delays in AV fistula (AVF) maturation cause increased catheter dependency and costs. Forearm fistulae have very poor maturation rates compared to upper arm AVF. Increased distention pressure, nitric oxide release, and intermittent wall shear stress may help dilate forearm veins after AVF creation. Early use of non-invasive devices may help assist clinical AVF maturation and dilation.

Methods: One week after AVF creation, a novel, intermittent pneumatic compression device [Fist Assist (FA)] was applied 15 cm proximal to the AVF in order to apply intermittent, cyclic compression for 60 mm Hg for six hours daily for 30 days. Forty (n=46) AVF patients were enrolled in an IRB approved study to test vein maturation at baseline and with the FA. Controls (n=17) used a sham device. Vein size was measured and recorded at baseline and after 30 days by duplex measurement. Clinical results (percentage increase) were recorded and tested for significance using standard t-tests.

Results: No patients experienced immediate thrombosis or adverse effects. Patient compliance and satisfaction was high. After one month, the mean percentage increase in vein diameter in the FA treatment group for all fistulas was significantly larger (p=0.05) than controls (n=17) used a sham device. Vein size was measured and recorded at baseline and after 30 days by duplex measurement. Clinical results (percentage increase) were recorded and tested for significance using standard t-tests.

Conclusions: Early application of an intermittent pneumatic compression device may assist in AVF maturation and success. Novel, non-invasive devices like Fist Assist may have clinical utility to create functional fistulae development and decrease costs as they may help in maturation. FA may assist in forearm vein dilation and may provide the first wearable for the renal community to assist in AVF dilation especially at the forearm vein region.

FR-OR043

Procedural Burden Following Successful Arteriovenous Fistula Maturation in the United States

1University of Michigan, Ann Arbor, MI; 2Arbor Research Collaborative for Health, Ann Arbor, MI.

Background: Over the last decade, the number of arteriovenous fistula (AVF) in the prevalent US hemodialysis (HD) population has increased. We have previously reported that just under half of patients required interventional procedures for successful maturation of AVF. Herein, we sought to determine the procedural burden following successful AVF maturation (defined as first-use) among newly placed AVF in United States.

Methods: Using the United States Renal Data System (USRDS), Medicare claims and CROWNWeb data, we analyzed patients new to HD from 7/1/12 to 6/30/13 who had first-time AVF placements (after HD start) between 7/1/12 and 6/30/2014. Successful maturation was defined as documentation of first AVF use in the CROWNWeb monthly reporting of vascular access in use. Patients were followed until 12/31/2015.

Results: Among the 102,703 incident HD patients, there were 24,416 first-time AVF placements of which 72.6% were successfully utilized, 24.0% had no recorded use, and 3.4% were lost to follow-up. Of those AVF that successfully matured, 30.0% required interventions during the maturation phase ("assisted maturation"), with about half (55.1%) of these interventions requiring angioplasty. Rates of interventions during the maintenance phase, expressed as a rate per patient per year (ppy), are summarized in the Table. AVF that required interventional assistance to mature also had higher procedural burden for AVF maintenance.

Conclusions: While there have been improvements in AVF prevalence in the HD population, interventions on these AVF were exceedingly common. Future work will examine factors predisposing to greater requirements for intervention, cost effectiveness, patient outcomes, and comparisons with alternative vascular access types. Funding: NIDDK Support

FR-OR044

Intermittent Pneumatic Compression Increases Forearm AV Fistula Maturation: The First Medical Wearable for the Renal Community

Tej M. Singhi, M. Stephen, J. Harvest, El Camino Hospital, Mountain View, CA; 2Fist Assist Devices, LLC, Los Altos Hills, CA.

Background: Delays in AV fistula (AVF) maturation cause increased catheter dependency and costs. Forearm fistulae have very poor maturation rates compared to upper arm AVF. Increased distention pressure, nitric oxide release, and intermittent wall shear stress may help dilate forearm veins after AVF creation. Early use of non-invasive devices may help assist clinical AVF maturation and dilation.

Methods: One week after AVF creation, a novel, intermittent pneumatic compression device [Fist Assist (FA)] was applied 15 cm proximal to the AVF in order to apply intermittent, cyclic compression for 60 mm Hg for six hours daily for 30 days. Forty (n=46) AVF patients were enrolled in an IRB approved study to test vein maturation at baseline and with the FA. Controls (n=17) used a sham device. Vein size was measured and recorded at baseline and after 30 days by duplex measurement. Clinical results (percentage increase) were recorded and tested for significance using standard t-tests.

Results: No patients experienced immediate thrombosis or adverse effects. Patient compliance and satisfaction was high. After one month, the mean percentage increase in vein diameter in the FA treatment group for all fistulas was significantly larger (p=0.05) than controls (n=17) used a sham device. Vein size was measured and recorded at baseline and after 30 days by duplex measurement. Clinical results (percentage increase) were recorded and tested for significance using standard t-tests.

Conclusions: Early application of an intermittent pneumatic compression device may assist in AVF maturation and success. Novel, non-invasive devices like Fist Assist may have clinical utility to create functional fistulae development and decrease costs as they may help in maturation. FA may assist in forearm vein dilation and may provide the first wearable for the renal community to assist in AVF dilation especially at the forearm vein region.
FR-OR045
VasQ™ External Support Device Improves Functionality of Arteriovenous Fistulas: Randomized Controlled Study Results

Nikolaos Karydis,1 Paul Bevis,2 Gary Maytham,3 Moshe Halak,4 Noam Zilberman,5 Guy’s Hospital, Guy’s and St Thomas’ NHS Foundation Trust, London, United Kingdom; 2Bristol, Bath and Weston Vascular Network; Bristol, United Kingdom; 3Vascular Institute, St George’s University Hospital NHS Foundation Trust, London, United Kingdom; 4Vascular Surgery, Sheba Medical Center, Ramat - Gan, Israel; 5Laminate Medical Technologies, Tel-Aviv, Israel.

Background: Inadequate maturation is a major drawback of the Arteriovenous Fistula (AVF). Non-laminar flow at the peri-anastomotic area and venous exposure to arterial circulation are associated with development of neointimal hyperplasia, impairing venous remodeling. VasQ™ is a novel external support device designed to optimize anastomosis geometry, regulate flow patterns and support the venous wall, thus improving AVF outcomes. Interim results of a randomized controlled study designed to evaluate VasQ™ usability, safety and efficacy are presented here.

Methods: Sixty patients referred for a Brachiophaclic AVF (BCAVF) in 4 different hospitals were recruited and randomized to the ‘Device’ group (End-to-side BCAVF + VasQ™, n=40), or the ‘Control’ group (End-to-side BCAVF, n=20). Patients were followed up 1, 3, and 6 months post AVF creation.

Results: Device implantation easily integrated with the BCAVF procedure. All patients were free from device related complications. Of patients with patent AVFs undergoing hemodialysis, significantly higher rates of AVF use, larger diameter veins, and less stenosis were seen in the ‘Device’ group 3 months post AVF creation (Table 1). Primary patency rates 6 months post AVF creation were 79% vs. 67%, and the secondary patency rates were 88% vs. 79% in the ‘Device’ and ‘Control’ groups respectively.

Average blood flow rates (mL/min) were 1214 vs. 1208 at 1 month, 1426 vs. 1173 at 3 months, and 1269 vs. 1175 at 6 months post AVF creation, for the ‘Device’ and ‘Control’ groups respectively.

Conclusions: A significant increase in functionality 3 months post AVF creation was observed in the Device group. This may be associated with an increase in laminar flow and a decrease in venous wall tension promoted by VasQ™.

Funding: Commercial Support - Laminate Medical Technologies

Table 1 - AVF functionality 3 months post creation

<table>
<thead>
<tr>
<th>Access-Mediated (%)</th>
<th>Average Blood Diameter (mm) (n=136/137)</th>
<th>AVF w/ hospital reuse (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device (n=40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>9.76</td>
<td>16.66</td>
</tr>
<tr>
<td>Control (n=20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>7.04</td>
<td>38</td>
</tr>
</tbody>
</table>

* Patients with a patent AVF, on active hemodialysis

FR-OR046
Does Regional Compared to Local Anaesthesia Influence Outcome after Arteriovenous Fistula Creation? One Year Follow-Up of a Randomised Controlled Trial

Emma L. Arkin,1 Andrew J. Jackson,2 Rachel J. Kearns,3 John Kinsella,4 Alan J. Macfarlane,5 Marc J. Clancy,6 Glasgow Royal Infirmary, Glasgow, United Kingdom; 2NHS Greater Glasgow and Clyde, Glasgow, United Kingdom; 3NHS Greater Glasgow & Clyde, Glasgow, United Kingdom; 4University of Glasgow, Glasgow, United Kingdom.

Background: AVF are the optimal form of vascular access but have a high early failure rate. Although regional compared to local anaesthesia produces vasoconstriction and increases short-term blood flow there is no evidence that anaesthesia modality influences long-term fistula patency. This study investigated whether regional compared to local anaesthesia improved long-term AVF patency. The early (3 month) patency rates were recently published in The Lancet. 1 year follow-up data is now presented.

Methods: An observer-blinded randomised controlled trial was performed at three university hospitals in Glasgow, UK. Adults undergoing primary radiocephalic (RCF) or brachiocephalic (BCF) AVF creation were randomly assigned (1:1, in blocks of eight) using a computer-generated allocation system to receive either local anaesthesia (LA) or regional (brachial plexus block (BPP)) anaesthesia. Patients were excluded if they were conglutopatic, had no suitable vessels or had a previous failed ipsilateral fistula. The primary end point was AVF patency at 3 months. Secondary end points included functional patency at 3 months and 1 year, vessel diameters and brachial artery blood flow before and after anaesthesia (NCT01703654).

Results: 163 patients were assessed for eligibility and 126 patients were randomly assigned to LA (n=63) or BPP (n=63). All patients completed follow-up on an intention-to-treat basis. Primary patency at 3 months was higher in the BPP group than the LA group (53 [84%] vs 39 patients [62%]; odds ratio [OR] 3.3, p=0.005) and was greater in RCF (20 [77%] vs 12 patients [48%]; OR 3.6, p=0.03). In the subsequent year, 18 revisional procedures aimed at improving functional patency were performed on 10 patients. Functional patency at 1 year was higher in the BPP group than the LA group (51 [81%] vs 35 patients [56%]; OR 3.4, p<0.001). This difference remained more marked for RCF than BCF.

Conclusions: BPP significantly improved 3 month primary and functional patency and 12 month functional patency rates. This difference was more marked in RCF. The low early functional patency rates observed in our previously published data are not reproduced in 1 year follow-up data.

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

Underline represents presenting author.

FR-OR047
Locking Solutions Impact on Biofilm Formation in Tunneled Hemodialysis Catheters (T-HDC) and Activation of the Inflammatory Response

Mario Jimenez Hernandez,1 Nephrology, Hospital Clinic de Barcelona, BARCELONA, Spain.

Background: The surface of the T-HDC proves an optimal environment for the development of bacterial biofilm. The presence of these biofilms facilitates the generation of catheter-related infections (CRI) and possibly thrombosis, which can significantly reduce catheter life as well as its relationship with higher inflammatory state. Use locking solutions into catheter with antibacterial and anticoagulant activity seems reduced those complications. To date, there are no studies comparing locking solutions and biofilm formation on catheter surface and their possible relation with inflammatory response.

Methods: Objective: To analyze biofilm formation into THDC locked with heparin solution 10%, citrate 4% or taurodine + heparin 500UI + citrate 4% mixed solution through confocal microscopy and activation of the inflammatory response Prospective study, 35 patients in HD were included in whom the catheter was removed for non-infection-related reasons, according to the lock solution used in T-HDC were divided in three groups: 1) heparin 1:1000, 2) citrate 4% and 3) taurodine+citrate 4%+heparin 500UI. Microbiological growth were determined in each catheter. C-reactive protein, IL-6, IL-10 and Tumoral Necrosis Factor alpha were determined. We use confocal microscopy to determine the characteristics of biofilm.

Results: 35 patients were included, mean age 67.06±4.41 y, 80% were male sex; no significant differences were found related with clinical and demographical variables. Both catheters and blood cultures were negative. Catheter locking with taurodine had lower thickness of biofilm compared with citrate 4% and heparin (28.8±5.68 vs 49.99 ±15.6 vs 56.2 ±15.76mm; p=0.001) respectively, as well as volume of biofilm (1013967.2 ±1184812.3 vs 3706378.3 ±2512228.3 ±5553246.79 ±2448112.8 mm³; p<0.001). No significant differences were found in the inflammatory markers studied among the 3 locking solutions.

Conclusions: The presence of biofilm was found in all catheters, even in the absence of bacteria and regardless of the type of locking solution used, however, biofilm was thimer in those catheters locked with the taurodine-based solution which could be related with better outcome and lower bacteremia rates. No statistical differences were found in inflammatory response between the 3 groups; citrate and taurodine based solution.

Funding: Private Foundation Support

FR-OR048
Changes in Biomarker Profile and Left Ventricular Hypertrophy Regression: Results from the Frequent Hemodialysis Network Trials

Christopher T. Chan,1 George A. Kayser,2 Gerald J. Beck,1 Minwei Li,1 Joan C. Lo,2 Michael V. Rocco,3 Alan S. Kliger,4 Cleveland Clinic Foundation, Cleveland, OH; 5Kaiser Permanente Northern California, Oakland, CA; 6UC Davis, Davis, CA; 4NIDDK, NIH, Bethesda, MD; 5Wake Forest School of Medicine, Winston-Salem, NC; 7Toronto General Hospital, Toronto, ON, Canada; 8Yale New Haven Health System, New Haven, CT. Group/Team: FHN Trials Group.

Background: Regression of left ventricular hypertrophy (LVH) has been shown to be feasible within less frequent hemodialysis. We aimed to ascertain potential renal pathways associated with regression of left ventricular mass (LVM) in patients enrolled in the Frequent Hemodialysis Network (FHN) Trials.

Methods: FHN participants were stratified according to LVM response. Regressors were defined as patients who achieved a reduction of more than 10% in LVM at 12 months. Progressors were defined as patients who had a minimum of 10% increase in LVM at 12 months.

Results: Among 332 randomized patients, there were 77 regressors and 45 progressors. LVM change differed between the 2 groups (-37.2 g) p <0.001. Regressors had a median increase in diastolic frequency (from 3.3 (3.3) to 4.9 (3.7) per week, p = 0.001) and median reductions in pre-dialysis systolic (from 149 (136, 162) to 136 (123, 152) mmHg, p<0.001) and diastolic (from 83 (71, 91) to 76 (68, 73)]
FR-OR049
A Light Dialysis Session Makes a Heavy Heart: Extended Haemodialysis Offers Cardio-Protection [Oral Abstract]
Daren R. Churchward,1 Katherine L. Hull,2 Daniel S. March,3 Matthew P. Graham-Brown,1,2 James Burton1,2 None,1 Leicester, United Kingdom;2 University Hospitals of Leicester NHS Trust, Coventry, United Kingdom;3 University of Leicester, Leicester, United Kingdom.

Background: Internationally, there is a growing body of observational data that extended hours haemodialysis (HD) improves morbidity, mortality and quality of life. Limited experimental data are available comparing conventional HD (CD) to in-centre programmes of extended HD. This study examined the effects of extended in-centre nocturnal HD (INHD) on left ventricular geometry and circulating markers of cardiac injury, compared to CD.

Methods: The MIDNIGHT trial (ISCTRN16672784) is a non-randomised controlled trial of INHD (3x5-hours, n=10) vs CD (3x3-hours, n=12), with patients matched for age, gender and HD vintage. Left ventricular mass index (LVMi) was assessed by cardiac magnetic resonance imaging; levels of heat shock protein 70 (HSP70), fibroblast growth factor-23 (FGF-23) and troponin-I (Trop-I) were analysed from blood samples taken prior to HD. All measures were completed at baseline and 6-months. LVMi results are shown as median with standard deviation (Mdn[SD]), blood markers are presented as median with lower and upper quartiles (Mdn[Q1,Q3]).

Results: LVMi significantly reduced in the INHD group (63.6±20.7 vs 55.0±17.3, p=0.02) and tended to increase in the CD group (51.4±8.6 vs 54.6±11.1, p=0.46). No change to HSP70 was seen in either group. Reductions in FGF-23 were seen in the INHD group (498.7[156.3, 1515.0] vs 88.3[49.7,400.6], p=0.043) but not the CD group (399.24[174.1,4670] vs 657.3[158.9,1097.9], p=0.735). Similarly, no change to Trop-I in the INHD group (15.3[5.0,25.6] vs 6.0[0.2,25.0], p=0.917) but a trend to increase in the CD group (11.0[6.3,20.3] vs 15.0[3.8,38.1], p=0.096).

Conclusions: In this study, INHD patients demonstrated favourable changes in circulating biomarkers of cardiovascular disease as well as regression of left ventricular hypertrophy, compared to controls. These results provide further evidence that extended HD regimens may improve cardiovascular outcomes and therefore warrant further investigation.

FR-OR050
Reduction in Post-Dialysis Recovery Time in the FREEDOM Study of Frequent Home Haemodialysis [Oral Abstract/Friday]
Bertrand L. Jaber,1 Eric D. Weinhandl,2 James Burton,1 None,1 Leicester, United Kingdom;2 EUCRITON Group, Minneapolis, MN;1 None, San Clemente, CA.

Background: The Frequent Hemodialysis Network has recently demonstrated that a novel measure of interdialytic fluid volume overload, the time-integrated estimate of fluid load (TIFL), is inversely associated with left ventricular mass reduction and could therefore be used to evaluate the effect of volume overload on cardiac stress (Raimann et al, Blood Purif 2016). The relative importance of clinical factors, such as dietary sodium intake (NaI), interdialytic weight gain (IDWG) and dialysate sodium concentration (diaNa), on TIFL during conventional and more frequent haemodialysis (HD) are incompletely understood.

Methods: We compared the effect of clinical factors on the mean interdialytic excess of extracellular fluid volume (eECV) and TIFL using mathematical model simulations. A conventional model of sodium and fluid kinetics was used to simulate intradialytic and interdialytic changes in serum sodium and extracellular fluid volume (Kimura & Gotech, Int J Artif Organs 1984). TIFL was calculated using the approach of Raimann et al (Blood Purif 2016) that assumes rapid post-dialytic fluid intake to maintain the sodium set-point and accounts for the length of the interdialytic interval. Residual kidney urine volume was assumed negligible. We compared eECV and TIFL for conventional HD, daily HD and nocturnal HD.

Results: As expected, eECV and TIFL were strongly and positively associated with IDWG. In contrast, eECV and TIFL were inversely associated with NaI when not accompanied by increased IDWG. The effects of treatment modality and dialaNa are tabulated.

Conclusions: More frequent (daily and nocturnal) HD result in substantial reductions in eECV and TIFL. Similar reductions in these measures cannot be achieved with dietary Na restriction or reductions in dialysate Na concentration.

Funding: Commercial Support - NxStage Medical.

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

FR-OR051
Determinants of Intradialytic Volume Overload During More Frequent Hemodialysis: Time-Integrated Estimate of Fluid Load (TIFL) [Oral Abstract/Friday]
L. Ken Leypoldt1, Allan J. Collins1, Eric D. Weinhandl,1 Chronic Disease Research Group, Minneapolis, MN;1 None, San Clemente, CA.

Background: The Frequent Hemodialysis Network has recently demonstrated that a novel measure of interdialytic fluid volume overload, the time-integrated estimate of fluid load (TIFL), is inversely associated with left ventricular mass reduction and could therefore be used to evaluate the effect of volume overload on cardiac stress (Raimann et al, Blood Purif 2016). The relative importance of clinical factors, such as dietary sodium intake (NaI), interdialytic weight gain (IDWG) and dialysate sodium concentration (diaNa), on TIFL during conventional and more frequent haemodialysis (HD) are incompletely understood.

Methods: We compared the effect of clinical factors on the mean interdialytic excess of extracellular fluid volume (eECV) and TIFL using mathematical model simulations. A conventional model of sodium and fluid kinetics was used to simulate intradialytic and interdialytic changes in serum sodium and extracellular fluid volume (Kimura & Gotech, Int J Artif Organs 1984). TIFL was calculated using the approach of Raimann et al (Blood Purif 2016) that assumes rapid post-dialytic fluid intake to maintain the sodium set-point and accounts for the length of the interdialytic interval. Residual kidney urine volume was assumed negligible. We compared eECV and TIFL for conventional HD, daily HD and nocturnal HD.

Results: As expected, eECV and TIFL were strongly and positively associated with IDWG. In contrast, eECV and TIFL were inversely associated with NaI when not accompanied by increased IDWG. The effects of treatment modality and dialaNa are tabulated.

Conclusions: More frequent (daily and nocturnal) HD result in substantial reductions in eECV and TIFL. Similar reductions in these measures cannot be achieved with dietary Na restriction or reductions in dialysate Na concentration.

Funding: Commercial Support - NxStage Medical.
Methods: We analyzed data from the KIHDNeY (Knowledge to Improve Home Hemodialysis Network in Europe) cohort, which comprises HHD patients at 9 centers in 5 Western European countries. All patients used the NxStage System One. Data about the HD prescription and 24-hour urine volume were collected at HHD initiation, 6 months, and 12 months. We retained patients with 24-hour UVol ≥500 mL at baseline and ≥4 sessions/week. We used generalized estimating equations to model changes in UVol between HHD initiation and 12 months.

Results: Baseline UVol was recorded in 98 (54%) of 182 patients, 44 (45%) of 98 had UVol ≥500 mL, and 43 (98%) of 44 dialed ≥4 sessions/week. Mean age was 51 years, 49% were female, median dialysis duration before HHD was 11.5 months, 9% had diabetes, and 19% had glomerulonephritis. Treatment frequencies were 5 and 6 sessions/week in 70% and 30% of patients, respectively, and mean treatment time was 12.2 hours/week. Mean UVol decreased (P = 0.001) from 1310 mL at baseline to 1080 mL at 6 months and 910 mL at 12 months. Cumulative incidence of anuria (UVol ≤50 mL) was 6% at 6 months and 18% at 12 months. Concurrently, mean ultrafiltration volume increased from 0.69 L at baseline to 0.85 L at 6 months and 0.96 L at 12 months. Antihypertensive medication use declined from 1.62 agents/day at baseline to 1.35 agents/day at 12 months.

Conclusions: RRF decreased during 12 months of frequent HHD, with treatment time per week comparable to conventional HD. However, cumulative incidence of anuria was lower than with nocturnal HD in FHN (Daurgidas, Kidney Int, 2013), as well as lower 5-year survival was 77% for HHD patients and 52% for PD patients. In the adjusted analysis, patient mortality was lower with HHD compared to PD (adjusted hazard ratio [AHR] 0.48, 95% CI 0.42-0.72, p<0.001).

FR-OR054
Vascular Audit Checklist in Home Hemodialysis: A Prospective Cohort Study
Miten Dhruv,² Christopher T. Chan,³ Toronto General Hospital, Toronto, ON, Canada; ¹University Health Network, Toronto, ON, Canada.

Background: Vascular access related infections lead to increased morbidity and mortality in the home hemodialysis (HHD) population. We had previously reported that errors made on nurse – administered vascular access audit were associated with higher rate of access-related infection. In the present study, we hypothesize that repeat administration of vascular audit, will result in a decrease in the number of errors performed. Furthermore, increase in errors will augment the future risk of vascular related infection.

Methods: We conducted a prospective cohort study of all HHD patients from 2013 to 2016. Vascular access audits errors were obtained from checklists that were nurse administered and occurred on average every six and a half (0 – 32) months.

Results: 370 audits were performed on 122 patients with an average HHD vintage of 6.7 (0.8 – 19.5) years. At baseline the mean number of errors was 1.24 ± 1.75. This decreased significantly to mean of 0.33 ± 0.49 by 8th audit. Patients with multiple audits demonstrated a significant decrease in median number of errors (baseline median 1, (0-2) end of study median 0, (0-1) p<0.01). There was a significant relation between ≥2 errors and future risk of infection, (p<0.001 (Table 1). The overall infection rate was 0.57 infections per patient year.

Conclusions: Vascular access audits have a significant role to play in identification of errors in HHD population with repeat audits leading to a decrease in the number of errors. There exists a strong relation between 2 or more errors and increased risk of future infection. Vascular audit tool should be utilized in HHD programs to identify patient errors in aspiration of decreasing infection rates.

TABLE 1: Chi Square analysis to assess relation between 2 or more errors and future risk of infection.

<table>
<thead>
<tr>
<th>No. of Errors</th>
<th>No. of Patient with Infection</th>
<th>No. of Patient without Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 or None</td>
<td>44</td>
<td>33</td>
</tr>
<tr>
<td>1</td>
<td>39</td>
<td>54</td>
</tr>
<tr>
<td>≥2</td>
<td>18</td>
<td>15</td>
</tr>
</tbody>
</table>

FR-OR055
Therapy Attrition on Nocturnal versus Diurnal Home Hemodialysis
Eric D. Weinhandl,¹ Allison J. Collins,¹ ²Northwestern Medical Center, Victoria, MN; ³University of Minnesota, Minneapolis, MN.

Background: Nocturnal hemodialysis offers several clinical advantages over diurnal hemodialysis, including slower ultrafiltration rate and increased cumulative phosphorus clearance. In addition, because nocturnal hemodialysis transfers treatment time to overnights, patients may gain daytime hours for activity unrelated to health care. Recently, the NxStage System One (NSO) was cleared by the US Food and Drug Administration for nocturnal home hemodialysis (NHHD). We aimed to identify the relative risk of all-cause and cause-specific therapy attrition in NHHD patients and diurnal HHD patients using the NSO.

Methods: We analyzed data in prescription records maintained by NxStage Medical (Lawrence, MA). We identified all US patients who initiated NHHD between April 1, 2015, and December 31, 2016. We also identified all US patients who initiated HHD between April 1, 2006, and December 31, 2016. For all patients, we collected age, race, sex, and year of therapy initiation among NHHD patients and diurnal HHD patients who were treated with either peritoneal dialysis (PD) or home hemodialysis (HHD).

Results: The study included 14 589 PD patients and 721 HHD patients. Unadjusted 5-year survival was 77% for HHD patients and 52% for PD patients. In the adjusted analysis, patient mortality was lower with HHD compared to PD (adjusted hazard ratio [AHR] 0.62, 95% confidence interval [CI] 0.50-0.78, p<0.001) and the association was demonstrated a significant decrease in median number of errors (baseline median 1, (0-2) end of study median 0, (0-1) p<0.01). There was a significant relation between ≥2 errors and future risk of infection, (p<0.001 (Table 1). The overall infection rate was 0.57 infections per patient year.

Conclusions: Vascular access audits have a significant role to play in identification of errors in HHD population with repeat audits leading to a decrease in the number of errors. There exists a strong relation between 2 or more errors and increased risk of future infection. Vascular audit tool should be utilized in HHD programs to identify patient errors in aspiration of decreasing infection rates.

TABLE 1: Chi Square analysis to assess relation between 2 or more errors and future risk of infection.

<table>
<thead>
<tr>
<th>No. of Errors</th>
<th>No. of Patient with Infection</th>
<th>No. of Patient without Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 or None</td>
<td>44</td>
<td>33</td>
</tr>
<tr>
<td>1</td>
<td>39</td>
<td>54</td>
</tr>
<tr>
<td>≥2</td>
<td>18</td>
<td>15</td>
</tr>
</tbody>
</table>

FR-OR056
Improvement in Health-Related Quality of Life in the FREEDOM Study of Frequent Home Hemodialysis
Fredric O. Finkelstein,² Eric D. Weinhandl,¹ Allison J. Collins,¹ Bertrand L. Jaber, ³Northwestern Medical Center, Victoria, MN; ²St. Elizabeth’s Medical Center, Boston, MA; ³Yale University, New Haven, CT; ⁴University of Minnesota, Minneapolis, MN.

Background: Poor health-related quality of life (HRQOL) is common in dialysis patients. Increasing treatment frequency improved physical HRQOL in the FREEDOM Hemodialysis Network trials. The FREEDOM (Following Rehabilitation, Economics and
Everyday-Dialysis Outcome Measurements) Study was a 12-month prospective cohort study of short daily home hemodialysis (SDHD). Interim analysis of the FREEDOM Study indicated that SDHD led to improvements in HRQOL. We sought to confirm these findings in a final analysis.

**Methods:** We analyzed HRQOL in intention-to-treat (ITT), conditional ITT (cITT), and as-treated (AT) cohorts. The ITT, cITT, and AT cohorts comprised all patients who initiated SDHD, those who completed 2 months of follow-up, and those who completed 12 months of follow-up, respectively. HRQOL was measured with the Short Form-36 health survey at baseline, 4 months (if the patient remained on SDHD), and 12 months (if the patient remained on SDHD). Patients were censored at death or kidney transplantation. We used adjusted mixed models to analyze changes in HRQOL domains, the physical-composite summary (PCS), and the mental-composite summary (MCS).

**Results:** The ITT, cITT, and AT cohorts included 487, 408, and 247 patients, respectively. In the ITT cohort, mean PCS increased from 34.8 at baseline to 37.1 at 12 months, while mean MCS increased from 45.8 to 48.0. In the AT cohort, mean PCS increased from 35.5 to 38.6, while mean MCS increased from 48.4 to 50.4. Modeled changes in HRQOL domains between baseline, 4 months, and 12 months are displayed in Table 1. Changes were uniformly positive.

**Conclusions:** In a 12-month prospective cohort study, SDHD was associated with widespread improvements across domains of both physical and mental HRQOL.

<table>
<thead>
<tr>
<th>HRQOL domain</th>
<th>ITT cohort</th>
<th>12 months</th>
<th>cITT cohort</th>
<th>15 months</th>
<th>AT cohort</th>
<th>15 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCS</td>
<td>37.1</td>
<td>+2.2</td>
<td>37.8</td>
<td>+2.2</td>
<td>38.6</td>
<td>+2.2</td>
</tr>
<tr>
<td>MCS</td>
<td>48.0</td>
<td>+1.6</td>
<td>48.6</td>
<td>+1.8</td>
<td>49.4</td>
<td>+1.8</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>1.2</td>
<td>+0.3</td>
<td>1.5</td>
<td>+0.4</td>
<td>1.8</td>
<td>+0.4</td>
</tr>
<tr>
<td>Role-physical</td>
<td>1.0</td>
<td>+0.3</td>
<td>1.3</td>
<td>+0.4</td>
<td>1.5</td>
<td>+0.4</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>0.9</td>
<td>+0.1</td>
<td>1.0</td>
<td>+0.1</td>
<td>1.1</td>
<td>+0.1</td>
</tr>
<tr>
<td>General health</td>
<td>0.5</td>
<td>+0.1</td>
<td>0.5</td>
<td>+0.1</td>
<td>0.5</td>
<td>+0.1</td>
</tr>
<tr>
<td>Vitality</td>
<td>0.6</td>
<td>+0.1</td>
<td>0.7</td>
<td>+0.1</td>
<td>0.7</td>
<td>+0.1</td>
</tr>
<tr>
<td>Social functioning</td>
<td>0.3</td>
<td>+0.1</td>
<td>0.4</td>
<td>+0.1</td>
<td>0.5</td>
<td>+0.1</td>
</tr>
<tr>
<td>Role-emotional</td>
<td>0.3</td>
<td>+0.1</td>
<td>0.3</td>
<td>+0.1</td>
<td>0.3</td>
<td>+0.1</td>
</tr>
<tr>
<td>Mental health</td>
<td>0.5</td>
<td>+0.1</td>
<td>0.6</td>
<td>+0.1</td>
<td>0.6</td>
<td>+0.1</td>
</tr>
</tbody>
</table>

*P < 0.05, with adjustments for demographics and comorbidity.

**FR-OR057**

Angiogenin Knockout in Rats Causes Proteinuria Xiaoli Zheng,1 Jerold m. Ward,2 Zakir Hossain,3 Sik Yin Foo,2 Isaac Liu,2 Chang-Yen Chan,2 Zi Jin Sun,2 Hu Kim Yap,2 Kar Hui Ng,2 1 National University Hospital, Singapore, Singapore, 2 National University of Singapore, Singapore, Singapore, 3 Global VetPathology, Montgomery Village, MD.

**Background:** Angiogenin was originally identified as angiostatin binding proteins and implicated in the regulation of endothelial cell migration and tube formation. Recent studies have shown that Angiogenin plays a central role in tube junction maintenance via the development formed with ARHGAP17, which acts by regulating the uptake of polarity proteins at tube junctions. This study aimed to investigate the renal functions of Angiogenin with an Angiogenin knockout (Amot KO) rat model.

**Methods:** Using CRISPR/Cas9 system, we created an Amot KO founder rat with a 5 bp deletion in the coding region (p < 0.01). Pathological changes in the rat kidneys were examined.

**Results:** Increased urine albumin:creatinine ratio was found as early as 4 month age in the Amot KO rats. The ratio increased progressively with age and reached 547 ± 254.6 µg/mg in the 6 month old Amot KO rats, while the ratio is 150 ± 117.4 µg/ for the wild type control (p < 0.01). Pathological changes in the kidneys were systematically examined with H&E and PAS staining. While wild type control rats showed normal histology, glomeruli and tubules, prominent thickening of Bowman’s capsule, casts or crystal in distal tubule, thicker tubular basement membrane and hyperplastic epithelium as well as podocyte atypia can be seen in the 6 and 10 month old Amot KO rats. RNA-Seq results showed more than 300 differentially expressed genes including Smad7, Rac1 and pdd1. Analysis using IPA revealed altered effector pathways in glomerular injury, renal necrosis, and nephritis.

**Conclusions:** Amot appears to play important roles in regulating renal functions. Amot may exert its function through Rich1/Gap complex affecting activation status of Rho GTPases or via interactions with slit diaphragm and actin cytoskeleton proteins.

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

**FR-OR060**


**Background:** FSGS is the most common primary glomerular disorder causing in at least 4% of patients with ESRD. The current SOC includes renin-angiotensin-aldosterone (RAAS) inhibitors, steroids and/or immunosuppressants. Several lines of evidence support a role for chemokine receptor 2 (CCR2) positive monocyte/macrophages in the pathogenesis of FSGS, and inhibition of CCR2 provides a potential therapeutic treatment of FSGS.

**Methods:** Two murine models of FSGS, 5/6 nephrectomy and Adriamycin nephropathy were used to investigate the efficacy of either CCRI2 antagonist alone or its combination with RAAS inhibition. CCR1 and CCR2 expression was assessed by proteinuria (UAER), UACR, BUN, creatinine and histopathology.

**Conclusions:** This work demonstrates a clear role for the PAR-1 receptor in proteinuria, and strengthens the hypothesis that circulating factor(s) may act via this receptor. Additionally, this is a novel model for circulating factor NS, to test therapies in vivo.

**Funding:** Government Support - Non-U.S.
FR-OR061

A New Mouse Model of Chronic Proteinuria Due to a Glomerular Basement Membrane Laminin-521 Polymorphism Defect

Steven D. Funk, Raymond H. Bayer, Jeffrey H. Minor. Washington University School of Medicine, St. Louis, MO.

Background: The glomerular basement membrane (GBM) is a dense extracellular matrix that separates endothelium from podocytes. The GBM is thought to stabilize foot processes and slit diaphragms and, together with podocytes and endothelium, forms the glomerular filtration barrier. GBM integrity is maintained by: 1) polymerization of laminin α5β2γ1 (LM-521) via tripartite αβγ chain NHE2-enzymic LN domains; 2) attachment of the LM65 C-terminal LG domain to podocyte & endothelial cell integrins; and 3) linkage of the laminin network to the type IV collagen network by nidogen. Null and missense mutations in the LM62 chain of LM-521 cause nephrotic syndrome. In previous studies of Lamb2-/- mice proteinuria preceded both foot process effacement and loss of slit diaphragms. Thus, Lamb2LN domain missense mutations in nephrotic patients may cause disease by impairing laminin polymerization.

Methods: In vitro mutational editing was used to generate a point mutation in the LN domain of mouse LAMB2, but DNA analysis of 1 founder showed an unexpected in-frame, 44 amino acid deletion within the LN domain. Homozygous Lamb2-/- mice were observed for up to 8 months. Urine, blood, and tissues were taken at select time points to evaluate albuminuria, BUN, histopathology, and GBM composition and ultrastructure.

Results: The unexpected Lamb2-/- mutation is analogous to the dy-2 mutation in mouse Lmα2 that causes severe muscular dystrophy due to defective LM-211 polymerization. The GBM of LAMB2-/- mice contained a normal level of LAMB2, but the mice exhibited modest proteinuria between 4-6 wks of age and nephrotic range by 8 wks. Foot process swelling was observed at 6 wks of age, with effacement at 8 wks. LAMB2-/- mice died spontaneously from 4 months onward, but some lived over 8 months. Moderate glomerulosclerosis, tubular dilations, protein casts, and occasional immune infiltrates were commonly observed features.

Conclusions: LAMB2-/- mice exhibit modest proteinuria early but have intact foot processes. Chronic nephrotic range proteinuria is accompanied by effacement. This mutant gene editing approach is a novel and innovative method for strengthening our understanding of the GBM’s laminin network and reducing proteinuria. More generally, this new genetic model of nephrotic syndrome will be useful for investigating disease progression.

Funding: NIDDK Support

FR-OR062

The miRNA-29a to Claudin-1 Pathway Is an important Regulator of Glomerular Alumimun Permeability in Diabetic Nephropathy

Yongteng Gong,1,2 Gerald Jarad,2 Ming-Zhi Zhang,2 Raymond C. Harris,1,3,4,5 Janghui Hou,2,3 Vanderbilt University Medical Center, Nashville, TN; 2Vanderbilt University School of Medicine, Nashville, TN; 4Washington University School of Medicine, St. Louis, MO.

Background: Diabetic nephropathy (DN) is characterized by alteration in glomerular filtration barrier, which include thickening of the glomerular basement membrane (GBM), podocyte foot process effacement, reduced slit width and loss of slit diaphragm (SD). The disappearance of the SD is associated with the appearance of the tight junction (TJ) and is a hallmark of claudin-1 in podocytes, suggesting a previously unknown role for TJ in DN. Hyperglycemia has been shown to suppress the expression of miRNA-29 family members in podocytes, which is known to modulate the expression of claudin-1 and extracellular matrix (ECM). This data suggest that miRNA-29 family might play roles in the development of podocyte dysfunction and glomerular phenotype of DN.

Methods: We have generated a series of transgenic mouse models to study the role of claudin and microRNAs in diabetic nephropathy. We have generated podocyte specific overexpression of claudin-1 in tetracycline inducible manner. Using gene targeting approach, we have generated a miRNA-29a knockout mouse model in the kidney.

Results: Expression of miRNA-29a is downregulated in the podocytes from the db/db, db/eNO mice model of DN. In a knockdown of miRNA-29a, the innate regulator of claudin-1 and ECM in podocytes, resulted in progressive proteinuria, accompanied by deassembly of podocyte SD and thickening of the GBM, which are the hallmarks of DN. Mechanistically, such pathologic changes are derived from increased expression of claudin-1 and its paralog - claudin-4 in podocytes - collagen IV alpha34.5 and laminin beta2, all of which are direct targets of miRNA-29a. 3. Induction of claudin-1 gene expression in mature podocytes caused albuminuria. Using freeze fracture techniques, we confirmed the cell junction mediated by claudin-1 overexpression, which culminate in the transformation of podocyte SD into TJ. Immunolabeling of SD proteins revealed that claudin-1 overexpression destabilized the SD protein complex, which was a significant contribution and altered localization of neprhin and podocin.

Conclusions: Our data attest to a novel concept that a central signaling pathway from neprhin to claudin-1 may cooperatively regulate a wide spectrum of podocyte lesions important to DN. Such a pathway may lead to a new therapeutic approach to treat DN by manipulating microRNA expression.

Funding: NIDDK Support

FR-OR063

The Potential Significance of Complement Factor D Bypass in ID-Targeted Treatment for C3G

Yuzhou Zhang,1 Adam C. Keenan,2 Margaret A. Lindorfer,3 Carla M. Nester,4 Ronald P. Taylor,5 John Lambiris,3 Richard J. Smith,6 1University of Iowa, Iowa City, IA; 2University of Pennsylvania School of Medicine, Philadelphia, PA; 3University of Virginia School of Medicine, Charlottesville, VA.

Background: C3 glomerulopathy (C3G) is characterized by predominant deposition of immunoglobulins in the glomerulus in the absence of circulating immune complexes. The underlying disease mechanism is uncontrolled activity of the C3 convertase of the alternative pathway (AP). Convertase activity is normally tightly controlled by the fluid-phase AP regulator factor H (FH). Mice with a targeted deletion of Fc D (Cfd-) develop features of C3G, with intense C3 deposition along glomerular capillary walls accompanied by subendothelial electron-dense deposits. The rate-limiting protease, Fc D, is the only enzyme known to cleave C3. Several AP inhibiting small-molecule antagonists against Fc D have been developed.

Methods: To assess ID-targeted therapy, we backcrossed Cfd-/- mice with Cfd-/- mice for >10 generations and evaluated complement dysregulation and renal pathology in Cfd-/-, Cfd-/- mice and Cfd-/-, Cfd-/- mice. We developed an in vitro iB-cleavage assay using a recombinant protein that contains the active catalytic domain of mannose-binding lectin-associated serine protease protease 3 (MASP-3). Results: In vitro iB-activation and enhanced activity can be observed in Cfd-/- mice. Addition of the Cfd-/- mouse serum leads to increased AP activity and enhanced C3 deposition in renal glomeruli. The combination of Cfd-/- serum and MASP-3 further increases AP activity.

Conclusions: We confirmed the cell junction induced by claudin-1 overexpression, which culminate in the transformation of podocyte SD into TJ. Immunolabeling of SD proteins revealed that claudin-1 overexpression destabilized the SD protein complex, which was a significant contribution and altered localization of neprhin and podocin.

Funding: NIDDK Support

FR-OR064

Ex Vivo Formation of CSb9 on Endothelial Cells Differentiates Complement-Mediated Renal Failure from Hypertensive Nephrosclerosis

Yuzhou Zhang,1 Adam C. Keenan,2 Margaret A. Lindorfer,3 Carla M. Nester,4 Ronald P. Taylor,5 John Lambiris,3 Richard J. Smith,6 1University of Iowa, Iowa City, IA; 2University of Pennsylvania School of Medicine, Philadelphia, PA; 3University of Virginia School of Medicine, Charlottesville, VA.

Background: C3 glomerulopathy (C3G) is characterized by predominant deposition of immunoglobulins in the glomerulus in the absence of circulating immune complexes. The underlying disease mechanism is uncontrolled activity of the C3 convertase of the alternative pathway (AP). Convertase activity is normally tightly controlled by the fluid-phase AP regulator factor H (FH). Mice with a targeted deletion of Fc D (Cfd-) develop features of C3G, with intense C3 deposition along glomerular capillary walls accompanied by subendothelial electron-dense deposits. The rate-limiting protease, Fc D, is the only enzyme known to cleave C3. Several AP inhibiting small-molecule antagonists against Fc D have been developed.

Methods: To assess ID-targeted therapy, we backcrossed Cfd-/- mice with Cfd-/- mice for >10 generations and evaluated complement dysregulation and renal pathology in Cfd-/-, Cfd-/- mice and Cfd-/-, Cfd-/- mice. We developed an in vitro iB-cleavage assay using a recombinant protein that contains the active catalytic domain of mannose-binding lectin-associated serine protease protease 3 (MASP-3). Results: In vitro iB-activation and enhanced activity can be observed in Cfd-/- mice. Addition of the Cfd-/- mouse serum leads to increased AP activity and enhanced C3 deposition in renal glomeruli. The combination of Cfd-/- serum and MASP-3 further increases AP activity.

Conclusions: We confirmed the cell junction induced by claudin-1 overexpression, which culminate in the transformation of podocyte SD into TJ. Immunolabeling of SD proteins revealed that claudin-1 overexpression destabilized the SD protein complex, which was a significant contribution and altered localization of neprhin and podocin.

Funding: NIDDK Support

FR-OR065

Ex Vivo Formation of CSb9 on Endothelial Cells Differentiates Complement-Mediated Renal Failure from Hypertensive Nephrosclerosis in Severely Hypertensive Patients

Jordi Timmermans,1 Chris Reutelingsperger,2 Pieter V. Paassen,2,3 Maastricht University, Maastricht, Netherlands; 2Maastricht University Medical Center, Maastricht, Netherlands. Group/Team: Limburg Renal Registry.

Background: Severe hypertension (HTN) can induce renal failure due to hypertensive nephrosclerosis, a diagnosis rarely confirmed by biopsy assuming that the kidney is the victim rather than culprit of HTN. Underlying acute thrombotic microangiopathy (TMA), HTN therefore be missed, particularly in patients not presenting with microangiopathic hemolysis and thrombocytopenia. Moreover, it is critical to distinguish TMA due to shear stress from TMA dominated by complement dysregulation, having major impact on treatment and prognosis.

Methods: To differentiate complement-mediated HTN from shear stress-induced kidney injury in patients with severe HTN (blood pressure >180/120 mmHg) and renal failure, we analyzed serum-induced CSb9 formation on resting and ADP activated human microvascular endothelial cells (HMEC) by using samples from patients with severe HTN either with active TMA or hypertensive nephrosclerosis on kidney biopsy. Serum samples with typical hemolytic uremic syndrome (aHUS) and dense deposits disease (DDD) were used as positive and negative controls; all samples were compared with normal human serum run in parallel.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: Serum from 12 patients with HTN-associated TMA induced extensive C5b9 formation (49%) (p<0.01) and activated KCl (318%), Pod+ ECs and cells of renin lineage (podocyte, parietal epithelial cell (PEC)). Th17 cells were measured in TMA samples (n=3; 344% and 394%, respectively). In contrast, samples from 5 patients with hypertensive nephrosclerosis induced scanty C5b9 formation on both resting (98%, P=1.0) and activated HMEC (108%, P=0.7), identical to DCC (n=5; 89% and 90%, respectively). Detailed imaging on kidney sections linked complement activation to TMA but not to nephrosclerosis. Moreover, genetic analysis confirmed complement defects in 6 (50%) out of 12 patients with HTN-associated TMA.

Conclusions: In conclusion, intrarenal solid phase complement dysregulation and ongoing TMA appears the dominant cause of renal failure in a subset of patients with severe HTN. The HMEC test differentiates complement-mediated TMA from other causes of HTN associated kidney injury, such as shear stress.

FR-OR065 Stem Cell-Derived Extracellular Vesicles Protect from VEGF-Induced Glomerular Endothelial Damage in the Kidney Sargsi Sedrakyan,1 Valentina Villani,1 Stefano Da Sacco,1 Nikita Tripuraneni,1 Stefano Porta,2 Andrea Achen,1 Maria J. Lavarrada-Pearce,1 Astigik Petrosyan,1 Hasmik Soloyan,1 Roger E. De Filippo,1 Benedetta Bussolati,2 Laura Perin,1 1Children’s hospital Los Angeles, Los Angeles, CA; 2University of Torino, Torino, Italy

Background: Tight regulation of paracrine VEGF signaling between podocytes and glomerular endothelial cells (GEC) is required for maintenance of the glomerular filtration barrier structure and function. Disruption of VEGF signaling has been implicated in various types of glomerular diseases. However, current therapies neither specifically target the glomerulus nor the local VEGF but in addition, present multiple side effects. Therefore, identification of new approaches that will restore local VEGF signaling pathways and therapeutic targets for podocyte-related kidney disease is necessary. We previously showed that anamnetic fluid stem cells (AFSC) are reprogrammable in Alport Syndrome (AS), a model of CKD. They home within the diseased glomeruli and secrete extracellular vesicles (EVs). EVs play a key role in stem cell-mediated paracrine function, including the kidney. Herein, we demonstrate that AFSC derived EVs regulate VEGF/VEGFR2 signaling balance in AS GEC via a trapping mechanism involving VEGFR1 expression on the surface of EVs.

Methods: We measured VEGF activity in AS glomeruli by WB. We also assessed VEGF/EVGR1 activity in GEC. We characterized ASFEC-VGs cargo by FACS and by miRs arrays and evaluated their potential to affect VEGF biology in GEC and kidney function. EVs silenced for VEGFR1 were used to confirm VEGF trapping by VEGFR1.

Results: Glomeruli from AS mice at 3-months showed increased VEGF activity that was associated with GEC damage and subsequent onset of proteinuria. Treatment with EVs from AS mice improved the damaged kidney function and decreased levels of VEGF. We found VEGFR1, present on the surface of EVs, responsible for this mechanism of action. EVs lacking both the full and soluble VEGFR1-1 failed to rescue GEC from VEGF-induced damage.

Conclusions: We demonstrated for the first time the aberration of VEGF signaling within AS glomeruli. We further showed that ASFEC derived EVs play important role in maintaining glomerular homeostasis of VEGF signaling, presenting with a potential for new targeted therapies in CKD.

Funding: Private Foundation Support

FR-OR066 NG2 Lineage Cells Migrate onto the Glomerular Tuft and Bowman's Capsule with Expression of PEC Markers in Experimental FSGS Tahiha Suzuki,1 Jeffrey W. Pippin,1 Diana G. Eng,1 Stuart J Shankland,2 1University of Washington, Seattle, WA; 2Nephrology, University of Washington, Seattle, WA.

Background: Glomerular regeneration typically relies on local stem/progenitor cells. After podocyte loss, parietal epithelial cells (PECs) and cells of renin lineage serve as adult PEC stem/progenitors in glomerular disease. However, the majority of NG2 lineage cells that migrated to Bowman’s capsule served as PEC stem/progenitors in glomerular disease.

Conclusions: We observed that apoE knockout mice (Klf4Δ/Δ) were generated on a C57Bl6 background by crossing Klf4Δ/Δ mice with Podocin-Cre mice. Nephrotic serum (NTS) nephritis was used to induce RPNG. Klf4Δ/Δ mice were backcrossed to a background susceptible to FSGS (FVB/n). Finally, human podocytes with stable knockdown of KLF4 (KLF4-shRNA) and overexpression of KLF4 (lentORF-KLF4), with appropriate controls, were generated.

Results: Glomerular KLF4 expression was increased 7 days after NT. NTS-treated Klf4Δ/Δ (C57Bl6/n) mice exhibited increased crescent formation, parietal epithelial cell (PEC) proliferation (Claudin1, Ki67), serum creatinine, and STAT3 signaling (phospho-STAT3, p-Akt, Sox2 expression) as compared to NTS-treated wildtype mice. KLF4-deleted (Klf4Δ/Δ) (p/Akt) mice exhibited STAT3 activation, cellular FSGS with PEC proliferation, renal failure, and a 50% increase in mortality as compared to wildtype mice at 12 weeks of age. Furthermore, basal STAT3 activation was significantly increased in wild-type FVB/n as compared to the C57Bl6/n strain. Differentiated KLF4-overexpressing cells also exhibited increased STAT3 activation with mitotic catastrophe (entry into cell cycle, actin destabilization) leading to reduced survival as compared with EV-shRNA podocytes. Conversely, these changes were reversed with re-induction of KLF4 (lentORF-KLF4) in cultured podocytes.

Conclusions: Collectively these data suggest that KLF4 is a key regulator of STAT3-mediated aberrant GEC proliferation in RPN and FSGS.

Funding: NIDDK Support, Private Foundation Support

FR-OR067 Effects of the Potassium Binding Polymer Patiromer on Markers of Mineral Metabolism David A. Bushinsky,1 David M. Spiegel,1 Jinwei Yuan,2 Suzette Warren,3 Pablo E. Pergola,4 Division of Nephrology, University of Rochester Medical Center, Rochester, NY; 3Relypsa, Inc., a Vifor Pharma Company, Redwood City, CA; 4Renal Associates, PA, San Antonio, TX.

Background: Patiromer is a non-absorbed potassium (K)-binding polymer approved for treatment of hyperkalemia (HK), which uses calcium (Ca) as the counter-exchange ion. The 4-week TOURMALINE study in patients with HK demonstrated that patiromer once-daily (QD) reduces serum K when given without food similarly to when given with food. Here we report data from TOURMALINE on markers of mineral metabolism.

Methods: Initial patient dose was 8.4 g QD and was adjusted to achieve and maintain serum K between 3.8-5.0 mEq/L. In this pre-specified analysis, baseline and week 4 (wk) 4 serum and 24-hour urine (u) markers of mineral metabolism normalized for u-creatinine (Cr) excretion, to correct for collection errors, are reported for the overall population and mean serum P in patients with hyperphosphatemia, 2D both decreased. In the 16 patients with elevated serum P (>4.8 mg/dL) at baseline, PTH and 1,25(OH)2D without changing serum Ca. PTH and 1,25(OH)2D without changing serum Ca.

Conclusions: In addition to lowering serum K, patiromer decreased mean u-Cr excretion in the overall population and mean serum P in patients with hyperphosphatemia, while not changing mean u-Cr or mean serum Ca. PTH and 1,25(OH)2D without changing serum Ca.

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

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-OR069
Erythropoietin Is Associated with Total FGF23 Levels in Mice and Humans with CKD Mark R. Hanude,1 Maxime Rappaport,2 Victoria R. Gabayan2,3 Tomas Ganz,2 Elizaveta Nemeth,2 Isidro B. Salusky,2 1Department of Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, CA; 2Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA.

Background: We have previously demonstrated that exogenous erythropoietin (EPO) increases bone and circulating FGF23 levels in mice and humans with normal kidney function. It is unknown if EPO has similar effects on FGF23 in the setting of CKD.

Methods: We administered a single dose of EPO to wild type mice with adenine diet-induced CKD. We evaluated associations between serum EPO levels and circulating FGF23 in adult and pediatric non-dialysis CKD patients, and between recombiant human EPO (rhEPO) doses and circulating FGF23 in adult and pediatric dialysis patients.

Results: At six hours post-injection, compared to CKD mice injected with saline, CKD mice intraperitoneally injected with 70 µg/rhEPO demonstrated a 10-fold increase in bone Fgf23 mRNA expression and a 5-fold increase in plasma C-terminal (total) FGF23 (cFGF23) levels, but only a 3-fold increase in plasma intact FGF23 (iFGF23) levels, with a 40% decrease in percentage iFGF23 (iFGF23/total FGF23 x 100%). These data suggest that EPO-induced increases in FGF23 mRNA expression are coupled with increased FGF23 proteolytic cleavage. In 70 adult and pediatric non-dialysis CKD patients, after adjustment for eGFR (p=0.001) and phosphate (p=0.001), serum EPO levels positively associated with Log cFGF23 (std. coeff. 0.25, p=0.010; model adjusted R²=0.44). The association remained significant (p=0.003; model adjusted R²=0.42) after further adjustment for age, calcium, Log PTH, TSAT, Log ferritin, Hgb, Log CRP, none of which were independently associated with Log cFGF23. Unlike cFGF23, Log iFGF23 was not significantly associated with EPO levels. In 79 adult and pediatric dialysis patients, after adjustment for age (p=0.001), phosphate (p=0.001), calcium (p=0.013), Log CRP (p=0.015), and Log ferritin (p=0.018), Log rhEPO dose positively associated with Log cFGF23 (std. coeff. 0.23, p=0.013; model adjusted R²=0.44). The association remained significant (p=0.016; model adjusted R²=0.43) after further adjustment for Log PTH, TSAT, and Hgb, none of which were independently associated with Log cFGF23. Similar to the non-dialysis CKD patients, Log rhEPO dose was not significantly associated with Log iFGF23.

Conclusions: In CKD patients, erythropoietin has stronger associations with total FGF23 than intact FGF23, suggesting coupling of increased production with increased cleavage.

Funding: NIDDK Support, Other NIH Support - NIH Loan Repayment Program

FR-OR070
Ferric Citrate Administration Reduces FGF23 Production and Improves Renal Function in a Mouse Model of CKD Connor Francis,2 Guillaume Courbon,2 Samantha Neuburg,2 Claire Gerber,2 Xueyan Wang,2 Corey Duosold,1 Linxi Qi,3 Aline Martin,2 Myles S. Wolf,1 Valentim David.2 1Duke University, Durham, NC; 2Northwestern University - Feinberg School of Medicine, Chicago, IL.

Background: Elevated levels of fibroblast growth factor 23 (FGF23) are strongly associated with cardiovascular disease, mortality, and progression of chronic kidney disease (CKD). Hyperphosphatemia and iron deficiency are powerful stimuli of FGF23 production. This suggests that reducing dietary phosphate intake or absorption and increasing serum iron may lower FGF23 levels and improve clinical outcomes in CKD.

Methods: We tested the hypotheses that ferric citrate treatment will simultaneously correct iron deficiency and also bind to dietary phosphate in the Col4a5−/− mouse model of diet-induced CKD. We fed 4-week-old wild-type (WT) and Col4a5−/− (CKD) mice, a control (Ctrl) or a 5% Ferric Citrate enriched (FC) diet for 6 weeks and performed biochemical, molecular and histological analyses.

Results: At 6 weeks, Ctrl-CKD animals displayed a decline in renal function, as shown by a 8% increase in Blood Urea Nitrogen (BUN) and a 52% increase, sign of iron deficiency anemia, evidenced by low serum iron (99±12 vs 128±5 mg/dL) and hemoglobin (15±1 vs 19±1 g/dL), as well as a 2 fold increase in serum phosphate (p=0.05 vs WT). This was concomitant with a marked increase in both total (FGF23, which includes intact and cleaved proteins) and intact FGF23 (iFGF23) serum levels, compared to WT (1142±623 vs 433±32 and 731±2749 vs 207±57 µg/mL, respectively, p<0.05). In addition, serum 1,25 Vitamin D levels were low (34±7 vs 143±45 µg/mL) in Ctr-CKD animal (p=0.05, vs. Ctrl-WT). Ferric citrate increased serum iron levels by 1.6 fold in CKD mice and resulted in a 5.5 fold serum phosphate reduction (p=0.05, vs. Ctrl-WT). In addition, iFGF23 and FGF23 were reduced by 4 and 3 fold respectively and serum 1,25 Vitamin D levels increased by 2 fold in FC-CKD mice (p=0.05 vs. Ctrl-CKD). Interestingly, the FC diet also decreased BUN (127±21 vs 216±24 mg/dL) and 24h urine albumin (101±69 vs 586±49 µg) (p<0.05 vs. Ctrl-CKD). Reductions in intestinal fibrosis and tubular dysuphoria were also evident by histology in FC-CKD animals compared to Ctrl-CKD group.

Conclusions: Our data show that ferric citrate administration in CKD mice reduces the burden of FGF23 increase and slows disease progression. This suggests that ferric citrate might mitigate renal injury.

Funding: Commercial Support - Keryx Biopharmaceuticals

FR-OR071
Occurrence of Hypophosphatemia Following IV Iron Treatment: Results from a Randomized Controlled Trial Myles S. Wolf,1 William Strauss,2 Kristine Bernard,3 Naomi V. Dahl,1 Robert F. Kaper,1 Julie S. Krop.1 1AMAG Pharmaceuticals, Inc., Waltham, MA; 2Duke University, Durham, NC.

Background: Hypophosphatemia is a common complication of administration of certain IV iron. For example, 32.1% of patients with gastrointestinal disorders who received treatment with ferric carboxymaltose (FCM) developed hypophosphatemia, <0.6 mmol/L (1.5 mg/dL) (Schafer et al., PLoS ONE 2016). Acute increases in circulating levels of intact fibroblast growth factor 23 (FGF23) mediate hypophosphatemia due to renal phosphate wasting in response to FCM, but not iron dextran, suggesting that the specific carbohydrate moieties might be involved in the differential FGF23 response to IV iron (Wolf et al., Bone Min Res, 2013). While initially considered a transient and benign laboratory finding, reports are accumulating of significant clinical sequelae associated with chronic FCM-associated hypophosphatemia.

Methods: In a large RCT (NCT026949978) that compared the safety and efficacy of standard courses of ferumoxylot (FER, 510mg x 2 doses; N=997), vs. FCM (750mg x 2 doses; N=1000) in patients with iron deficiency anemia of any etiology except dialysis-dependent CKD, we measured serum phosphate and fractional excretion of phosphate (FEPi) at baseline, day 9 (prior to dose 2), week 2 and week 5.

Results: Mean baseline serum phosphate was 1.22 mmol/L (3.8 mg/dL) and FEPi was 15.7% in both groups. Among patients receiving FCM, serum phosphate decreased significantly, and FEPi increased significantly at all time points compared to ferumoxylot-treated patients (P<0.0001; Figure). Serum phosphate <0.6 mmol/L (1.9 mg/dL) occurred in 38% of FCM patients, and only 0.4% of FER patients.

Conclusions: FCM induced a marked drop in blood phosphate occurring as soon as 8 days following 750mg of FCM secondary to a significant increase in FEPi. Almost 40% of patients developed at least moderate hypophosphatemia. These changes did not occur following FER.

Funding: Commercial Support - AMAG Pharmaceuticals, Inc.

FR-OR072
Cardiac Hypertrophy Elevates Serum FGF23 Karin Shimada, Isao Matsui, Tatsufumi Oka, Daisuke Mori, Nobuhiro Hashimoto, Ayumi Matsumoto, Satoshi Yamaguchi, Keiichi Kubota, Sayoko Yonemoto, Yusuke Sakaguchi, Takayuki Hamano, Yoshitaka Isaka. Osaka University Graduate School of Medicine, Suita, Japan.

Background: FGF23 is a potent phosphaturic hormone predominantly produced by the bone. Although several studies have revealed FGF23 induces left ventricular hypertrophy (LVH), effect of LVH on FGF23 remains uncertain.

Methods: The activation of calcineurin/NFAT pathway plays pivotal roles in the development of pathological LVH. Therefore, we performed experiments using cardiomyocyte-specific calcineurin A transgenic (TG) mice.

Results: The TG mice at 6-week-old showed severe LVH. Body weight, systolic blood pressure, food intake, water intake, urinary volume, and creatinine clearance were not different between wild type (WT) and the TG mice. We found that serum intact FGF23 (iFGF23) in the TG mice were elevated (TG 125.6 ± 6.1 vs. WT 87.5 ± 10.1 pg/mL, P=0.0107). Both real time PCR and immunohistochemistry revealed that the elevation of iFGF23 in the TG mice was derived from hypertrophic cardiomyocytes but not from the bone. The promoter region of the FGF23 gene contained two putative NFAT-binding sites. Luciferase assay showed that NFAT1 activates the promoter in a proximal NFAT-binding site dependent manner. Although serum level of iFGF23 was elevated in the TG mice, all parameters — serum, urinary, and fractional excretion of calcium/phosphate, and serum 1,25(OH) vitamin D — were not different between the WT and the TG mice. Renal levels of α-klotho were also at comparable levels between the two groups. We found that plasma ADH levels in the TG mice were higher than those of the WT mice (TG 1.01 ± 0.68 vs. WT 0.40 ± 0.46 pg/mL, p=0.0396). To investigate the effects of ADH on the function of FGF23, we injected ADH and/or FGF23 into WT mice. As previously reported, FGF23 suppressed renal mRNA levels of CYP27B1. The suppression of CYP27B1 was restored by ADH. In addition, FGF23-dependent elevation of CYP24 was suppressed by ADH. Both FGF23 and ADH did not affect expression levels of α-klotho in the kidney.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
Conclusions: Hypertrophic cardiomyocyte produces FGF23. Proximal NFAT-binding site in the FGF receptor is important for the transcriptional regulation of FGF23. ADH causes FGF23-resistance in the kidney.

Funding: Private Foundation Support

FR-OR073

Different Outcome of Cardiac Remodeling in Two Mouse Models with FGF23 Excess and Klotho Deficiency

Beatrice Richter,1 Melis Basaran,2 Ioana Alesutan,2 Jakob Voelkl,4 Florian C. Lang,1 Dieter Haffner,1 Maren Leifheit-Nestler. 2 Department of Cardiology, Vascular Medicine and Physiology, University of Tuebingen, Tuebingen, Germany; 2 Department of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany; 3 Department of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany; 4 Department of Internal Medicine and Cardiology, Center for Cardiovascular Research, Charité University Medicine, Berlin, Germany; 1 Department of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany; 6 Department of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany

Background: High levels of fibroblast growth factor-23 (FGF23), phosphate and parathyroid hormone (PTH) as well as deficiency in active vitamin D (1,25D) and klotho are strongly associated with the development of cardiovascular disease, including left ventricular hypertrophy and myocardial fibrosis. In vivo, klotho and 1,25D improve cardiac hypertrophy and in vitro, klotho inhibits fibroblast activation and collagen synthesis in the heart and protects against FGF23-induced oxidative stress.

Methods: Heart tissue from two mouse models with high FGF23 serum levels and klotho deficiency was analyzed: 1) klotho hypomorph (K/-) mice displaying both high phosphate and 1,25D levels, but low PTH; 2) Hyp mice presenting high PTH, but low plasma levels of phosphate and 1,25D. Results: For both mouse models an enhanced relative heart weight and raised cross-sectional area of cardiomyocytes were detected when compared to respective wild type controls. In K/- mice, a clear increase of cardiac Fgf23, Fgf4, activation of calcineurin/ NFAT signal transduction and inhibition of pro-inflammatory genes Rcan1, Lcn2 and HMGB1 was seen. Furthermore, K/- mice showed an enhanced expression of transcription factors (Celpb4, Gata4) and fibrosis-related factors (Tgfb1, collagen 1, Mmp2) that are involved in cardiac remodeling events. In contrast, Hyp mice presented a strong increase of cardiac Fgf23 mRNA and intact cardiac Fgf23 protein as well, but missed the induction of the Fgf4/calcineurin/NFAT pathway. Moreover, the expression of the pro-hypertrophic markers BNP, ANP, HMC and pro-fibrotic factors was absent in Hyp mice.

Conclusions: Despite the FGF23 excess, high PTH, low 1,25D and reduced klotho, it seems that Hyp mice mice are protected from the development of pathological heart changes may be due to hypophosphatemia. Contrary, K/- mice show induced cardiac hypertrophy and fibrosis though high 1,25D plasma levels.

FR-OR074

Fibroblast Growth Factor 23 (FGF23) Regulates PTH Levels through FGF Receptor Signaling In Vivo at Normal, but Not at Low, Plasma Calcium

Maria L. Mace,1 Eva Gravesen,1 Anders Nordholm,2 Jacob Hofman-Bang,1 Klaus Olgaard,1 Ewa Lewin,1 Copenhagen University, Copenhagen, Denmark; 2 Herlev Hospital, Herlev, Denmark; 3 Rigshospitalet, Copenhagen, Denmark

Background: The regulation of PTH secretion is primarily mediated by calcium. FGF23 is a bone derived phosphatonin that requires klotho as a co-receptor for binding to the FGF receptors (FGFR). Parathyroid cells express both Klotho and FGFRs, however, the physiological function of FGF23 in the parathyroid gland is not fully clarified. Parathyroid cells lose rapidly their calcium-sensing responsiveness ev vivo, and no functional parathyroid cell line has been established. Therefore the aim of the present investigation was to study FGF23’s regulation of PTH levels in vivo.

Methods: Wistar rats were randomized to FGF23 injection by PiD17304 (20-40mg) or vehicle. Acute hypocalcemia was induced by a continuous intravenous EGTA infusion (40mM, 3m/h) in normal rats and rats after prior FGF23 inhibition. Increasing doses (0.1, 1, and 10 µg) of recombinant FGF23 were given to normal rats and rats after prior FGF23 inhibition. Plasma Ca⁺, phosphate, FGF23 and PTH were measured.

Results: Acute inhibition of FGF23 resulted in a decrease in p-FGF23 (36.4±22 to 154±18 pg/ml, p<0.05) and a concomitant increase in PTH levels (154±54 to 685±285 pg/ml, p<0.01). The PTH secretory response was challenged by acute severe hypocalcemia (p-Ca⁺ from 1.37±0.01 to 0.98±0.03 mmol/l, p<0.01). Again at normocalcemia PTH increased in FGF23 inhibited rats (85±13 to 182±10 pg/ml), while the maximal PTH secretion at low p-Ca⁺ was not different in FGF23 inhibited rats compared to vehicle treated rats (35±7 to 61±9 pg/ml, p>0.05). Exogenous FGF23 0.1 µg inhibited rats for 20 min, PTH levels in normal rats (137±71 to 10±9 pg/ml, p<0.05). In FGF23 inhibited rats 0.1 µg FGF23 did not suppress PTH levels (275±50 vs. 374±62 pg/ml). Higher doses of FGF23 resulted in very high levels of p-FFG23 (12,000 & 120,000 pg/ml), still these high levels had no effect on PTH levels when the FGF23 was inhibited.

Conclusions: FGF23 regulates PTH tonus in vivo via the FGF receptor. The inhibitory effect of FGF23 on PTH is present at normal range of plasma Ca⁺, but not at low Ca⁺ levels, when increased PTH secretion is needed.

Funding: Government Support - Non-U.S.

FR-OR075

Acute and Mid-Term Mineral Disturbances Following Kidney Donation

Kenneth Lim,1 Jane C. Smith,1 Carmel M. McEniery,1 Laurie A. Tomlinson,1 Ian Wilkinson,4 Thomas F. Hiemstra,3 1Division of Nephrology, Massachusetts General Hospital, Harvard Medical School, Boston, MA; 4London School of Hygiene and Tropical Medicine, London, United Kingdom; 2University of Cambridge, Cambridge, United Kingdom; 3School of Clinical Medicine, University of Cambridge, Cambridge, United Kingdom

Background: Unilateral nephrectomy performed for live transplant donation is increasing due to a greater demand for available organs. To counteract the growing transplant waiting list, the opportunity to donate organs has been extended to a broader population. However, these expanded criteria donors (ECDs) may be at greater risk from a fall in GFR following unilateral nephrectomy. While emerging studies have demonstrated profound mineral disturbances that occur following kidney donation, whether acute disturbances in mineral homeostasis occur following unilateral nephrectomy is currently unknown.

Methods: We conducted the KARMA (Effect of Kidney Donation on Bone and Mineral Metabolism) study, a prospective controlled observational cohort study. Biochemical parameters were determined before and acutely after kidney donation on days 1-3 with mid-term follow-up at 6 weeks and 12 months in the donor group and at baseline, 6 weeks and 12 months in the control group.

Results: We enrolled 34 donors (59% male) and 34 healthy controls (47% male). Both groups had similar characteristics: mean (±SD) age (53±10 vs 50±14 years, p=0.33), BMI (26±2.8 vs 25±9.7, p=0.59), systolic BP (128±13 vs 130±6, p=0.59), diastolic BP (80±6 vs 81±9, p=0.68) and baseline GFR (84±4.2 vs 82±3.6±5 ml/min/1.73m², p=0.25). No renal donation induced Rcan1 and hydroxyapatite conversion.

Conclusions: Despite the FGF23 excess, high PTH, low 1,25D and reduced klotho, acute mineral disturbances in phosphate and calcium occur independently of changes in the phosphate hormonal axis. PTH and FGF23. Serum α-Klotho levels decline acutely following unilateral nephrectomy.

Funding: Private Foundation Support

FR-OR076

Quantitative Systems Pharmacology (QSP) Model of Metabolic Bone Disease in ESRD

Michael E. Brieg,1 Matthew J. Graves,1 Eleanor D. Lederer,2 Adam E. Gaweda,1 1University of Louisville, Louisville, KY; 2University of Louisville; Robley Rex VA Medical Center, Louisville, KY

Background: Metabolic bone disorder (MBD), a universal complication of chronic kidney disease (CKD), is a recognized contributor to the accelerated mortality of CKD patients but achieving established goals for therapy is challenging. We tested the hypothesis that a QSP model of MBD-CKD could provide a precision medicine tool to guide pharmacologic interventions for MBD.

Methods: We modified the Peterson-Riggs (Bone 2010) model of phosphate (PO4), calcium (Ca), PTH, and Calcitriol (CTL) in CKD to apply to end-stage renal disease patients. The model consists of a set of nonlinear differential equations describing the regulation of serum PO4, Ca, PTH, and Calcitriol (CTL) implemented in Matlab, and includes the effect of intermittent hemodialysis and the administration of phosphate binders, cinacalcet, and vitamin D analogs. We tested the model by simulating the administration of different agent dosages on end-stage renal disease patients and identified key model components. Data were obtained from in-center dialysis patients at the University of Louisville.

Results: The QSP model accurately predicts the concentration time profile of PTH following repeated administration of cinacalcet and CTL and the impact of intermittent hemodialysis on the serum concentrations of Ca and PTH. Sensitivity Analysis results for the top 5 100 parameters along with the contribution of each of the individual components are shown. The table entries represent the correlation between the model parameters and goodness of fit for an individual patient. The model is most sensitive to flux of PO4, lesion volume, excretion, and Ca on PTH production and hydroxyapatite conversion.

Conclusions: We conclude that a QSP model of MBD-CKD accurately predicts the serum concentrations of PO4, Ca, PTH, and CTL and that these predictions are heavily influenced by PO4 flux, PO4 excretion sensitivity, and availability of Ca.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author. 56
FR-OR077

FGF23 Trajectories Among Patients Undergoing Chronic Hemodialysis in the HEMO Study. Anna J. Jovanovich, Zheng Zhou, Kricki L. Nowak, Lilia Cervantes, Tamara Cervantes, Myles S. Wilf, Michel Trouilloud, Jessica B. Kendrick. 1Denver Health, Denver, CO; 2Denver VA / University of Colorado, Denver, CO; 3Duke University, Durham, NC; 4Feinberg School of Medicine, Northwestern University, Chicago, IL; 5UC Denver, Aurora, CO; 6University of Colorado Denver and Denver Health Medical Center, Denver, CO; 7University of Colorado Denver: Anschutz Medical Campus, Aurora, CO.

Background: Single measurements of elevated circulating levels of fibroblast growth factor 23 (FGF23) are associated with all-cause mortality in patients with end stage kidney disease (ESKD). However, long-term patterns in FGF23 levels have been poorly characterized. The objective of this study was to identify common FGF23 trajectories in patients with ESKD, and to evaluate predictors and outcomes among trajectories.

Methods: We identified 5 distinct FGF23 trajectories during the initial 2 years of the HEMO study: low-stable (16.8%; n=154), moderate-increasing (17.3%; n=159), elevated-increasing (27.5%; n=253); elevated-stable (25.4%; 233) and moderate-decreasing (13.1%; n=120). The only predictors of the moderate decreasing trajectory versus the low-stable trajectory were lower serum calcium (OR: 0.95; 95% CI 0.90-0.99, p=0.007) and higher calcium-phosphate product (OR: 1.03; 95% CI 1.02-1.05, p=0.001). The objective of this study was to identify common FGF23 trajectories in patients undergoing hemodialysis and very high FGF23 trajectories are associated with an increased risk of death. Lower serum calcium and interleukin-6 appear to be important predictors of decreasing FGF23 levels.

Funding: NIDDK Support

FR-OR078

Athena Study Outcomes on Allograft Function after 12 Months with Everolimus-Based versus Tacrolimus-MPA Regimen in De Novo Renal Transplant Recipients Friedberg, Stephen, Barbara M. Scalbert, Claudia Sommerer, Duska Dragaun, Ingeborg A. Hauser, Peter Schenker, Oliver Witzke, Christian Hugo, Nassim Kamar, Pierre Merville, Martina Jung, Bjorn Nashan, Benzard, Christoph, Novartis Pharma GmbH Germany, Nuremberg, Germany; PELLEGRIN HOSPITAL, Bordeaux, France; Ruhr-University Bochum, Bochum, Germany; University Hospital, Toulouse, France; University Duisburg-Essen, Essen, Germany; University Hospital, Hamburg, Germany; University Hospital Charite, Campus Virchow, Berlin, Germany; University Hospital of Heidelberg, HEIDELBERG, Germany; University of Dresden, Dresden, Germany, Dresden, Germany. Group/Team: Athena Study Group.

Background: The ATHENA study was designed to compare efficacy, safety and outcomes on renal function [GF] of everolimus [EVR] combined with tacrolimus [TAC] or cyclosporine A [CyA] vs. a standard regimen of mycophenolic acid [MPA] + TAC in de novo renal transplant recipients.

Methods: In this 12 months [M], prospective, randomized study with 15 German and 12 French sites, 612 patients [pts] were randomized 1:1:1 at time of Tx to either EVR (3-6ng/ml M1-M2) + TAC (4-8ng/ml M1-M3; 5-8ng/ml M1-M2) or EVR (3-8ng/ml M1-M12) + CyA (75-125mg/ml M1-M3; 50-100mg/ml M1-M12) or control TAC (4-8ng/ ml M1-M3; 3-5ng/ml M3-M12) + MPA. Steroids were to be continued. Here we report M12 outcomes on allograft function from IFT full analysis set with 208 EVR/ TAC vs 199 EVR/ CyA vs 205 TAC/ MPA pts.

Results: From rnd to M12 allograft recovery was good in all 3 treatment groups with increase in GFR (Nankivel) as AcEVR/M1-M2: a) EVR + TAC -6.6ml/min, b) EVR + CyA +9.6ml/min, c) TAC/MPA +7.6ml/min (not significantly different). Analysis of donor age categories [-35; 35-49; 50-64; >65 years] showed that donor age >65years had worst allograft outcomes, regardless of treatment. Urinary protein excretion at M12 was different between groups with a category analysis showing only 3.7% of TAC+MPA vs 1.3% of EVR+ vs 0.7% of CyA+EVIR pts had proteinuria in nephrotic range [>339mg/mmol] at M12.

Conclusions: ATHENA, the largest European KT study, showed comparable incidence in renal allograft function among all treatment groups with no difference in measured urinary protein excretion after 12 Mo drug exposure. Strongest impact on post Tx GFR appears to be determined by donor age, which is shown here for the first time in a large prospective study.

Funding: Commercial Support - Novartis Pharma GmbH, Germany

FR-OR080

Donor-Derived Cell-Free DNA Improves DSA-Informed Diagnosis of ABMR in Kidney Transplant Patients

Methods: Patients with primary kidney transplants performed between 2007 and 2015 were included. Patients were classified as having either zero HLA-DQ MM, one or two HLA-DQ MM. Primary outcomes were death-censored graft survival (DCGS), and incidence of acute rejection.

Results: Among 95,664 patients were included in the analysis, with median follow-up time of 3.45 years. Of these, 22,379 (23.39%) and 73,294 (76.61%) received zero and one or two HLA-DQ MM kidneys, respectively. After adjusting for HLA-ABDR, various recipient and donor variables and initial immunosuppression, HLA-DQ MM was associated with an increased risk of graft loss in living donor transplant (LDKT) recipients with an adjusted hazard ratio (HR): 1.42 (95% CI 1.01-1.93) in LDKT, but not in deceased donor kidney transplant (DDKT) recipients (HR 1.07, 95% CI, 0.99-1.53; p=0.066).

Conclusions: HLA-DQ mismatching is a predictor for graft survival and acute rejection independent mismatching of HLA-ABDR and initial immunosuppression. Cold ischemic times of longer than 17 hours appear to obviate the benefit of zero HLA-DQ MM.

Funding: Commercial Support - CareDx, Brisbane, CA

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

57
The primary diagnosis for 2410 consecutive indication and SOC renal transplant biopsies are plotted together on a logarithmic timescale after transplantation.
Increased Expression of the Co-Inhibitors PD-1 and BTLA on CMV-Specific T-Cells Is Associated with Symptomatic CMV Infection in Renal Transplant Patients

Oliver Witzke.1 Sebastian Erdel.1,2 Katrin Blaut.3 Siegfried Wagner.1 Jan H. Braesen.1 Verena Broecker.1 Vivette D. D’Agati.1 Cinthia Drachenberg.1 Evan A. Farkash.2 Alton B. Farris.3 Laurette Geldenhuys.4 Volker Nickeleit.5 Parmeet S. Randhawa.6 Heinz Regele.1 Michael Mengele.7 Columbia University College of Physicians and Surgeons, New York, NY; 8 Sahlgrenska University Hospital, Gothenburg, Sweden; 9 Emory University, Atlanta, GA; 10 Medical University of Vienna, Vienna, Austria; 11 Medizinische Hochschule Hannover, Hannover, Germany; 12 Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada; 13 The University of North Carolina at Chapel Hill, Chapel Hill, NC; 14 University of Alberta, Edmonton, AB, Canada; 15 University of Maryland School of Medicine, Baltimore, MD; 16 University of Michigan, Ann Arbor, MI; 17 University of Pittsburgh, Pittsburgh, PA.

Background: Cytomegalovirus (CMV) infections occur frequently in renal transplant patients due to immunosuppressive therapy inhibiting CMV-specific T-cell immunity. Prophylaxis with antiviral agents or preemptive strategies to monitor viral load and then treat do not prevent infections sufficiently. It was the aim of this study to investigate if the expression of inhibitory molecules on CMV specific T-cells is associated with the clinical course of renal transplant patients.

Methods: 30 renal transplant patients were recruited. Peripheral blood was sampled and stimulated with CMV lysate, SEB or control serum. The coinhibitors PD-1 and BTLA expression was determined on CMV-specific T-cells. Clinical data was collected retrospectively from patient files. Symptomatic CMV infection was defined as detectable CMV replication in peripheral blood and absence of signs indicating CMV syndrome/tissue invasive disease. Asymptomatic CMV infection was defined as detectable CMV replication in peripheral blood and absence of signs indicating CMV syndrome/tissue invasive disease.

Results: Two renal transplant patients were at low risk for CMV infection according to donor/recipient CMV IgG sero-status at the time of transplantation (D neg / R neg). Seven patients had a high risk according to sero-status (D pos / R neg) and the remaining 21 patients were confined to the intermediate risk group (D pos R pos or D neg / R pos). Patients with low risk were excluded for further analysis. PD-1 expression was significantly enhanced on CMV-specific CD3+ T-cells in patients with a history of symptomatic CMV infection (n=6) as compared to patients with asymptomatic CMV infection (n=14) (CD3+CD154+% of PD-1+ 63.8 ±16.0% vs. 37.2 ±19.4%, p=0.006). Likewise, expression of BTLA on CMV-specific T-cells was significantly increased in patients with symptomatic versus asymptomatic CMV infection (CD3+CD154+% of BTLA+ 89.3 ±29.5% vs. 66.0 ±22.0%, p=0.005).

Conclusions: Patients with symptomatic CMV infection had enhanced expression of PD-1/BTLA on virus-specific T-cells. The coinhibitors PD-1/BTLA usually promote T-cell suppression. Therefore, increased expression of PD-1/BTLA on CMV-specific T-cells may compromise viral control and could serve as biomarker to stratify patients at risk.

Comparison of Outcomes after DAA Therapy among HCV Infected Kidney Transplant Recipients Who Received Grafts from Either HCV Positive or Negative Donors

Camillo Cortesi1, Paul Martin,2 David Roth3, Kalyan R. Bhamidimarri4,5 University of Miami, Miami, FL; 6 University of Miami Miller School of Medicine, Miami, FL; 7 University of Miami/Jackson Memorial Hospital, Miami, FL.

Background: Direct acting antivirals (DAA) have transformed hepatitis C virus (HCV) treatment. In the kidney transplant (KT) setting, HCV-infected patients (R+) can now receive deceased donor KT (DDKT) from HCV positive donors (D+) and undergo treatment in the post-transplant period. However, a few cases of rejection have been reported in this HCV D+R+ cohort. We sought to compare outcomes among R+ receiving grafts from HCV negative donors (D-) versus D+.

Methods: This is a case series of 39 KT recipients of which 14 R+ have been transplanted with a kidney from D- and the rest from D+. All patients completed a full course of DAA. Time to transplantation, efficacy of DAA therapy, rejection episodes, tacrolimus dose adjustments, and renal function were assessed in both groups.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
FR-OR089

Effect of SGLT-2 Inhibitors to Proximal Tubular Function and Injury in Patients with Type 2 Diabetes: A Randomized Controlled Trial Patharaman Korkiapitak,1 Bancha Satirapoj,2 Naowan Nata,2 Amnart Chaiprasert,3 Pimhana Tasanavipas,4 Theerasak Tangwongler,5 Ouppatham Supasyndh,1 Phramongkutklao Hospital, Pathumthani, Thailand; 2Phramongkutklao hospital, Bangkok, Thailand; Group-Team: phramongkutkla.

Background: Intensive glucose control reduces the risk for microvascular complications in type 2 diabetes (T2DM). Recently, sodium-glucose co-transporter 2 (SGLT2) inhibitors have the potential to exert renoprotection beyond glycemic control, the effects of SGLT2 inhibitors on the organs are not well known. There is limited data of SGLT2 inhibitors on biomarkers of kidney injury in T2DM patients.

Methods: T2DM patients with persistent HbA1c >7% randomly assigned to add dapagliflozin 10 mg/day or standard treatment for 12 weeks. Proximal tubular injury biomarkers including urine kidney injury molecule-1 (KIM-1), urine cystatin-C, urine albumin to creatinine ratio (UACR), fraction excretion of phosphate (FEPO4) and uric acid (FEURic) were measured at baseline and the end of study.

Results: Patients were randomized to receive dapagliflozin (N=28) and control (N=29). Baseline characteristics were comparable across treatment groups. After 12 weeks, dapagliflozin-treated versus standard-treated patients showed reductions in HbA1c (-0.75 ± 0.21 vs -0.07 ± 0.25 %, p-value=0.882), fasting plasma glucose (-15.99 ± 8.26 vs -11.07 ± 8.71 mg/dL, p-value=0.481) and serum uric acid -0.06 ± 0.18 vs 0.18 ± 0.12 mg/dL). There were significant between-group differences in the reduction of UACR (-3.31 ± 10 vs 19.88 ± 11.54 mg/cmp, p-value=0.010) and urine KIM-1 to creatinine ratio (-2.70 ± 98.2 vs 422.19 ± 181.05 mg/cm, p-value=0.036), but no significant in changes of urine cystatin-C to creatinine ratio between two groups. There was no significant change of glomerular filtration rate, serum phosphorus, FEURic and FEPO4 in the dapagliflozin. No serious renal-related adverse events were observed in any group.

Conclusions: This study indicates that dapagliflozin in T2DM patients can decrease urinalysis proximal tubular biomarkers which refer to nephroprotective effects. SGLT2- Inhibitors may be useful in treating T2DM for protect renal tubular injury and may lead to a reduced long-term renal outcome.

Funding: Other NIH Support - This study was supported by a grant from the National Science and Technology Development Agency (NSTD, P-13-00505), Bangkok, Thailand.

FR-OR090

Effect of the SGLT-2 Inhibitor Dapagliflozin on Glomerular and Tubular Injury Markers Claire Dekkers,1 Serge Petrykiv,1 Goezijwijn D. Laverman,2 Ron T. Gasnevoort,3 Hiddo J. Lambers Heerspink,4 None, Groningen, Netherlands; 1ZGT Almelo, Almelo, Netherlands; 2UMC Groningen, Groningen, Netherlands; 3University Medical Center Groningen, Groningen, Netherlands.

Background: Sodium-glucose co-transporter 2 (SGLT2) inhibitors have been shown to delay progression of kidney function decline in type 2 diabetes. However, an FDA communication reported potential risk of acute kidney injury (AKI) particular during the first weeks of treatment, potentially due to tubular injury. Here we assessed effects of the SGLT2 inhibitor dapagliflozin (DAPA) on markers of subclinical tubular injury.

Methods: Data was used from a randomized controlled cross-over trial in 33 patients with type 2 diabetes and albuminuria ≥100 mg/g designed to assess the safety and tolerability of dapagliflozin 10 mg/day for 6-weeks treatment. Patients were randomly assigned to receive dapagliflozin (group DAPA) or placebo (group P) for 6 weeks and then crossed over between these groups.

Results: Compared to placebo, DAPA decreased IgG and IgG4 excretion, but did not change the glomerular charge selectivity index (table 1). Compared to placebo, DAPA decreased urinary KIM-1 excretion, whereas no change in NGAL and LFAFB was observed. The inflammatory marker IL-6 significantly decreased during DAPA therapy. DAPA also decreased albuminuria (36.2% [95%CI 22.9, 47.2]) and eGFR (5.3 ml/mint 1.73m2 [8.0, 2.7]). Albuminuria tended to correlate with eGFR change during DAPA therapy (p=0.06). Tubular injury markers did not correlate with change in eGFR. Changes in IgG, MCP-1 and IL-6 significantly correlated with change in albuminuria (all p<0.02).

Conclusions: DAPA lowers urinary excretion of glomerular and tubular injury markers as well as inflammation markers. These data indicate that the fall in eGFR after start of dapagliflozin reflects a hemodynamic response and not (subclinical) tubular injury.

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

Table 1

<table>
<thead>
<tr>
<th>Injury markers</th>
<th>Mean change % from baseline compared to placebo (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>-28.4 (-42.6, -4.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>IgG4</td>
<td>-34.3 (-50.3, -18.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>KIM-1</td>
<td>-22.6 (-33.6, -3.8)</td>
<td>0.05</td>
</tr>
<tr>
<td>NGAL</td>
<td>-13.1 (-33.6, 18.6)</td>
<td>0.53</td>
</tr>
<tr>
<td>LFAFB</td>
<td>0.9 (-12.4, 13.2)</td>
<td>0.91</td>
</tr>
<tr>
<td>MCP-1</td>
<td>-23.1 (-44.0, -0.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>MCP-2</td>
<td>-18.4 (-32.8, 8.0)</td>
<td>0.20</td>
</tr>
</tbody>
</table>
**FR-OR091**

Effect of the SGLT2 Inhibitor Dapagliflozin in Patients with Type 2 Diabetes and Stages 3b-4 CKD

David C. Wheeler, Claire Dekkers, David Sjostrom, Bergur V. Stefansson, Valerie Cain, Hiddo J. Lambers Heerspink, Astrazeneca, Molndal, Sweden; AstraZeneca LP, Molndal, Sweden; University College London, London, United Kingdom; University Medical Center Groningen, Groningen, Netherlands; Bogert Clinical and IT Solutions, Inc, Haddonfield, NJ.

**Background:** Dapagliflozin, an anti-diabetic drug targeting the sodium-glucose co-transporter 2, decreases HbA1c, body weight, blood pressure (BP), and albuminuria (UACR) in patients with type 2 diabetes. Although the glucose lowering capacity of dapagliflozin is diminished in patients with reduced kidney function, the effects of this drug on body weight, BP, and UACR as well as its safety have not been properly defined in patients with type 2 diabetes and stages 3b-4 chronic kidney disease (CKD).

**Methods:** In a pooled analysis of 11 phase 3 randomized controlled clinical trials, we determined changes in HbA1c, body weight, BP, hematocrit, eGFR, and UACR over 24 weeks in patients with type 2 diabetes and an eGFR ≥45 ml/min/1.73m² receiving placebo (n=70) or dapagliflozin 5 mg or 10 mg (n=151). Effects on UACR were determined in a subgroup of patients with baseline UACR ≥30 mg/g (n=137).

**Results:** Placebo-corrected changes in HbA1c with dapagliflozin 5 and 10 mg were -0.02 (95% CI: -0.36, 0.33) and -0.03 (95% CI: -0.34, 0.28). Dapagliflozin 5 and 10 mg compared to placebo changed eGFR after 24 weeks by -1.5 (95% CI: -4.6, 1.5) and -2.6 (95% CI: -5.3, 0.2) and UACR by -48.3% (95% CI: -67.4, 17.8), and -32.7% (95% CI: -56.2, 3.5), respectively. Additionally, dapagliflozin at both 5 and 10 mg compared to placebo increased hematocrit and decreased body weight and BP. The overall frequency of adverse events was similar among treatment groups. Adverse events associated with renal function occurred more frequently in the dapagliflozin 10 mg group. These events included many asymptomatic increases in serum creatinine of which none qualified as a serious adverse event.

**Conclusions:** Dapagliflozin does not decrease HbA1c in patients with type 2 diabetes and stages 3b-4 CKD. However, the drug decreases UACR, BP, and body weight to a clinically meaningful extent without major side effects. These actions of dapagliflozin support a large outcomes trial in this population to confirm long-term safety and efficacy in reducing adverse clinical endpoints.

**Funding:** Commercial Support - AstraZeneca

---

**FR-OR092**

Are the Renal Effects of Empagliflozin Consistent in Patients Already Using Medications That Alter Renal Hemodynamics? An Exploratory Analysis from EMPA-REG OUTCOME

Gert J. Mayer, Christoph Wanner, Matthew R. Weir, Silvio E. Inzucchi, Audrey Kotikova-Weber, Stefan Hantel, Maximilian von Eynatten, Bernard Zinnman, David Cherney, Dept of Internal Medicine IV (Nephrology and Hypertension), Medical University Innbruck, Innsbruck, Austria; Dept of Medicine, Wurzburg Univ Clinic, Wurzburg, Germany; Dept of Nephrology, University of Maryland School of Medicine, Baltimore, MD; Yale University School of Medicine, New Haven, CT; Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; Lunenfeld-Tanenbaum Research Inst, Mount Sinai Hospital, Toronto, ON, Canada; Toronto General Hospital, Univ of Toronto, Toronto, ON, Canada.

**Background:** Among patients with type 2 diabetes (T2D) at high cardiovascular (CV) risk, the SGLT2 inhibitor empagliflozin (EMPA) decreases progression of kidney disease, likely via reduction in intraglomerular pressure. These patients often receive other agents to prevent development or progression of both CV disease (CVD) and chronic kidney disease (CKD). Some of these agents may also alter renal hemodynamics, such as RAS inhibitors, diuretics, NSAIDs and CCBs. We investigated whether the renal effects of EMPA are consistent across background medication subgroups, with no heterogeneity of treatment effect (Figure). RAS inhibitors were the most commonly used background medication (4.5%, 2.7%).

**Methods:** In a pooled analysis of 11 phase 3 randomized controlled clinical trials, we compared placebo-corrected changes in HbA1c with EMPA (10 mg: n=700, 25 mg: n=700) or placebo during 2 consecutive periods of 6 weeks each, with a 6-week wash-out in between. Plasma C-terminal FGF23 was measured with ELISA (Immutopics Inc), 25(OH) vitamin D with LC-MS/MS. Data are shown as mean (95% CI).

**Results:** Thirty-three patients (age 61±9 yrs; 24% female; median 24h UAE 1470 mg/24h) completed the study. Baseline characteristics and results are shown in table 1. EMPA increased serum phosphate, PTH and FGFR23 compared to both baseline and placebo. Serum calcium and 25(OH)D levels remained unchanged. In light of the high prevalence of bone and mineral disorders in patients with diabetes and kidney disease, future studies should assess the clinical significance of these alterations.

**Funding:** Commercial Support - Astra Zeneca provided study medication., Government Support - Non-U.S.

Table 1: baseline values and mean change (95%CI) vs. baseline during Dapa and Placebo study periods.

**FR-OR093**

Effects of SGLT2 Inhibition on Fibroblast Growth Factor 23 and 25(OH) Vitamin D

Vitamin D Maarten A. de Jong, Sergey Petryk, Gozewijn D. Lavern, Dick de Zeeuw, Stephan J. Bakker, Hiddo J. Lambers Heerspink, Martin H. De Borst, University Medical Center Groningen, Groningen, Netherlands; ZGT Almeio, Almeio, Netherlands.

**Background:** Sodium-glucose co-transporter 2 (SGLT2) inhibitors like dapagliflozin are novel drugs for the treatment of diabetes mellitus, which also promise to slow the progression of kidney disease. Previous studies found that SGLT2 inhibition increases serum phosphate and PTH. However, the effects on fibroblast growth factor 23 (FGF23) and vitamin D are less well studied.

**Methods:** This is a post-hoc analysis of a double-blind, randomized, cross-over trial, enrolling patients on stable RAAS blockade, albumin:creatinine ratio between 100 and 3500 mg/g, eGFR ≥45 ml/min/1.73m² and HbA1c ≥55 and <100 mmol/mol. Patients were treated with dapagliflozin 10 mg/d (DAPA) or placebo during 2 consecutive periods of 6 weeks each, with a 6-week wash-out in between. Plasma C-terminal FGF23 was measured with ELISA (Immutopics Inc), 25(OH) vitamin D with LC-MS/MS. Data are shown as mean (95%CI).

**Results:** Thirty-three patients (age 61±9 yrs; 24% female; median 24h UAE 1470 mg/24h) completed the study. Baseline characteristics and results are shown in table 1. EMPA increased serum phosphate, PTH and FGFR23 compared to both baseline and placebo. Serum calcium and 25(OH)D did not change (p=0.9, p=0.8). DAPA reduced eGFR, but change in eGFR and change in bone and mineral parameters were not correlated (all P>0.5). All effects of EMPA were reversed 6 weeks after discontinuation.

**Conclusions:** Dapagliflozin treatment induced a significant rise in serum phosphate, PTH and FGFR23 levels, independent of concomitant effects on eGFR. Serum calcium and 25(OH)D levels remained unchanged. In light of the high prevalence of bone and mineral disorders in patients with diabetes and kidney disease, future studies should assess the clinical significance of these alterations.

**Funding:** Commercial Support - Astra Zeneca provided study medication., Government Support - Non-U.S.

**Table 1:** baseline values and mean change (95% CI) versus baseline during Dapa and Placebo study periods. * denotes P< 0.01 vs. baseline. † denotes P<0.01 vs placebo.

---

**FR-OR094**

AKI in Patients on SGLT2 inhibitors: A Propensity Matched Analysis

Girish N. Nadkarni, Rocco Ferrandino, Alex R. Chang, Aditya L. Surapaneni, Kinshuk Chauhan, Priti Poojary, Aparna Saha, Bart Ferreti, Morgan Grams, Steven G. Coca, Geisinger Medical Center, Danville, PA; Icahn School of Medicine, New York, NY; Icahn School of Medicine at Mount Sinai, New York, NY; Johns Hopkins University, Baltimore, India; Icahn School of Medicine at Sinai, New York, NY.

**Background:** Sodium-glucose co-transporter-2 inhibitors (SGLT2i) improve both renal and cardiovascular outcomes in type 2 diabetes (T2D) patients. However, the FDA has issued alerts regarding increased acute kidney injury (AKI) with canagliflozin/dapagliflozin. We aimed to assess real world AKI risk with SGLT2i separately in two health-care cohorts.

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

Underline represents presenting author.
Methods: We utilized the Mount Sinai chronic kidney disease (MScRD) registry and the Kidney Health System (KHS) cohort. We selected SGLT2i users/non-users and determined AKI by KDIGO definition (AKI<30). We used nearest neighbor: 1:1 propensity matching and calculated unadjusted and adjusted (accounting for covariates poorly balanced in the propensity match) hazard ratios (HRs).

Results: We analyzed 377 SGLT2i users: non-user pairs in MScRD, and 1,242 SGLT2i users: non-user pairs in KHS. During median follow-up time of 14 months, 4% in Mount Sinai and 3% of SGLTI users experienced an AKI<30 event, vs. 10% and 7% of non-users, respectively. Unadjusted HRs for AKI<30 were 0.46 (95% CI 0.26–0.82) and 0.43 (95% CI 0.29–0.63) in MScRD and KHS, respectively. After propensity score adjustment, reduced risk persisted (aHR 0.48; 95% CI 0.25–0.91, and aHR 0.63, 95% CI 0.39–1.09, respectively). These estimates did not qualitatively change across sensitivity analyses, including by SGLTI type. (Table 1)

Conclusions: These pharmacoepidemiologic findings suggest there may not be increased AKI risk in SGLT2i users vs. comparable T2D patients. In fact, all three SGLTI were associated with lower AKI risk, similar to empagliflozin trials. Our results suggest that perceived AKI risk with canagliflozin/dapagliflozin may be attributable to the high-risk population taking these medications and not to inherent nephrotoxicity.

Funding: NIDDK Support

Table 1. Hazard Ratios for AKI in SGLT2 Users vs. Propensity Matched Non-users in Mount Sinai and Geisinger Cohorts

<table>
<thead>
<tr>
<th>AKI defined by KDIGO</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis</td>
<td>Unadjusted HR (95% CI)</td>
<td>Adjusted HR (95% CI)</td>
</tr>
<tr>
<td>AKI defined by KIDOG</td>
<td>0.4 (0.2–0.8)</td>
<td>0.4 (0.2–0.8)</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>0.5 (0.3–0.9)</td>
<td>0.5 (0.3–0.9)</td>
</tr>
</tbody>
</table>

Results: Following the derivation of kidney organoids from GAPDHdual:SIX2Cre PSCs for fate-mapping studies, we used CRISPR/Cas9 to insert the Cre recombinase gene within the endogenous SIX2 locus of GAPDHdual PSCs (GAPDHdual:SIX2Cre). Kidney organoids were generated from GAPDHdual:SIX2Cre PSCs and monitored for mCherry expression.

Results: Following induction of mesendoderm, addition of retinoic acid, FGF2, and BMP4 induced aM expressing up to 95% GATA3, 88% HOXB4, 78% PAX2, 74% WTI, and 71% LHX1 in both human embryonic stem cells and induced pluripotent stem cells. Subsequent treatment of aM with noggin generated CD11b+ PAX2*GATA3* tubular epithelia consistent with putative Wolffian duct (WD). Ewing treatment of WD with GDNF and retinoic acid to induce ret signaling upregulated SALL4 in tubular epithelial structures, consistent with tubulogenic bud (UB) induction. In contrast, 3D culture of mGFP-aM cells treated with noggin and FGFs (2, 7, 10) generated presumptive WD organoids. Co-culture of WD-GFP and nephron organoids induced GFP CDH1*GATA3* tubular epithelial structures connected in series with CDH1 GFP distal segments of MM organoids, consistent with the addition of an in-series distal tubule-collecting duct structural linkage. Moreover, UB organoids provided Wnt signaling to the nephron organoids, negating the need for a transient CHIR pulse. Conclusions: hPSC-GFP lines, generated from the transduction with a CMV-GFP lentiviral construct, permittend lineage tracing in co-culture experiments with distinction between UB and nephron organoids.

Results: Following induction of mesendoderm, addition of retinoic acid, FGF2, and BMP4 induced aM expressing up to 95% GATA3, 88% HOXB4, 78% PAX2, 74% WTI, and 71% LHX1 in both human embryonic stem cells and induced pluripotent stem cells. Subsequent treatment of aM with noggin generated CD11b+ PAX2*GATA3* tubular epithelia consistent with putative Wolffian duct (WD). Ewing treatment of WD with GDNF and retinoic acid to induce ret signaling upregulated SALL4 in tubular epithelial structures, consistent with tubulogenic bud (UB) induction. In contrast, 3D culture of mGFP-aM cells treated with noggin and FGFs (2, 7, 10) generated presumptive WD organoids. Co-culture of WD-GFP and nephron organoids induced GFP CDH1*GATA3* tubular epithelial structures connected in series with CDH1 GFP distal segments of MM organoids, consistent with the addition of an in-series distal tubule-collecting duct structural linkage. Moreover, UB organoids provided Wnt signaling to the nephron organoids, negating the need for a transient CHIR pulse. Conclusions: hPSC-derived UB organoids, whether alone or in co-culture with nephron organoids, will provide a human tissue tool for the study of kidney development and human disease modeling with implications for drug discovery and regenerative medicine.

Funding: Other NIH Support - T32

FR-OR097

Ureteric Bud Organoids Derived from Human Pluripotent Stem Cells Facilitate Self-Organization of Neprhon Organoids

Methods: CRISPR-modified hPSC lines encoding fluorescently-tagged reporters were used to generate several other Cre-drivers to interrogate lineage relationships of other cellular compartments within the developing kidney that remain largely unknown.

FR-OR095

Organelles in Kidney Organoids: Live Imaging of Human Mini-Kidneys Using Targeted Tracers Reveals Dynamic Intracellular Responses to Kidney Injury

Methods: We utilized the Mount Sinai chronic kidney disease (MScRD) registry and the Kidney Health System (KHS) cohort. We selected SGLT2i users/non-users and determined AKI by KDIGO definition (AKI<30). We used nearest neighbor: 1:1 propensity matching and calculated unadjusted and adjusted (accounting for covariates poorly balanced in the propensity match) hazard ratios (HRs).

Results: We analyzed 377 SGLT2i users: non-user pairs in MScRD, and 1,242 SGLT2i users: non-user pairs in KHS. During median follow-up time of 14 months, 4% in Mount Sinai and 3% of SGLTI users experienced an AKI<30 event, vs. 10% and 7% of non-users, respectively. Unadjusted HRs for AKI<30 were 0.46 (95% CI 0.26–0.82) and 0.43 (95% CI 0.29–0.63) in MScRD and KHS, respectively. After propensity score adjustment, reduced risk persisted (aHR 0.48; 95% CI 0.25–0.91, and aHR 0.63, 95% CI 0.39–1.09, respectively). These estimates did not qualitatively change across sensitivity analyses, including by SGLTI type. (Table 1)

Conclusions: These pharmacoepidemiologic findings suggest there may not be increased AKI risk in SGLT2i users vs. comparable T2D patients. In fact, all three SGLTI were associated with lower AKI risk, similar to empagliflozin trials. Our results suggest that perceived AKI risk with canagliflozin/dapagliflozin may be attributable to the high-risk population taking these medications and not to inherent nephrotoxicity.

Funding: NIDDK Support

Table 1. Hazard Ratios for AKI in SGLT2 Users vs. Propensity Matched Non-users in Mount Sinai and Geisinger Cohorts

<table>
<thead>
<tr>
<th>AKI defined by KDIGO</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis</td>
<td>Unadjusted HR (95% CI)</td>
<td>Adjusted HR (95% CI)</td>
</tr>
<tr>
<td>AKI defined by KIDOG</td>
<td>0.4 (0.2–0.8)</td>
<td>0.4 (0.2–0.8)</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>0.5 (0.3–0.9)</td>
<td>0.5 (0.3–0.9)</td>
</tr>
</tbody>
</table>

Results: Following induction of mesendoderm, addition of retinoic acid, FGF2, and BMP4 induced aM expressing up to 95% GATA3, 88% HOXB4, 78% PAX2, 74% WTI, and 71% LHX1 in both human embryonic stem cells and induced pluripotent stem cells. Subsequent treatment of aM with noggin generated CD11b+ PAX2*GATA3* tubular epithelia consistent with putative Wolffian duct (WD). Ewing treatment of WD with GDNF and retinoic acid to induce ret signaling upregulated SALL4 in tubular epithelial structures, consistent with tubulogenic bud (UB) induction. In contrast, 3D culture of mGFP-aM cells treated with noggin and FGFs (2, 7, 10) generated presumptive WD organoids. Co-culture of WD-GFP and nephron organoids induced GFP CDH1*GATA3* tubular epithelial structures connected in series with CDH1 GFP distal segments of MM organoids, consistent with the addition of an in-series distal tubule-collecting duct structural linkage. Moreover, UB organoids provided Wnt signaling to the nephron organoids, negating the need for a transient CHIR pulse. Conclusions: hPSC-derived UB organoids, whether alone or in co-culture with nephron organoids, will provide a human tissue tool for the study of kidney development and human disease modeling with implications for drug discovery and regenerative medicine.

Funding: Other NIH Support - T32

FR-OR098

Fluidic Shear Stress Induces Vascular and Glomerular Development in Kidney Organoids

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

Underline represents presenting author.
imperfect and vasculature is neither perfusable nor remains viable longitudinally, limiting both the degree of relevant applications and potential extent of translatable to human physiology in vivo.

Methods: Early nephron organoids (renal vesicle stage) derived from both human embryonic stem cells (hESCs) and induced pluripotent stem cells (hiPSCs) were embedded on extracellular matrix (ECM) in 3D perfusable chips. The degree of vascularization and maturation of vascular networks were evaluated by immunostaining, RT-qPCR, and flow cytometry for FLK1, CD146, and CD31 at regular intervals when subject to variable degrees of fluidic shear stress as well as of growth factors including VEGF, as compared to static conditions without flow.

Results: By subjecting renal organoids to the right combination of underlying ECM, medium components, and fluidic shear stress, the abundance of vasculature, the incidence of capillary invasion of glomerular clefts, and the number of vascularized glomerular structures as well as peritubular vasculature are significantly enhanced. We also demonstrate that the vasculature contains open lumens which can be visualized with fluorescent beads, indicating that vasculature in the organoids is perfusible.

Conclusions: Culturing renal organoids under fluidic shear stress has the potential to unlock new opportunities for glomerular disease modeling, podocyte/vascular maturation, and development of a glomerular filtration barrier in vitro.

Funding: NIDDK Support

FR-OR099

A Microfluidic Kidney Organoid System Reveals Real-Time Dynamics of Nutrient Absorption

Ramilia E. Gulieva,1 Jonathan Himmelfarb,1 Benjamin S. Friedman2, 'Kidney Research Institute, Seattle, WA; 'University of Washington, Seattle, WA.

Background: Human mini-kidney organoids derived from pluripotent stem cells have great potential for kidney disease modeling and regeneration. Microfluidic flow is an essential component of the nephron for reabsorption and filtration, but is absent from existing organoid cultures. To more accurately model nephron functions in vitro, we tested whether intrinsically high fluid flow into kidney organoids could be used to visualize absorption of transport cargos and nutrients in real time.

Methods: Human mini-kidneys were either differentiated de novo from hiPSCs or transferred into chambers from cryopreserved stocks in microfluidic flow chambers. Fluorescently-labeled glucose, albumin and dextran were introduced and monitored live every 15 minutes over the course of 24 hours, under constant perfusion conditions.

Results: Organoid proximal tubules, distal tubules, and podocytes differentiated normally, expressed SGLT2 and LR2P2 transporters, and remained stable under flow for as long as two weeks. Accumulation of glucose occurred very rapidly, while absorption of albumin and dextran increased gradually in a linear fashion and eventually reached a plateau over 24 hours. The magnitude of absorption was significantly increased and featured increased signal to noise under flow conditions, compared to static conditions where absorption was minimal. Inhibition of SGLT transporters blocked glucose absorption in a dose-dependent manner.

Conclusions: The combination of kidney organoids with microfluidics enables visualization of nutrient and transport cargo absorption in nephron-like structures with high spatial and temporal resolution. Organoids under flow exhibit increased ability to absorb nutrients, relative to other cells in these cultures or organs without flow. Our results indicate that this system can be utilized to accurately model absorption dynamics of specific substrates and to test the effects of therapeutic compounds, such as SGLT2 inhibitors. As flow is an essential component of the nephron, these experiments also build towards more sophisticated organ microphysiological systems and artificial kidney devices.

Funding: NIDDK Support, Other NIH Support - NCATS Tissue Chips, Commercial Support - Northwest Kidney Centers (Unrestricted Gift), Private Foundation Support

FR-OR100

Multi-Segmented Kidney Organoids Derived from Human ES Cells by Stepwise Transcription Factor Administration

Ken Hiratsuka,1 Toshiaki Momkawa,1 Shintaro Yamaguchi,2 Ruji Morizane,3 Shigeru K. Ko,1 Hiroshi Ishii,1 Minoru S. Ko,2 Brigham and Women’s Hospital, Boston, MA; 3National Institutes of Health, Phoenix, AZ; 1Keio University School of Medicine, Tokyo, Japan.

Background: We have recently reported a method to differentiate renal tubule-like cells from human Embryonic Stem Cells(hESCs) by a combinatorial administration of defined transcription factor(TF) mRNAs. However, a critical problem of this protocol, referred as direct reprogramming, is that it generates only proximal and distal tubular cells, but not other cell types. Here, we identified TFs that can induce the formation of SIX2+ metanephric mesenchyme/renal vesicles, which can be further differentiated into all other renal linages.

Methods: We used the human ES line with doxycycline-inducible transcription factors (~700 genes), analyzed correlation of gene expression response to the induction of human TFs with tissue-specific gene expression in silico, and identified candidates for differentiating towards renal linages. Modified mRNAs for TFs were synthesized by in vitro transcription. hESCs were transfected with several combinations of synthetic mRNAs for four days by lipofection and cultured for up to 14 days to form kidney organoids, mimicking renal developmental stage. hESCs-derived kidney organoids were used for RNA-sequencing analysis(RNA-Seq) and were tested functional assays to model kidney injury.

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

Underline represents presenting author.

63

FR-OR101

Nephron Organoids Derived from Patients with ARPKD Model Polycystic Kidney Disease Respond to a CAMP Inducer and an Src Inhibitor and Provide a Platform for Drug Screening

Ken Monkawa,1 Y amaguchi,2 Ken Morizane,2 Jonathan Nelson,1 Albert G. Yuji Morizane,1 Rajasree Menon,2 Cristina Cebrian Ligero,1 Jing Zhou,1,3 M. Todd Valerius,1,3 Joseph V. Bonventre.1,3 Brigham & Women’s Hospital/Harvard Medical School, Boston, MA; 2Brigham and Women’s Hospital, Boston, MA; 3Harvard Stem Cell Institute, Cambridge, MA.

Background: Nephron organoids, derived from human pluripotent stem cells (hPSCs), represent a method to study inherited kidney diseases and perform drug screening in vitro. Previously, we established proof of concept by modeling autosomal dominant polycystic kidney disease (ADPKD), an adult-onset form, using PKD1 or PKD2 CRISPR mutant hPSC lines that generated 6% cystic organoids. Here, we sought to model autosomal recessive PKD (ARPKD), an early-onset form, using patient derived pluripotent stem cells (hPSCs) to generate cystic organoids with greater efficiency, establishing a suitable system for studying kidney morphogenic mechanisms in vitro.

Methods: Nephron organoids were generated in 96-well culture plates from a human embryonic stem cell (hESC) line and a hiPSC line derived from subjects without cystic kidney disease (controls), and 2 ARPKD patient-derived hiPSC lines using our established protocol. Cyst formation was assessed by organoid size and demonstrated enhanced cystogenesis with forskolin treatment. The effect of Src inhibition on cystogenesis was assessed by organoid size.

Results: Patient-derived ARPKD nephron organoids spontaneously formed cysts and demonstrated enhanced cystogenesis with forskolin treatment. Bright field imaging detected cysts in >90% of ARPKD organoids, while control hiSC and hiPSC organoids contained few cysts. Forskolin treatment enhanced cystogenesis in ARPKD organoids, but not in controls. Mislocalization of the Na+/K+-ATPase to the apical membrane was observed in ARPKD organoids, while control organoids demonstrated Na+/K+-ATPase basolateral restriction. Src inhibition decreased the size of ARPKD organoids.

Conclusions: Patient-derived ARPKD organoids efficiently demonstrated cystic phenotypes that retain known pathophysiology: proliferative response to CAMP and loss of tubular epithelial cell polarity. Src treatment suppressed cystogenesis in a 96-well format, indicating the feasibility of drug screening in vitro.

Funding: NIDDK Support, Commercial Support - AJINOMOTO, TORAY

FR-OR102

Defining Cellular Ontologies in Inducible Pluripotent Stem Cell (iPSC)-Derived Kidney Organoids by Mapping into Human Nephrogenesis via ssRNAseq

Jennifer L. Harden,1 Edgar A. Otto,1 Rajasree Menon,2 Cristina Cebrian Ligero,1 Jizhong Zhou,2 Benjamin S. Friedman,4 Robert G. Nelson,1 Matthias Kretzler,1 University of Michigan, Ann Arbor, MI; 2NHLBI, NIH, Bethesda, MD; 3National Institutes of Health, Phoenix, AZ; 4University of Washington, Seattle, WA.

Background: Generation of kidney organoids from iPSCs offers a novel method to study genetic effects of kidney phenotypes, and may provide useful models of kidney development and disease. Techniques to address the variable cell heterogeneity of these organoids are needed to enhance their utility.

Methods: iPSCs were derived from peripheral blood mononuclear cells from individuals with diabetic kidney disease and kidney organoids were generated using a Matrigel sandwich technique. Droplet-based single cell RNA-Seq (ssRNAseq) was performed on dissociated cells and sequencing data were aligned to the human genome. Downstream clustering and further analyses were performed using various R statistical packages (Seurat, SC3, Limma). Organoid single cell gene expression was compared to human fetal kidney ssRNAseq data and to publicly available expression datasets. Results: ssRNAseq signatures of cells from iPSC-derived organoids were clustered into 3 clusters with distinct patterns of differential gene expression reflecting differentiated kidney cell lineages: podocyte(PODXL, NPHS1, NPHS2, CLC5, tub), (IGFBP7, SLC3A1, VIL11, CUBN, CLDN16), and stromal/mesangial(COL5A1, TAGLN, ACTA2). Gene expression of these clusters mapped to cell clusters from ssRNAseq analysis of early second trimester human fetal kidney. When compared to bulk RNA expression patterns of human fetal and adult tissues, iPSC-derived kidney organoid
clusters overlapped prominently with microdissected developing and adult murine kidney tissues for validation.

**Conclusions:** Human iPSC-derived kidney organoid cultures contain subsets of cells with unique gene expression patterns that recapitulate distinct tissue states of developing and adult human kidney. Identification of individual cells with specific markers of interest provides the ability to analyze co-expression genes within an individual cell in a heterogeneous environment and a method to isolate cells of interest within organoid experiments. These results highlight the benefits of modeling human kidney disease with human iPSCs in a kidney organ culture system and provide strategies to address the system’s inherent cellular heterogeneity.

**Funding:** NIDDK Support

**FR-OR103**

**Defining the Cellular Composition of Human Kidney Organoids Using High-Throughput Single Cell Sequencing**

**Alexander S. Combes,1 Luke Zappia,1 Belinda Chipson,1 Pei Xuan Er,1 Alicia Oshlack,1 Melissa H. Little,1,2 Murdoch Children’s Research Institute, Melbourne, VIC, Australia; 2Anatomy and Neuroscience, University of Melbourne, Parkville, VIC, Australia; 3Peadiatrics, University of Melbourne, Parkville, VIC, Australia.

**Background:** Single cell sequencing is a rapidly developing method for transcriptional analysis that has resulted in new insight into the cellular composition of complex tissues. Our lab and others have recently established protocols to directly differentiate human pluripotent stem cells to a kidney fate. This resulted in the formation of self-organizing structures that contain the basic components of the developing kidney. Understanding the cellular composition of these organoids is important to clarify the extent of tissue-specific diseases that may be modelled in this system, and to determine whether all known renal progenitors have been generated.

**Methods:** Kidney organoids were generated as previously described and harvested after 18 days of culture. We used the 10x Genomics Single Cell platform to profile ~7000 cells from three independent organoids.

**Results:** Clustering the single cell data identified multiple cell types enriched for markers of early proximal tubule, podocyte, pre-podocyte, collecting duct, ureter, vasculature, neural, and multiple interstitial populations. Cell types such as the vasculature and podocytes expressed multiple markers that enable unequivocal identification and give an insight into the state of maturity and fidelity of those cell types. Two distinct populations were identified which were enriched for podocyte markers such as PODXL, NPHS1, NPHS2, PTPRO, and SYNPO. While these both suggest podocyte identity, this may infer distinctions between early visceral and parietal epithelial cell types. The two populations did segregate along the loop of Henle and distal tubal-hairpin and were not clearly identified. However, remaining epithelial clusters may represent progenitors of mature nephron segments. This is consistent with organoid morphology, which suggests nephron segmentation equivalent to Stage III/capillary-loop formation.

**Conclusions:** The analysis of organoid cellular composition using single cell transcriptional profiling has enabled a rapid survey of cellular diversity and fidelity of the cell types generated. The major cell types previously identified in kidney organoids were confirmed and extended with gene expression profiles for each. This data suggests that our kidney organoids will be useful for modelling development and disease of the early proximal tubule, collecting duct, and podocytes.

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

**FR-OR104**

**Defining Kidney Organoid Cell Diversity by scRNA-Seq**

**Haojia Wu,1 Kohei Uchimura,1 Erin L. Donnelly,1 Samantha A. Morris,2 Benjamin D. Humphreys,1 Division of Nephrology, Washington University in St. Louis, Saint Louis, MO; 2Department of Developmental Biology, Washington University in St. Louis, Saint Louis, MO.

**Background:** Kidney organoids differentiated from pluripotent stem cells hold great promise for understanding organogenesis, disease modeling and ultimately as a source of replacement tissue. Realizing this potential requires a comprehensive evaluation of the extent of tissue-specific diseases that may be modelled in this system, and to determine whether all known renal progenitors have been generated.

**Methods:** Kidney organoids were generated as previously described and harvested after 18 days of culture. We used the 10x Genomics Single Cell platform to profile ~7000 cells from three independent organoids.

**Results:** Clustering the single cell data identified multiple cell types enriched for markers of early proximal tubule, podocyte, pre-podocyte, collecting duct, ureter, vasculature, neural, and multiple interstitial populations. Cell types such as the vasculature and podocytes expressed multiple markers that enable unequivocal identification and give an insight into the state of maturity and fidelity of those cell types. Two distinct populations were identified which were enriched for podocyte markers such as PODXL, NPHS1, NPHS2, PTPRO, and SYNPO. While these both suggest podocyte identity, this may infer distinctions between early visceral and parietal epithelial cell types. The two populations did segregate along the loop of Henle and distal tubal-hairpin and were not clearly identified. However, remaining epithelial clusters may represent progenitors of mature nephron segments. This is consistent with organoid morphology, which suggests nephron segmentation equivalent to Stage III/capillary-loop formation.

**Conclusions:** The analysis of organoid cellular composition using single cell transcriptional profiling has enabled a rapid survey of cellular diversity and fidelity of the cell types generated. The major cell types previously identified in kidney organoids were confirmed and extended with gene expression profiles for each. This data suggests that our kidney organoids will be useful for modelling development and disease of the early proximal tubule, collecting duct, and podocytes.

**Funding:** NIDDK Support

**FR-OR105**

**Transcription Factor Meis1 Is Upregulated in Kidney Stroma after Injury and in Aging, and Regulates Tubulointerstitial Cross-Talk**

**Monica Chang Panessoz,1 Farid F. Kadyrov,2 Flavia G. Machado,3 Benjamin D. Humphreys,1 1Washington University School of Medicine, Clayton, MO; 2Washington University in St Louis, St Louis, MO; 3Washington University in St Louis, School of Medicine, St Louis, MO; 4Washington University in St. Louis, St. Louis, MO.

**Background:** P16Ink4a, a cell cycle regulator and mediator of cellular senescence, accumulates during aging including in kidney. Meis1 is a transcription factor known to regulate p16Ink4a and other cycin-dependent kinases. We hypothesized that Meis1 may mediate kidney senescence in kidney and investigated the expression and function of Meis1 in kidney injury and aging.

**Methods:** We used Meis1/Epf reporter mice and antibody-based detection of endogenous Meis1. We also deleted Meis1 from kidney stroma by crossing a FoxD1-GrPr with the cells to a floxed allele.

**Results:** Meis1 was strongly expressed in PDGFRβ+ pericytes and fibroblasts based on both immunofluorescence and Meis1/Epf reporter mice. Meis1 mRNA and protein was upregulated after bilateral ischemia-reperfusion injury (IR). It was also strongly upregulated in myofibroblasts of aged (23 mo) mice. To examine the functional role of Meis1 in kidney stroma, we generated bigenic Meis1f/f;FoxD1Cre/+ mice. Examination by qPCR and IF staining showed efficient Meis1 deletion of approximately 90% compared to controls. There was no gross histological abnormality at either P0 or P30 in the Meis1f/f;FoxD1Cre/+ compared to littermate controls. However P30 kidneys of Meis1f/f;FoxD1Cre/+ mice weighed less compared to controls and had a higher BUN. Further histological evaluation at P30, revealed unexpected expression of Kidney Injury Molecule-1 (Kim1) protein expression in the outer medulla, indicating tubular injury. Kim1 induction was confirmed by qPCR. There was no NGAL expression indicating that the injury pattern was restricted to the S3 proximal tubular segment. Meis1 knockout mice had normal peritubular capillary density, normal numbers of glomeruli and no atubulurum.

**Conclusions:** Meis1 is upregulated in myofibroblasts during kidney fibrosis and in aging. Surprisingly, conditional deletion of Meis1 in the stromal lineage led to focal injury of the S3 segment of the proximal tubule in the absence of structural kidney abnormalities. These findings suggest that Meis1 expression in kidney stroma regulates proximal tubule health by a non-cell-autonomous mechanism.

**Funding:** NIDDK Support

**FR-OR106**

**Renal Tubular-Specific Jagged1 Deletion Ameliorates Kidney Fibrosis via Mitochondrial Transcription Factor A (TFAM) Regulation and Metabolic Reprogramming**

**Shizheng Huang, Jiwan Park, Chengxiang Qiu, Szu-Yuan Li, Katalin Susztak, University of Pennsylvania, Philadelphia, PA.

**Background:** Notch is a basic cell-cell communication pathway where expression of the ligand, Jagged1,2 or Delta1,3,4 on signal-sending cells, Notch1-4 on the signal-receiving cell. Our group previously established that tubular epithelial cell (TEC) Notch signaling plays a key role in kidney fibrosis development. However, the precise ligand and receptor pairs that contribute to kidney fibrosis still remain unknown. Here we performed a systematic approach to analyze the specific ligands and molecular pathways of Notch-induced fibrosis development in TEC.

**Methods:** To examine Notch ligands and receptors expression profiles, we used genome wide gene expression arrays from well phenotyped microdissected human kidney tubule samples (n=94). Mechanistic studies were performed by generating mice with tubule-specific deletion of Jagged1 ([Kspcre/Jagged1flox/flox]) and the kidney injury induced by administering folic acid (FA) intra-peritoneally. In vitro studies were performed using a co-culture system of rat tubule epithelial cells (NRK52E) and mouse stromal cells that express Jagged1. Direct targets of Notch signaling were identified by ChIP-Seq with co-transfection factor Rbpj.

**Results:** In microdissected human kidney tissue samples, of the ligands, Jagged1 showed the best correlation with the degree of interstitial fibrosis. Increased Jagged1 expression was recapitulated in the FA-induced kidney fibrosis model and in primary cultured TEC treated with TGFβ1. Mice with tubule specific deletion of Jagged1 mice showed no kidney specific alterations at baseline, but were protected from FA-induced kidney injury. There was no FA-induced reduction in inflammatory and profibrotic gene expression and improvement of histology in the Jagged1 knockout mice following FA injection. In vitro co-culture studies indicated that Jagged1 expression induces proliferation and dedifferentiation of TEC. We found that mitochondrial transcription factor A (TFAM) is a direct target of Notch signaling. In vitro expression of TFAM could rescue the metabolic defect and protect from Jagged1-induced fibrosis development in co-culture system.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
Conclusions: The effect of Notch in TEC induced fibrosis development is mediated by Jagged1. Jagged1 induces epithelial dedifferentiation and fibrosis via TFA mediated metabolic reprogramming.

Funding: NIDDK Support

FR-OR107

Myokines Mediate Muscle-Kidney Crosstalk Suppressing Metabolic Reprogramming and Fibrosis in Damaged Kidneys

Han,1,2 Yulong Fu,1 Jun-yi Zhu,1 Children’s National Health System, Washington, DC; 2Dept. of Pediatrics, George Washington University, Washington, DC.

Background: Kidney injury initiates metabolic reprogramming in tubule cells that contributes to the development of chronic kidney disease (CKD). Because exercise might benefit the outcomes of CKD, we hypothesized that the induction of myokines will improve kidney energy metabolism and suppress kidney damage.

Methods: We investigated how a substitute for exercise, overexpression of PGC-1α only in skeletal muscles (mPGC-1α), affects recovery from kidney tubule cell damage in three mouse models including folic acid nephropathy (FAN), unilateral ureteral obstruction (UUO), or subtotal nephrectomy (CKD).

Results: Despite injury from folic acid, unilateral ureteral ligation or subtotal nephrectomy, kidney tubules from mPGC-1α mice resisted progressive cellular damage and subsequent fibrogenesis. Metabolomics analysis revealed improved energy metabolism and ATP production in injured kidneys from mPGC-1α mice. A myokine-enriched serum fraction from mPGC-1α mice (>50 kDa but > 10 kDa) improved energy metabolism in primary cultures of tubule cells. Specifically, the myokine, irisin, protected kidney cells from injury by suppressing metabolic reprogramming. A neutralizing anti-irisin antibody blocked improvements in kidney cell metabolism engendered by serum from mPGC-1α mice. Recombinant irisin administration to mice with kidney injury attenuated kidney damage and fibrosis. The mechanism underlying irisin-initiated improvements is that irisin competes with TGF-β1 for binding to the TGF-β type 2 receptor, thereby impairing activation of the TGF-β1 type 1 receptor and Smad3 signaling, as result, suppression of metabolic reprogramming and fibrogenesis.

Conclusions: myokine-mediated crosstalk between muscle and kidney can protect kidney tubule cell from damage. Myokine, irisin counteracts metabolic reprogramming in injured kidney cells with improvement in kidney function and suppression of kidney fibrosis.

Funding: Other NIH Support - NIASM, Government Support - Non-U.S.

FR-OR108

RNA of APOL1 Risk Alleles Causes Cellular Toxicity through the PKR Pathway

Zhe Han,1,2 Yulong Fu,1 Jun-yi Zhu,1 Children’s National Health System, Washington, DC; 2Dept. of Pediatrics, George Washington University, Washington, DC.

Background: African Americans are at higher risk for developing chronic kidney diseases due to APOL1 risk alleles (RA), but the mechanism of the cellular toxicity remains unclear. We generated Drosophila models of APOL1 nephropathy by expressing APOL1-Ra in nephrocytes, which shares striking similarities with podocytes. Using the genetic screen, we identified genes that interact with APOL1-Ra. One of these genes is Pyk, homolog of human protein kinase R (PKR). PKR was suggested to interact with APOL1-Ra RNA. Here we test the hypothesis that the APOL1-Ra RNA induce toxicity through activating the PKR pathway.

Methods: A series of transgenic flies carrying APOL1-Ra with different mutations were generated. Some carry an early stop codon so that these APOL1 proteins are gone. Some carry synonymous mutations so that the RNA remains same (STOP mutations), some carry synonymous mutations so that the RNA remains same (STOP mutations), some carry synonymous mutations so that the RNA remains same (STOP mutations), some carry an early stop codon so that these APOL1 proteins are gone. Using the fly genetic screen, we identified genes that interact with APOL1-Ra. One of these genes is Pyk, homolog of human protein kinase R (PKR). PKR was suggested to interact with APOL1-Ra RNA. Here we test the hypothesis that the APOL1-Ra RNA induce toxicity through activating the PKR pathway.

Methods: A series of transgenic flies carrying APOL1-Ra with different mutations were generated. Some carry an early stop codon so that these APOL1 proteins are gone. Some carry synonymous mutations so that the RNA remains same (STOP mutations), some carry synonymous mutations so that the RNA remains same (STOP mutations), some carry synonymous mutations so that the RNA remains same (STOP mutations), some carry an early stop codon so that these APOL1 proteins are gone. Using the fly genetic screen, we identified genes that interact with APOL1-Ra. One of these genes is Pyk, homolog of human protein kinase R (PKR). PKR was suggested to interact with APOL1-Ra RNA. Here we test the hypothesis that the APOL1-Ra RNA induce toxicity through activating the PKR pathway.

Results: We found that expression of either STOP or Synonymous mutations of APOL1-Ra lead to cellular toxicity. In the fly wing, phenotypes caused by APOL1 RNA and protein appear different, suggesting that APOL1 RNA and protein have different molecular mechanisms of cellular toxicity. In the nephrocytes, however, APOL1 STOP and Synonymous mutations cause similar phenotype, characterized as nephrocyte hypertrophy followed by functional decline and cell death. Knocking down of Pyk could rescue the toxicity caused by APOL1-Ra with STOP mutations but not by APOL1-Ra with synonymous mutations, suggesting that PKR interaction is uniquely required for the APOL1 RNA toxicity. Feeding with PKR inhibitor reduced the overall toxicity of APOL1-G1 and G2, suggesting that inhibiting the PKR pathway is beneficial for reducing the cellular toxicity caused by the RNA of APOL1-Ra.

Conclusions: Our findings demonstrated that both the RNA and the protein of APOL1-Ra contribute to the overall cellular toxicity. We provided the in vivo evidence for the mechanism of APOL1 RNA toxicity through the PKR pathway, and showed that PKR inhibitor could be used as a potential therapeutic treatment to reduce APOL1 RNA toxicity.

Funding: NIDDK Support

FR-OR109

Potential Therapeutic Targets for CKD by Comparative Analysis of Conserved Transcriptional Changes in Human and Mouse Kidney Fibrosis

Rojesh Shrestha,1 Jihwan Park,1 Chengyang Qiu,1 Shizheng Huang,1 Szu-Yuan Li,1 Yi-An Ko,2 Thomas Bell,2 Aaron Donner,2 Emily Brand,2 Katalin Susztak.1 University of Pennsylvania, Philadelphia, PA; 2Ionis Pharmaceuticals, Carlsbad, CA.

Background: Kidney fibrosis is the histological manifestation of chronic kidney disease (CKD). Kidney fibrosis is associated with global gene expression changes and while some of them might be causally related to disease development, others could be a consequence of the disease. While not all aspect of CKD is recapitulated in mouse models, changes that consistent in a different species could have a higher likelihood to be causal. Furthermore, genetic modification of mouse models can be used to understand causality.

Methods: We performed expression profiling for a large cohort (n=95) of human microdissected normal and CKD tubule samples. Using an adjusted linear regression model, we identified genes whose expression levels were significantly associated with phenotypic changes including GFR and tubulointerstitial fibrosis. By using RNA sequencing, we examined gene expression changes in four mouse fibrosis models; folate induced fibrosis (FA), unilateral ureteral obstruction (UUO), tubule specific Notch transgenic and podocyte specific risk allele APOL1 transgenic mice.

Results: We identified 761 conserved expression changes and 10 transcription factors between mouse and human kidney disease. Here, we focused on E74-like factor 4 (Elf4), which is mainly expressed in immune cells and fibroblasts. It is also an important transcription factor that mediates the effect of interferon response. Then, we generated Elf4−/− and tested the effectiveness of antisense oligonucleotide (ASO) both in vitro and in vivo for Elf4 knock-down. ASO mediated knockdown of ELF4 in prevented interstitial fibrosis in FA model. Mice injected with Elf4 ASO showed lower expression of fibrosis markers (vimentin, fibronectin, collagen) compared to control FA injected mice. In addition, Elf4 ASO mice also showed marked histological improvement in fibrosis.

Conclusions: Thus, comparative analysis of human and mouse kidney fibrosis have identified conserved genes and pathways in kidney fibrosis. These genes can serve as potential new biomarkers or therapeutic targets for kidney disease development.

Funding: NIDDK Support, Commercial Support - Ionis pharmaceuticals

FR-OR110

Smad Anchor for Receptor Activation (SARA) Overexpression in Pericytes Prevents Renal Fibrosis

Tomoko Hayashida,1,2 Zhe Han,1 Constance Runyan,2 H. William Schnaper,3 Xiaoyan Liang.2 ‘Children’s National Medical Center, Washington, DC; 2Northwestern University, Chicago, IL; 3Lurie Children’s Hospital, Chicago, IL.

Background: We previously reported that overexpressing SARA in cultured proximal tubular epithelial cells prevents transforming growth factor (TGF)-β-induced mesenchymal phenotypic transition, and SARA knockdown alone is sufficient to induce such changes, suggesting that SARA is critical for maintenance of cellular phenotype. Here we tested whether maintaining SARA levels could ameliorate mouse and fly models of kidney fibrosis.

Methods: A SARA-overexpressing (SARA-Tg) mouse was generated by inserting full-length human cDNA for SARA1 preceded by a lox-stop-lox cassette at the ROSA26 locus, and was crossed with either PDGFRα-Cre or tamoxifen-inducible Cre-ERT2 mice to induce ectopic SARA expression specifically in pericytes or systemically, respectively. Aristolochic acid (AA), 5 mg/kg, was given intraperitoneal 3x week for 4 weeks beginning at 8 weeks old, to SARA-Tg-Cre mice and their Cre-negative littermates. The mice were sacrificed for analysis one week after AA treatment was stopped. Drosophila heart tube/nephrocyte fibrosis model was generated using a 4xHand-Gal4 driver and iRNA for Wds or Ada2b.

Results: Severe interstitial fibrosis was observed in wild-type mice subjected to AA and whole kidney SARA expression was significantly lower than in non-AA control mice. On the other hand, SARA levels remained similar even after AA administration to SARA-Tg-Cre-ERT2 mice treated with tamoxifen. Cre expression in PDGFRα-Cre mice started completely at E12.5, but SARA-Tg PDGFRα-Cre mice developed normally and were fertile. PDGFRα-Cre expression was detected in pericytes and in some mesangial cells as expected. AA-induced fibrosis as detected by COL1a1 and α-smooth-muscle actin staining and mRNA levels were significantly less in PDGFRα-Cre SARA-Tg mice compared to their Cre-negative littermates. In Drosophila, cardioblast/nephrocyte-specific knockdown of Wds or Ada2b caused fibrosion around the heart tube as shown by increased pericardin expression. SARA knockdown significantly enhanced, and SARA overexpression virtually prevented, pericardin expression.

Conclusions: SARA maintains renal cell phenotype in murine kidney disease and decreases the collagen-producing response in mice and flies. Our data support the recent findings by others that pericytes are essential for renal fibrosis, and suggest a role for SARA in ameliorating fibrogenesis.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Erythrocyte Adenosine A2B Receptor (ADORA2B) Promotes Oxygen Release to Counteract Renal Tissue Damage

Zhangze Peng,1,2  Renna Luo,1 Lijian Tao,3 Yang Xia.1 The First Affiliated Hospital of Dalian Medical University; Dalian, China; Université of Texas-Medical School, Houston, TX; Xiangya Hospital, Central South University, Changsha, China; Nankai Medical University, Dalian, China; Department of Biochemistry and Molecular Biology, McGovern Medical School, the University of Texas Health Science Center, Houston, TX.

**Background:** Hypoxia, defined as inadequate oxygen supply to the whole body or a region of the body, is commonly seen in patients with chronic kidney disease (CKD) and frequently promotes renal failure. As the only cell type responsible for delivering oxygen, erythrocytes quickly respond to hypoxia by increasing their oxygen delivery ability. However, there is an enormous gap in our understanding of the role of erythrocytes in renal tissue damage.

**Methods:** Non-biased metabolomics screening was conducted in the whole blood of Angiotensin II (Ang II) treated WT mice. Subsequently, we infused Ang II to mice with specific deletion of ADORA2B in erythrocytes (Adora2b-f/f-Cre), and examined tissue hypoxia, damage, and erythrocyte function. Human studies were conducted on CKD patient samples.

**Results:** First, metabolomics profiling revealed that 2,3-BPG, an erythrocyte-specific metabolite regulating oxygen release, was highly elevated in the whole blood of Ang II treated mice. Erythrocyte-specific ADORA2B deficiency suppressed Ang II-induced 2,3-BPG production and 2,3-BPG mutation activity. After Ang II infusion, erythrocyte oxygen release ability (P50) was significantly elevated in EpOr-Cre' mice but not in ADORA2B(−/−)-EpoR-Cre'. Moreover, renal and cardiac hypoxia was more severe in ADORA2B(-/-)EpOr-Cre' mice. Ang II also significantly increased proteinuria in ADORA2B(-/-)EpOr-Cre' mice. In addition, both the protein and mRNA levels of HIF-1α in heart and kidney were further increased in kidneys and hearts of ADORA2B(-/-)EpOr-Cre' mice infused with Ang II, together with the mRNA levels of collagen I, fibronectin, and vimentin. Mechanistically, we revealed that AMPK is an intracellular signaling molecular which functions downstream of ADORA2B underlying elevated 2,3-BPG production by inducing BPG mutase activity, thereby increasing the ratio of the two forms of BPG.

**Conclusions:** Our findings reveal a previously unrecognized beneficial role of erythrocyte ADORA2B signaling in Ang II-induced systemic hypoxia and renal tissue damage and thereby identify novel and important therapeutic possibilities for hypoxia-induced tissue damage.

**Pik3c3-Dependent mTORC1 Signaling Mediates Compensatory Nephrin Hypertrophy**

Ting Liu,1 Jinxian Xu,1 Benjamin D. Humphreys,2 Caihong Dai,1 Jian-Kang Chen.1 Augusta University, Augusta, GA; Washington University School of Medicine, Clayton, MO.

**Background:** Nephron loss stimulates the residual nephrons to undergo compensatory nephrin hypertrophy (CNH), which is implicated in progressive nephron damage. Activation of the mechanistic (formerly mammalian) target of rapamycin complex 1 (mTORC1) mediated nephrin hypertrophy (UNX)-induced CNH. We recently observed class 3 phosphatidylinositol 3-kinase (PI3Kc3) activation in the remaining kidney after nephron hypertrophy (CNH), which is implicated in progressive nephron damage. We hypothesized that PI3Kc3 activation in the remaining kidney is attributable to upregulation of renal EPO expression or increased RBC adenosine A2B (ADORA2B) signaling.

**Methods:** Mice with genetic Keap1 hypomorphism were studied as a pharmacomimetic model of chemical Nrf2 inducers to delineate physiologic effects of Nrf2 activation on renal and vascular function. Keap1f/f mice exhibited 5-fold upregulation of Nrf2 target gene NQO1 in the kidney and were polyuric. Co-administration of aminophylline decreased both polyuria and persistent proteinuria. Co-administration of Nrf2 inhibitor N-acetyl cysteine (NAC) prevented the polyuric effects of Aminophylline.

**Results:** Keap1f/f mice exhibited 2-fold elevation in renal cycolooxygenase-1 and prostanoid synthase-1 and 2 in Keap1f/f mice suggests crosstalk between Nrf2 and prostaglandin signaling, and resulted in reduced renal cycolooxygenase-1 and 2 and in Keap1f/f mice suggests crosstalk between Nrf2 and prostaglandin signaling, and resulted in reduction in vasoactivity of angiotensin II (Ang II) in Keap1f/f mice, indicating involvement of ACh metabolism pathway in the regulation of renal prostaglandin production.

**Conclusions:** Our findings reveal a previously unrecognized beneficial role of erythrocyte ADORA2B signaling in Ang II-induced systemic hypoxia and renal tissue damage and thereby identify novel and important therapeutic possibilities for hypoxia-induced tissue damage.

**FR-OR113**

**Dysfunction of Proteasome in Podocytes Results in CKD**

Shinichi Makino,1 Naritoshi Shirata,1 Kanee Nonaka,1 Motoko Yanagita,2 Katsukiko Asanuma,1 1Chiba University Graduate School of Medicine, Chiba, Japan; 2Kyoto University Graduate School, Kyoto, Japan; 3Kyoto University Graduate School of Medicine, Kyoto, Japan; 4Mitsubishi Tanabe Pharma Corporation, Toda, Japan.

**Background:** Ubiquitin-proteasome (UP) and autophagy had been known as major integral degradation systems. The importance of autophagy in podocytes has already been reported, however, the role of UP has not well been understood.

**Methods:** To investigate the role of UP in podocyte, we generated podocyte-specific proteasome knockout mice (Rpt3(−−) by deletion of Rpt3, which is essential for construction of 26S proteasome, using Cre-loxP system under the regulation of the podocyte specific podocin promoter. To evaluate autophagy activity, LC3 was visualized by crossing with GFP-PC3 transgenic mice.

**Results:** Rpt3(−−) mice developed albuminuria starting at 4 weeks of age and increased significantly higher than littermates on 12 weeks of age. The ratio of sclerotic glomeruli and serum creatinine levels were significantly increased. The KO mice exhibited a significantly lower survival ratio than the littermates due to severe renal failure. Ubiquitinated proteins were accumulated and the oxidative stress marker 8OHdG intensity was increased in podocytes of Rpt3(−−) mice. Expressions of p33 and cleaved caspase3 to regulate apoptosis were increased in podocytes of the KO mice. On the other hand, LC3 positive dots in the KO podocytes were not increased, and accumulation of p62 which is detected in autophagy failure, was seen in the KO podocytes.

**Conclusions:** Ubiquitin-proteasome plays an important role in podocytes, resulting in severe renal failure.

**Funding:** NIDDK Support, Veterans Affairs Support, Commercial Support - Mitsubishi Tanabe Pharma

**FR-OR114**

Keap1/Nrf2 Signaling Reveals Homeostatic Function in Renal and Cardiovascular Physiology

Soma Jobbagy,1 Dario A. Vitturi,2 Sonia R. Salvador,3 Scott Hahn,4 Adam Straub,5 Arohan R. Subramanya,6 Francois Possemiers,1 Francesco J. Schopfer.1 Pharmacology and Chemical Biology, University of Pittsburgh School of Medicine, Pittsburgh, PA; 2Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA.

**Background:** Keap1/Nrf2 signaling is well-established as a master regulator of cellular responses to oxidative stress; however, recent findings suggest that this pathway additionally performs key functions in renal solute and water homeostasis. Herein we study the functional consequences of constitutive graded Nrf2 activation on renal salt and water handling and integrate renal and cardiovascular endpoints.

**Methods:** Wild-type, Keap1 hypomorphic (Keap1f/f), and Nrf2−/− mice were studied under control conditions or in response to dietary sodium maneuvers, and renal and plasma biomarkers were assessed by IIF, PCR, immunoblot and HPLC-MS/MS. Cardiovascular function was assessed by radiotomometry and wire myography.

**Results:** Keap1f/f mice exhibited 5-fold upregulation of Nrf2 target gene NQO1 in the kidney and were polyuric. Consistent with a urine concentrating defect and volume depletion, hematocrits were higher in the Keap1f/f cohort (45.5% vs. 37.2% WT). The latter was not attributable to upregulation of renal EPO expression or increased RBC adenosine A2B receptor expression, and resolved after salt loading. 2-fold down-regulated expression of total NCC2 and NBCN by western blot implicated a distal nephron defect. Compensatory activation of WKY signaling was consistent with 2-fold elevation in plasma renin activity and led to 3-fold increase in phospho- to-total NCC ratio in Keap1f/f mice after sodium depletion. Reduced renal cortical prostaglandin E1-1 and 2 in Keap1f/f mice suggests crosstalk between Nrf2 and prostaglandin signaling, and resulted in reduction in vasodilatory PGI2. Blood pressure was unchanged between WT and Keap1f/f mice, however heart rate was significantly depressed in the Keap1f/f cohort. Wire myography revealed impaired vasodilation of resistance arteries in response to ACh.

**Conclusions:** Mice with genetic Keap1 hypomorphism were studied as a pharmacomimetic model of chemical Nrf2 inducers to delineate physiologic effects of this pathway. Keap1f/f mice display distal nephron defect with reduced urine concentrating function due to volume depletion. Compensatory activation of RAAS and WKY-signaling likely serves to mitigate solute and water loss in this model. Differences in prostanoid biosynthesis suggest a mechanism underlying renal and vascular effects of constitutive Nrf2 activity.

**Funding:** NIDDK Support, Private Foundation Support
proteinuria and hematuria. Kidney biopsies are consistent with chronic tubulointerstitial nephritis. The causes of this epidemic remain obscure and systematic epidemiological data are scarce.

Methods: In the context of a joint effort between Regione Toscana and the Department of Leon we performed a screening of the population in the city of Malpasillo-Larreyagna, in the Department of Leon, Nicaragua, of the general population of 23885 inhabitants we selected 18510 subjects, age ≥ 12 years, (mean age ± SD) 36.3 ± 18 years, 8771 M, 9739 F, and extracted a sample of 2786 subjects (1310 M, 1458 F), of these 1915 subjects (723 M and 1192 F; mean age 38.9 ± 18 years) were enrolled. All participants filled in all of (N=340) collected blood and urine samples to estimate glomerular filtration rate (eGFR) (CKD-EPI mL/min/1.73m²), and urine albumin excretion (UAE= albumin, mg / creatinine, g).

Results: Among participants, 1410 (73.6%, 483 M and 927 F) had normal eGFR, and 505 (26.4%, 240 M and 265 F) manifested CKD (Stage 1=21.6%; Stage 2=14.8%; Stage 3a=25.5%; Stage 3b=15.8%; Stage 4=16%; Stage 5=6.5%). Male subjects (33.2%) were more affected than females (22.2%). Among participants with CKD Stage 3-5, 160 (50%) had UAE ≤ 30 and 162 (50%) had UAE > 30. Among the latter, only 20 (25%) of subjects manifested UAE >300. No patient manifested nephrotic syndrome.

Conclusions: For the first time a systematic epidemiological approach to estimate the prevalence of Men has been used. We report an alarming prevalence of CKD affecting a relatively young population in Malpasillo-Larreyagna, Leon, Nicaragua. The disease is in large part asymptomatic and characterized by minimal proteinuria in keeping with a diagnosis of tubulointerstitial disease. The cause(s) of this disease remain to be determined. *Perfil epidemiologico de la enfermedad renal cronica y sus principales factores de riesco en el municipio Larreyagna-Malpasillo, Leon, Nicaragua.

Funding: Government Support - Non-U.S.

FR-OR116

CKDu in Mexico: The Case of Poncitlán, Jalisco

E. Magriço,1 Miguel Bigotte Vieira,2 Cataria Viegas dias,3 Lia Leitão,4 João Sérgio Neves5 (Nephrology Department, Hospital Garcia de Orta, Almada, Portugal; 2Nephrology and Renal Transplantation Department, Centro Hospitalar Lisboa Norte, Lisboa, Portugal; 3Dafundo Family Health Unit, Agrupamento de Centros de Saúde Lisboa Ocidental e Oeiras, Lisboa, Portugal; 4Neurology Department, Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal; 5Department of Endocrinology, Diabetes and Metabolism, Hospital de São João, Faculdade de Medicina, Universidade do Porto, Porto, Portugal)

Background: An elevated prevalence of CKD of unspecified cause (CKDu) has been documented in various developing countries. It has been reported by the media a high prevalence of CKDu in towns located by Chapala Lake, Mexico, particularly in the communities of San Pedro Itzican, Agua Caliente, and Mezcala, in Poncitlán, Mexico. Environmental factors have been blamed as the probable cause of the pandemia.

Methods: Since 2006, we pioneered screening people at risk for the presence of CKD using mobile units that travel to rural and urban communities of Jalisco. Trained personnel collected demographic and clinical data, and obtained blood and urine for serum chemistry and dipstick urinalysis. Those individuals who were aware they had kidney disease were not assessed; all others were eligible to participate. GFR was estimated with the MDRD formula. CKD was defined as an eGFR < 60 ml/min/1.73m².

Results: Between 2007-2016, 50,909 adults were screened with the mobile units. Findings in individuals residing in Poncitlán were compared with those living in other Jalisco municipalities (Table) Changes in three-fold higher among the adult population in comparison with other Jalisco municipalities. Prevalence of proteinuria was three-fold higher than in other communities of Jalisco. Undergoing studies will provide information on the causes of this epidemic.

Funding: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Support

FR-OR117

SPRINT Trial: Intensive Hypertension Treatment and CKD Incidence Rita Magriço,1 Miguel Bigotte Vieira,2 Cataria Viegas dias,3 Lia Leitão,4 João Sérgio Neves5 (Nephrology Department, Hospital Garcia de Orta, Almada, Portugal; 2Nephrology and Renal Transplantation Department, Centro Hospitalar Lisboa Norte, Lisboa, Portugal; 3Dafundo Family Health Unit, Agrupamento de Centros de Saúde Lisboa Ocidental e Oeiras, Lisboa, Portugal; 4Neurology Department, Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal; 5Department of Endocrinology, Diabetes and Metabolism, Hospital de São João, Faculdade de Medicina, Universidade do Porto, Porto, Portugal)

Background: The Systolic Blood Pressure Intervention Trial (SPRINT) showed that in non-diabetic patients with high cardiovascular risk, intensive systolic blood pressure reduction was associated with lower rates of major cardiovascular events and mortality. However, intensive treatment was associated with increased CKD incidence. We evaluated the association between mean arterial pressure (MAP) reduction and CKD incidence in the intensive-treatment group.

Methods: We performed a secondary analysis of the SPRINT trial. We categorized patients in the intensive-treatment group according to MAP reduction: <20 mmHg; 20 to <40 mmHg; ≥40 mmHg. We defined the primary outcome as ≥30% reduction in eGFR to <60 ml/min/1.73m², and the secondary outcomes as cardiovascular events or death. We also performed a propensity score analysis, matching patients in each MAP reduction category from the intensive-treatment group with patients from the standard-treatment group, in order to calculate the number needed to treat (NNT) regarding cardiovascular events and the number needed to harm (NNH) regarding CKD incidence.

Results: 1138 (34.4%) patients presented MAP reduction <20 mmHg, 1857 (56.3%) presented 20 to <40 mmHg and 309 (9.4%) ≥40 mmHg. Adjusted hazard ratios for CKD incidence were 2.14 (95% CI, 1.25-3.66) for MAP reduction between 20 and 40 mmHg and 6.35 (95% CI, 3.72-11.49) for MAP reduction ≥40 mmHg. In the propensity score analysis, MAP reduction <20 mmHg presented a NNT of 43.5 and a NNH of 65.4, MAP reduction between 20 and <40 mmHg presented a NNT of 41.7 and a NNH of 35.1 and MAP reduction ≥40 mmHg presented a NNT of 95.2 and a NNH of 15.9.

Conclusions: Higher categories of MAP reduction were associated with increased risk of CKD incidence. The benefit-risk balance of intensive treatment was less favourable as MAP reduction increased.

Funding: NIDDK Support

Figure 1. Unadjusted least-square means and standard error of eGFR, urinary ACR and urinary biomarkers at baseline and the 4-year follow-up.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Longitudinal Changes in Plasma Biomarkers Strongly Associate with Risk for DKD Progression in the VA NEPHRON-D Trial
Steven G. Coca,1 Yuan Huang,2 Dennis G. Molechina,1 Veena Rao,3 Divya A. Vergheese,1 Wasim Obied,1 Girish N. Nadkarni,1 Bart Ferket,1 Linda F. Fried,1 Chirag R. Parikh,1 1Uehn School of Medicine at Mount Sinai, New York, NY; 2VA Cooperative Study Program, West Haven, CT; 3Yale School of Medicine, New Haven, CT; 4VA Pittsburgh Healthcare System, Pittsburgh, PA; 5Yale University and VAMC, New Haven, CT.

Background: While baseline levels of plasma TNFR-1, TNFR-2, and KIM-1 are independently associated with risk for renal function decline in diabetic kidney disease (DDK), the prognostic value of longitudinal changes in these biomarkers is unknown.

Methods: In this ancillary study of the Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) Trial, plasma biomarkers were included in plasma samples at both baseline and 1-year in 636 participants. We measured plasma TNFR-1, TNFR-2 and KIM-1 via MesoScale Discovery multiplex assay. We assessed the association between the change in plasma biomarker concentrations at 12 months from baseline with the renal endpoint (decline in eGFR or ESRD as defined in the trial) using Cox Proportional Hazards Models with adjustment for study arm, biomarker, eGFR and albuminuria at baseline and change in eGFR and albuminuria by 12 months.

Results: In the 123 (16%) participants who experienced the renal endpoint after 12 months, plasma TNFR1, TNFR2 and KIM-1 increased by 34%, 17%, and 6% respectively by 12 months (TABLE). In the 636 participants that did not reach the renal endpoint, plasma TNFR1 and TNFR2 increased by 11% and 3%, respectively, whereas KIM-1 decreased by 6%. After multivariable adjustment, including baseline biomarker concentration, eGFR, and change in eGFR from baseline at 12 months, increases in TNFR1, TNFR2 and KIM-1 over time were associated with increased hazards of developing the renal end point (TABLE). There were no statistically significant differences in the change in the three biomarkers or interactions on the outcomes between the combination-therapy and placebo therapy arms.

Conclusions: Longitudinal changes in plasma TNFR1, TNFR2 and KIM-1 add additional prognostic information to baseline concentrations of these markers, even after accounting for clinical variables, including changes in eGFR and albuminuria.

Funding: NIDDK Support, Veterans Affairs Support

---

Sustainable Urokinase Plasminogen Activation Receptor and Cardiovascular Mortality in Persons Undergoing Coronary Angiography
Claudia Sommerer,1 Marcus E. Kleber,1 Christian Morath,2 Jochen Reiser,2 Martin G. Zeier,1 Winfried März,1 Heidelberg University, Heidelberg, Germany; 3Rush University Medical Center, Chicago, IL; 4Synlab Services GmbH, Mannheim, Germany; 5Nephrology, University Hospital of Heidelberg, HEIDELBERG, Germany; 6University of Heidelberg, Germany.

Background: Soluble urokinase plasminogen activation receptor (suPAR) is an emerging biomarker for prediction and progression of kidney disease and cardiovascular outcomes. To further validate the value of suPAR as a cardio-renal biomarker we studied German persons undergoing coronary angiography having a follow-up of ten years.

Methods: suPAR was measured in baseline samples of participants of the Ludwigshafen Risk and Cardiovascular Health (LURIC) study. We estimated overall risk of cardiovascular death by Cox proportional hazards regression according to quartiles of suPAR, including age, sex, use of lipid-lowering drugs, body mass index, diabetes and proteinuria. The association between suPAR and cardiovascular outcomes were analyzed in a fully adjusted model, including eGFR or inflammation (IL-6 and CRP) did not materially alter this relationship. In a fully adjusted model HRs for cardiovascular death were 1.52 (95% CI 1.11-2.09), 1.56 (95% CI 1.14-2.15), and 1.78 (95% CI 1.28-2.46) in quartiles two to four.

Conclusions: suPAR predicts cardiovascular death over a period of ten years in persons undergoing coronary angiography, independent of kidney function and markers of systemic inflammation. su-PAR has the potential to stratify the risk in patients with cardiovascular disease and kidney disease. suPAR could be a useful and additional biomarker in cardiovascular and renal medicine.

Funding: Private Foundation Support

---

Treatment of Metabolic Acidosis in CKD with Fruits and Vegetables Yields Better Overall Health Outcomes Than Oral NaHCO3
Nimrat Goraya,1,2 Jan Simoni,1 Yolanda Munoz Maldonado,1 Donald E. Wesson,3 1Biostatistics, Baylor Scott & White Health, Temple, TX; 2Diabetes Health and Wellness Institute, Dallas, TX; 3Surgery, Texas Tech University Health Sciences Center, Lubbock, TX; 4Internal Medicine, Baylor Scott and White Health, Temple, TX; 5Internal Medicine, Texas A and M School of Medicine, Temple, TX.

Background: Dietary acid reduction added to pharmacologic anti-angiotensin II therapy appears to provide adjunctive kidney protection and KDIGO guidelines recommend Na+-based alkali for treatment of metabolic acidosis in chronic kidney disease (CKD). Nevertheless, base-producing fruits and vegetables (F+V) also improve cardiovascular disease and kidney disease. su-PAR could be a useful and additional biomarker in cardiovascular and renal medicine.

Methods: One hundred eight macroalbuminuric, non-diabetic CKD 3 subjects with metabolic acidosis but with serum [HCO3] between 22-44 meq/L were randomized to receive F+V (n=36) in amounts to reduce dietary potential renal acid load by half, oral NaHCO3 (HCO3, n=36) or Usual Care (UC, n=36). All had a systolic blood pressure (SBP) goal < 130 mm Hg using drug regimens including ACE inhibitors. The primary outcome was a composite of cardiovascular death or ESRD as defined in the trial) using Cox Proportional Hazards Models accounting for clinical variables, including changes in eGFR and albuminuria.

Results: In the 123 (16%) participants who experienced the renal endpoint after 12 months, plasma TNFR1, TNFR2 and KIM-1 increased by 34%, 17%, and 6% respectively by 12 months (TABLE). In the 636 participants that did not reach the renal endpoint, plasma TNFR1 and TNFR2 increased by 11% and 3%, respectively, whereas KIM-1 decreased by 6%. After multivariable adjustment, including baseline biomarker concentration, eGFR, and change in eGFR from baseline at 12 months, increases in TNFR1, TNFR2 and KIM-1 over time were associated with increased hazards of developing the renal end point (TABLE). There were no statistically significant differences in the change in the three biomarkers or interactions on the outcomes between the combination-therapy and placebo therapy arms.

Conclusions: Longitudinal changes in plasma TNFR1, TNFR2 and KIM-1 add additional prognostic information to baseline concentrations of these markers, even after accounting for clinical variables, including changes in eGFR and albuminuria.

Funding: NIDDK Support, Veterans Affairs Support

---

FR-OR122

Treatment of Metabolic Acidosis in CKD with Fruits and Vegetables Yields Better Overall Health Outcomes Than Oral NaHCO3
Nimrat Goraya,1,2 Jan Simoni,1 Yolanda Munoz Maldonado,1 Donald E. Wesson,3 1Biostatistics, Baylor Scott & White Health, Temple, TX; 2Diabetes Health and Wellness Institute, Dallas, TX; 3Surgery, Texas Tech University Health Sciences Center, Lubbock, TX; 4Internal Medicine, Baylor Scott and White Health, Temple, TX; 5Internal Medicine, Texas A and M School of Medicine, Temple, TX.

Background: Dietary acid reduction added to pharmacologic anti-angiotensin II therapy appears to provide adjunctive kidney protection and KDIGO guidelines recommend Na+-based alkali for treatment of metabolic acidosis in chronic kidney disease (CKD). Nevertheless, base-producing fruits and vegetables (F+V) also improve cardiovascular disease and kidney disease. su-PAR could be a useful and additional biomarker in cardiovascular and renal medicine.

Methods: One hundred eight macroalbuminuric, non-diabetic CKD 3 subjects with metabolic acidosis but with serum [HCO3] between 22-44 meq/L were randomized to receive F+V (n=36) in amounts to reduce dietary potential renal acid load by half, oral NaHCO3 (HCO3, n=36) or Usual Care (UC, n=36). All had a systolic blood pressure (SBP) goal < 130 mm Hg using drug regimens including ACE inhibitors. The primary outcome was a composite of cardiovascular death or ESRD as defined in the trial) using Cox Proportional Hazards Models accounting for clinical variables, including changes in eGFR and albuminuria.

Results: In the 123 (16%) participants who experienced the renal endpoint after 12 months, plasma TNFR1, TNFR2 and KIM-1 increased by 34%, 17%, and 6% respectively by 12 months (TABLE). In the 636 participants that did not reach the renal endpoint, plasma TNFR1 and TNFR2 increased by 11% and 3%, respectively, whereas KIM-1 decreased by 6%. After multivariable adjustment, including baseline biomarker concentration, eGFR, and change in eGFR from baseline at 12 months, increases in TNFR1, TNFR2 and KIM-1 over time were associated with increased hazards of developing the renal end point (TABLE). There were no statistically significant differences in the change in the three biomarkers or interactions on the outcomes between the combination-therapy and placebo therapy arms.

Conclusions: Longitudinal changes in plasma TNFR1, TNFR2 and KIM-1 add additional prognostic information to baseline concentrations of these markers, even after accounting for clinical variables, including changes in eGFR and albuminuria.

Funding: NIDDK Support, Veterans Affairs Support

---

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-OR123

Blood Pressure Lowering and Risk of Mortality in CKD: A Meta-Analysis of Randomized Controlled Trials Rakesh Malhotra, Hoang Anh Nguyen, Oscar Benavente, Mihriye Mete, Jonathan Mant, Michelle Odden, Carmen A. Peralta, Alfred K. Cheung, Girish N. Nadkarni, Ruth L. Coleman, Holman Rury, Alberto Zanchetti, Ruth Peters, Nigel Beckett, Jan A. Staessen, Joachim H. Ix, Ichon School of Medicine, New York, NY; Medstar Health Research Institute, Hyattsville, MD; Oregon State University, Corvallis, OR; Studies Coordinating Centre, Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Diseases, University of Leuven, Leuven, Belgium; UCSD Department of Nephrology and Hypertension, San Diego, CA; University of British Columbia, Vancouver, BC, Canada; University of California San Francisco/SFVAMC, San Francisco, CA; University of Cambridge, Cambridge, United Kingdom; University of Utah, Salt Lake City, UT; UCSD, San Diego, CA; University of Oxford, Oxford, United Kingdom; Instituto Auxologico Italiano, University of Milan, Milan, Italy; Imperial College London, London, United Kingdom; Guys and St Thomas’ NHS Foundation Trust, London, United Kingdom.

Background: Trials in hypertensive patients demonstrate that intensive blood pressure (BP) lowering reduces CVD and mortality risk, but may increase risk of chronic kidney disease (CKD) progression. Whether intensive BP lowering is associated with a lower mortality in patients with prevalent CKD remains uncertain.

Methods: We conducted a meta-analysis of randomized controlled trials (RCTs) that enrolled patients with CKD stage 3-5 and determined whether randomization to more vs. less intensive BP control was associated with mortality. Ovid Medline, Cochrane Library, Embase, Pubmed, and ClinicalTrials.gov electronic databases were searched. All RCTs that compared two defined BP targets (either active treatment vs. placebo or no treatment, or intensive vs. less intensive BP control) and enrolled persons with CKD stages 3-5 exclusively or as CKD subgroup between January 1950 and June 2016 were included. The main outcome was mortality during the active phase of each trial.

Results: We identified 31 RCTs, among which we were able to extract the CKD subset mortality data in 19 trials. There were 1300 deaths among 15,861 participants with CKD. More vs. less-intensive BP control resulted in 14% lower risk of all-cause mortality (Odds Ratio (OR) 0.86; 95% CI 0.76-0.96, p = 0.009) (Figure 1), a finding that was without significant heterogeneity (p<non-sig) across subgroups including type of treatment in the comparator arm (placebo vs. less intensive BP target), length of follow-up, presence of diabetes, baseline SBP, achieved SBP during the trial and degree of SBF differences across the treatment arms.

Conclusions: Randomization to more intensive BP control is associated with lower mortality risk among CKD trial participants.

Figure 1. Effect of Intensive BP Lowering on Risk of Mortality in Participants with CKD

FR-OR124

Influence of Altitude on the Prevalence of Anemia of CKD Christos Argyropoulos, V. Shane Pankratz, Orrin Myers, Mark L. Urru, Keith C. Norris, Joseph A. Vassalotti, Ichan School of Medicine at Mount Sinai, New York, NY; UCLA, Marina Del Rey, CA; UMN Health Sciences Center, Albuquerque, NM; University of New Mexico, Albuquerque, NM.

Background: Hypoxia is the major regulator of erythropoietin production in the kidney. There are currently minimal data about the prevalence of anemia in patients with varying degrees of CKD who reside in high altitudes.

Methods: We undertook an exploratory analysis of the National Kidney Education Program Early Evaluation Program. Participant’s address were geo-coded to geographic coordinates using National Elevation US Database and the altitude of the residence of each participant in KEEP was determined. We examined prevalence of anemia (Hemoglobin, Hgb < 10g/dl) against the severity of CKD (eGFR) and other predictors after stratifying the KEEP participants to the US census, in order to account for the self-selection bias in KEEP.

Results: In multivariate analyses, race, ACR, personal history of anemia (Table), age (a relationship that differed between women Figure A and men Figure B), eGFR and altitude were significant predictors of the odds of anemia (p<0.001). Predicted prevalence of anemia was half at 2.0 km elevation vs. sea level for all eGFR values (Figures CD). There was no interaction between altitude and eGFR.

Conclusions: The odds of anemia differ for individuals residing at different altitudes. This relationship likely contributes to geographic disparities of CKD complications. Further studies should examine the response to iron and ESA according to altitude.

Funding: Commercial Support - Dialysis Clinic Inc

Categorical associations with anemia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Race (Caucasian vs.)</th>
<th>Gender (Men vs. Women)</th>
<th>ACR (&gt;30 vs. ≤30)</th>
<th>ACR (&gt;3.5 vs. ≤3.5)</th>
<th>Peripheral Hb of Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>Odds Ratio (95% CI)</td>
<td>Odds Ratio (95% CI)</td>
<td>Odds Ratio (95% CI)</td>
<td>Odds Ratio (95% CI)</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Women</td>
<td>1.2 (0.89 - 1.64)</td>
<td>1.6 (1.28 - 2.08)</td>
<td>1.7 (1.4 - 2.17)</td>
<td>2.0 (1.8 - 3.40)</td>
<td>10.4 (7.6 - 13.6)</td>
</tr>
</tbody>
</table>

FR-OR125


Nephrology, University of Florida, Gainesville, FL; Mayo Clinic College of Medicine, Rochester, MN; Nephrology, NF/SVHs, Gainesville, FL.

Background: Hypokalemia is associated with increased ammonia excretion, but neither the specific proteins that signal this response nor the functional role of increased ammonia excretion are known. This study’s purpose was to determine NBCCel-A’s role in the effect of hypokalemia on renal ammonia metabolism and potassium homeostasis.

Methods: We used mice with NBCCel-A deletion generated using TALEN techniques. We compared mice with homozygous deletion (KO) to wild-type (WT) littermates. Hypokalemia was induced by feeding a K-free diet for 7 days. Results: A K-free diet caused persistently increased urinary ammonia excretion in WT mice, whereas in KO mice urinary ammonia increased only on day 1 and 2, and then returned to baseline. In proximal convoluted tubule (PCT), NBCCel-A KO had significantly lower expression, compared to WT, of key ammonogenetic proteins, phosphoenolpyruvate carboxykinase (PEPCK) and phosphate-dependent glutaminase (PDG), and greater expression of the ammonia-recycling protein, glutamine synthetase (GS). In contrast, in the proximal straight tubule (PST) in the outer medulla, where relatively little NBCCel-A expression is found compared to the PCT, hypokalemic KO mice exhibited PEPCK and PDG expression that was greater and GS expression that was less than in hypokalemic WT. NBCCel-A deletion also altered renal K handling during hypokalemia. Serum K did not differ on normal diet, but was lower in KO mice on K-free diet (KO 1.80±1.0; WT 3.2±0.1 mM, P<0.01). Despite more severe hypokalemia, urinary K was significantly higher, 75%±16% greater in KO than WT during days 3-7, when maximal K conservation occurred in both WT and KO. Total NCC expression was unchanged, but phosho-NCC, which decreases renal K excretion, was significantly less in hypokalemic KO than WT mice.

Conclusions: 1) NBCCel-A is essential to the signaling pathway that increases ammonia excretion in response to hypokalemia; 2) KO mice partially compensate to NBCCel-A deletion with supranormal responses in PST; and, 3) NBCCel-A is critical for PT signaling to distal sites to conserve K through a mechanism that may involve NCC phosphorylation. Thus, hypokalemia’s induction of ammonia metabolism via NBCCel-A may be a critical signaling mechanism regulating distal epithelial K transport.

Funding: NIDDK Support, Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-OR126
Expression, Localization, and Role of Slc4a8 (NDBCE) in Acid Base Transport in Kidney Tubules Jie Xu,1,2Sharon L. Barone,1,2Marybeth Brooks,1Manoocher Soleimani,1,21University of Cincinnati, Cincinnati, OH;2Research Services, Veterans Administration, Cincinnati, OH.

Background: The sodium-dependent bicarbonate transporter Slc4a8, also known as NDBCE, mediates the cotransport of sodium and bicarbonate in exchange for chloride (Na-dependent Cl-/HCO3- exchanger). NDBCE is abundantly detected in the brain, with very low expression levels in the kidney. The cell distribution, subcellular localization and role of NDBCE in acid/base and electrolyte homeostasis in the kidney have been the subject of conflicting reports. There are no localization studies (such as immunolabeling and/or in situ hybridization) and no functional studies to pinpoint the location and demonstrate the function of NDBCE in the kidney.

Methods: Molecular techniques including RT-PCR, Northern Hybridization and in situ hybridization experiments using FISH (Fluorescence In Situ Hybridization) showed very little to no expression for NDBCE in the cortex or in cortical collecting ducts (CCD). NDBCE was predominantly detected in the kidney medulla with significant expression in medullary collecting ducts. NDBCE was targeted to the basolateral membrane of MDCK cells when grown in hypertonic medium, a physiologic environment for cells in medullary collecting duct. NDBCE deficient mice showed altered urea and bicarbonate wasting phenotypes under baseline condition, and their urine pH remained comparable to wild type mice in response to bicarbonate loading or salt restriction. Expression levels of pendrin and NCC were comparable in kidney cortices of NDBCE KO and wild type mice.

Conclusions: Slc4a8 (NDBCE) is predominantly detected in mouse medullary collecting duct, is targeted to the basolateral membrane, shows increased activity in hypertonic environment and its deletion does not cause any noticeable acid base perturbation either under baseline conditions or in response to bicarbonate loading or salt restriction.

Funding: Veterans Affairs Support, Private Foundation Support
FR-OR127
Robust Circadian Clock Oscillation and Osmotic Rhythms in the Inner Medulla Reflecting Cortico-Medullary Osmotic Gradient Rhythm in Rodent Kidney Masayuki Haru,1,2Toichi Minami,1 Nobuya Koike,1 Tetsuro Kubasa,2Keichi Tamagaki,2 Kauzihiro Yagita.1 1Physiology and Systems Bioscience, Kyoto Prefectural University of Medicine, Kyoto, Japan; 2Nephrology, Kyoto Prefectural University of Medicine, Kyoto, Japan.

Background: Circadian clocks in mammals function in most organs and tissues throughout the body. Various renal functions such as the glomerular filtration and excretion of electrolytes exhibit circadian rhythms. Although it has been reported that the expression of the clock genes composing molecular oscillators show apparent daily rhythms in rodent kidneys, functional variations of regional clocks are not yet fully understood.

Methods: 1) To monitor the molecular clock work and localization, we applied the method of chromoluminescence imaging method of the PER2::Luciferase knock-in mouse. 2) We analyzed the circadian fluctuation of the cortico-medullary osmotic pressure gradient. 3) We analyzed diurnal expression patterns of genes contributing to high osmotic pressure and reabsorption of water in mice kidneys. 4) To analyze the effect of molecular clock gene knockout on osmotic pressure gradient, we measured osmotic pressure gradient in systemic pressure and reabsorption of water in mice kidneys. 5) To analyze the effect of molecular clock gene knockout on osmotic pressure gradient and of expression of genes (V1aR, V2R, UT-A2, and Aqp2) show diurnal variations in the inner medulla. 4. Systemic Bmal1 deficient mice impaired circadian rhythm of osmotic pressure gradient and of expression of genes (V1aR, V2R, UT-A2, and Aqp2) in the inner medulla.

Results: 1) PER2::Luciferase knock-in mice exhibited strong and robust circadian clock oscillation in the medulla. 2) Signficant diurnal rhythm of the tissue osmolality with peaking at night (active phase) was found in the medulla but not in the cortex. This suggests that cortico-medullary osmotic pressure gradient changes diurnally depending on osmotic pressure rhythm in the inner medulla. 3. Vasopressor receptors (V1aR, V2R), urea transporter (UT-A2) and water channel (Aqp2) show diurnal variations in the inner medulla. 4. Systemic Bmal1 deficient mice impaired circadian rhythm of osmotic pressure gradient and of expression of genes (V1aR, V2R, UT-A2, and Aqp2) in the inner medulla.

Conclusions: The circadian clocks in the medulla of the kidney regulate the circadian rhythm of genes expressed in relation to the water reabsorption and subsequent cortico-medullary osmotic pressure gradient, resulting in the physiological day-night rhythm of urination.

Funding: USDA, NIH, and JSPS
FR-OR128
Global Identification of Protein Phosphorylation Changes Following CRISPR-Cas9-Deletion of aCAMP-Dependent Protein Kinase (PKA) in Collecting Duct Cells Jie Xu,1 Huijun Hou,1 Mark A. Knepper,11NHLIB/NHLBI, Bethesda, MD.

Background: Vasopressin regulates water and sodium transport in collecting duct principal cells by binding to the V2 receptor and increasing cAMP, thereby activating cAMP-regulated protein kinase PKA catalytic subunits PKA-Cα and/or PKA-Cβ. Signaling downstream from PKA is poorly understood.

Methods: To identify PKA-dependent phosphorylation changes, we deleted both PKA catalytic subunits using CRISPR-Cas9 in vasopressin-sensitive mKCC6 cells. Indel mutations were confirmed by Sanger sequencing. We carried out large-scale quantitative phosphoproteomic analysis using mass protein spectrometry in three pairs of PKA-knockout (KO) vs. control clones. The cells were grown on permeable supports in the presence of 0.1 mM IBMX.

Results: The PKA-KO cells maintained viability and polarity. Phosphoproteomics identified 229 PKA substrate sites. These sites contained the motif R-(R/K)-Y-P and were significantly decreased in PKA-KO. Most of these PKA targets are not annotated in public databases. Surprisingly, a large number of phosphorylation sites with the motif X-(pS/pT)P showed increased phospho-occupancy, pointing to increased activity of one or more MAP kinases in PKA-KO cells. Indeed, a marked increase in phosphorylation of ERK2 at T183 and Y185 (which activates ERK2) was seen in PKA-KO cells. The ERK2 is downstream from a direct PKA site in Sipa11, which directly inhibits Raf1 through Rap1 inactivation. Aquaporin-2 phosphorylation at S256 was not decreased in PKA-KO cells. The datasets were integrated to identify a causal neuronal pathway describing PKA signaling that explains vasopressin’s actions to regulate membrane trafficking and gene transcription. The model predicts that, through PKA activation and interaction of MAP kinase signaling, vasopressin is converted to vasopressin-responsive genes (confirmed by ChIP-seq).

Conclusions: We conclude that PKA-dependent signaling is more complex than previously believed with both primary and secondary effects on phosphorylation that explain vasopressin responses.

Funding: Other NIH Support - NHLBI

FR-OR129
Proteomics and Water Channel Function of AQP2-Rich Extracellular Vesicles in Human Ursula Y. Kalin,1 Yuki Miyazawa,1 Saki Mikami,1 Masaki Sakai,1 Takahiro Suzuki,1 Kenichi Ishimatsu,2 Sei Sasaki,2 1Meiji Pharmaceutical University, Kiyose-shi, Japan; 2Tokyo Medical and Dental University, Tokyo, Japan.

Background: AQP2 water channel is a key membrane protein which determines urine concentrating ability. AQP2 is excreted in urine in a form of extracellular vesicles (EVs), mostly in exosomes and urine AQP2 is now measured as a useful biomarker for diagnosis and treatment of water-balance disorders. However, proteomic and functional analysis of AQP2-bearing EVs have not yet been performed.

Methods: Urine EVs were obtained from healthy volunteers by the differential centrifugation. Membrane-disrupted (freeze-thaw) AQP2-bearing EVs were obtained by immunoprecipitation with an AQP2-specific antibody and the proteins were digested with tryptic and applied to LC/MS based peptide mass analysis. The proteins were also analyzed by Western blots. Osmotic water permeability (Pf) of the AQP2-enriched EVs was measured by a stopped flow method monitoring 90 degree scattered light intensity in response to outwardly directed osmotic gradient created by glycerol.

Results: 1) The MS analysis of the EVs co-immunoprecipitated with the AQP2 antibody identified 137 proteins, surprisingly, 103 of these 137 proteins have been shown to express in collecting duct cells, suggesting that our co-immunoprecipitation successfully gather AQP2-bearing EVs membranes. Pathway analysis show the presence of water channels, urea transporters, and multiple vesicular body-related proteins such as TSG101, ALIX, CHMP1-6, VPS4,7,9,25. MS analysis of urine EVs showed the phosphorylation of AQP2 at Ser256 and Ser261. Western blot analysis confirmed the presence of these proteins and Ser256, S261, and S269 phosphorylated AQP2. 2) Pf of 160,000 xg EVs was 4.75 ± 0.38 x 10^-10 cm/s which was inhibited by 0.3 mM HgCl2 pretreatment. The activation energy was 3.51 kcal/mol which is consistent with a water channel activity. Pf was not detectable when EVs membranes were disrupted by extensive sonication. The measured Pf values of EVs samples were proportional to the protein amounts of AQP2 (r=0.95, p<0.014). A positive correlation was also observed between the EVs Pf and osmolality of the urine from which urine EVs were prepared (r=0.879, p=0.049).

Conclusions: Urine AQP2 excretion is mediated by late endosome-multiple vesicular body pathway, and AQP2 at EVs preserve the original water channel function. AQP2 is excreted in urine in a form of extracellular vesicles (EVs), mostly in exosomes and urine AQP2 is now measured as a useful biomarker for diagnosis and treatment of water-balance disorders. However, proteomic and functional analysis of AQP2-bearing EVs have not yet been performed.

Funding: Government Support - Non-U.S.

FR-OR130
RNA-Seq in Microdissected Rat Cortical Collecting Ducts during Development of Lithium-Induced Nephrogenic Diabetes Insipidus Chih-chien Sung,1 Chung-Lin Chou,1 Li-Mei Chen,2 Hyun Jun Jung,3 Mark A. Knepper,11NHLIB/NHLBI, Bethesda, MD; 2Tri-Service General Hospital, Taipei, Taiwan.

Background: Lithium has been widely used to treat bipolar disorder, but many patients develop nephrogenic diabetes insipidus (NDI). Our previous studies in rats have demonstrated rapid activation of ERK1/ERK2 in collecting ducts after oral lithium administration (Trepiccione et al., KI, 2014). Associated gene expression changes early in patients develop nephrogenic diabetes insipidus (NDI). Our previous studies in rats have demonstrated rapid activation of ERK1/ERK2 in collecting ducts after oral lithium administration (Trepiccione et al., KI, 2014). Associated gene expression changes early in treatment were explored using a whole-transcriptome RNA-Seq approach.

Methods: RNA-Seq in Microdissected Rat Cortical Collecting Ducts during Development of Lithium-Induced Nephrogenic Diabetes Insipidus.

Conclusions: AQP2 is a water channel that regulates urine concentrating ability. AQP2 is excreted in urine in a form of extracellular vesicles (EVs), mostly in exosomes and urine AQP2 is now measured as a useful biomarker for diagnosis and treatment of water-balance disorders. However, proteomic and functional analysis of AQP2-bearing EVs have not yet been performed.

Funding: Other NIH Support - NHLBI
Results: Lithium-treated rats showed increased water intake within 24 hr, consistent with a fluid secretion (osmotic water transport). RNA-Seq data at 72 hr revealed moderate decreases in AQP2, AQP3, and AQP4 mRNA. The three subunits of ENaC showed more profound decreases. A large number of transcripts coding for other transporters and receptors were decreased with lithium treatment including the vasopressin V2 receptor and the chloride channel ClC-Kb. Several known aldosterone-regulated genes showed decreases in mRNA including Sgk1, eNaC, and Gadd45g. Immediate early genes (typical of MAP kinase activation) and transcriptional targets of NF-κB were significantly more frequent among transcripts increased with lithium than among decreases (not shown and Supplement). Similar responses were observed in affected transcripts were seen for two other pathways, e.g. cell cycle signaling, and Wnt signaling. No association with lithium treatment was found for several pathways including cyclic AMP signaling, estrogen receptor signaling and insulin signaling. In contrast to the CD, significant changes were found in mRNA levels in CTALs in response to lithium, indicating the effect of lithium was selective for CCD.

Conclusions: Cellular signaling during development of lithium-induced NDI is consistent with known responses to increased MAP kinase activation and includes major gene expression changes characteristic of NF-κB-dependent inflammatory signaling.

Funding: Other NIH Support - NIDDK

FR-OR131

Identification of miRNAs Regulating the Water Transporter in the Collecting Duct

Irpino, Italy; 2University of Aarhus, Aarhus, Denmark; 3Biogem scarl, Ariano Irpino, Italy; 4Laboratoire National de Santé, Dudelange, Luxembourg; 5Univ. of Campinas Luigi Vanvilliti, Napoli, Italy; 6Dpt of Cardio-Thoracic and Respiratory Science, University of Campina, Naples, Italy.

Background: Principal cells (PC) contribute to water reabsorption in the collecting duct (CD). In response to vasopressin, they express on their apical membrane the AQP2, and so increase water permeability of the CD. Finally, an interstitium driven osmotic gradient leads the water to be reabsorbed. Although several molecular mechanisms have been identified as master regulators of this process, both dependent and independent by vasopressin stimulation, no miRNAs involved in the water reabsorption are known. miRNAs are post-transcriptional regulators of gene expression and, thus, are appealing targets for new therapy. We aim to identify the miRNAs involved in urinary concentrating mechanism to fill this gap.

Methods: To identify whether the miRNAs are crucial for the water reabsorption in the CD, the gene expression profile of the CD was studied in the AQP2 KO mice using the Affymetrix gene chips. By microarray analysis we compared the miRNAs expressing profile of the inner medulla from Dicer cKO and their littermate control mice. miRNAs target prediction and IPA analysis was used to build a network of interaction between miRNAs and target proteins.

Results: Single segment evaluation of Dicer expression confirmed its ablation only in the CD. Dicer-AQP2 cKO mice present with a severe water concentrating defect that is resistant to AVP administration. Loss of expression of AQP2 and AQP2 protein abundance (western blotting). RNA-Seq data at 72 hr revealed moderate decreases in AQP2, AQP3, and AQP4 mRNA. The three subunits of ENaC showed more profound decreases. A large number of transcripts coding for other transporters and receptors were decreased with lithium treatment including the vasopressin V2 receptor and the chloride channel ClC-Kb. Several known aldosterone-regulated genes showed decreases in mRNA including Sgk1, eNaC, and Gadd45g. Immediate early genes (typical of MAP kinase activation) and transcriptional targets of NF-κB were significantly more frequent among transcripts increased with lithium than among decreases (not shown and Supplement). Similar responses were observed in affected transcripts were seen for two other pathways, e.g. cell cycle signaling, and Wnt signaling. No association with lithium treatment was found for several pathways including cyclic AMP signaling, estrogen receptor signaling and insulin signaling. In contrast to the CD, significant changes were found in mRNA levels in CTALs in response to lithium, indicating the effect of lithium was selective for CCD.

Conclusions: Cellular signaling during development of lithium-induced NDI is consistent with known responses to increased MAP kinase activation and includes major gene expression changes characteristic of NF-κB-dependent inflammatory signaling.

Funding: Other NIH Support - NIDDK

FR-OR132

ILDR1 Expression in the Tricellular Junction Regulates Epitelial Water Permeability

Nina Himmerkus, Yongfeng Gou, Susanne Milatz, Cosima Merkel, Jianghui Hou, Markus Bleich, Christian Albrechts University Kiel, Kiel, Germany; 2Washington University School of Medicine, Saint Louis, MO.

Background: The ability to produce a wide range of urine osmolality depends on the epithelial water permeability of the thick ascending limb (TAL). The collecting duct (CD) is responsible for producing a wide range of urine osmolality by changing the transepithelial water permeability under control of anti-diuretic hormone (AVP). Water tightness of the space in between the CD segments TAL and CD and it confers paracellular water tightness. Impaired water tightness in the TAL by ILDR1 knockout impedes the dilution of the luminal fluid as well as the concentration of the medullary interstitium. ILDR1 might therefore be a new target to regulate renal concentrating ability.

Funding: Other NIH Support - RO1DK084059

FR-OR133

Renal Phenotype of P2Y12 Receptor Knockout Mice

Bellamkonda K. Kishore, Kenny M. Hansson, Tao Liu, Kerstin Magnell, Noel G. Carlson, Yue Zhang, AstraZeneca, Cardiovascular and Metabolic Diseases iMED, Mölndal, Sweden; 2AstraZenecaR&D, Mölndal, Sweden; 3Univ. of Utah & VA Medical Center, Salt Lake City, UT; 4Univ. of Utah and VA Medical Center, Salt Lake City, UT; 5VA Salt Lake City Health Care System, Salt Lake City, UT.

Background: Previously we reported that pharmacological blockade of P2Y12 receptor (R) potentiates the action of arginine vasopressin (AVP) on renal medullary collecting duct (mCD). To establish that the observed effect is mediated through P2Y12-R, we evaluated the renal phenotype of P2Y12-R global knockout (KO) mice.

Methods: The P2y12 gene was disrupted by targeted homologous recombination in ES cells. Urinary excretion of AVP, cAMP, PGE2, Na and K was assayed in adult homozygous KO and syngeneic C57/B6 wild type (WT) mice under basal conditions. Primary cultures of mCD cells from KO and WT mice were stimulated with 0.1 mM of dDAVP for 24 hr, and assayed for cAMP generation, and mRNA expression of AQP2.

Results: The urine from KO mice showed significant increases in cAMP, PGE2 and K compared to WT mice (see Table). Comparisons between mCD cells derived from KO and WT mice showed significantly higher production of cAMP in response to stimulation with dDAVP (16-fold vs. 4-fold, P < 0.006, N = 6). Significantly higher level of mRNA expression of AQP2 was observed in mCD from KO vs. WT mice after dDAVP stimulation (2.43-fold, P < 0.004).

Conclusions: These findings are consistent with our previous observations and show that loss of P2Y12-R by either pharmacological blockade or genetic deletion potentiates the action of AVP/dDAVP on mCD. These data also reveal that P2Y12-R may play a role in renal handling of sodium and potassium.

Funding: Vibeke Affairs Support, Commercial Support - AstraZeneca AB, Clinical Revenue Support

Oral Abstract FR-OR134

Novel Imaging Techniques Reveal Axial Differences in Endo-Lysosomal Uptake Capacity along the Kidney Proximal Tubule

Claudia D. Schub, 1Marc-Antoine Reiner, 1Dominique Reiner, 1Evgeni Stoyanov, 1Urs Elsom, 2Olivier Devyust, 3Andrew Hall, 3University of Zurich, Zurich, Switzerland; 2University of Zurich, Zurich, Switzerland; 3University of Zurich, Center for Microscopy and Image Analysis, Zurich, Switzerland.

Background: The kidney filters low-molecular weight proteins (LMWPs) and albumin, which are reclaimed by the proximal convoluted tubule (PCT) to prevent wasting in urine. PCT cells take up proteins across the apical membrane by receptor- mediated endocytosis, which involves binding to megalin, internalization into early endosomes (EE), and subsequent trafficking to late endosomes (LE) and lysosomes. Early (S1) and late (S2) PCT segments show ultrastructural differences in the endolysosomal system by EM, but how these might relate to differences in uptake capacity is unknown.

Methods: Confocal microscopy of immuno-stained mouse kidney. Multiphoton intravital imaging and 3-D analysis of cleared post-mortem tissue.

Results: Using established antibody markers for EEs (Eh5b), LEs (Lrb 7), recycling endosomes (Rab11) and lysosomes (LAMP1), we found that expression levels of these 4 markers were far higher in S1 than in S2 segments. In contrast, expression of megalin was similar in both. Intravital imaging revealed that uptake of dye-labeled albumin and
LMWP lysosome occurred exclusively in S1, whereas uptake of 10 kDa dextran — a subcytoplasmic molecule — was distributed throughout all the segments in S2. This pattern was repeated using two different fluorescent labels for each ligand to exclude a confounding effect on substrate handling. Real-time imaging of lysosome uptake revealed the expected dynamic progression from brush border to EEs, and then EEs/lysosomes. Following saturation of S1 capacity with a high concentration of injected lysosome, some uptake was observed in S2 segments, but it remained far lower than in S1. Antibody staining in tissue fixed post-lysosome injection revealed that the uptake pattern closely matched the expression of endo-lysosomal proteins, but not megalin. A major constraint of the assay is the limited depth of immersion fixation. We therefore treated fixed kidneys chemically with a modified CLARITY protocol to increase transparency. Using this approach, we were able to image through the entire cortex and confirm that lysosome uptake was confined to early segments in all PCTs, whereas dextran uptake was more diffused.

**Conclusions:** We have found evidence for major axial differences in endo-lysosomal uptake capacity along the PCT, independent of megalin expression.

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

**SA-OR001**

**Novel Imaging Technique Reveals Changes in the Podocyte Actin Network following Injury**

Hani Sulaiman,1 Andy S. Shaw,2 Jeffrey H. Miner.3

1Genentech, South San Francisco, CA; 2Washington University, Saint Louis, MO; 3Washington University School of Medicine, St. Louis, MO.

**Background:** Actin stress fibers are abundant structures in cultured cells, including podocytes, yet no clearly equivalent structures have been observed in vivo. This disparity has been thought to be the result of preparation methods, which do not preserve actin structures in their intact forms. Here we developed a new method that allows us to view actin stress fibers in their native state in the whole kidney glomerulus using focused ion beam scanning electron microscopy (FIB-SEM).

**Methods:** Kidney glomeruli from wild-type and Col4a3-/- (Alport) mice were isolated, the cytoskeleton was stabilized, and all tissue sections were extracted with detergent. Samples were processed and imaged using FIB-SEM using the serial block-face imaging mode.

**Results:** Block-face imaging of membrane-extracted healthy glomeruli reveals that the whole glomerulus is a network of actin cables, with the capillary network as electron dense material, similar to their appearance by transmission electron microscopy. In contrast, the cellular edges were completely gone, leaving behind only the contours of the cytoskeleton. This method allowed us to view the cytoskeleton of the foot processes (FPs), which formed a continuous electron dense sheet, incorporating the slit diaphragm (SDs) and covering the glomerular basement membrane (GBM). Tracking this dense material across serial sections in the FPs revealed continuity with the central actin cables in individual FPs that fuse together to form thick membrane (GBM). Tracking this dense material across serial sections in the FPs revealed continuity with the central actin cables in individual FPs that fuse together to form thick membrane.

**Conclusions:** Here, we imaged the complete cytoskeleton of the podocytes in both health and disease. Our data indicate that in the normal podocyte, actin filaments in the FPs are connected to the SDs to form one continuous network enclosing the capillary wall, like a wire mesh, suggesting that podocyte FPs and the SDs work as one unit to form the outer structure of the glomerular filtration barrier. Our data also indicate that in injured wall, like a wire mesh, suggesting that podocyte FPs and the SDs work as one unit to form the outer structure of the glomerular filtration barrier. We therefore treated fixed kidneys chemically with a modified CLARITY protocol to increase transparency. Using this approach, we were able to image through the entire cortex and confirm that lysosome uptake was confined to early segments in all PCTs, whereas dextran uptake was more diffused.

**Funding:** National Institute of Biomedical Imaging and Bioengineering; Department of Veterans Affairs.

**SA-OR002**

**Deep Mapping of the Podocyte Proteome Unravels Altered Protein Dynamics during Differentiation**

Christina B. Schroeder,2 Thomas Benzing,3 Markus M. Rinschen,1 Paul T. Brinkkötter,2 CEACD, Cologne, Germany; 1University Hospital Cologne, Cologne, Germany; 2University of Cologne, Köln, Germany.

**Background:** Podocytes are epithelial postmitotic cells which maintain the renal filtration barrier. Immortalized podocyte cell lines are widely utilized tools to estimate podocyte foot process rearrangement processes in vitro. We intended to generate a comprehensive map of proteins expressed in proliferating and differentiated cultured human podocytes in vitro thereby providing a thorough database and useful tool for researchers in the podocyte field.

**Methods:** We analyzed 7037 proteins in depth and quantified 7230 of them. We performed additional in-depth analyses of the cultured human podocyte proteome in order to characterize changes regarding protein expression, protein synthesis and proteostatic mechanisms during differentiation of the cells. We included a detailed analysis on the expression of podocyte-specific proteins that govern the function and dysfunction of the slit diaphragm, and of gene products mutated in hereditary nephrotic syndrome. Notably, this data set detected general perturbations in protein expression, which are highly conserved across different species. We therefore treated fixed kidneys chemically with a modified CLARITY protocol to increase transparency. Using this approach, we were able to image through the entire cortex and confirm that lysosome uptake was confined to early segments in all PCTs, whereas dextran uptake was more diffused.

**Conclusions:** In conclusion, podocyte differentiation in vitro is largely associated with a proteostatic shift, and the deep proteomic mapping approach utilized here may demonstrate the limitations, but also the potential of podocyte cell culture.

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

**SA-OR003**

**Super Resolution Microscopy and Automated Digital Image Processing as a Novel and Rapid Diagnostic Tool for Podocyte Foot Process Effacement**

Nicole Endlich,1 Florian Siegertist,1 Silvia Ribback,2 Frank Dombrowski,3 Kerstin U. Arnarn,3 Karlhans Endlich.1 1Anatomy and Cell Biology, University Medicine Greifswald, Greifswald, Germany; 2Pathology, University Medicine Greifswald, Greifswald, Germany; 3Nephropathology, University Medicine Erlangen, Erlangen, Germany.

**Background:** Podocyte foot process morphology plays an essential role for proper glomerular filtration. In glomerular diseases like minimal change disease, podocyte foot processes are replaced by flattened cell processes. Since foot processes are around 200-300 nm in width, morphometrics could only be performed by time consuming electron microscopy. Recently, super resolution microscopy techniques have been developed which allow lightweight microscopic imaging beyond Abbe’s optical resolution limit of ~200 nm. Using one of those techniques, structured illumination microscopy (SIM), it is now possible to double the optical resolution limit. We hypothesized that SIM would allow the analysis of podocyte morphology and to diagnose foot process effacement.

**Methods:** 4µm sections were obtained from formalin fixed and paraffin embedded renal tissue of human and murine origin and stained with an antibody against the slit diaphragm protein nephrin. We developed SIM protocols for SIM microscopy enabling automated quantification of morphometric data.

**Results:** In human samples, we measured a mean foot process width of 0.249±0.68 µm in healthy, and 0.675±0.246 µm in MCD patients. By the use of our custom made software we measured a slit diaphragm density of 3.999±0.268 µm in healthy compared to 23.59±7.98 µm in MCD patients. Using both methods we found statistically significant differences between the MCD patients in comparison to the healthy control subjects. As we found out that the both results highly correlate (R=0.91) we show that the techniques can be used equivalently. Furthermore, we show that we can image and measure foot process morphology in murine kidneys.

**Conclusions:** Taken together, we have established a novel method which allows quick analysis of kidney sections for foot process effacement in an automated fashion. Including this technique into the diagnostic routine could effectively shorten the time until diagnosis of podocyte foot process effacement in patients and in animal models.

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

**SA-OR004**

**Intravital Imaging Reveals the Important Role of A-Synuclein in Podocytes**

Georgina Gyrari-Brisot,1 Janis Petri-Peterdi.2

1University of Southern California, Los Angeles, CA 90013, CA.

**Background:** Podocytes are known to functionally express a number of neuron-specific genes. Recent studies of SNCAs in the brain demonstrated the Parkinson’s and Alzheimer’s disease amyloid a-synuclein (SNCA) to be one of the top secretory proteins (PMID:23950145), and top 5 phosphorytated with increased expression in Fabry disease podocytes (PMID:27681560). SNCA was also recently linked to disruption of the autophagy-lysosome pathway and neuropathology in Fabry disease (PMID:24529306). The present study aimed to establish the functional importance of SNCA in podocytes.

**Methods:** Constitutive or tamoxifen-inducible podocyte-specific SNCA knockout mice (iPod-SNCA KO) were generated that also expressed the intensely green calcium indicator GCaMP5/Tomato or the green/red mTmG reporter only in podocytes. Serial high resolution intravital multiphoton microscopy (MPM) of the same glomeruli in the same intact living kidney consecutively for three weeks was performed non-invasively via a dorsal abdominal imaging window to directly visualize and track the changes in glomerular and podocyte function including cell [Ca2+] after SNCA deletion.

**Results:** Immunohistochemistry revealed that human and mouse kidney tissue sections confirmed the podocyte-specific expression of SNCA. Intact podocyte and glomerular functions were found at baseline in iPod-SNCA mice. However, within one week of tamoxifen-induced SNCA KO, podocytes developed an enlarged cell body with balled-up foot processes which gradually progressed within two additional weeks to the appearance of focally increased cell [Ca2+] of podocyte detachment and shedding into the tubular fluid and migration to the parietal Bowman’s capsule, leakage of plasma albumin-Alexa594 into the filtrate and tubular fluid, and glomerular capillary microthrombosis blocking blood flow. This confirmed PUB-MPM as a tool to study podocyte primary and secondary processes and foot process effacement. Histology of constitutive Pod-SNCA kidney sections found numerous tuft attachments and detached podocytes.

**Conclusions:** This study visually demonstrated the development and progression of glomerular pathology after SNCA knockout, suggesting the important role of SNCA in maintaining normal podocyte and glomerular functions.

**Funding:** NIDDK Support
SA-OR005

aPKC Independent Signaling Events of Par3 at the Glomerular Slit Diaphragm Sybille Köhler, Carsten M. Niessen, Sandra Iden, Wilhelm Bloch, Bernhard Schermer, Thomas Benzing, Barry Denholm, Paul T. Brinkkoe{"tzer} 1 CECD University clinic of Cologne, Cologne, Germany; 2 Edinburgh University, Edinburgh, United Kingdom; 3 German Sport University Cologne, Cologne, Germany; 4 University Hospital Cologne, Cologne, Germany; 5 University of Cologne, Köln, Germany

Background: Polarity signaling through the aPKC-Par polarity complex is essential for the development and maintenance of the podocyte architecture and the function of the glomerular filtration barrier of the kidney. Despite its well-established role in aPKC-mediated signaling, Par3A appears to be dispensable for the function of the glomerular filtration barrier.

Methods: Results: mRNA seq data from primary podocytes revealed high levels of Par3B in podocytes, which were much higher in comparison to Par3A levels. Interestingly, loss of Par3B also did not cause glomerulosclerosis or albuminuria. To study a potential compensatory mechanism between Par3A and Par3B, we generated podocyte-specific Par3A/B double knockout mice. Par3A/B double knockout mice were born following Mendelian rules. Within 8 weeks of age Par3A/B DKO mice developed severe proteinuria in comparison to control mice. To further study the interplay between the different Par3 proteins, we utilized Drosophila nephrocytes. Here, we show co-localization of the Par3A/B homolog bazooka and the nephrocyte diaphragm proteins Snell (Snep) and Duf (NEPH1) in different developmental stages at the nephrocyte diaphragm. Second, we analyzed the role of bazooka on nephrocyte function. Silencing bazooka expression resulted in a disturbed diaphragm morphology and severe filtration defects. To study the mammalian Par3 proteins in greater detail, we used the UAS-GAL4 system to re-express different murine Par3 variants in a bazooka knockdown background. Although the rescue capacity differed between the different mammalian Par3A isoforms, none of the isoforms resulted in a complete rescue. Even the 100KDa isoform, lacking the aPKC binding domain, resulted in partial rescue, suggesting an aPKC-independent function for Par3A in nephrocyte filtration. In line with these findings, an aPKC iota interactome from immortalized mouse podocytes, revealed Lgi2 and Par6 as predominant interactors of aPKC.

Conclusions: Taken together, the data establish an important role for Par3 function in podocytes and reveal this function is, at least partially, independent from aPKC.

SA-OR006

The Interaction between MAGI2 and RapGEF2 Sustains Podocyte Rap1GTPase Signaling and Is Critical for Glomerular Filter Function Bingbing Zhu, Jinhua Li, Jenny Wong, Kirk N. Campbell, Shazia Ashraf, Agnieszka Bierzyńska, Moin Saleem, Charles Sawyer, John C. He, Friedhelm Hildebrandt, Vivette D. D’Agati, Wen Peng, Lewis Kaufman, Icahn School of Medicine at Mount Sinai, New York, NY; Peking University International Hospital, Beijing, China; Shanghai University of Traditional Chinese Medicine, Shanghai, China; Boston Childrens Hospital, Harvard Medical School, Boston, MA; University of Bristol, Bristol, United Kingdom; MSKCC, New York, NY; Columbia University College of Physicians and Surgeons, New York, NY.

Background: The essential role of MAGI2 in proper podocyte function is reflected by the severe FSGS phenotypes of both MAGI2 knockout mice and of humans with congenital nephrotic syndrome (CNS) caused by mutations in MAGI2.

Methods: Results: In the current work, we perform co-immunoprecipitation experiments which show MAGI2 directly binds the Rap1 guanine nucleotide exchange factor, RapGEF2, and that this interaction is lost when expressing MAGI2 variants that cause CNS. In cultured cells, co-expression of RapGEF2 with wild-type MAGI2, but not MAGI2 variants known to cause CNS, dramatically enhanced activation of the small GTPase Rap1, a pathway we previously demonstrated to be essential for normal podocyte function. Furthermore, in mice, podocyte specific deletion of RapGEF2 resulted in spontaneous proteinuria with FSGS, substantiating the critical importance of RapGEF2 to sustain normal podocyte function. Although the FSGS phenotype of MAGI2 knockout mice is considerably more severe than that of RapGEF2, both mouse models show comparable qualitative glomerular features including mesangial expansion, focal segmental and global sclerosis, podocyte loss, and glomerular epithelial cell proliferation, suggesting mechanistic similarities. Indeed, knockdown of either RapGEF2 or MAGI2 in cultured podocytes caused nearly identical reductions in levels of Rap1GTPase activation, dramatic reductions in many Rap1 downstream signalling targets, and similarly high rates of podocyte apoptosis. Finally, Immunostaining of glomerular sections from CNS patients with MAGI2 mutations also suggested reduced glomerular Rap1GTPase mediated signaling.

Conclusions: We conclude that Rap1 activation induced by the complex of MAGI2 and RapGEF2 is indispensable for normal podocyte homeostasis.

Funding: NIDDK Support

SA-OR007

Confocal Imaging of the Glomerular Filtration Barrier in Expanded Kidney Tissue Samples David Universio-Jess, Lena Scott, Sonia Zambrano Sevilla, Jaacko Patrakka, Hans Blom, Hjalmar Brismar, Karolinska Institutet, Solna, Sweden; Royal Institute of Technology, Solna, Sweden.

Background: When studying the glomerular filtration barrier (GBF), one is normally restricted to electron microscopy (EM). However, using EM, it is not trivial to perform volumetric imaging and multiple labelling of different epitopes. We have recently demonstrated an optical clearing protocol that in combination with super-resolution STED microscopy enables epitope-specific nanoscale imaging of the GBF. STED microscopy is presently an expensive and complex technique, and thus it would be highly relevant to develop more conventional bioimaging methods which resolve the GBF.

Methods: We apply a sample preparation protocol which isotropically expands kidney tissue samples approximately 5 times, while making them optically transparent. We then use immunofluorescence and confocal microscopy to image components of the GBF.

Results: Kidney samples were sufficiently expanded to allow for nanoscale localizations of different parts of the GBF (e.g. glomerular basement membrane, podocyte foot processes and the slit diaphragm), at an effective resolution below 70 nm. 2-color z-stacks of glomeruli were acquired, giving the unique possibility to study the 3D localization of GBF proteins in intact tissue samples, including the detection of foot process effacement in mice with induced glomerulonephritis. Additionally, by applying super-resolution STED microscopy on expanded kidney samples, a resolution below 20 nm could be obtained.

Conclusions: We show that an expansion protocol in combination with confocal microscopy can be used to perform sub-70 nm resolution imaging of the GBF using standard lab equipment and reagents. This finding has an impact for researchers and clinical pathologists, since conventional light microscopy can for the first time be used to study kidney fine-morphology and protein topology on the effective nanoscale.

Expanded kidney sample stained for podocin (magenta) and cytosolic podocyte-specific tdTomato (pod-cre-tdTomato, green), showing podocyte foot processes and the filtration slit. The sample was imaged using confocal microscopy.

SA-OR008

APOL1 Risk Variant Induced Kidney Injury in Podocytes Is Mediated by Caspase-1 Dorothy Laczko, Paxit Beckerman, Jing Bi Karchin, Frank S. Chiang, Katalin Szaszzik, University of Pennsylvania, Philadelphia, PA.

Background: Coding variants of APOL1 (termed as G1 and G2) are associated with increased risk of kidney disease in African Americans. Recently, we developed a new mouse model that recapitulates APOL1 associated renal disease by conditional inducible expression of G1 and G2 APOL1 variants in podocytes. While these animals develop albuminuria, glomerulosclerosis and azotemia, the exact pathomechanism of APOL1 variant induced kidney disease remains poorly understood. Here, we tested whether caspase-1 (Cas1) / IL-1β mediated pyroptotic cell death play a role in disease development.

Methods: Podocyte specific G2 APOL1 transgenic mice was generated by crossing TRE-G2 APOL1 animals with mice carrying the nphin rTa. Transgene expression was controlled by doxycycline. To test the role of Cas1, we crossed nphin rTa TRE-G2 G2 with Cas1 knockout (KO) mice. To test the role of IL-1β we treated mice with IL-1β neutralizing antibody Anakinra. Histological changes were evaluated by PAS staining and the level of proteinuria was determined by albumin specific ELISA. The mRNA levels of kidney injury markers (KIM1, Col4a1, SMA) were analyzed by qPCR. For in vitro testing cells with inducible G2 APOL1 expression were generated, and the effect of pan-caspase, Cas1 and -3 were tested.

Results: In vitro expression of G2 APOL1 resulted in increased cleaved Cas1 and IL-1β levels. Pan-caspase and Cas1 inhibitors ameliorated cell death induced by G2 APOL1. In vivo, Anakinra injection for 21 days failed to significantly reduce albuminuria or glomerulosclerosis of G2 APOL1 mice. In line with these findings, no change in the important level of kidney injury markers was observed after neutralization of IL-1β compared to their control saline injected littermates. In contrast, renal disease was ameliorated in G2 APOL1 Cas1 KO mice as evidenced by decreasing level of proteinuria over the 21 days doxycycline treatment period as opposed to their Cas1 wild type littermates. In addition to this, Cas1 KO mice displayed marked reduction of kidney fibrosis confirmed by PAS staining.

Conclusions: Our initial data suggest that Cas1 plays a crucial role in the development of G2 APOL1 induced kidney damage, albeit the mechanism still needs to be elucidated. We propose that inhibition of Cas1 can offer a potential therapeutic target for APOL1 associated kidney damage.

Funding: Other NIH Support - SR01DK105821-02

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

Underline represents presenting author.
SA-OR009

COSMC, the Molecular Chaperone of O-Linked Glycosylation, Is Essential for Podocyte Function

Brian R. Stotter,1,2 Brianna Talbot,1 Johannes S. Sch condolr,1,2 Div of Nephrology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; 2Div of Nephrology, Boston Children’s Hospital, Harvard Medical School, Boston, MA.

Background: Proper podocyte function is required to maintain the glomerular filtration barrier. Many podocyte proteins undergo post-translational O-linked glycosylation (OLG), which requires Tn-synthase and its molecular chaperone Cosmc. Prior studies have shown that global COSMC knockout produces immature glycoproteins that express Tn antigen. We hypothesize that podocyte-specific COSMC deletion causes albuminuria, renal failure, and glomerulosclerosis due to aberrant OLG.

Methods: Male podocin-Cre mice were bred with female COsmc+/fl mice to produce males devoid of COSMC in podocytes (Podo-COsmc+/fl) and females with mosaic COSMC loss in podocytes (Podo-COsmc−/−). Serum creatinine (SCr) and urine albuminuria were measured at 1 and 2 months of life for experimental and control mice. Kidneys were harvested for histology, immunofluorescence (IF), electron microscopy (EM), and biochemical analysis. Immature OLG was detected by staining for Tn antigen with lectin HPA.

Results: Podo-COsmc+/fl males have heavy albuminuria by 1 month, with mesangial expansion and glomeruloneglogous on histology and diffuse foot process effacement by EM. By 2 months, SCr is elevated compared to controls and histology shows extensive glomerulosclerosis, interstitial fibrosis, and tubular atrophy. Podo-COsmc−/− females have mosaic glomerular Tn antigen expression, mild albuminuria, and normal SCr by 1 and 2 months. Podo-COsmc+/fl females have normal histology at 1 month but both rare segmental sclerosis and foot process effacement by 2 months. IF shows diffuse lectin HPA staining in Podo-COsmc−/− male podocytes and mosaic staining in Podo-COsmc−/− female podocytes. Podocalyxin, an O-linked podocyte glycoprotein, is normally expressed in 1 month Podo-COsmc−/− male and 1 and 2 month Podo-COsmc−/− females, but is lost in 2 month Podo-COsmc−/− males. In contrast, staining of O-linked glycoprotein podoplanin is reduced in COSMC-deficient podocytes by 1 month, confirmed by Western blot of glomerular lysates.

Conclusions: Loss of COSMC in podocytes causes albuminuria and renal failure with glomerulosclerosis, interstitial fibrosis, and tubular atrophy. This phenotype is most severe in male mice that have complete COSMC excision, and less severe in mosaic females. The mechanism of podocyte injury may be due to aberrant function of podocalyxin, podoplanin, and other O-linked glycoproteins.

Funding: NIDDK Support

SA-OR010

Dilution-Induced Maf and Egr1 Upregulation Triggers Differentiation of Podocytes

Masahiko Okabe,1,2 Masaru Motojima,1 Yoichi Miyazaki,2 Takashi Yokoo,2 Taiji Matusaka,2 Tokai University School of Medicine, Isehara, Japan; 1Jikei University School of Medicine, Tokyo, Japan.

Background: Podocytes quickly lose their characteristics when they are cultured in vitro, suggesting that detachment from the glomerular basement membrane (GBM) may trigger dedifferentiation. We aimed to explore gene expression changes induced by podocyte dissociation from the GBM.

Methods: We obtained dissociated podocyte-specific RNA by two methods. One method was to dissociate glomerular cells and purify RNAs from FACS-sorted podocytes that are transgenically labeled with fluorescent protein. The other was to utilize RiboTag technology to dissociate podocyte from the GBM.

Results: We obtained podocyte-specific RNAs by two methods. One method was to dissociate glomerular cells and purify RNAs from FACS-sorted podocytes that are transgenically labeled with fluorescent protein. The other was to utilize RiboTag technology to dissociate podocyte from the GBM.

Conclusions: These findings indicate that detachment from the GBM activates Maf and Egr1 in podocytes, which actively facilitate dedifferentiation by competing with other transcriptional activators.

Funding: Government Support - Non-U.S.

SA-OR011

Impact on Blood Pressure of Mobile-Based Application (eKidneyCare) in Patients with CKD: A Randomized Controlled Trial

Sarbjit V. Jassal,1 Kelly Min,2 Akib Uddin,2 Eveline C. Porter,2 George Tomlinson,2 Alexander G. Logan,3,4 Mount Sinai Hospital, Toronto, ON, Canada; 1University Health Network, Toronto, ON, Canada.

Background: We have previously demonstrated feasibility and acceptability of an integrated app (eKidneyCare) used for CKD management (CIASN 2016). It allows patients to monitor blood pressure (BP), manage medication, assess symptoms and track laboratory results. Customizable algorithms provide real-time personalized patient feedback and alerts to providers. Currently we are performing a one-year randomized controlled trial comparing eKidneyCare (intervention) to MyMedRec (control). The latter is a commercially available app that records medical information without providing feedback. Study midpoint results are presented.

Methods: Consenting patients with CKD 3b-5 or 5 were recruited from 6 outpatient renal clinics or dialysis units at University Health Network (UHN) and randomized to using either eKidneyCare or MyMedRec monitoring. Outcome assessments include BP at 6 and 12 months and medication reconciliation, questionnaires on self-management and, at study end, in-person interviews.

Results: A total of 182 patients were enrolled and randomly allocated to the intervention (n=91) or the control (n=91) group. A total of 157 patients completed the 6 month BP assessment using the automated oscillometric device, BpTRU. Premature withdrawals included 11 transferred or incomplete data, 8 who withdrew consent and 6 withdrawn after medical complications. At 6m, the fall in BP of patients with uncontrolled hypertension at baseline was -0.7±2.0 mmHg in the eKidneyCare group (median reduction in systolic BP -18 vs 13 mmHg respectively, p=0.05; diastolic BP -5 vs 5.5 mmHg p=0.03). There was no between group difference in normotensive patients.

Conclusions: Hypertensive patients allocated to the eKidneyCare app had a significantly greater BP reduction than those using the commercially available app. This preliminary analysis suggests that real time patient feedback and integrated mobile apps are critical components for success with mHealth monitoring.

Funding: Other NII Support - Canadian Institute for Health Research, Government Support - Non-U.S.

SA-OR012

Reducing Health Disparity – PCORI Supported Home Based Kidney Care Approach in Zuni Indians

V. Shane Pankratz,1 Donica M. Ghahate,1 Jeanette Bobelu,1 National Institutes of Health, Phoenix, AZ, 2University of New Mexico Health Science Center, Albuquerque, NM.

Background: To conduct a randomized trial of home based kidney care (HBKC) of patient activation measure (PAM) with lifestyle intervention to reduce risk factors for chronic kidney disease (CKD) in Zuni Indians.

Methods: Randomized families with more than one individual with CKD (1:1) to a usual care (UC) or an HBKC intervention group. After initial lifestyle coaching in both groups, the HBKC received reinforcement of healthy behaviors through alternate weekly home visits by the community health representatives, and with quarterly group sessions. The primary outcome was change in PAM. The secondary outcomes were changes in measures of T2D, CKD, BP, lipid profiles, BMI, Morsi score), KDQOL and diet. Tests of changes compared between intervention and control groups were performed using mixed models analysis of variance with a per-protocol analysis.

Results: Patients in the HBKC group increased PAM total score by 9.5±26.1 points, compared to a decrease of 0.7±14.0 points in the UC group (p=0.04). Similarly, 16.7% more of the UC group were in the PAM “activated” group at the study’s end, while 12.5% fewer of the UC group were in the PAM “activated” group at the study’s end. In our secondary analyses, progression of multiple risk factors for kidney disease, especially BMI, AIC, and lnCtP, slowed by the HBKC intervention. We also observed greater improvements in QOL in the HBKC group; SF12 mental scores significantly increased in the HBKC compared to the UC (p=0.02), with an average 5.0 point change in the HBKC group of 7.5±1.10 compared to a -0.2±9.0 point change in the control group. Conclusion: A HBKC intervention of continuous patient engagement, a potentially scalable approach to providing care to patients with CKD, was effective in improving PAM levels and in reducing risk factors for CKD.

Funding: Other U.S. Government Support

SA-OR013

Loss of Renal Function and Benefits of Measured GFR among Lung Transplant Patients

Nans Flores,1,2 Laurence Dubourg,1 Agathe Senechal,1 Francois Philil,1 Laurent Juillard,2 Sandrine Lemoine,1 Hospices Civils de Lyon, Lyon, France; 2University of Lyon, Lyon, France.

Background: There are approximately 4000 lung transplant patients over the world. Renal dysfunction and chronic kidney disease among this population are underestimated. The aim of the study was to evaluate the loss of glomerular filtration rate (GFR) after a lung transplantation.

Methods: All the lung transplant patients in the university hospital of Lyon between January 2012 and April 2016 were studied retrospectively. Patients had a pre- and/or post-transplantation measurement of their GFR (mGFR) either by the inulin gold standard

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
method or by iohexol clearance. Estimation of the GFR was achieved with CKD-EPI equation.

Results: 111 lung transplantations were performed between January 2012 and April 2016. 91 patients had a pre-transplantation mGFR. Among those patients, 13 deceased during the follow-up period, 28 had a mGFR after 1 or 2 years of their transplantation and 6 patients underwent maintenance hemodialysis after their transplantation. Mean pre-transplantation mGFR was 106 mL/min/1.73m² and 58 mL/min/1.73m² after transplantation (p=0.05) with a mean loss per patient of 48 mL/min/1.73m². 6 % of the patients had a CKD stage 3 or more before the transplantation while 66% after. In pre-transplantation patients, GFR and mGFR were significantly different (16 ± 6 mL/min/1.73m², p<0.05) not in post-transplantation. The risk of developing a CKD stage 3 after the transplantation was higher for patients with a pre-transplantation mGFR under 90 mL/min/1.73m² (RR = 2.1; 95% CI: 1.2-3.6). Patients undergoing a maintenance hemodialysis had a lower pre-transplantation mGFR than all the other patients with a post-transplantation CKD (74 ± 7 mL/min/1.73m² vs 108 ± 5, p<0.05).

Conclusions: The prevalence of CKD among lung transplant patients is important as the loss of kidney function is about 50 mL/min/1.73m² per patient. Lung transplant candidates with a mGFR under 90 mL/min/1.73m² need an increased monitoring of their renal function and patients with an initial GFR< 50 mL/min/1.73m² had to be discussed for a double-lung and kidney transplant.

SA-OR014
Racial and Ethnic Disparities in Access to Predialysis Nephrology Care in the US: Have We Made Any Progress over the Last Decade? Tanjala S. Purnell, Xun Luo, Sunjane Bae, Deidra C. Crews, Lisa A. Cooper, Dorry L. Segev. Johns Hopkins School of Medicine, Baltimore, MD.

Background: Over the past decade, there has been increased attention and efforts to improve overall access and redress racial and ethnic disparities in access to predialysis nephrology care in the US. The goal of this study was to investigate whether these efforts have been successful.

Methods: Using USRDS patient data, we performed multivariable logistic regression models to quantify temporal changes in racial and ethnic disparities in receipt of predialysis nephrology care among 934,599 adults who initiated chronic dialysis treatment between 2005 and 2015. We adjusted regression models for differences in patient sociodemographic factors.

Results: Over the last decade, racial and ethnic disparities in access to predialysis nephrology care slightly worsened. In 2005-2007, Blacks were 14% (aOR: 0.86, 95% CI: 0.85-0.88) and Hispanics were 22% (aOR: 0.78, 95% CI: 0.76-0.80) less likely to receive predialysis nephrology care than Whites. In 2008-2010, Blacks were 14% (aOR: 0.86, 95% CI: 0.84-0.87) and Hispanics were 29% (aOR: 0.71, 95% CI: 0.70-0.73) less likely than Whites. In 2011-2013, Blacks were 18% (aOR: 0.82, 95% CI: 0.81-0.84) and Hispanics were 30% (aOR: 0.70, 95% CI: 0.69-0.72) less likely than Whites. In 2014-2015, Blacks were 19% (aOR: 0.81, 95% CI: 0.79-0.83) and Hispanics were 29% (aOR: 0.71, 95% CI: 0.69-0.73) less likely than Whites. (Figure 1)

Conclusions: Disparities in access to predialysis nephrology care worsened (versus narrowed) over the past decade. Targeted interventions to effectively reduce these disparities should be identified and adopted widespread to improve outcomes for patients with ESRD in the US.

Funding: NIDDK Support, Other NIH Support - NHLBI, NIMHD, AHRQ, Other U.S. Government Support

SA-OR015
Disease-Specific Stress Experienced by Patients with CKD Julie A. Wright Nunez,1 Eve Kerr,2 Emily P. Chen,1 Gunjan Garg,1 Angela Fagerlin,1
1University of Michigan, Ann Arbor, MI; 2University of Michigan, Ann Arbor, MI; 3University of Michigan Health System, Ann Arbor, MI; 4University of Utah, Salt Lake City, UT.

Background: Increased psychological stress is independently associated with decreased social functioning, poor quality of life and morbidity. We developed a new scale to assess patient psychological stress about a chronic kidney disease (CKD) diagnosis and examined whether stress varies across different patient demographics.

Methods: Adults with CKD Stages 1-5 were enrolled to take a cross-sectional survey from April 2015-May 2016. Eight questions (stress scale) assessed how often patients thought about their CKD, had trouble sleeping because of it, and felt fearful and worried (scale “0 not at all” to “3 extremely”). We also asked participants to rank CKD importance compared to other conditions. An a priori model was used to examine for validity. Reliability was calculated using Cronbach’s alpha. Associations were examined using linear regression.

Results: 203 patients were enrolled with a mean (SD) age 59 (16) years; 49% were men, 78% Caucasian, 16% African American (AA), 5% other races, 73% had CKD Stage 3-5, 48% had an annual income < $50K, and 95% had a H.S. education. Cronbach’s alpha was 0.89 (excellent reliability). The mean (SD) of the 8-item scale was 1.1 (0.6), range 0-7 (seven percent scored as either very important or their top health priority. Age was negatively associated [β = -0.01 (CI -0.02, -0.005); p=0.01] and AA race positively associated [β=0.4 (0.1, 0.6); p<0.01] with CKD stress scores. In adjusted analysis, age remained independently and negatively associated with stress scores [β = -0.01 (-0.02, -0.001); p=0.03], while AA race and CKD stage trended towards a positive association [β=0.33 (0.004, 0.7); p=0.05] and [β=0.2 (-0.02, 0.5); p=0.08], respectively.

Conclusions: Our scale exhibits excellent internal reliability and evidence of validity assessing disease-specific stress in patients with CKD. Despite the majority of patients ranking CKD as very important/top health priority, overall patients reported low stress about their diagnosis. African American race conferred more perceived stress related to CKD. Future education and awareness interventions must consider the impact that disease knowledge has on patient stress, in particular for African American patients—and integrate individualized psychosocial support for all patients into education programs.

Funding: NIDDK Support

SA-OR016
Reported Kidney Disease Awareness and Medical Subspecialty Use before and after the Affordable Care Act Implementation among National Health Interview Survey Participants Anna J. Lee,1 Kael Segev,2 Sunjae Crews,2 Deidra C. Crews,3 Zhiying You,1 Denver VA / University of Colorado, Denver, CO; 2 UC Denver, Aurora, CO; 3University of Colorado, Aurora, CO.

Background: In the U.S., individual awareness of chronic kidney disease (CKD) is low. Nephrology referral improves CKD awareness and clinical outcomes. The Affordable Care Act (ACA) implementation on January 1, 2014 increased insurance coverage and access to health care for people with chronic disease. It is unknown if the ACA has impacted people with CKD.

Methods: Using National Health Interview Survey (NHIS) data, we compared kidney disease awareness and medical subspecialty use during 2012, a full year before the ACA implementation, and 2015, a full year after. The sample included 66,624 non-institutionalized U.S. citizens ages 19-64. In this quasi-experimental analysis, we used logistic regression to examine whether kidney disease awareness and medical subspecialty use increased after the ACA implementation, using weights as appropriate.

Results: Baseline characteristics among NHIS participants in the years 2012 and 2015 were similar: age 47 years, 52% female, and 80% white. The percentage of participants reporting no health insurance coverage decreased from 17% in 2012 to 10% in 2012 (p <0.0001). Kidney disease awareness, medical subspecialty use, and a combination of both increased from 2012 to 2015: 1.6% to 2.0% (p = 0.002), 26% to 28% (p <0.002), and 1.0% to 1.3% (p = 0.006), respectively. After adjustment for age, sex, race, ethnicity, marital status, education, income, and region, 2015 NHIS participants were 27% (odds ratio [OR] 1.27 [95% CI, 1.01-1.46]) more likely to report kidney disease awareness, 6% (OR 1.06, [95% CI, 1.00 to 1.11]) more likely to report medical subspecialty use, and 27% (OR 1.27 [95% CI, 1.07 to 1.50]) more likely to report both. When insurance was added to the models, the magnitude of all the odds ratios was attenuated suggesting that insurance status influences reported kidney disease awareness and medical subspecialty use.

Conclusions: Kidney disease awareness and medical subspecialty use reported by NHIS participants significantly increased from 2012 to 2015, after the ACA implementation, while participants reporting no health insurance significantly decreased. These data suggest that the ACA improves access to care among people with CKD, and thus, may be key to improving clinical outcomes.

Funding: Veterans Affairs Support

SA-OR017
The Association between Participation in a Specialized Renal Disease Management Program and Economic Outcomes Chunhui A. Chien,1 Kael Haig, Matt Ryaner, Ana R. Stankovic. OptumHealth, Minneapolis, MN.

Background: A 2016 meta-analysis of efficacy of chronic kidney-focused disease management (DM) programs in improved quality of life among chronic kidney disease (CKD) patients. However, published evaluations of DM program impact on medical spend, utilization, and transplantation have been inconsistent. We measured the association between participation in a specialized renal disease management (DM) program and all-cause medical spend, utilization outcomes, and transplantation among patients with Stage 4 or 5 CKD or ESRD.

Methods: The study included commercially insured members 18 years or older identified as having Stage 4 or 5 CKD or ESRD during January 2013 – December 2016. All members included in the study were eligible for the DM program. We compared members who participated in a nurse-based telephonic DM program (CKD = 1,428 and
Interaction of Socioeconomic Status with Genetic Factors in Kidney Function Outcomes

Chris H. Thio,1 Harold Snieder,1 Ute Bültmann,3 Ron T. Gaasenbeek,1,2
1Epidemiology, UMCG, Groningen, Netherlands; 2Epidemiology, UMCG, Groningen, Netherlands; 3Health Sciences, UMCG, Groningen, Netherlands; Nephrology, UMCG, Groningen, Netherlands.

Background: Chronic kidney disease (CKD) is potentially caused by genetic and environmental factors. Previous studies suggested joint effects of socio-economic status (SES) and genetic risk in obesity and diabetes, but this issue has not been investigated in CKD. We therefore tested whether SES and genetic risk interact in their association with eGFR decline and incident CKD (CKDi).

Methods: In the community-based PREVEND cohort, we calculated eGFR from creatinine and cystatin C at five examinations. We defined CKD as eGFR<60 mL/min/1.73m² during follow-up in those without baseline CKD. SES was measured by educational level and categorized into low, medium, and high (<secondary; secondary equivalent; >secondary school). To quantify genetic risk, we used a genetic risk score (GRS) comprising 53 eGFR SNPs, weighted for published effects. In longitudinal analyses, we tested main effects of SES and GRS, as well as their interaction. Covariates were age, sex, smoking, BMI, urinary albumin, diabetes, hypertension, high cholesterol, and cardiovascular disease.

Results: We included 3,393 subjects (Caucasian, 52% male, median age 49 yrs [IQR 40-60], median follow-up duration 11 yrs [IQR 4.7-12], N=109 baseline CKD, N=190 CKDi). Mean GRS did not differ between SES levels. In univariate analyses, both high GRS and low SES were associated with lower eGFR levels. Low SES was associated with steeper eGFR decline, but higher GRS was not. However, their interaction was significant (SESxGRS*time, p=0.01). A higher GRS was associated with steeper decline only in those with low SES (see Figure). Covariate adjustment did not affect these conclusions. Both SES and GRS were univariately associated with CKDi, but their interaction was not significant.

Conclusion: Our data suggest that in subjects with low SES the effects of genetic risk for kidney function decline are stronger, independent of CKD risk factors. Future studies need to corroborate these findings in larger samples and focus on aspects of SES that mediate this relation.

Funding: Commercial Support - UnitedHealth Group

SA-OR019
Qualitative Assessment of an Online Peer Mentoring Platform for Patients with CKD

Awaib Ammar,1 Mary Morrow-Sutton,1 Tabitha Semancik,2 Tara Lughiat,1 Umar Farooq,1 Nasrollah Ghahramani,1 Penn State College of Medicine, Hershey, PA; 2Kidney Foundation of Central Pennsylvania, Harrisburg, PA.

Background: Peer mentoring (PM) is an effective model for patients with the same chronic disease to share knowledge and experience to which others often cannot relate. PM occurs in various settings, including face-to-face, via telephone or online. This study is a qualitative assessment of the communications in an online PM platform designed for patients with chronic kidney disease (CKD).

Methods: Twenty-one patients were assigned to trained peer mentors with whom they had regular online communication in a PM relationship. The interactive online platform allowed patients to post their concerns and questions about specific symptoms or treatment decisions through a private network. Patients used an intuitive user interface, utilizing mood and symptom icons, to indicate their current status. The program currently monitored the patient’s “posts” and mentors’ “responses” (on a sliding scale: 1-10), as subjectively indicated by the patients, were used to quantitatively assess the severity of their concerns.

Results: A total of 213 posts, initiated by 21 patients, were included in the analysis. The posts were categorized into 15 general topics areas. The largest number of posts (n=34) related to family relationship concerns, followed by posts regarding weakness and lack of energy (n=25), weight change (n=19), overall prognosis (n=18) and financial stressors (n=16). Quantitatively, the most stressful concerns related to financial matters (77%) and family relationships (61%).

Conclusions: Patients communicate with their peers via an online platform regarding a variety of concerns and questions. Concerns about finances and family relationships form a significant aspect of the communication. These findings underscore the patients’ concern about the impact of their disease on their families. Funding source: Patient Centered Outcomes Research Institute

Funding: Other U.S. Government Support

SA-OR020
Trajectories of HRQOL in Children with CKD

Arlene C. Gerson,1 Matthew Matheson,2 Rebecca J. Johnson,3 Stephen R. Hooper,3 Shrinivas,4 Bradley A. Wardy,4 Susan L. Furth,4 Cynthia Wong,4 Amy Kogon,4 Marc Lande,4 Lyndsay Harshman,1 Susan R. Mendylo,1 Johns Hopkins School of Medicine, Baltimore, MD; 2Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; 3Children’s Mercy Hospital, Kansas City, MO; 4University of North Carolina School of Medicine, Chapel Hill, NC; 5Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY; 6The Children’s Mercy Hospital, Kansas City, MO; 7The Children’s Hospital of Philadelphia, Philadelphia, PA; 8Stanford University, Stanford, CA; 9Nationwide Children’s Hospital, Columbus, OH; 10University of Rochester, Rochester, NY; 11University of Iowa Children’s Hospital, Iowa City, IA; 12University of Maryland, Baltimore, MD.

Background: Trajectories of health related quality of life (HRQOL) may offer valuable insights into psychosocial aspects of disease progression in children with chronic kidney disease (CKD). Few longitudinal studies have evaluated the impact of CKD duration on HRQOL. The aim of this study was to determine how HRQOL changes over the time course of CKD.

Methods: The subjects in this study were participants in the Chronic Kidney Disease in Children (CKiD) cohort who completed the Pediatric Quality of Life Inventory (PedsQL) on three or more occasions over the course of two or more years. Generalized gamma (GG) mixed effects models were applied to assess the effect of CKD duration on HRQOL, controlling for confirmed covariates from previous cross-sectional analyses.

Results: 660 children (median age: 11.3) with a median of 8.5 years duration of CKD were evaluated. GG models with child self-report PedsQL data indicated that longer CKD duration was associated with improved overall, Physical, Emotional, Social and School HRQOL. GG models with parent-proxy PedsQL data indicated that longer duration was associated with worse School HRQOL. Increasing trajectories of child self-report HRQOL were observed in the majority of subjects (ranging from 64% to 96% depending on subscale and baseline HRQOL level), while lower percentages of increasing trajectories were observed on parent-proxy scales. In the overall group there was no significant relationship between HRQOL and time varying FGR.

Conclusions: Longer duration of disease is associated with improved HRQOL on all child self-report scales. This finding may be a function of changes in internal standards, values or conceptualization of illness.

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

Table 1. Significance of CKD duration from generalized mixed effects models and effects on PedsQL scores at the 25th percentile.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-OR021

Protective Role of Type III Sodium-Dependent Phosphate Transporter, PIT-2, in Uremic Vascular Calcification Shunsuke Yamada, Elizabeth M. Sober, Timothy C. Cox, Mei Y. Speer, Cecilia M. Giachelli, University of Washington, Seattle, WA.

Background: Vascular calcification (VC) is prevalent in patients with chronic kidney disease (CKD) and increases the risk of cardiovascular deaths. PIT-2 is a type III sodium-dependent phosphate (Pi) transporter expressed in various tissues and a causative gene for Familial basal ganglia arterial calcification. However, it is unknown whether PIT-2 plays a role in the pathogenesis of VC related to CKD.

Methods: To determine the role of PIT-2 in VC, wild-type (WT) and global PIT-2 heterozygous (Het) knockout mice were challenged with CKD. At two weeks after the two-step 5/6th nephrectomy, mice were fed a normal (0.5%) or high (1.5%) Pi diet for 11 days and terminated. At termination, blood, aorta, kidney, and femur were collected. Serum chemistry, histology, and micro CT analyses were performed. Primary vascular smooth muscle cells (VSMCs) isolated from the aortas of WT and PIT-2 Het mice were used for in vitro Pi-induced calcification and P-scarble experiment. WT-derived VSMCs were also treated with scramble or PIT-2 small interfering RNA (siRNA) and used for gene and protein expression analysis.

Results: Uremic mice fed a high Pi diet developed VC in the medial layer of the aorta, which was alleviated by Alizarin red staining and calcium quantification of the blood vessels. PIT-2 haplosufficiency greatly enhanced VC in the setting of CKD and high Pi diet. No differences were observed in the serum levels of calcium, Pi, and FGF23, kidney function, and renal mRNA expression of SLC34A1 and SLC34A3 between the WT and PIT-2 Het mice. Micro CT showed that high Pi diet of PIT-2 decreased trabecular bone mineral density and thickness in CKD. In vitro, Pi uptake activity was decreased in the cultured VSMCs isolated from the PIT-2 Het mice compared with those from the WT mice. Under high Pi medium condition, PIT-2 haplosufficiency increased calcification of the cultured VSMCs. Similar results were also found in WT VSMC treated with PIT-2 siRNA. Finally, mRNA expression and protein levels of osteoprotegerin, an inhibitor of VC, were decreased in VSMCs treated with PIT-2 siRNA compared to scramble controls.

Conclusions: PIT-2 plays a protective role in the pathogenesis of VC and bone disorders in CKD mice, and can be a promising therapeutic target in the CKD population.

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

SA-OR022

Large Secondary Calciprotein Particles Are Associated with Vascular Calcification Wei Chen,1 Viktoria Aronkina,1 Benjamin L. Miller,1 Gregory Diedonne,1 Matthew K. Abramowitz,2 Randeep Kashyap,3 Chen Yan,1 Tong tong Wu,1 David A. Bushinsky,1 University of Rochester School of Medicine, Rochester, NY; 2Albert Einstein College of Medicine, Bronx, NY.

Background: Vascular calcification (VC) is common and contributes to cardiovascular mortality in patients with CKD. Calcification propensity as measured by the serum assay of Pasch et al. using nephelometry is associated with cardiovascular events; however, whether it is a biomarker for VC is unknown. We modified this assay through the use of microplate-based dynamic light scattering, which allowed us to measure both time for half-maximal transformation (T50) of 1° to 2° calciprotein particles (CPPs) and size of 2° CPPs (CPP2) (instead of only T50 with nephelometry). A fast T50 and/or a large CPP2 would be associated with VC.

Methods: We measured T50 and CPP2 in 46 subjects with stage 4-5 CKD and 17 healthy volunteers. T50 and CPP2 were examined as continuous and categorical variables (dichotomized at the median). VC was measured on plain radiographs and defined as a large CPP2 would be associated with VC.

Results: There were 327 deaths, 287 global CV and 228 ASCV events in the entire cohort. In the CKD group, there were 97 (34.5%) deaths, 76 (34.5%) global CV and 62 (27.9%) ASCV events. Median (IQR) MCP-1 was 164.7 (120.3, 220.9) pg/mL in non-CKD vs. 192.2 (143.6, 269.8) in CKD individuals, P=0.001, and negatively correlated with eGFR, r=-0.23, P=0.001. While MCP-1 does not predict global CV and ASCV events after adjusting for traditional CV risk factors (age, sex, race, hypertension, diabetes, current smoking, total and HDL cholesterol) and eGFR.

Conclusions: Increasing MCP-1 might lead to reductions in cardiovascular events and death in subjects with ESRD.

Funding: Government Support - Non-U.S.
SA-OR025

Metabolic and Hypertensive Complications of Pregnancy in Women with Nephrolithiasis

Jessica S. Tangren, Elizabeth D. Ankers, Ravi I. Thadhani. Massachusetts General Hospital, Boston, MA.

Background: Kidney stones are associated with future development of hypertension, diabetes and the metabolic syndrome. The relationship between nephrolithiasis and pregnancy complications, including gestational dysglycemia and gestational hypertension has not previously been evaluated. We assessed whether stone formation prior to pregnancy was associated with metabolic and hypertensive complications in pregnancy. We hypothesized that stone formation is a marker of metabolic disease and associated with increased risk for maternal complications in pregnancy.

Methods: We conducted a retrospective cohort study of women who delivered infants at the Massachusetts General Hospital from 2006 to 2016. Women with abdominal imaging (CT or ultrasound) prior to pregnancy were included in the analysis. Pregnancy outcomes in women with documented stones on imaging (stone formers, n=174) were compared to women without stones on imaging (controls, n=1,330). Women with pre-existing CKD, hypertension and diabetes were excluded.

Results: Maximum systolic blood pressure (mSBP) in pregnancy was increased in stone formers versus controls despite similar first trimester blood pressure. Gestational diabetes and gestational hypertension were more common in stone formers (18% vs. 6%, p<0.01 and 19% vs. 13%, p=0.04). After multivariate adjustment, stones were associated with increased risk of preterm delivery, gestational diabetes and preeclampsia (1A). Stone formation was an effect modifier of the relationship between mSBP and BMI (1B).

Conclusions: In women without preexisting diabetes and hypertension, a history of nephrolithiasis was associated with gestational dysglycemia and hypertension. Nephrolithiasis may be a marker of increased metabolic risk in women without traditional risk factors for pregnancy complications.

Funding: Private Foundation Support

SA-OR026

Antibiotic Use and Risk of Incident Kidney Stones

Eric N. Taylor,¹,² Pietro Manuel Ferraro.¹ ¹Channing Division of Network Medicine, Brigham and Women’s Hospital, Boston, MA; ²Fondazione Policlinico Universitario A. Gemelli, Rome, Italy; ¹Maine Medical Center, Portland, ME.

Background: Intestinal microbiota may play a role in the formation of kidney stones. Antibiotics alter the gut microbiome and therefore represent a potential risk factor for kidney stones.

Methods: We prospectively examined the independent associations between antibiotic use at age 20 to 39 and age 40 to 59 with risk of a subsequent symptomatic, incident kidney stone in the Nurses’ Health Study I (NHS I; N=67,051 women). We also examined antibiotic use at age 20 to 39 and age 40 to 49 in the Nurses’ Health Study II (NHS II; N=74,467 women). Medical record review of a subset of cases confirmed ≥ 95% of self-reported incident kidney stones in each cohort, and the majority of stones (≥ 77%) were predominantly calcium oxalate. Validated food frequency questionnaires were used to update dietary intakes every four years. Cox proportional hazards regression was used to adjust for age, body mass index, thiazide use, family history of kidney stones, hypertension, diabetes, fluid intake, supplemental calcium, and dietary factors.

Results: We documented 1,318 incident kidney stones over a combined 14 years of follow-up. At baseline, mean age was 68 in NHS I and 50 in NHS II. Compared with non-users, women who used antibiotics for ≥ 2 months between age 20 to 39 had a multivariable relative risk (MVRR) for kidney stones of 1.41 (95% CI 1.01 to 2.09) in NHS I and 1.28 (95% CI 0.87 to 1.89) in NHS II. Compared with non-users, women who used antibiotics for ≥ 2 months between age 40 to 59 in NHS I and between age 40 to 49 in NHS II had MVRRs for kidney stones of 1.62 (95% CI 1.01 to 2.60) and 1.35 (95% CI 1.00 to 1.84), respectively. Excluding women with self-reported urinary tract infections before the symptomatic kidney stone event did not change the results. There was no statistically significant interaction between dietary oxalate, antibiotic use, and kidney stone risk.

Conclusions: Long-term antibiotic use in early and middle adulthood may be independently associated with a higher risk of kidney stones later in life.

Funding: NIDDK Support
Effect of Dietary Phosphate Intake on Blood Pressure in Healthy Humans

Background: Despite strong epidemiologic evidence for CV toxicity of high dietary phosphate (Pi) in humans with normal renal function, controlled Pi intervention effects on systemic human health have not been reported. Vitamin D is known to increase intestinal Pi absorption, thereby increasing Pi load. Conversely, vitamin D supply has been associated with better CV outcome.

Methods: Prospective outpatient study with blinded assessment in 20 young healthy humans with normal renal function randomly assigned to high (HP, regular diet, RD, + 1 mmol/kg bw/d of Pi as neutral NaPO4) or low Pi (LP, RD + lanthanum 750 mg p.o. TID plus 0.7 mmol/kg bw/d NaCl to correct for excess Na intake in HP group) for 11 weeks (w). At end of w6, each subject received 600 000 U of vitamin D3 (i.m.) and continued on HP and LP for another 5w. Recovery visits on RD were performed 2 months after w11. Plasma and 24h urinary assays were performed at BL, w6 and w11. CV endpoints: 24h ABPM, endothelial function (reactive hypoxia index), arterial elasticity (pulse wave velocity). Data are means of 3 consecutive daily measurements/period.

Results: Mean fasting [Pi]p increased significantly by 0.23±0.11 (SEM) mmol/l in HP group as did 24h SBP and DBP, both in comparison to own baseline and to the LP group: +4.1 (range 2.1-6.1) and 3.2 (1.2-5.2) mmHg, respectively. 24h U Pi was 14.6 ± 1.8, 21.9 ± 2.4 and 41.5 ± 4.1 mmol/24h in LP, RD and HP. Mean 24h pulse rate increased significantly in HP group. Plasma creatinine, concentration of 24h urinary excretion rates of Na, aldosterone and free cortisol did not differ among the 2 groups. 24h urinary excretion of metanephrin increased significantly (intra- and intergroup) in the HP group by +60 (50-70) µg/24h. Vitamin D had no effect on the HP-induced increases in BP, pulse rate, metanephrin or renalin/aldosterone values and increased BP in 1/24h only in the LP group. Serum FGF23, PTIH, α-Klotho and urinary Klotho increased significantly in HP vs. LP. Recovery RD visits showed reversal of the elevated 24h ABPM and pulse rates in the HP group. Neither modulation of Pi intake nor vitamin D affected endothelial function or arterial elasticity tests significantly.

Conclusions: Increased Pi intake (controlled for sodium intake) significantly increases SBP, DBP and pulse rate in normal humans, an effect explained at least in part by increased sympathoadrenergic activity.

Funding: Government Support - Non-U.S.

Chlorthalidone Is Superior to Potassium Citrate in Reducing Calcium Phosphate Stone Formation in Genetic Hypercalciuric Stone-Forming Rats

Background: Despite strong epidemiologic evidence for CV toxicity of high dietary phosphate (Pi) in humans with normal renal function, controlled Pi intervention effects on systemic human health have not been reported. Vitamin D is known to increase intestinal Pi absorption, thereby increasing Pi load. Conversely, vitamin D supply has been associated with better CV outcome.

Methods: Prospective outpatient study with blinded assessment in 20 young healthy humans with normal renal function randomly assigned to high (HP, regular diet, RD, + 1 mmol/kg bw/d of Pi as neutral NaPO4) or low Pi (LP, RD + lanthanum 750 mg p.o. TID plus 0.7 mmol/kg bw/d NaCl to correct for excess Na intake in HP group) for 11 weeks (w). At end of w6, each subject received 600 000 U of vitamin D3 (i.m.) and continued on HP and LP for another 5w. Recovery visits on RD were performed 2 months after w11. Plasma and 24h urinary assays were performed at BL, w6 and w11. CV endpoints: 24h ABPM, endothelial function (reactive hypoxia index), arterial elasticity (pulse wave velocity). Data are means of 3 consecutive daily measurements/period.

Results: Mean fasting [Pi]p increased significantly by 0.23±0.11 (SEM) mmol/l in HP group as did 24h SBP and DBP, both in comparison to own baseline and to the LP group: +4.1 (range 2.1-6.1) and 3.2 (1.2-5.2) mmHg, respectively. 24h U Pi was 14.6 ± 1.8, 21.9 ± 2.4 and 41.5 ± 4.1 mmol/24h in LP, RD and HP. Mean 24h pulse rate increased significantly in HP group. Plasma creatinine, concentration of 24h urinary excretion rates of Na, aldosterone and free cortisol did not differ among the 2 groups. 24h urinary excretion of metanephrin increased significantly (intra- and intergroup) in the HP group by +60 (50-70) µg/24h. Vitamin D had no effect on the HP-induced increases in BP, pulse rate, metanephrin or renalin/aldosterone values and increased BP in 1/24h only in the LP group. Serum FGF23, PTIH, α-Klotho and urinary Klotho increased significantly in HP vs. LP. Recovery RD visits showed reversal of the elevated 24h ABPM and pulse rates in the HP group. Neither modulation of Pi intake nor vitamin D affected endothelial function or arterial elasticity tests significantly.

Conclusions: Increased Pi intake (controlled for sodium intake) significantly increases SBP, DBP and pulse rate in normal humans, an effect explained at least in part by increased sympathoadrenergic activity.

Funding: Government Support - Non-U.S.

Chlorthalidone Is Superior to Potassium Citrate in Reducing Calcium Phosphate Stone Formation in Genetic Hypercalciuric Stone-Forming Rats

Background: Despite strong epidemiologic evidence for CV toxicity of high dietary phosphate (Pi) in humans with normal renal function, controlled Pi intervention effects on systemic human health have not been reported. Vitamin D is known to increase intestinal Pi absorption, thereby increasing Pi load. Conversely, vitamin D supply has been associated with better CV outcome.

Methods: Prospective outpatient study with blinded assessment in 20 young healthy humans with normal renal function randomly assigned to high (HP, regular diet, RD, + 1 mmol/kg bw/d of Pi as neutral NaPO4) or low Pi (LP, RD + lanthanum 750 mg p.o. TID plus 0.7 mmol/kg bw/d NaCl to correct for excess Na intake in HP group) for 11 weeks (w). At end of w6, each subject received 600 000 U of vitamin D3 (i.m.) and continued on HP and LP for another 5w. Recovery visits on RD were performed 2 months after w11. Plasma and 24h urinary assays were performed at BL, w6 and w11. CV endpoints: 24h ABPM, endothelial function (reactive hypoxia index), arterial elasticity (pulse wave velocity). Data are means of 3 consecutive daily measurements/period.

Results: Mean fasting [Pi]p increased significantly by 0.23±0.11 (SEM) mmol/l in HP group as did 24h SBP and DBP, both in comparison to own baseline and to the LP group: +4.1 (range 2.1-6.1) and 3.2 (1.2-5.2) mmHg, respectively. 24h U Pi was 14.6 ± 1.8, 21.9 ± 2.4 and 41.5 ± 4.1 mmol/24h in LP, RD and HP. Mean 24h pulse rate increased significantly in HP group. Plasma creatinine, concentration of 24h urinary excretion rates of Na, aldosterone and free cortisol did not differ among the 2 groups. 24h urinary excretion of metanephrin increased significantly (intra- and intergroup) in the HP group by +60 (50-70) µg/24h. Vitamin D had no effect on the HP-induced increases in BP, pulse rate, metanephrin or renalin/aldosterone values and increased BP in 1/24h only in the LP group. Serum FGF23, PTIH, α-Klotho and urinary Klotho increased significantly in HP vs. LP. Recovery RD visits showed reversal of the elevated 24h ABPM and pulse rates in the HP group. Neither modulation of Pi intake nor vitamin D affected endothelial function or arterial elasticity tests significantly.

Conclusions: Increased Pi intake (controlled for sodium intake) significantly increases SBP, DBP and pulse rate in normal humans, an effect explained at least in part by increased sympathoadrenergic activity.

Funding: Government Support - Non-U.S.
SA-OR031
Dementia and Alzheimer’s Disease Among Older Adults Initiating Hemodialysis
Mara McAdams-DeMarco,1 Matthew Daubresse,4 Sunjai Bae,2 Dorry L. Segev,3 Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; 4Johns Hopkins School of Medicine, Baltimore, MD; 3Johns Hopkins University, Baltimore, MD; 2Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.

Background: Older end-stage renal disease (ESRD) patients experience rapid declines in executive function after initiating hemodialysis; these impairments might lead to high rates of dementia and Alzheimer’s disease (AD) in this population. We estimated incidence, risk factors, and sequence of dementia and AD among older ESRD patients initiating hemodialysis.

Methods: We studied 356,668 older (age>=66) hemodialysis patients (1/1/2001-12/31/2015) from national registry data [United States Renal Data System] linked to Medicare. We estimated dementia and AD risk (cumulative incidence), studied factors associated with these disorders using competing risks models, and estimated the risk of subsequent mortality using Cox proportional hazards models.

Results: The 1-year, 10-year, and lifetime dementia risks were 4.6%, 22.1%, and 25.1% for women and 3.7%, 18.9%, and 21.3% for men. The corresponding AD risks were 0.6%, 4.3%, and 7.5% for women and 0.4%, 3.4%, and 4.2% for men. The strongest independent risk factors for dementia and AD were age=68 years (dementia: HR=2.11, 95%CI:1.99-2.23; AD: HR=2.33, 95%CI:2.06-2.63), African American race (dementia: HR=1.70, 95%CI:1.64-1.75; AD: HR=1.92, 95%CI:1.79-2.06), and institutionalization (dementia: HR=1.50, 95%CI:1.41-1.59; AD: HR=1.49, 95%CI:1.31-1.69). Older HD patients with dementia were at 2.17-fold (95%CI:1.25-1.99) increased risk of subsequent mortality (with AD at 1.92-fold (95%CI:1.88-1.95) increased mortality risk.

Conclusions: Older hemodialysis patients are at substantial risk of dementia and AD, and these disorders increase subsequent mortality risk 2-fold. Hemodialysis may be inadequate to treat ESRD patients; the role of renal replacement therapy, particularly in older adults, should be expanded to protect cognitive function.

Funding: Other NIH Support - NIA

SA-OR032
Randomized, Placebo-Controlled Study on the Efficacy of CR845 in Improving the Quality of Life of Hemodialysis Patients with CKD-Associated Pruritus
Frederique Menzagli, Catherine Munera, Maria S. Oberdick, Joseph W. Stauffer, Robert H. Spencer. Cara Therapeutics, Inc., Stamford, CT.

Background: Chronic kidney disease-associated pruritus is a serious itching disorder associated with poor quality of life (QOL), linked to sleep disturbance, depressed mood and increased mortality. The present trial evaluated the anti-pruritic efficacy of the novel kappa-opioid receptor agonist CR845 and its impact on QOL in hemodialysis (HD) patients suffering from moderate-to-severe pruritus.

Methods: 174 HD patients with a mean baseline numerical rating score (NRS) for worst itching intensity ≥4 were enrolled [no itching up to 10=worst itching imaginable]. Patients were randomized to receive one of 3 intravenous doses of CR845 (0.5 mcg/kg, n=44; 1 mcg/kg, n=41 and 1.5 mcg/kg, n=44) or placebo (n=45) at the end of each dialysis over an 8-week treatment period. Worst itching intensity (NRS, primary endpoint) and QOL measures due to itching (secondary/exploratory endpoints) were recorded, with efficacy being defined as the change from baseline to the last week of the treatment (i.e. Week 8). Changes in QOL was assessed using multidimensional questionnaires including the Skindex-10 (with measures of emotional distress and social functioning), 5-D itch subscale (with measures of sleep and social functioning) and the MOS sleep disturbance scale.

Results: CR845 was well tolerated and reduction in itch NRS scores over placebo was observed at all doses, with a change from baseline ≥3 NRS points by end of Week 8 for 64% of the patients treated with CR845 0.5 mcg/kg vs 29% of the placebo patients (p<0.001). Improvement in QOL measures was significantly different from placebo for all doses of CR845 with respect to the Skindex-10 and the 5-D itch scale (p values ranging from <0.001 to <0.026), along with a significant improvement in sleep at doses of 0.5 and 1 mcg/kg (p=0.006). The mean change in QOL measures correlated with the change in itch intensity (Pearson’s correlation ranging from r=0.67 to 0.74, p<0.0001).

Conclusions: CR845 produced a substantial improvement in multiple measures of itch-related QOL associated with a clinically important reduction in itch intensity in HD patients with moderate-to-severe pruritus that was sustained over 2 months of treatment.

Funding: Commercial Support - Cara Therapeutics, Inc.

SA-OR033
Conservative Kidney Profile Prior to Transitioning to Dialysis and Early Dialysis Outcomes in US Veterans: A Transition of Care in CKD Study
Melissa Soochoo,1 Elani Streja,1 Yoshitsugu Obi,1 Connie Rhee,1 Daniel L. Gillen,2 Keelichi Sumida,3 Danh V. Nguyen,4 Csaba P. Kovetsy,4 Kamyar Kalantar-Zadeh,1 UC Irvine, Orange, CA; 2Nephrology, Center Toranomon Hospital Kajiyama, Kawasaki, Japan; 3University of Tennessee Health Science Center, Memphis, TN.

Background: National data has shown that more patients transition to end-stage renal disease (ESRD) at a higher estimated glomerular filtration rate (eGFR), yet mortality is high in the first months upon ESRD transition and studies have questioned the contribution of aggressive dialysis initiation to this outcome. We hypothesized that among US veterans transitioning to ESRD, a more conservative kidney profile in the pre-ESRD (prelude) period, including lower kidney function level and slower eGFR slope, is associated with better outcomes.

Methods: In 19,985 veterans transitioning to ESRD in 2007-2014, we examined the association of eGFR at transition and its slope over the final 12 months of the prelude period with 12-month post-ESRD mortality and hospitalization rates, using Cox and Poisson regression models, respectively. Two groups of low vs. high eGFR (dichotomized at 10 mL/min/1.73m²) and slow vs. fast slope (dichotomized at <0 mL/min/1.73m²/year) were combined into four groups.

Results: Patients had a median[95% CI] of eGFR at transition and slope of 9.7[7.1,13.3] mL/min/1.73m² and -0.5[-18.8,-5.9] mL/min/1.73m²/year, respectively. Patients with a conservative kidney profile (low eGFR and slow slope), had the lowest 12-month all-cause and cardiovascular (CV) mortality risks (Figure), and hospitalization rate. Conversely, patients with a high eGFR and fast slope had the highest adjusted all-cause (HR [95% CI]: 1.80 [1.62, 1.99]) and CV mortality risks (1.57 [1.32,1.83]) and hospitalization rate (IRR [95% CI] 1.39 [1.34, 1.44]) compared to conservative kidney profile patients.

Conclusions: A kidney profile characterized by slower chronic kidney disease progression and a later transition to ESRD is associated with more favorable early dialysis outcomes. Trials to examine a more conservative approach to dialysis are warranted.

Funding: NIDDK Support

SA-OR034
Residual Kidney Function and Ultrafiltration Rate: Their Association with Mortality
Jason A. Chou,1 Yoshitsugu Obi,1 Connie Rhee,1 Elani Streja,1 Danh V. Nguyen,1 Melissa Soochoo,1 Csaba P. Kovetsy,2 John J. Sim,2 Kamyar Kalantar-Zadeh,1 UC Irvine, Orange, CA; 2University of Tennessee Health Science Center, Memphis, TN; 1*Kaiser Permanente Southern California, Pasadena, CA.

Background: Residual kidney function (RFK) among both peritoneal dialysis and hemodialysis (HD) patients has been associated with improved survival. Although faster ultrafiltration rates (UFR) with HD have been observed to have greater mortality risk among incident HD patients with RFK, the ideal UFR goals are unknown. We hypothesize that in incident HD patients with RFK, a lower UFR will have improved survival.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-OR036
Impact of Transition of Care Visits on Readmission Rates in Dialysis Patients
Terry L. Ketchersid, Michael P. Martin, Daniel E. Geary, Greg S. Garza, Maria Radonova, Marta Reviriego-Mendoza, John W. Larkin, Len A. Usyvatl, Chris Richmond, Anna Alanis, Franklin W. Maddux, Fresenius Medical Care North America, Waltham, MA; Fresenius Health Partners, Austin, TX.

Background: End stage renal disease (ESRD) patients discharged from an acute care facility have 30-day readmission rates that approach 30% (USDS, 2015). In a fee for service environment, the Centers for Medicare & Medicaid Services (CMS) Transitional Care Management Services cannot be submitted by a physician billing for ESRD Monthly Capitation Payment services. Through the Comprehensive ESRD Care (CEC) Model, FMCNA has partnered with CMS to identify, test, and evaluate new ways to improve care for Medicare beneficiaries with ESRD. Utilizing the ESRD Seamless Care Organization (ESCO) care coordination waterfall, we hypothesized that nephrology providers could feasibly conduct ESRD specific Transition of Care (TOC) visits that would lower readmission rates. We are obligated to disclose that the statements contained in this document are solely those of the authors and do not necessarily reflect the views or policies of CMS. The authors assume responsibility for the accuracy and completeness of the information contained in this document.

Methods: We established an ESRD specific TOC template. Nephrology providers were paid a care coordination fee for completing the ESCO within 14 days of discharge. We analyzed claims data from May 2016 to December 2016 using a 3 month claims run out for 6 ESCOs representing 7,248 discharges. We determined the frequency of TOC visits conducted by the nephrology practice within 14 days of discharge. We measured 30-day readmission rates for each ESCO for the patients who had a TOC visit within 14 days of discharge.

Results: Completion of the TOC visits varied among the 6 ESCOs from a low of 11% to a high of 36%; TOC completion rates were inversely correlated with the ESCOs number of discharges (correlation coefficient -0.93). Among 5 ESCOs, 30-day readmission rates were 0.6% to 4.2% lower in patients who received a TOC visit; at one ESCO there was 0.9% increase.

Conclusions: Conducting a formal TOC visit within 14 days of discharge is associated with reductions in 30-day readmission rates. Smaller ESCOs completed TOC visits at a higher rate as compared to larger ESCOs.

Funding: Commercial Support - Fresenius Medical Care North America

SA-OR035
Renal Function Recovery in Incident US Dialysis Patients
Paul L. Kimmel,1 Ching-Wen Fuw,2 Kevin C. Abbott,2 Paul Eggers.1 National Institute of Diabetes and Digestive Kidney Diseases (NIDDK), Bethesda, MD; Retired, Obney, MD; Social & Scientific Systems, Inc., Silver Spring, MD.

Background: Recovery of renal function (RF) in ESRD patients is thought to be uncommon, but there are few recent descriptive data. Factors associated with RF as well as outcomes after RF are unknown.

Methods: Using USRDS data, we included incident dialysis patients between 2006 and 2015, followed until 6/30/2016. RF was physician-determined and reported by dialysis facility. Logistic regression examined associations of RF 6m after dialysis initiation with demographic characteristics and diagnoses causing ESRD. Percent of RF patients who died, returned to ESRD, and alive and not on ESRD therapy 3y after RF were determined.

Results: 1,087,954 incident dialysis patients from 2006 through 2015 were included. 68,711 patients (6%) recovered renal function during the study. The incidence of RF within 6m, accounting for 77% of all RF, was 9.0 cases/1,000 person-months (95% CI, 8.9-9.1). Mean patient age with RF was 62±15 y compared with 63±15 y for those without RF (p<0.001). Males, non-Hispanic Whites, younger patients, those receiving hemodialysis as first modality, patients with higher eGFR, and patients with central catheters had greater likelihood of RF, compared with their counterparts (all p<0.001). Acute interstitial nephritis (AIN; percent with RF, odds ratio and 95% CI: 40%, 1.28, 1.17-1.40), acute tubular necrosis (ATN; 35%, 8.8, 8.6-9.1), nephrotoxins (18%, 5.1, 4.7-5.5), traumatic or surgical loss of kidney (19%, 4.8, 4.1-5.6), and multiple myeloma (16%, 3.5, 3.3-3.7) had higher odds of RF, while patients with cystic kidney (1%, 0.4, 0.3-0.4) had lower odds of RF, compared with patients with diabetes (4%) as primary cause of ESRD. AIN and ATN patients together account for 3% of incident patients, but comprised 18% of all recoveries. At 3y, 53% of recovered patients were still alive and not on ESRD therapy, 32% had died, and 15% were living on ESRD therapy.

Conclusions: RF is not uncommon, occurs later than previously reported, and is associated with acute kidney injury diagnoses. A majority of patients survive after RF, but more than 45% of patients with RF return to ESRD and/or die within the following 3y. To better detect RF earlier, for the benefit of patients, practitioners and dialysis providers, patients with acute diagnoses and abrupt presentations should receive more intensive monitoring after initiation of dialysis than is currently practiced.

Funding: NIDDK Support
Scheduled versus Emergency Dialysis in ESRD Saves Lives and Lowers Utilization: A Quasi-Randomized Study

Background: In many states across the U.S., individuals with end-stage renal disease (ESRD) lacking federal funding for scheduled dialysis instead receive intermittent emergency dialysis only for life-threatening indications. The effects on health outcomes and utilization compared to scheduled dialysis are unknown. We sought to compare these strategies through a natural experiment among individuals with ESRD on emergency dialysis who were newly eligible and applied for private insurance coverage for scheduled dialysis, with nearly half receiving coverage in a quasi-randomized fashion.

Methods: Retrospective cohort study of 193 adults on emergency dialysis in Dallas, Texas who applied for private insurance in February 2015. Patient characteristics and outcomes were ascertained using medical record and all-payer regional claims data. Overall, 112 were enrolled in scheduled dialysis; 81 were declined for non-patient-related reasons (i.e., their dialysis center declined to participate) and remained on emergency dialysis (controls). We compared emergency department (ED) visits and hospitalizations in a 6-month baseline and a 12-month follow-up period after enrollment with a 1-month washout, using intention-to-treat negative binomial difference-in-differences (DiD) regression analyses.

Results: At baseline, the scheduled group was younger (45 vs. 52 yrs., p<0.001), had more frequent dialysis (1.0 vs. 0.6 sessions/week, p=0.04), more ED visits (7.6 vs. 4.3 median visits/month, p<0.001), and similar hospitalizations (median 2.5 vs. 3.2 per 6 months, NS) vs. controls. After enrollment, the scheduled group had fewer deaths (6% vs. 16%, p=0.01). In adjusted analyses, compared to baseline, the scheduled group had a larger net decrease in ED visits (-6.7 vs. -0.1 visits/month, p<0.001; BID of 6.6 fewer visits/month, 95% CI 5.5-7.7) and similar net decrease in hospitalizations (-1.7 vs. -1.4 per 6 months, p=0.46) during follow-up vs. controls.

Conclusions: In this quasi-randomized controlled study, individuals enrolled in a scheduled dialysis program had far lower rates of death and ED utilization in the year after enrollment compared to those remaining on emergency dialysis, despite being sicker at baseline. Universal scheduled dialysis improves health outcomes and may also be more cost-effective.

Funding: Other NIH Support - NIH/NCATS K23 TR001103

Opiate Analgesics and Adverse Outcomes in Hemodialysis Patients

Background: Pain is a highly prevalent symptom in hemodialysis patients and has been associated with worse quality of life and survival. Hemodialysis patients may be particularly vulnerable to adverse events from the use of opiate analgesics, but studies evaluating their risk are scarce and have not examined associations with dose or specific agents. Methods: From the USRDS, we identified 140,899 Medicare-covered adults on in-center hemodialysis with Part D coverage in 2011. Using Cox regression models in which we adjusted for demographics, comorbidities, number of medications, and use of potentially confounding concomitant medications (e.g., sedatives/hypnotics), we investigated the association between receipt of opiate analgesics, modeled as a time-varying exposure, and time to first emergency room visit or hospitalization for altered mental status (AMS), fall, and fracture defined by ICD-9 and CPT codes. We evaluated risk according to average daily dose (high >60 mg, low <=60 mg, and per 10 mg) and specific agents (hydrocodone, oxycodone, tramadol, codeine, hydromorphone, fentanyl, morphine, methadone per 10 mg). Doses are expressed in standardized oral morphine equivalents (OME), and exposure was time-lagged (i.e., ascertained from the prior day) for fall and fracture to account for the possibility of effect-cause.

Results: There were 90,124 (64%) patients who received opiate analgesics and 39,173 (28%) who had an episode of AMS, fall, or fracture in 2011. Opiate use was associated with risk of AMS, fall, and fracture in a dose-dependent manner (Table). Agents were associated with significantly higher rates of adverse outcomes (hazards per 10 mg OME): all agents for AMS (2.22% higher hazard); hydromorphone, hydrocodone, oxycodone, tramadol, and morphine for fall (2.27% higher hazard); and hydrocodone, oxycodone, and tramadol for fracture (3.10% higher hazard).

Conclusions: Opiate analgesics are associated with a high risk of adverse outcomes in hemodialysis patients, even at lower doses and for agents recommended by guidelines. Future research intended to predict and mitigate risks of opiate use in this population is warranted.

Funding: NIDDK Support

Adverse Outcomes by Opiate Dose

<table>
<thead>
<tr>
<th>Hazard Rate (95% Confidence Interval)</th>
<th>AMS</th>
<th>Fall</th>
<th>Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid &lt;0 mg vs. none</td>
<td>1.30 (1.20-1.35)</td>
<td>1.30 (1.22-1.38)</td>
<td>1.50 (1.38-1.62)</td>
</tr>
<tr>
<td>Opioid &gt;0 mg vs. none</td>
<td>1.39 (1.66-1.90)</td>
<td>1.51 (1.37-1.65)</td>
<td>1.75 (1.54-1.99)</td>
</tr>
</tbody>
</table>

SA-OR040

Utilizing Symptom Targeted Intervention to Help Dialysis Patients Remain Vocationally Active

Background: Ongoing vocational activity among patients with end-stage renal disease receiving dialysis is associated with considerable benefits, including better financial/insurance status, higher quality of life, and greater likelihood of receiving a kidney transplant. In spite of these benefits, most dialysis patients are not vocationally active. Perceived barriers to vocational activity include lack of access to transportation, depression, and lack of motivation. Here, we tested the utility of social workers applying Symptom Targeted Intervention (STI) to mediate psychosocial challenges and support ongoing vocational activity among dialysis patients.

Methods: In this pilot study (2016-2017), 85 specifically trained social workers at a large US dialysis organization provided 6 or more STI counseling sessions, delivered over a period of ~10 weeks, to dialysis patients who were either vocationally active (employed, student/trainee, volunteer) or interested in becoming vocationally active. Following completion of STI, each patient was matched to a control subject (no STI) based on geographic area, vocational status, and dialysis vintage. Subjects were followed until the earliest of transplant, death, loss to follow-up, or 6 months post-enrollment.

Results: Of 246 patients who received STI in the pilot study, 210 were matched to eligible controls (15 were withheld from matching due to enrollment in additional intervention programs; appropriate controls could not be identified for the remainder). A larger proportion of pilot patients were vocationally active during follow-up as compared to controls.

Conclusions: Previous work has shown that STI benefits patients who display difficulty with adjustment to dialysis. Here, we demonstrate that proactive incorporation of STI by social workers may support ongoing vocational activity among patients on dialysis.

Funding: Commercial Support - DaVita, Inc
SA-OR041

Haemodilfiltration (HDF) Improves the Cardiovascular Risk Profile Compared to Conventional Haemodialysis (HD) in Children – The HDF, Heart, and Height (3H) Trial Rukshana Shroff,1 Colette J. Smith,2 Karolis Azukaitis,3 Constantinos J. Stefanidis,4 Nur Campolat,5 Saousen Krid,6 Mieczyslaw P. Litwin,7 Franz S. Schaefer,8 Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom; University College London, London, United Kingdom; Vilnius University, Lithuania; and University of Heidelberg, Heidelberg, Germany.

Background: Fluid overload, hypertension and cardiovascular disease are common in children on dialysis. In adults, HDF is shown to reduce cardiovascular mortality, but causes for this are not clear and data in children are scarce.

Methods: We performed a non-randomized parallel-arm clinical trial within the International Pediatric Hemodialysis Network registry to assess changes in fluid status, BP, biochemistry and cardiovascular measures in children on HDF compared with conventional HD. The primary outcome measure was change in carotid intima-media thickness standard deviation score (cIMT SDS) at 1-year. (ClinicalTrials.gov NCT0263776)

Results: 190 children (from 28 centres across Europe and North America) were recruited, and 179 fulfilled inclusion criteria. 134 children (78 on HD and 56 on HDF) completed one-year follow-up. There was no difference between HD and HDF groups in age, gender, underlying renal disease, dialysis vintage, access type, blood flow or residual renal function. There were 45 drop-outs, mainly (75%) due to transplantation; there were no deaths. The median convective volume achieved in the HDF group was 13.3 (interquartile range 12.4 to 14.5) ml/min/session. At 1-year, children on HDF had lower cIMT SDS and lower pulse wave velocity SDS compared to those on conventional HD (1.98 vs 2.64; p<0.001; 0.97 vs 1.99; p<0.001 respectively). Annualised change in cIMT SDS was 10-fold lower in HDF compared to HD (0.03 vs 0.18; p=0.002). 24-hour mean arterial pressure, left ventricular mass index and parathyroid hormone level were also significantly lower on HDF (p<0.01 for all). On univariable analysis the HDF vs HD group, serum phosphate and PTH and dialysate water quality significantly associated with baseline cIMT-SDS. Multivariable linear regression analysis, the annualised change in cIMT SDS was 0.3 higher (95%CI -0.01 to 0.61) and PWV SDS was 0.26 higher (95%CI -0.4 to 0.9) in children on HD compared to those on HDF. All data were adjusted for centre and baseline cIMT-SDS.

Conclusions: In children, HDF attenuates the progression of vascular disease compared to conventional HD. This may be due to improved fluid and BP control as well as normalisation of phosphate and PTH levels.

SA-OR043

The Effect of Prenatal Lead Exposure and Gestational Age on Blood Pressure among Children Alison P. Sanders,1 Katherine Svensson,2 Chris Gennings,2 Chitra Amarasiriwardena,2 Priyanka Basnet,2 Maria L. Pizano,1 Lourdes Schnaas2,3 Marcela Tamayo y ortiz,4 Lisa M. Satin,5 Andrea A. Baccarelli,6 Martha M. Tellez-Rojo,7 Robert O. Wright,2 National Institute of Public Health, Cuernavaca, Mexico; 2Incan School of Medicine at Mount Sinai, New York, NY; 3Columbia University, New York, NY; 4National Council of Science and Technology (CONACYT) - National Institute of Public Health, Cuernavaca, Mexico; 5National Institute of Perinatology, Mexico City, Mexico.

Background: Prenatal metal exposure occurs during a susceptible period of renal development and may program later cardiovascular and renal outcomes. Our objective was to evaluate the association between prenatal lead exposure and gestational age on childhood blood pressure measured at 4 years of age.

Methods: Maternal blood lead levels (BLLs) collected in the second trimester were analyzed via inductively coupled plasma mass spectrometry. We defined AKI using changes in serum creatinine (sCr) based on the latest AKI definition, serum B2M performs well to predict AKI using changes in serum creatinine (sCr) based on the latest AKI definition, serum B2M performs well to predict AKI.

Results: 1 Maternal second trimester BLLs ranged from 0.7 to 17.8 µg/dl, with 112 (20%) above the CDC guideline level of 5 µg/dl. We identified a threshold lead level of concern of 2.5 µg/dl. When data were stratified at this lead level, shorter gestations were associated with increased SBP for subjects with BLLs ≥ 2.5 µg/dl, whereas shorter gestations were not associated with SBP for BLLs < 2.5 µg/dl. Specifically, for BLLs ≥ 2.5 µg/dl, SBP was 0.6 higher (95%CI: 0.4, 2.9) mmHg higher per each week shorter gestation among females shorter than 36.9 weeks; and among gestations longer than 36.9 weeks, this relationship was attenuated yet remained significant [β: 0.9, 95%CI (0.2, 1.6)].

Conclusions: Prenatal lead exposure may contribute to subclinical changes in the developing kidney or cardiovascular system leading to elevated SBP in childhood. We found that higher prenatal blood lead modified the association between shorter gestation and higher blood pressure. Ongoing studies will assess renal molecular changes due to early life lead exposure.

Funding: Other NIH Support - NIEHS

SA-OR044

Long-Term Renal Outcomes in Children Who Had Surgical Repair of Congenital Heart Disease Chirag R. Parikh,1 Jason H. Greenberg,2 Eric McArthur,1 Heather Thiessen Philbrook,2 Ron Wald,3 Michael Zappitelli,4 Rahul Chanchlani,5 Amit X. Garg,6 Institute for Clinical Evaluative Sciences, London, ON, Canada; 7London Health Sciences Centre, London, ON, Canada; 2McGill University Health Centre, Montreal Children’s Hospital, Montreal, QC, Canada; None, Hamilton, ON, Canada; 8St. Michael’s Hospital, Toronto, ON, Canada; Yale University, New Haven, CT; Yale University and VAMC, New Haven, CT.

Background: The risk of mortality in children who require surgery for congenital heart disease (S-CHD) has markedly reduced in recent years due to advances in pediatric and surgical care. However, there are limited data on long-term kidney outcomes in children after S-CHD compared with the general population of children.

Methods: A registry-based, matched-cohort study was conducted across 7 administrative Canadian databases. Children were included if they were born between April 1, 2002 and March 31, 2015 and underwent surgery for CHD. Follow-up and comorbidity data were collected until March 2015. Children serving as controls (10 controls for each patient with S-CHD), were matched for age, sex, neighborhood income quintile, and county, and were randomly selected from the general population. Survival analyses were performed with Cox proportional hazards models.
**SA-OR045**

**Amniotic Fluid Peptide Biomarkers for In Utero Prediction of Postnatal Renal Function in CAKUT**

Julie Klein,1 Benedictue Buffin-Meyer,2 Franck Boizard,3 Pedro Magalhães,4 Petra Zárubí,5 Benjamin Breuil,6 Elena N. Levitchenko,7 An Hindryckx,2 Lounis Nadia,3 François Auclair,4 Jean-loup Bascard,5 Stéphane Decramer,7 Joost Schansstra.1

**Background:**

Clinical management of fetuses with bilateral CAKUT is hampered by the lack of methods able to predict evolution toward kidney failure. Here we explored the amniotic fluid (AF) peptideome of 152 bilateral CAKUT pregnancies in order to identify biomarkers predictive of disease progression.

**Methods:**

Using capillary electrophoresis coupled to mass spectrometry, comparison of the AF peptideome from 32 fetuses with normal postnatal renal function at 2 years and 18 fetuses with early renal failure allowed the identification of 59 differentially abundant peptides, including fragments from extracellular matrix proteins, osteopontin, proSAAS or thymosin beta-4.

**Results:**

Modelling the 59 peptides into a random forest classifier combined with clinical features (AF volume and the age of the fetus at the time of sampling) predicted the renal outcome at 2 years in a separate validation cohort of 68 CAKUT fetuses with 89% sensitivity, 98% specificity and a positive likelihood ratio of 24. Next, we used the classifier to discriminate 34 CAKUT fetuses subjected to termination of pregnancy (TOP) but where fetopathology analysis either failed to demonstrate severe renal damage or was absent or inconclusive. The classifier scores suggested that TOP without severe renal damage could have been avoided in 80% of the cases.

**Conclusions:**

We believe that identification of the 59 AF peptide biomarkers is a significant step forward for antenatal prediction of the postnatal renal function outcome in CAKUT fetuses and should be of great help for early prenatal counselling and improved clinical management of CAKUT pregnancies, hence alleviating the psychological burden imposed on the parents.

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

---

**SA-OR046**

**Survival and Morbidity of Children with Posterior Ureteral Valves**

Gina Lockwood,1,2 Katherine W. Herbst,3 Cynthia J. D’Alessandro-Silva,1,3 Connecticut Children’s Medical Center, Hartford, CT; 2Urology, University of Connecticut Health Center, Farmington, CT; 3Pediatrics, University of Connecticut Health Center, Farmington, CT.

**Background:**

Posterior ureteral valves (PUV) is a severe urologic condition causing a spectrum of sequelae. PUV can lead to end-stage renal disease, dialysis, renal transplantation, and premature death. Predicting outcomes is challenging as prognostic measures remain imprecise. We aimed to describe outcomes for children with PUV in United States children’s hospitals.

**Methods:**

The Pediatric Health Information System (PHIS) database was searched for children diagnosed with PUV (ICD-9 code 753.6; congenital urethral stenosis) with initial hospitalization between 1992 and 2006 in their first year of life. Valve ablation or mortality following urinary drain placement was used to confirm diagnosis of PUV. Primary outcomes of dialysis catheter placement, renal transplant and mortality were determined by disposition and ICD-9/ICD-10 codes found in subsequent hospitalizations through 12/31/2016. Dialysis catheter insertion was used as a proxy for dialysis treatments, as these are not generally captured in the PHIS dataset. Subjects from hospitals without a transplant program were excluded from transplant analysis.

**Results:**

Our cohort included 754 males with median age upon hospitalization of 7 days (IQR 1-38 days). Over 90% were discharged at one month of age or less. The majority (621; 82%) did not experience any of the outcomes described, and 232 (37%) did not have a subsequent PHIS hospitalization. Of 60 (7.9%) subjects who underwent dialysis catheter placement, 34 (57%) did so during their initial hospitalization. Only 10 (16.7%) underwent placement at >5 years. Thirty-six (6.5%) subjects underwent renal transplant at a median age of 3.2 years (IQR 2.0-8.1 years), with 26 (43%) of those who underwent dialysis catheter placement undergoing transplantation. Twelve (33%) subjects underwent transplant after five years of age. Of 33 (4.4%) patients who died, 32 (97%) did so at <5 years, with 19 (58%) expiring during their initial hospitalization.

**Conclusions:**

Relatively small but significant proportions of children with PUV at PHIS hospitals undergo dialysis, renal transplantation and/or premature death. Most outcomes occur at <5 years of age, as expected in those born with severe nephropathy. As risk factors for renal deterioration are studied, these statistics from a large cohort can help to counsel parents and guide physician management.

**Funding:** Clinical Revenue Support

---

**ORAL ABSTRACTS**

**SA-OR047**

**IL-6/Stat3 Signaling Promotes Antimicrobial Peptide Expression and Limits Epithelial Invasion and Ascending Infection by Uropathogenic Escherichia coli**

Nadine Gupta1, Christina B. Ching,2 Birong Li,3 Hanna H. Cortado,4 Ashley R. Jackson,4 Kirk M. McHugh,4 Brian Becknell.4

1Nephrology, Nationwide Children’s Hospital, Columbus, OH; 2Nephrology, Nationwide Children’s Hospital, Columbus, OH; 3Urology, Nationwide Children’s Hospital, Columbus, OH; 4Anatomy, Ohio State University, Columbus, OH; 5Urology, Nationwide Children’s Hospital, Columbus, OH.

**Background:**

Despite dramatic recent improvements in outcomes after S-CHD, the incidence of long-term hypertension, CKD, ESRD and mortality remains high in these patients compared to general populations. Further interventions aimed at improving renal outcomes in this vulnerable group are required.

**Funding:** NIDDK Support, Veterans Affairs Support

---

**Table: Long-Term Outcomes following Surgical Repair of Congenital Heart Disease**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Status</th>
<th>N.</th>
<th>%</th>
<th>Indicence rate per 1000 person-years</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CHD</td>
<td>998</td>
<td>150</td>
<td>78%</td>
<td>1.25</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>304</td>
<td>150</td>
<td>15%</td>
<td>1.80</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>KD</td>
<td>217</td>
<td>150</td>
<td>15%</td>
<td>1.60</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>AI</td>
<td>76</td>
<td>150</td>
<td>5%</td>
<td>1.00</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Background: Copy number variations (CNVs) play an important role in the pathogenesis of human birth defects.

Methods: We performed a genome-wide CNV study in 2,824 cases compared to 21,498 controls to elucidate the genomic landscape of disease across the whole phenotypic spectrum of CUKAT.

Results: CUKAT cases carried a significant increased burden of rare CNVs and were highly enriched for known genomic disorders (GD) compared to controls (OR 6.6, \(P=5.7 \times 10^{-10}\)). Renal hypoplasia (RHD) showed the highest enrichment (OR 12.7, \(P=8.5 \times 10^{-12}\)), followed by obstructive uropathy (OU; OR 3.5, \(P=6.0 \times 10^{-9}\)) and posterior urethral valves (PUV) OR 5.9, \(P=2.2 \times 10^{-13}\). The most frequent CNVs in both cases and controls were gains of 16p11.2 (17q21 (n=26), 22q11.2 (n=20), the 1q21 (n=10), and 16p11.2 (n=9). While the 17q12, 22q11.2, and 1q21 were specific for RHD, the 16p11.2 showed high pleiotropy. At the loci where deletions were associated to RHD, duplications were associated to PUV or duplicated collecting system. Deletion mapping in silico annotation identified 1720 genes and 35 molecules which are expressed in a variety of human biofluids. These molecules are potential etiologies of increased VUR in the mutant mice.

Conclusions: Our study describes the genomic landscape across the phenotypic spectrum of CUKAT, identifies recurrent CNVs for urinary tract developmental phenotypes and identifies 1720 as a genetic driver of CUKAT in the 16p11.2 deletion syndrome. We identified a de novo frameshift mutation in 1720 in a case with scoliosis and CUKAT. Analysis of mouse models for two different 1720 alleles identified highly penetrant CUKAT recapitulating the high pleiotropic effect observed in humans with 16p11.2 deletions.

Funding: NIDDK Support

SA-OR049
Loss of Dicer Activity in the Peri-Wolffian Duct Stroma Leads to Increased Rates of Vesicoureteral Reflux

Melissa J. Ansley, Jacqueline Ho, Carlton M. Bates, Andrew J. Bodnar, Sunder Sims-Lucas, Children’s Hosp of Pittsburgh of UPMC, Pittsburgh, PA; Children’s Hospital of Pittsburgh, Pittsburgh, PA; Pediatric Nephrology, Children’s Hospital of Pittsburgh of UPMC, Pittsburgh, PA

Background: Vesicoureteral reflux (VUR) is associated with urinary tract infections, hypertension, and reflux nephropathy, which is the 4th most frequent cause of end-stage renal disease in children. The formation of the vesicoureteral junction occurs during development through induction of the urachic bud from the Wolffian duct, which requires signaling factors from both the Wolffian duct and surrounding stroma. VUR is known to play a role in VUR.

Methods: We generated a transgenic mouse model with loss of Dicer in the peri-Wolffian duct stroma. Dicer is a key component in the production of mature, functional miRNAs. Euthanized cystograms and 3D reconstructions of the ureters and bladders were performed on mutants (Tbx18Cre+;Dicerflx/flx) and controls (Tbx18Cre negative) mice.

Results: Euthanized cystograms demonstrated significantly higher rates of VUR in the mutant mice compared to controls (6.5 pg/ml, p<0.01). Of the mutant mice, two had bilateral VUR. Preliminary 3D reconstruction data suggests lower ureteral insertion into the bladder in mutant compared to control mice.

Conclusions: Together, these data suggest for the first time that miRNAs play a role in VUR, and that this may be due to lower ureteral insertion into the bladder in mutant mice. Future work will further assess for ureretic bud induction abnormalities and explore other potential etiologies of increased VUR in the mutant mice.

Funding: NIDDK Support, Other NIH Support - T32 Grant, Private Foundation Support

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

SA-OR050
Conditional Ablation of the Prorenin Receptor (PRR) in Nephron Progenitor Cells (NPCs) Results in Developmental Hypertension

Renfang Song, Adam T. Janssen, Laura R. Kidd, Ihor V. Yosypiv, Tulane University, New Orleans, LA

Background: The PRR is a receptor for renin and prorenin, and an accessory subunit of the vacuolar proton pump V-ATPase. Previously, we demonstrated that conditional ablation of the PRR in Srr2-/- NPCs in mice (cko) causes reduced nephron endowment and early neonatal lethality (Baxi et al., 2016).

Methods: Here, we: 1) Investigated PRR-regulated genes and pathways in Srr2-/- NPCs FACS-isolated from cko and control (CO) kidneys on embryonic day E15.5 (n=3 pooled samples/ genotype) using whole-genome-based analysis of gene expression; 2) Tested whether the Srr2-/- PRR gene dosage in Srr2+/+ mice (Het) is associated with development of hypertension during later life; and 3) Tested the hypothesis that soluble PRR (sPPR), PRR cleavage product generated subcellularly and secreted into the urine by renal tubular cells, can contribute to BP programming in Het mice.

Results: Top 10 genes included Hmga2, Mapt, Mtg5 and Gpc2. The functional groups of differentially expressed genes within the altered gene set in cko mice included genes involved in embryonic development, tissue/cell morphology, cellular assembly and organization, cell death and survival. While the number of gliomeruli per kidney section was reduced at 2 months of age (69±4 vs. 178±4, p<0.001), conscious systolic blood pressure was increased in Het compared to CO mice. Electron microscopy showed segmental thickening of the GMB with focal podocyte foot process effacement in Het mice. Urine sPPR levels measured by ELISA at 2 months of age were increased in Het compared to CO mice (262±28 vs. 146±13 pg/ml, p<0.01).

Conclusions: These data demonstrate that PRR performs essential functions during nephrogenesis via control of hierarchy of genes that regulate critical cellular processes. Reduced nephron endowment, glomerular injury and augmented urine sPPP likely contribute to programming of hypertension in Het mice.

Funding: NIDDK Support, Commercial Support - Novo Nordisk, Private Foundation Support

SA-OR051
Circulating miRNAs Profile and Risk of ESRD in Type 1 Diabetes Echinorhyncatake, Marcus G. Pizzolato, Adam Smiles, Monika A. Niewczas, Andrzej S. Krolewski, Joslin Diabetes Center, Boston, MA; University of Utah, Salt Lake City, UT

Background: MicroRNAs (miRNAs) are short endogenous, non-coding RNA molecules which are expressed in a variety of human biofluids. These molecules are involved in gene regulation and play important roles in the pathogenesis of various renal diseases, including diabetic nephropathy. However, miRNA signatures associated with diabetic nephropathy in Type 1 diabetes (T1D) has not been fully established. The objective of this study was to determine the circulating miRNA signature that is associated with risk of end-stage renal disease (ESRD) in T1D patients with chronic kidney disease (CKD).

Methods: The levels of 2,083 miRNAs from the human miRNA genome were measured in baseline plasma samples from 196 T1D patients with CKD3. We applied a new technology, High Throughput Genomics (HTG) Edge Sequence platform for miRNA sequencing and quantitation. Data were normalized by quantile normalization with sample weights.

Results: Among 196 patients, there were 90 patients who progressed to ESRD within 10 years follow-up. After filtering out miRNAs with low expression level, a total of 988 miRNAs were detectable in plasma samples from these study participants. To identify miRNAs associated with risk of ESRD, we performed fold change analysis and Cox model analysis. In total, there were 28 miRNAs significantly correlated to risk of ESRD (p-value < 0.10). For these candidate miRNAs, we divided them into 5 groups according to the Cox model analysis, and selected 5 representative miRNAs (exemplars) from each group. Multivariate Cox analysis showed that 4 of them were still associated with risk of ESRD after adjusting for baseline ACR and eGFR. Pathway analysis revealed that 3 exemplars were associated with insulin signaling pathway and/or the TGF-β pathway.

Conclusions: We discovered a profile of circulating miRNAs that is a very strong predictor/determinant of progression to ESRD in patients with T1D. This profile is represented by exemplar miRNAs which can be used to develop a multi-miRNA prognostic biomarker to predict time to onset of ESRD. Furthermore, some of these miRNAs can be used as therapeutic targets to prevent or treat progressive renal decline that leads to ESRD in diabetes.

Funding: NIDDK Support, Commercial Support - Novo Nordisk, Private Foundation Support

SA-OR052
Immunolocalization of Apolipoprotein L1 with Specific Antibodies Suzie J. Scales, Ndidi Gupta, Kathy J. Hotzel, Andrew A. Pierce, Georgios Koukos, Paul Moran, Michael T. Lipari, Xinhua Wang, Daniel Kirchhofer, Randall J. Brezski, Oded Foreman, Andrew S. Peterson, Genentech, Inc., South San Francisco, CA

Background: Human Apolipoprotein (ApoL1) is the only secreted member of the apolipoprotein (Apol) family (ApoL1-ApoL6), with 53% amino acid identity (63% similarity) to its closest relative, Apolipoprotein-A (Apol-A). We previously studied the protective role against Trypanosoma infections and the association of its variants G1 and
G2 with chronic kidney disease. To better understand the role of ApoL1 in kidney disease, it is important to identify its localization within the kidney. By immunohistochemistry, ApoL1 is reportedly strongest in proximal tubules but only just detectable in podocytes, the susceptible kidney cell type in ApoL1 nephropathies. There are conflicting reports of immunofluorescent ApoL1 subcellular localization using different commercially available antibodies: in the endoplasmic reticulum, on the plasma membrane, endosomes and even mitochondria. However, these antibodies have not been well characterized for cross-reactivity with other members of the ApoL family, giving rise to misleading results.

**Methods:** We generated monoclonal antibodies to ApoL1 and characterized their cross-reactivity with all members of the ApoL family in parallel with the commercially available polyclonal antibodies. ApoL family expression in podocytes was determined by Taqman analysis. ApoL1-specific antibodies were used to determine the true localization of ApoL1 in kidney and liver by immunohistochemistry, and in cultured podocytes by dual immunofluorescence labeling.

**Results:** All the commercially available antibodies previously published for localization studies cross-react with ApoL2, as did half of our monoclonals. Human podocytes express ApoL1, 2 and 6 mRNAs. In tissues, ApoL1 was specifically and robustly detected in serum, liver hepatocytes and kidney podocytes, but not in most podocytes. In cells, overexpressed ApoL1 and ApoL2 were found on opposite faces of the endoplasmic reticulum. Endogenous ApoL1 was also detected inside the endoplasmic reticulum (but not endosomes or mitochondria) of wild type podocytes and was enhanced by gamma interferon. The specificity of the staining was proven by its absence from ApoL1 knockout (CRISPR) podocytes.

**Conclusions:** Non-ApoL2 cross-reactive antibodies are essential for determining the true localization of endogenous ApoL1.

**Funding:** Commercial Support - Genentech

**SA-OR053**

**Metabolic Profiling of APOL1 Risk Alleles Adrienne Tin,10 Girish N. Nadkarni,1 Cheryl A. Winkler,1 Erwin P. Bottiger,1 Lesley Inker,3 Andrew S. Levey,2 Michael S. Lipkowitz,2 Lawrence J. Appel,1 Dan Arking,1 Josef Coresh,4 Morgan Gramps,5 Berlin Institute of Health, Berlin, Germany; 1Georgetown University Medical Center, Washington, DC; 2Ichac School of Medicine, New York, NY; 3Johns Hopkins Medical Institutions, Baltimore, MD; 4Johns Hopkins University, Baltimore, MD; 5Johns Hopkins School of Medicine, Baltimore, MD; 6NCI, NIH, Frederick National Laboratory, Frederick, MD; 7Tufts Medical Center, Boston, MA; 8Welch Center for Prevention, Epidemiology & Clinical Research, Baltimore, MD; 9Epidemiology, Johns Hopkins University, Baltimore, MD.

**Background:** Apolipoprotein L1 (APOL1) risk alleles have been associated with chronic kidney disease (CKD) progression. Metabolic profiling by APOL1 risk allele status may inform our understanding of the pathogenesis of APOL1-associated kidney disease.

**Methods:** We evaluated the association between 1,133 serum metabolites identified via an untargeted approach at Metabolon and the number of APOL1 high risk alleles (0,1, or 2) in the African American Study of Kidney Disease (AASK) \((n=699)\). The significance threshold was set at 2.4e-4 based on principal component analysis. Significantly associated metabolites were then tested in a second cohort of African American patients with CKD (BioMe; \(N=680\)). Metabolites that replicated were evaluated as risk factors for CKD progression, defined as ESRD or at least doubling of serum creatinine.

**Results:** Of the six metabolites significantly associated with APOL1 in AASK, one, 5-bromotryptophan, was also significant in BioMe, with lower levels associated with higher number of risk alleles (beta per APOL1 risk allele, AASK: -0.23, p=2.5e-5; BioMe: -0.14, p=4.1e-3). In further analysis in AASK, lower levels of 5-bromotryptophan, a product of tryptophan metabolism, were associated with CKD progression adjusting for demographics, study assignments, baseline GFR, proteinuria, and APOL1 high-risk status (adjusted HR by tertile \(T\); T2 vs T1 (lowest) 0.86 (95% CI: 0.64, 1.16); T3 (highest) vs T1: 0.63, 95% CI: 0.45, 0.88, \(p\) for trend: 0.008, figure).

**Conclusions:** Metabolomic profiling identified an association of APOL1 high risk alleles with lower 5-bromotryptophan levels, which was also associated with CKD progression, a finding which was consistent in two cohorts.

**Funding:** NIDDK Support

**SA-OR054**

**Apolipoprotein L1 Risk Variants and Soluble Urokinase Plasminogen Activator Receptor Synergistically Mediate CKD in African Americans Salim Hayek,1 Kwi Hye Koh,12 Morgan Gramps,4 David C. Wei,11 Hyun Lee,1 Ranadheer Dande,4 Ha Won Lee,12 Eunsih Hahn,12 Vassil Pevs,1 Nicholas I. Tardi,12 Vineet Gupta,12 Mehmet M. Altintas,12 Nikolima Stoianovic,12 Cheryl A. Winkler,1 Michael S. Lipkowitz,1 Adrienne Tin,1 Lesley Inker,13 Andrew S. Levey,1 Martin G. Zeier,1 Barry I. Freedman,1 Jeffrey B. Kopp,1 Karl Skorecki,1 Josef Coresh,9 Sanja Sever,9 Jochen Reiser,13 Emory University School of Medicine, Atlanta, GA; 14Univ. of Illinois at Chicago, Chicago, IL; 15Georgetown University Medical Center, Washington, DC; 16Johns Hopkins University, Baltimore, MD; 17MGH, Charlestown, MA; 18Massachusetts General Hospital, Charlestown, MA; 19NCI, NIH, Frederick National Laboratory, Frederick, MD; 20NIDDK, NIH, Bethesda, MD; 21None, Baltimore, MD; 22Rambam Health Care Campus, Haifa, Israel; 23Rush University, Chicago, IL; 24Rush University Medical Center, Chicago, IL; 25Tufts Medical Center, Boston, MA; 26Wake Forest University School of Medicine, Winston-Salem, NC; 27Welch Center for Prevention, Epidemiology & Clinical Research, Baltimore, MD; 28Division of Nephrology, Ruhtep Arch Center, Heidelberg, Germany.

**Background:** Apolipoprotein L1 (APOL1) gene variants G1 and G2 but not the reference allele G0 are associated with an increased risk for chronic kidney disease (CKD) in African Americans, but the mechanisms are unknown. Soluble urokinase plasminogen activator receptor (suPAR) strongly predicts CKD.

**Methods:** We characterized APOL1 genetic variants and plasma suPAR levels in two separate cohorts of African-American patients, the Emory Cardiovascular Biobank (EmCAB, \(n=487\)) and the African American Study of Kidney Disease and Hypertension (AASK, \(n=607\)). We studied the biochemical interaction between ApoL1, suPAR, and integrin \(\beta3\) by immunoprecipitation and surface plasmon resonance (SPR).

**Results:** Here we show that individuals carrying the high-risk APOL1 genotype, i.e. 2 copies of risk variants, manifest a steeper decline in kidney function with increasing suPAR levels compared to individuals harboring low-risk genotypes. SPR identified high affinity interactions between ApoL1, suPAR, and cvr3 \(\beta3\) integrin. ApoL1 protein variants G1 and G2 exhibited higher affinity for suPAR-activated cvr3 \(\beta3\) integrin than ApoL1 G0, and activated podocyte cvr3 \(\beta3\) integrin. APOL1 G1 or G2 expression causes proteinuria in mice in a suPAR dependent manner.

**Conclusions:** The synergistic activation of cvr3 \(\beta3\) integrin by circulating factor suPAR and ApoL1 G1 or G2 is a mechanism for CKD in patients of recent African ancestry.

**Funding:** NIDDK Support
Metabolites Associated to Mortality and ESRD in a Brazilian CKD Cohort: The Progredir Study
Silvia M. Titan,1 Gabriela Venturini,2 Kallysay Padilha,2 Paulo Lotufo,3 Isabelra M. Bensonor,4 Ravi I. Thadhani,4 Eugenio P. Rhee,4 Alexandre C. Pereira.5 Nephrology Division, Massachusetts General Hospital, Boston, MA; 1Laboratório de Cardiologia Molecular, InCor; Hospital das Clínicas, Faculty of Medicine, University of Sao Paulo, Sao Paulo, Brazil; 2Nephrology Division, Faculty of Medicine, Sao Paulo University, Sao Paulo, Brazil; 3Clinical Research Center, University Hospital, Sao Paulo University, Sao Paulo, Brazil; 4Laboratorio de Cardiologia Molecular, InCor; Hospital das Clínicas, Faculty of Medicine, University of Sao Paulo, Sao Paulo, Brazil.

Background: Recent studies have evaluated metabolomics in relation to eGFR and to incident CKD. However, very few studies have evaluated metabolomics biomarkers in the context of prevalent CKD and hard outcomes. Objective: To evaluate specific metabolites related to death, ESRD, and a composite outcome of both in a CKD population (n=454).

Methods: Metabolomics was performed by GC and Mass Spectrometry. Metabolites were identified using Agilent Fiehn GC/MS Metabolomics and NIST libraries (Agilent MassHunter Workstation Quantitative Analysis, version B.06.09). From initial 10940 metabolites, we excluded those present <50% of the samples, leaving 293. We selected candidate metabolites by applying a FDR q value <0.05 in a Cox model on the composite outcome adjusted only for batch. Among the 34 selected metabolites, Cox regression models were built on death (n=93), ESRD (n=36) and composite outcome (n=126).

Results: Mean age was 68±12y, mean eGFR-CrDEPI was 38.4 (±14.6) ml/min/1.73m² and 57% were diabetic. After adjustment for batch, sex, age, DM and eGFR, 18 metabolites were significantly related to the composite outcome, with lactate, D-threitol, docosahexaenoic acid (DHA), butanoic acid and mannitol among the top. For mortality only, 9 metabolites remained significantly associated with death, with D-malic acid (TCA cycle), OR 1.84, 95% CI 1.32 – 2.56, p=0.006, butanoic acid (colon microbiota; 1.59, 95% CI 1.17 – 2.15, p=0.003), and DHA (omega3 fatty acid, OR 0.58, 95% CI 0.39 – 0.88, p=0.009) among the top 3. For ESRD, 4 metabolites remained significantly associated to its risk: lactate, 2-O-glyceryl-G-d-galactopyranoside, D-threitol and tyrosine (Table 1), findings confirmed by the competing analysis except for D-threitol.

Conclusions: Our results identify specific metabolites related to hard outcomes in a CKD population. These can be further confirmed in an independent sample.

Funding: Government Support - Non-U.S.

Table 1. Cox proportional hazard models on the risk of ESRD after adjustment for batch, sex, age, eGFR and DM.

<table>
<thead>
<tr>
<th>Metabolite (lgG)</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate</td>
<td>1.68</td>
<td>1.71</td>
<td>2.31</td>
</tr>
<tr>
<td>2-O-Glyceryl-G-d-galactopyranoside</td>
<td>1.17</td>
<td>1.11</td>
<td>2.54</td>
</tr>
<tr>
<td>D-threitol</td>
<td>2.34</td>
<td>1.01</td>
<td>7.30</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>0.59</td>
<td>0.30</td>
<td>0.98</td>
</tr>
</tbody>
</table>

The global burden of chronic kidney disease attributable to elevated PM₂.₅ expressed in disability adjusted life years (D ALY) per 100,000 population.

SA-OR055

A Machine Learning Approach to Predicting ESRD
Girish N. Nadkarni,1 Edward Lee,2 Oliver L. Fielding,2 Teddy Chu,3 Hai Po Sun,4 Chris Kipers,5 William D. Paiva,6 Elvena Fong,7 Steven G. Coca.1 Icahn School of Medicine at Mount Sinai, New York, NY; 2puleData, Inc., New York, NY; 3Center for Health Systems Innovation (Oklahoma State University, Stillwater, OK.

Background: Risk prediction of end stage renal disease (ESRD) for population management and care intervention is both a research priority and unmet public health need. The use of electronic medical records (EMR) can be leveraged for improved assessment of ESRD onset. However, traditional risk scoring may not provide accurate risk prediction or complete population coverage if EMR data is incomplete. To handle missing data we developed a machine learning (ML) approach and compared it to traditional risk scoring in two EMR cohorts.

Methods: We utilized longitudinal data from the Mount Sinai Chronic Kidney Disease registry and a data set from the Center for Health Systems Innovation at Oklahoma State University provided by the Corner Corporation. Using a random forest ML technique and imputation we can predict risk of ESRD (defined as administrative codes for dialysis or transplant). We then compared it to the Tangri 4-Variable kidney failure risk equation (KFRE) by comparing area under curve (AUC) measures and the percent of the population on which each metric can be calculated.

Results: We analyzed data from 318,292 patients. The median age was 65 years, 54% were female and 20% were African American. 60% of the cohort had at least one estimated glomerular filtration rate (eGFR) measurement before ESRD onset, however, only 6% had both an eGFR measurement and a urine albumin creatinine ratio (UACR) value before failure. The AUC of the 4-Variable KFRE was 0.89 (95% CI [0.88, 0.91]), while the ML approach had an AUC of 0.94 (95% CI [0.94, 0.95]). Importantly, the improvement in AUC was achieved while risk-scoring 10 times more of the population.

Conclusions: The ML approach outperformed traditional risk scoring such as the 4-Variable KFRE both in risk discrimination and in population coverage. Therefore, future efforts to risk stratify for population management and care intervention will benefit from utilizing ML approaches.

Table. Comparison of 4-Variable KFRE and ML approach

<table>
<thead>
<tr>
<th>Population coverage (%)</th>
<th>4-Variable KFRE</th>
<th>Machine Learning Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>19.2%</td>
<td>0.89</td>
</tr>
<tr>
<td>60%</td>
<td>19.4%</td>
<td>0.91</td>
</tr>
<tr>
<td>70%</td>
<td>19.5%</td>
<td>0.91</td>
</tr>
<tr>
<td>80%</td>
<td>19.5%</td>
<td>0.91</td>
</tr>
<tr>
<td>90%</td>
<td>19.5%</td>
<td>0.91</td>
</tr>
<tr>
<td>100%</td>
<td>19.5%</td>
<td>0.91</td>
</tr>
</tbody>
</table>

SA-OR057

Association between Pre-ESRD RAAS Blockade and Post-ESRD Mortality
Miklos Z. Molnar,1 Adnan Naseer,2 Keichi Sumida,3 Ariel R. Kiezenman,4 Praveen Kumar Potukuchi,4 Abdusghaar Gapow,4 Elani Streja,4 Kamyar Kalantar-Zadeh,3 Csaba P. Kovovsky,4 Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; 1Nephrology Center, Toramnon Hospital Kaigaya, Kawasaki, Japan; 2University of California Irvine, School of Medicine, Orange, CA; 3University of Texas Health Science Center, Memphis, TN; 4University of Tennessee Health Science Center - Memphis, Memphis, TN; 5VAMC, Germantown, TN.

Background: Renin-Angiotensin-Aldosterone system inhibitor (RAASI) use is associated with slower progression of chronic kidney disease (CKD) and lower mortality in patients with CKD. However, the association between pre-end stage renal disease (ESRD) RAASI use and post-ESRD mortality is unclear.

Methods: We examined 15,866 US veterans initiating dialysis during 2007-2014. We divided patients into three groups of RAASI use pattern in the last 3 pre-dialysis years: never exposed (n=7,294), exposed but discontinued in the last pre-dialysis years (n=6,833) and uninterrupted use (n=1,889). Associations of RAASI use patterns with all-cause mortality were examined in multivariable adjusted Cox models.

Results: Patients were 72±11 years old, 98% male, 23% African-American, and 65% diabetic. The all-cause mortality rates were 303 (95% CI 294-311)/1000 patient-years (PY) in patients who never exposed to RAASI, 276 (95% CI 268-284)/1000PY in patients who discontinued RAASI and 240 (95% CI 227-254)/1000PY in patients on uninterrupted
RAASi, respectively, during a median of 2.2 years of follow-up. Uninterrupted RAASi use was associated with lower risk of death after dialysis start in unadjusted and various adjusted analyses (Figure).

**Conclusions:** Uninterrupted RAASi use prior to dialysis is associated with lower risk of death after dialysis start. There was no post-ESRD survival benefit observed in patients who discontinued RAASi in the final year before MHD initiation.

**Funding:** NIDDK Support

### SA-OR059

**High FGF-23 Is Associated with Coronary Calcification Only in Patients with High Adiponectin:** From the KNOW-CKD Study

Young Youl Hyun,1 Curie Ahn,1 Yong-Soo Kim,3 Soo Wan Kim,3 Yeong Hoon Kim,3 Chonnam National University Medical School, Dongku, Republic of Korea; Inje University Medical School, Busan, Republic of Korea; The Catholic University of Korea College of Medicine, Seoul, Republic of Korea; Seoul National University Hospital, Seoul, Republic of Korea; Yonsei University College of Medicine, Seoul, Republic of Korea; Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea. Group/Team: KNOW-CKD Study Group.

**Background:** Both FGF-23 and coronary artery calcification (CAC) are known as predictors of high cardiovascular and all-cause mortality. However, previous studies on the association between FGF-23 and CAC were inconclusive. Recently, it has been shown that adiponectin modulates renal handling of phosphate and calcium, important factors in vascular calcification. We hypothesized that adiponectin play a role in the effect of FGF-23 on CAC, and explored whether this association between FGF-23 and CAC is modified by serum adiponectin level in CKD patients.

**Methods:** This cross-sectional study analyzed 1,153 predialysis CKD patients from the KNOW-CKD cohort who measured coronary artery calcium scores (CACS), serum FGF-23 and serum adiponectin. Participants were divided into three groups according to modified half of adiponectin.

**Results:** Median [interquartile range] CACS were not different between low and high adiponectin group (3.25 [1.53-6.91] vs 3.00 [1.50-6.42], P=0.30). The CACS ratio in the high FGF-23 group compared to the low group were significantly increased only in the high adiponectin group (Table).

**Conclusions:** High serum FGF-23 was associated with CAC only in CKD patients with high adiponectin, but not in those with low adiponectin. Further studies are warranted to verify the role of adiponectin in FGF-23-related coronary calcification.

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

### SA-OR060

**HDL Cholesterol and Its Associations with Cause-Specific Mortality in Patients with CKD**

Sankar D. Navaneethan,1 Jesse D. Schold,2 Susana Arriagada,3 Stacey Jolly,3 Carl P. Walther,4 Wolfgang Winkelmayer,4 Joseph V. Nally,2 1Baylor College of Medicine, Houston, TX; 2Cleveland Clinic, Cleveland, OH.

**Background:** Recent data suggest a U-shaped association between HDL cholesterol (HDL-c) and death in CKD. However, whether the increased mortality in patients with extreme levels is driven by specific causes of death remains unclear. Herein, we examined the associations between HDL-c and cause-specific mortality in a large CKD population.

**Methods:** We included 38,377 patients with eGFR 15-59 ml/min/1.73 m² who had lipid levels measured within 1 year of CKD diagnosis. We ascertained overall and cause-specific deaths from the State mortality data and classified deaths into 3 major categories: a) cardiovascular; b) malignancy; and c) non-cardiovascular/non-malignancy causes. We fitted Cox regression models for overall mortality and separate competing risk models for each major cause of death category to evaluate their respective associations with categories of HDL-c (≥30, 31-40, 41-50 [referent], 51-60, >60 mg/dl). Separate analyses were conducted for men and women.

**Results:** During a median follow-up of 4.5 years, 9,665 patients died. HDL-c ≥30 mg/dl was associated with higher all-cause and cardiovascular mortality in both sexes and higher risk of malignancy-related deaths in women (Table 1). HDL-c >60 mg/dl was associated with lower all-cause mortality in women only. HDL-c >60 mg/dl was associated with higher risk of non-cardiovascular/non-malignancy related deaths in men but not women. Exclusion of those with malignancy yielded results similar to primary analyses.

**Conclusions:** In a non-dialysis dependent CKD population, HDL-c ≥30 mg/dl was associated with higher all-cause and cardiovascular mortality, but not with non-cardiovascular mortality. HDL-c >60 mg/dl was associated with higher risk of non-cardiovascular/non-malignancy related deaths in men only. Additional studies examining the reasons for these different associations between HDL-c and cause-specific mortality, and potential effect modification by sex, are needed.

**Funding:** Commercial Support - Development of CCF CKD registry was supported by an unrestricted educational fund to the Department of Nephrology and Hypertension from Amgen, Inc

**Table 1. Associations between HDL-c (in mg/dl) and cause-specific mortality in CKD**

<table>
<thead>
<tr>
<th>Category</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-c (mg/dl)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>&lt;30</td>
<td>30,377</td>
<td>9,665</td>
</tr>
<tr>
<td>31-40</td>
<td>14,677</td>
<td>4,520</td>
</tr>
<tr>
<td>41-50</td>
<td>14,677</td>
<td>4,520</td>
</tr>
<tr>
<td>51-60</td>
<td>14,677</td>
<td>4,520</td>
</tr>
<tr>
<td>&gt;60</td>
<td>14,677</td>
<td>4,520</td>
</tr>
</tbody>
</table>

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

Underline represents presenting author.
**SA-OR061**

**Differential Effects of STCH and HSP70 on the Stability and Maturation of NKCC2**


**Background:** Mutations in the apically located Na-K-2Cl cotransporter, NKCC2, lead to type I Bartter syndrome, a life-threatening kidney disorder associated with salt wasting, hypokalemia, and metabolic alkalosis. Conversely, increased expression of NKCC2 promotes hypertension. We previously showed that export from the ER constitutes the limiting step in the maturation and cell surface expression of NKCC2 and its disease causing mutants. Yet the molecular mechanisms involved in this process remain unclear.

**Methods:** To identify the protein partners involved in ER associated degradation of NKCC2, we screened a kidney cDNA library through yeast two-hybrid using NKCC2 C-terminus as bait. NKCC2 protein expression was monitored in transiently transfected HEK cells, using immunofluorescence and confocal imaging. NKCC2 stability was assessed by cycloheximide chase assay.

**Results:** We identified STCH, a constitutively expressed member of the heat shock protein family, as a specific binding partner of NKCC2. STCH is known to be a microsome-associated chaperone. Co-immunoprecipitation and co-immunolocalization experiments confirmed NKCC2-STCH interaction in HEK cells. Interestingly, they also identified the cytoplasmic and stress-inducible heat shock protein 70 (HSP70) as an interactor with NKCC2. STCH and HSP70 binding to NKCC2 involve mainly the immature form of the co-exporter and takes place at the ER. STCH co-expression decreased the total cellular WT NKCC2 protein and its disease associated folding mutants, in a dose dependent fashion, whereas HSP70 co-expression had the opposite effect. Cycloheximide chase assay showed that in cells over-expressing STCH, NKCC2 stability was increased. Maturation of a NKCC2-K542E mutant impaired in STCH to HSP70 co-expression increased strikingly NKCC2 expression and maturation.

**Conclusions:** Our results are consistent with STCH and HSP70 having differential and antagonistic effects with regard to NKCC2 biogenesis, in particular under ER stress conditions. Most importantly, they may have an impact on our understanding and potential treatment of diseases related to aberrant NKCC2 trafficking and expression.

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

---

**SA-OR062**

**Modeling the Structural and Dynamical Changes of TRPV5 Caused by the A563T Variation Based on the Structure of TRPV6**

Lingyun Wang, Ji-Bin Peng, Div of Nephrology, Dept of Medicine, Nephrology Research and Training Center, University of Alabama at Birmingham, Birmingham, AL.

**Background:** TRPV5 is an epithelial Ca2+ channel that plays a key role in the active Ca2+ reabsorption process in the kidney. The single nucleotide polymorphism (SNP) rs4252499 in TRPV5 gene has a minor allele frequency of around 0.17 in African descendants. This SNP results in an A563T variation in the sixth transmembrane (TM) domain of TRPV5. Our previous study indicates that the variation increases Ca2+ uptake and alters Mg2+ sensitivity of TRPV5. To understand the molecular mechanism, molecular simulations have been performed based on the structure of TRPV1. Recently, the structure of TRPV6 was determined. Since TRPV5 is much more similar to TRPV6 than TRPV1, new molecular simulation based on TRPV6 structure would provide more accurate information on the A563T variation in TRPV5.

**Methods:** Using MODELLER, TRPV5 model was set up on a newly deposited structure of TRPV6 which shares 73% amino acid identity with TRPV5. This model contained all the six TM helices and the TRP domain of TRPV5. The A563T variation was introduced into TRPV5 using PyMOL. To mimic the membrane environment, the modeled TRPV5 was embedded in a lipid bilayer composed of 299 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) lipids using CHARMM-GUI, and then modeled TRPV5 was embedded in a lipid bilayer composed of 299 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) lipids using CHARMM-GUI, and then simulations have been performed based on the structure of TRPV1. Recently, the structure of TRPV5 was determined.

**Results:** The first patient was diagnosed with Bartter syndrome (BS) over 30 years ago. Re-evaluation demonstrated hypocalciuria and hypercalcemia, suggesting Gitelman syndrome (GS). However, serum magnesium was in the upper-normal to hypermagnesemic range, thiazide responsiveness was not blunted, and genetic analyses did not show mutations in genes associated with either GS or BS. A reduced urinary concentrating ability with a preserved aquaporin-2 response to desmopressin was demonstrated, with an intact to exaggerated response to furosemide. These findings are not in line with any known salt-transporting nephropathy. Whole exome sequencing revealed compound heterozygous CLDN10 sequence variants. A second unrelated patient was thereafter identified demonstrating a similar phenotype and compound heterozygous CLDN10 sequence variants. Both patients' phenotypes resemble a mouse model lacking distal tubular Claudin-10, that demonstrates a reduced TAL paracellular sodium reabsorption, induce hypokalemic alkalosis by increasing distal tubular flow and sodium delivery. However, the importance of paracellular transport also identified the cytoplasmic and microsome-associated chaperone. Co-immunoprecipitation and co-immunolocalization experiments confirmed NKCC2-STCH interaction in HEK cells. Interestingly, they also identified the cytoplasmic and stress-inducible heat shock protein 70 (HSP70) as an interactor with NKCC2.

**Conclusions:** Pathogenic CLDN10 mutations cause a novel tight junction disease, possibly affecting TAL paracellular ion transport, characterized by a non-Bartter non-Gitelman hypokalemic-alkalotic salt-losing phenotype and a renal concentration defect, with hypocalciuria and unexpectedly normal to high serum magnesium levels. Consistent with TRPV1-based simulation, the current simulation indicates that the identified sequence variants. Both patients' phenotypes resemble a mouse model lacking distal tubular Claudin-10, that demonstrates a reduced TAL paracellular sodium reabsorption, induce hypokalemic alkalosis by increasing distal tubular flow and sodium delivery. However, the importance of paracellular transport also identified the cytoplasmic and microsome-associated chaperone. Co-immunoprecipitation and co-immunolocalization experiments confirmed NKCC2-STCH interaction in HEK cells. Interestingly, they also identified the cytoplasmic and stress-inducible heat shock protein 70 (HSP70) as an interactor with NKCC2.

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

---

**SA-OR065**

**Effect of Sodium-Glucose Cotransporter 2 Inhibitor on Fluid Distribution: Comparison with Furosemide and Tolvaptan Ken Ohara, Takahiro Masuda, Takuya Murakami, Toshio Imai, Saki Nakagawa, Mari Okada, Hiromichi Yoshizawa, Atsushi Miki, Kentaro Oka, Maki Asakura, Taro Sugase, Akira Onishi, Tetsu Akimoto, Osamu Saito, Shigeaki Muto, Daisuke Nagata. Division of Nephrology, Department of Internal Medicine, Fuchi Medical University, Oyama, Japan.

**Background:** Sodium-glucose cotransporter 2 (SGLT2) inhibitor is a new antihyperglycemic drug that increases urinary glucose excretion. Recently, the diuretic effects of SGLT2 inhibitors (SGLT2i) have been reported, but the diuretic fluid distribution remains unclear. Therefore we examined the change of fluid distribution after the administration of SGLT2 inhibitor dapagliflozin (DAPA), and compared with loop diuretic furosemide (FR) and vasopressin V2 receptor antagonist tolvaptan (TLV).

**Methods:** Forty chronic kidney disease (CKD) patients with fluid retention (average cGFR 29.0±3.3 mL/min/1.73 m2) were enrolled in this study. The patients were divided into the three groups: DAPA (n=15, dose 5 mg/day), FR (n=15, dose 55.7±12.4 mg/day) and TLV (n=10, dose 7.5 mg/day). The fluid volume was measured using a bioimpedance cGFR...
**SA-OR066**

**Mobilization of Nonosmotically Stored Sodium after Water Loading in Healthy Individuals**  
Rosa D. Wouda, 1 Shoshia Dekker, 2 Joelle Reijm, 3 Rik H. Olde Engberink, 1 Liiffert Vogt, 1 Academic Medical Center, Amsterdam, Netherlands; 2 AMC Academic Medical Center, Amsterdam, Netherlands; 3 Amsterdam Medical Center, Amsterdam, Amsterdam, Netherlands.

**Background:** Recently it was discovered that significant amounts of sodium (Na+) can be stored without concurrent water retention. These observations indicate the presence of sodium-storing compartments in the body. The nonosmotic compartment for sodium retention is not known. In this study we investigated whether Na+ can be released from its nonosmotic stores after a hypotonic fluid load.

**Methods:** Twelve healthy male subjects had a water loading test (WL; 20 ml water/kg at 10 min). During a 240 min follow-up, we compared the observed plasma [Na+] to the predicted Na+ concentration using the Barsoum-Levine and Nguyen-Kurtz formula. These formulas are used for guidance of fluid therapy during dysnatremia and can be stored without concurrent water retention. These observations indicate the presence of sodium-storing compartments in the body. The nonosmotic compartment for sodium retention is not known. In this study we investigated whether Na+ can be released from its nonosmotic stores after a hypotonic fluid load.

**Results:** After 1 week, changes in body weight (DAPA -3.1±0.8, FR -4.6±0.8, TLV -2.6±1.0 kg, p<0.02) and urine volume (+81±220, +451±243, +187±230 mL/day, p<0.52) were not significantly different among the groups. BIA showed changes in intracellular water (+6.2±1.3, -7.3±1.2, -7.1±1.4 p=0.02) were similar among the groups, and changes in extracellular water (ECW) tended to increase in FR (+8.5±6.1, -2.6±1.6, -7.9±1.8%, p=0.10). Changes in the ratio of ECW to total body water (ECW/TBW) were significantly different (-1.3±0.5, -3.4±0.5, -0.3±0.6%, p<0.001). Changes in estimated glomerular filtration rate were not significantly different during the treatment (-20±2.3, 3.9±2.3, 0.4±1.1%, p=0.46).

**Conclusions:** SGLT2 inhibitor dapagliflozin predominantly decreases ECW, but the reduction rate of ECW/TBW differs from furosemide and tolvaptan. These results indicate that SGLT2 inhibitor has a novel property on fluid distribution not found in conventional diuretics.

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

**SA-OR068**

**Low Dietary Intake May Help the Kidneys Improve Exercise Capacity**  
Enni-Maria Hietavala, 1 Lynda A. Frassetto, 1 University of California San Francisco, San Francisco, CA; 2University of Jyväskylä, Jyväskylä, Finland.

**Background:** Diet influences the acid-base status of the body. The effects of differing acid balances may become more relevant as renal functional capacity declines with aging. We examined the effects of low (LD) versus high dietary acid load (HD) blood bicarbonate and exercise performance.

**Methods:** The 88 healthy volunteers who participated - 22 adolescents (AD), 33 young adults (YA) and 33 elderly (EL) - followed a 7-day LD and HD in a randomized order. At the end of both diet periods the subjects performed a cycle ergometer test (3x10 min at 35%, 55% and 75%, and (except EL) until exhaustion at 100% of VO2peak). At the beginning of, and after the diet periods, blood samples were collected at rest and after all workloads. Oxygen consumption, respiratory exchange ratio and heart rate were monitored during cycling. Glomerular filtration rate (GFR) was calculated with CKD-EPI formula. Two-way repeated measures ANOVA and Pearson correlation analyses were done on SPSS Statistics 22.0.

**Results:** Bicarbonate (HCO3-) decreased over the HD period in YA women (p<0.001), YA men (p<0.001), EL women (p<0.001) and EL men (p=0.011). HCO3- increased over the LD period in AD girls (p=0.005) and EL men (p<0.039). HCO3- was lower at rest after HD compared to LD in YA women (p<0.001), YA men (p=0.042) and in both EL groups (p<0.001). HCO3- was lower at submaximal workloads after HD compared to LD in YA women (p=0.022) and EL women (p=0.020). In young women, the maximal workload was 19 % shorter (p<0.001) and maximal cardiorespiratory measures (p=0.029) lower after HD compared to LD.

**Conclusions:** Our data uniquely suggests that better renal function is associated with higher availability of bases, which may diminish exercise-induced acidosis and improve performance. Glomerular filtration rate decreased with aging and was higher in men compared to women, likely explaining the larger effects of dietary acid load on acid-base status in the elderly compared to younger subjects and in women compared to men. The diet composition along with renal functional capacity affects acid-base status of the body at rest and in exercise.

**Funding:** Private Foundation Support

**SA-OR069**

**Impact of Fluid Balance on One-Year Mortality of Patients with Septic Shock**  
Tsering Dhondup, 1 Jong-Chie Claudia Tien, 1 Hon Liang Tan, 2 Alberto E. Marquez, 2 Kianoush Banai-Kashani, 1 Mayo Clinic, Rochester, MN; 2 Singapore General Hospital, Singapore, Singapore.

**Background:** Septic shock patients require early and aggressive volume resuscitation. However, current evidence shows higher risk with the intensity and duration of fluid overload in critically ill patients. In this report, we outline the impact of fluid balance and timing of volume de-resuscitation on outcomes in septic shock patients.

**Methods:** We retrospectively identified adult septic shock/ severe sepsis patients admitted to the ICU of Mayo Clinic Hospital from January 1st, 2007 to December 31st, 2009. Data was abstracted electronically and validated manually. We collected basic demographic, clinical, laboratory and outcome variables. Social security death index was used for missing mortality information. De-resuscitation day was defined as the 1st day with the negative fluid balance, and KDIGO criteria were used for AKI definition.

**Results:** A total of 633 patients were included with mean age of 68 years, with 348(55%) being males. Median ICU length of stay was 2.4 (IQR of 1.3-5.5) days, and median 24-hour fluid balance in ICU was 2352 (IQR of 990-4323) ml. The median day 1 SOFA score was 7 and 57 (9%) patients had pre-existing ESRD. In ICU, de-resuscitation was achieved in 443 (70%) patients within [median (IQR)] 2 (1-3) days of ICU admission. Among those starting de-resuscitation in ICU, the average cumulative fluid balance was −1.4 (±5.7) liters. 371 of 576 non-ESRD (64%) patients developed AKI of which 291 patients were admitted with AKI. Eighty (22%) of those with AKI required initiation of dialysis with 63 patients being initiated on CVVH and 17 on intermittent hemodialysis.

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

**Underline represents presenting author.**
Adjusted for age, Charlson Comorbidity Index, APACHE III score and day 1 SOFA score, even after the positive cumulative fluid balance was associated with increased hospital mortality (OR of 1.10; 95% CI: 1.06-1.16) in patients who achieved re-sursumation phase. More interestingly, every 1 liter positive cumulative fluid balance was also associated with increased 1-year mortality (OR of 1.07; 95% CI: 1.03-1.12). Association of fluid balance with increased risk of Hospital and 1-year death remained significant irrespective of pre-existing ESRD or AKI development.

Conclusions: In our cohort of patients with septic shock who achieved re-sursumation, positive cumulative fluid balance was associated with increased hospital and 1-year mortality.

SA-OR70

TRC101, a Novel Hydrochloric Acid Binder, Increases Serum Bicarbonate in Acidemic Patients with CKD

Methods: In this randomized, double-blind, placebo-controlled study, 135 acidemic CKD patients (eGFR 20 to <60 mL/min/1.73m²) were admitted to an in-patient unit and treated for 14 days with either daily TRC101 dosing regimens (1.5, 3.0, or 4.5 g BID; 6.0 g QD), or one of four TRC101 dosing regimens: (CT; 5Univ. of Rochester, Rochester, NY; 6Parsell Associates, Cedar Park, TX). Background: Metabolic acidosis is common in patients with chronic kidney disease (CKD) and has significant adverse effects on renal function, muscle, and bone. TRC101 is a novel, orally-administered, non-absorbed, metal and counterion-free polymer that selectively binds hydrochloric acid. In this study of acidemic CKD patients we evaluated the safety and tolerability of TRC101, and its effectiveness in increasing serum bicarbonate.

Results: Patients had a mean baseline eGFR of 34.8 mL/min/1.73m² and a mean baseline serum bicarbonate of 17.7 mEq/L. Comorbidities included hypertension (93%), diabetes (70%), and heart failure (22%). Within 72 hours of the first TRC101 dose, mean serum bicarbonate increased in each of the four TRC101 treatment groups by >1.4 mEq/L and was significantly increased (p<0.0001) by 3.1 - 3.8 mEq/L at the end of treatment compared to placebo. Mean serum bicarbonate continued to increase in all treatment groups over the course of the study while the mean bicarbonate in the placebo group remained stable. In the combined TRC101 treatment groups, serum bicarbonate was in the normal range (22 - 29 mEq/L) at the end of treatment in 34.6% of patients and in at least 50% of patients in all groups at the end of the study. Serum bicarbonate decreased nearly to baseline levels within 2 weeks. All adverse events were well-tolerated and led to a significant increase in the level of serum bicarbonate.

Conclusions: In this 14-day study of acidemic CKD patients TRC101 was safe and well-tolerated and led to a significant increase in the level of serum bicarbonate.

Funding: Commercial Support - Tricida

SA-OR71

Economic Evaluation of Contemporary Kidney Transplant Practice

Methods: Using contemporary modeling techniques including Discrete Event Simulation (DES) over a 10-year time horizon, we compared the cost effectiveness of KT from varying donor types and dialysis for patients with kidney failure. DES models were constructed using data drawn from the United States Renal Data System, the national transplant registry, University HealthSystem Consortium, and literature review. Graft failure rates, transplant cost, and disease transmission events were adjusted for donor characteristics.

Results: All KT options resulted in improved patient survival compared to long-term dialysis; however, the relative benefits and costs differed substantially (Table). Over a 10 year period, living donor KT with 0-3 HLA mismatches (mm) yielded 77.3 Quality Adjusted Life Months (QALM) at a cost of $53,982 per quality adjusted life year (QALY). By comparison, dialysis provided only 56.8 QALMs at a cost of $101,580 per QALY. HLA incompatible living donor KT was more expensive than dialysis, but resulted in an additional 12 QALM of survival over 10 years. Sensitivity analysis suggests that these results are robust over a clinically relevant range of inputs.

Conclusions: KT is cost effective over a spectrum of donor characteristics, despite higher costs for marginal organs and innovative living donor KT practices.

Funding: Private Foundation Support

SA-OR72

Association of Dialysis Facility Ownership on Access to Kidney Transplant Waitlist or Living Donor Transplant

Methods: We linked adult, incident ESRD, United States Renal Data System (2000-2014) patient data with facility ownership (Dialysis Facility Compare) and facility-level characteristics (Dialysis Facility Report). Access to KT was defined as incident waitlisting or receipt of living donor KT. Facility ownership was categorized into one of five groups as either for-profit, large company (Groups A and B), for-profit small clinics (Group C), for-profit independent clinics (Group D), or non-for-profit clinics (Group E). Hierarchical survival analysis assessed the association between access to KT and dialysis facility ownership while controlling for patient- and facility-level characteristics and patient-level clustering.

Results: Among 1,137,113 patients in our study cohort, 166,240 (14.6%) were waitlisted or received a living donor KT and among 6,263 U.S. facilities. In adjusted survival analysis, patients waitlisted or receiving a living donor KT were more likely to be Hispanic (HR=1.45; 95% CI 1.40, 1.51) and male (HR=1.39; 95% CI 1.33, 1.46), and less likely to have heart disease (HR=0.46; 95% CI 0.46, 0.47), and Medicaid insurance (HR=0.44; 95% CI 0.43, 0.45). ESRD patients receiving treatment from Group A and Group B facilities were less likely (HR=0.59; 95% CI 0.53, 0.66 and HR=0.57; 95% CI 0.51, 0.64) to be waitlisted or receive a living donor KT compared to non-profit facilities (Figure 1).

Conclusions: Dialysis facility ownership was found to be significantly associated with a patient’s access to KT. Facilities can influence their patients’ access to the KT waitlist and living donor KT. We urge CMS to adopt quality measures that hold dialysis facilities accountable for patient access to KT.

Funding: NIDDK Support

SA-OR73

Significantly Lower Rates of Transplantation and Increased Wait List Mortality among Kidney Transplant Candidates with VA Insurance

Methods: Among 1,137,113 patients in our study cohort, 166,240 (14.6%) were waitlisted or received a living donor KT and among 6,263 U.S. facilities. In adjusted survival analysis, patients waitlisted or receiving a living donor KT were more likely to be Hispanic (HR=1.45; 95% CI 1.40, 1.51) and male (HR=1.39; 95% CI 1.33, 1.46), and less likely to have heart disease (HR=0.46; 95% CI 0.46, 0.47), and Medicaid insurance (HR=0.44; 95% CI 0.43, 0.45). ESRD patients receiving treatment from Group A and Group B facilities were less likely (HR=0.59; 95% CI 0.53, 0.66 and HR=0.57; 95% CI 0.51, 0.64) to be waitlisted or receive a living donor KT compared to non-profit facilities (Figure 1).

Conclusions: Dialysis facility ownership was found to be significantly associated with a patient’s access to KT. Facilities can influence their patients’ access to the KT waitlist and living donor KT. We urge CMS to adopt quality measures that hold dialysis facilities accountable for patient access to KT.

Funding: NIDDK Support
centers nationwide. Recent SRTR reports show a lower observed vs. expected rate of transplant in VA centers. Because VA centers are affiliated with non-VA academic centers within the same donor service area (DSA), we sought to compare transplantation rates nationally and also between the four VA centers and their non-VA (NVA) affiliates.

**Methods:** SRTR data was used to identify adult patients listed for a primary kidney transplant from 2004 through 2016. Patients with VA insurance (n=3663) were compared to those with private insurance (PI) (n=141,523), Medicaid (n=25,245) and Medicare (n=132,026). Analyses were conducted using multivariable Cox and competing risks regression models for time to transplantation, and unadjusted cumulative incidence functions of death with transplant as a competing risk.

**Results:** Compared to PI, VA patients were older and mostly male, with more black patients, diabetes, and vascular disease. VA patients lived much further from the transplant center compared to other groups (med. 282 vs. 23 miles). VA patients had a lower likelihood of transplant compared to PI nationally (HR: 0.72(95% CI:0.69,0.76)), and compared to PI patients within the four NVA programs (HR: 0.78(95% CI:0.71,0.85)). This difference with NVA centers persisted after excluding living donors (HR of 0.84(95% CI:0.76,0.93)), and in a model with death as a competing risk. VA patients also had a lower rate of transplantation vs. Medicare nationally (HR of 0.86(95% CI:0.82,0.91)) but did not differ from Medicare in the NVA centers. The HR of VA vs. Medicare was not different nationally (HR 1.01(95% CI:1.00,1.02)).

This difference with NVA centers persisted after excluding living donors (HR of 0.84(95% CI:0.76,0.93)), and in a model with death as a competing risk. VA patients also had a lower mortality at 2 years was 7.0(95% CI:6.1,7.9) in VA patients, 5.8(95% CI:5.6,5.9) in PI nationally, and 4.6(95% CI:4.5,5.8) in PI within NVA centers.

**Conclusions:** VA patients had a lower rate of transplantation and greater waitlist mortality compared to PI patients both nationally and within four paired NVA academic centers that shared DSAs. The reasons for this discrepancy require further study, but may include differences in patient availability and organ acceptance between VA and non-VA centers.

**SA-OR074**

**Hospitalizations for AKI in Kidney Transplant Recipients in the United States, 2004–2014**

**Tripti Singh, Nilay Kumar, Sana Waheed, Arjang Djamali, Neetika Garg, School of Medicine and Public Health, University of Wisconsin, Madison, WI.**

**Background:** There is little information on the incidence of acute kidney injury (AKI) and mortality associated with AKI in hospitalized kidney transplant recipients.

**Methods:** We used the National Inpatient Sample 2004 – 2014 to identify hospitalizations with a primary or secondary diagnosis of AKI in the setting of known history of kidney transplantation. Survey analysis techniques were used to generate national estimates. Linear and logistic regression were used to test trends in outcomes.

**Results:** There were 36,457 hospitalizations for AKI representative of 176,128 hospitalizations nationally in renal transplant recipients during the study period. Mean age of kidney transplant recipients admitted for AKI was 55.5 years and 43.4% were females. There was a significant increase in the comorbidity burden during the period of study (Charlson comorbidity index 1.3 in 2004 to 2.8 in 2014, p<0.001). There was a nearly threefold increase in hospitalization rate for AKI (52 to 135/1000 transplant recipients, p<0.001) over 10 years. We found a concomitant decline in in-hospital mortality, dialysis requirement and length of stay (LOS) along with a modest but significant negative trend in cost. Utilization for intubation and mechanical ventilation increased during the study period.

**Conclusions:** Hospitalizations for AKI have increased in the kidney transplant recipients but in-hospital outcomes and resource utilization have improved significantly. Further study is warranted to understand the reasons for increasing rate of hospitalizations for AKI in renal transplant patients.

**SA-OR075**

**Consequences of Declining a Public Health Service Increased Risk (PHS-IR) Donor Kidney**

**Hilda E. Fernandez, Mariana C. Chiles, Marcus Pereira, Syed A. Husain, Sumit Mohan. NYP-CUMC, NYC, NY.**

**Background:** The risk of disease transmission from PHS-IR kidney donors is extremely low but the perception increased risk by patients may adversely impact their willingness to accept these organs.

**Methods:** We performed a retrospective, single-center study of all PHS-IR kidney offers made to patients at Columbia University Medical Center (CUMC) from 6/2004 to 5/2015 to 1) identify who was likely to accept these organs and 2) assess the potential consequences of declining such offer.

**Results:** Among 2423 candidates who received a PHS-IR kidney offer, 358 accepted and 2065 declined. On multivariate analysis, higher estimated post-transplant survival (EPTS) score (OR=1.005, p=0.025), male sex (OR=1.345, p=0.035), and higher educational achievement (OR=0.693, p=0.025) appear to influence organ offer acceptance. Among those who declined, 57.5% subsequently received a non-PHS-IR transplant while 16.5% remained on the waitlist. Acceptance of a PHS-IR offer was associated with a lower mortality (3.63% vs 11.6%); adjusted HR 0.467, p=0.0008 and PHS-IR allografts were associated with lower death censored allograft failure rates (HR = 0.677, p=0.041).

**Conclusions:** Declining a PHS-IR kidney offer appears to be associated with a survival disadvantage at our center. This underscores the importance of patient education regarding the risks and benefits of PHS-IR organs. Efforts must be made to increase acceptance of PHS-IR organs in order to improve outcomes for those on the waitlist.

**Funding:** NIDDK Support

**SA-OR076**

**Absarst Withdrawn**

**SA-OR077**

**Obesity Is a Risk Factor for New-Onset Diabetes Mellitus after Living Kidney Donation**

**Krista L. Lenteine, Farrukh M. Koriaishy, Abhisht S. Naik, Ngan Lam, David A. Axelrod, Mark Schnitzler, Zidong Zhang, Gregory P. Hess, Amit X. Garg, Bertram L. Kasiske, Daniel C. Brennan, Dorry L. Segev, Hennepin County Medical Center, Minneapolis, MN; 1LDI University of Pennsylvania/IMS, Plymouth Meeting, Pa; 1Lakey Hospital and Clinic, Burlington, MA; 2None, Ann Arbor, MI; 3Saint Louis University, St Louis, MO; 4Johns Hopkins University, Baltimore, MD; 5London Health Sciences Centre, London, ON, Canada; 6Saint Louis University, St Louis, MO;7University of Alberta, Edmonton, AB, Canada; 8Washington University in St. Louis, St. Louis, MO.**

**Background:** End-stage renal disease is uncommon in living kidney donors (LKD), but most kidney failure developing late after donation appears to be due to diabetes or hypertension. To improve understanding of the relationship of obesity and post-donation diabetes mellitus (PDDM), we examined a novel linkage of national transplant registry data with records from a pharmacy claims clearinghouse that identifies diabetes treatments.

**Methods:** Among 24,238 LKD with at least 1 year of pre-donation pharmacy records, fills for insulin and non-insulin diabetes agents were examined as measures of new-onset PDDM. Time to first fill of insulin or other diabetes agents in relation to body mass index (BMI), age, sex, race, and other clinical factors in the registry was examined by Kaplan-Meier analysis and Cox regression (adjusted hazard ratio, aHR). aHR (95% CI).

**Results:** Mean age at donation was 42.7 years. Of LKD, 65.7% were women; 75% white, 10.5% black, and 10.9% Hispanic; 40.8% were overweight (BMI 25<30 m2) and 22.8% were obese (BMI ≥30 kg/m2). The 5-year risk of non-insulin PDDM treatments rose in a graded manner with higher BMI, from 0.6% in normal weight to 3-fold increased risk in overweight (1.5%, aHR:1.09, 95% CI:1.03,1.14) and 3.4% in obese (3.4%, aHR:1.05, 95% CI:1.02,1.07). Among those who declined, 57.5% subsequently received a non-PHS-IR transplant while 16.5% remained on the waitlist. Acceptance of a PHS-IR offer was associated with a lower mortality (3.63% vs 11.6%); adjusted HR 0.467, p=0.0008 and PHS-IR allografts were associated with lower death censored allograft failure rates (HR = 0.677, p=0.041).

**Conclusions:** Declining a PHS-IR kidney offer appears to be associated with a survival disadvantage at our center. This underscores the importance of patient education regarding the risks and benefits of PHS-IR organs. Efforts must be made to increase acceptance of PHS-IR organs in order to improve outcomes for those on the waitlist.

**Funding:** NIDDK Support

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

**Underline represents presenting author.**
SA-OR078

Early Post-Donation eGFR and ESRD in Living Kidney Donors

Allan Massie,1 Lara Fahmy,2 Macey L. Henderson,1 Jon J. Snyder,3 Courtenay M. Holscher,4 Sandra R. Dibrito,1 Dorry L. Segev1 Johns Hopkins, Baltimore, MD; 2Johns Hopkins University School of Medicine, Detroit, MI; 3Johns Hopkins School of Medicine, Baltimore, MD; 4Johns Hopkins University, Baltimore, MD; 5Minneapolis Medical Research Foundation, Minneapolis, MN.

Background: Several studies have shown higher ESRD risk in living kidney donors (LKDs) compared to healthy non-donors. All LKDs may not equally tolerate nephrectomy. Identifying post-donation risk factors for ESRD would improve post-donation counseling and care. We studied the association between early post-donation eGFR and subsequent ESRD risk.

Methods: Using SRTR data, we studied 64,989 LKDs 1999-2015 who were ESRD-free 9 months post-donation and who had at least one valid post-donation SCR value reported to OPTN between 3-30 months post-donation. When eGFR measured between 3-9 months post-donation (6-month eGFR) was missing, we multiply imputed based on pre-donation eGFR and other post-donation eGFR values. We studied the association between 6-month eGFR and post-donation ESRD (via CMS linkage) using Cox regression, adjusting for age, sex, race (black vs nonblack), pre-donation eGFR, BMI, and 1st-degree biological relationship to recipient.

Results: Median (IQR) 6-month eGFR was 63.2 (54.2-74.3) mL/min/1.73 m². Out of 64,989 donors, 50 progressed to ESRD during the study period. Donors with lower 6-month eGFR had greater incidence of ESRD (Figure). There was no evidence of association between pre-donation eGFR and post-donation ESRD risk (p=0.3, Table). A 10-unit difference in 6-month eGFR was associated with 32% decreased risk of ESRD (aHR=0.68, 95% CI 0.61-0.78, p<0.01, Table).

Conclusions: Lower eGFR in the first 6 months post-donation is associated with higher subsequent risk of post-donation ESRD in living kidney donors. Careful monitoring of early post-donation eGFR is essential to provide adequate post-donation care and counseling.

Funding: NIDDK Support

SA-OR079

Estimated GFR before Living Kidney Donation as a Predictor of Postdonation Measured GFR

Marco van Londen, Jessica V. Weijden, Jan-Stephan Sanders, Stefan P. Berger, Stephan J. Bakker, Gerjan Navis, Martin H. De Borst. University Medical Center Groningen, Groningen, Netherlands.

Background: In living kidney donor screening, precise renal function measurement is vital to ensure adequate postdonation renal function. Measured GFR (mGFR) is the gold standard, but costly and laborious. We tested the capacity of predonation estimated GFR (eGFR) equations to predict postdonation mGFR.

Methods: In a single-center prospective cohort study in 750 living kidney donors, we determined predonation mGFR (continuous iothalamate) including dopamine stimulation, and creatinine-based eGFR (CKD-EPI, Cockcroft-Gault and MDRD equations), as well as mGFR at 3 months postdonation. We used linear regression, Receiver Operating Characteristic curves, and Bayesian statistics to test the performance of eGFR equations.

Results: Mean donor age was 51±11 years, 48% of donors were male. Predonation mGFR was 102±16 mL/min/1.73 m², stimulated mGFR was 110±18 mL/min/1.73 m², eGFR\text{MDRD} was 88±14 mL/min/1.73 m², eGFR\text{CKD-EPI} was 93±19 mL/min/1.73 m², and eGFR\text{CG} was 86±16 mL/min/1.73 m². Predonation mGFR and the results of the three eGFR formulas were positively associated with postdonation mGFR (mGFR R²=0.49, dopamine stimulated mGFR R²=0.34, eGFR\text{MDRD} R²=0.21, eGFR\text{CKD-EPI} R²=0.22, eGFR\text{CG} R²=0.14). A predonation eGFR\text{CG} >102 mL/min/1.73 m² (present in 16% of donors) excludes a postdonation mGFR <60 mL/min/1.73 m² with a specificity of 100% (AUC 0.74), for predonation eGFR\text{MDRD} this threshold is 114 mL/min/1.73 m² (AUC 0.78) and for eGFR\text{CKD-EPI} 114 mL/min/1.73 m² (AUC 0.70). A predonation eGFR\text{MDRD} >95 mL/min/1.73 m² (present in 30% of donors) excludes a postdonation mGFR of <50 mL/min/1.73 m² with 100% specificity (AUC 0.78), for predonation eGFR\text{CG} this threshold is 105 mL/min/1.73 m² (AUC 0.82) and for eGFR\text{CG} >97 mL/min/1.73 m² (AUC 0.74).

Conclusions: We provide cut-off values for predonation donor eGFR to select donors with a high probability of good renal function postdonation without requiring mGFR measurement. In order to avoid incorrect exclusion of a large proportion of donors, additional renal function tests such as measured GFR are warranted in donors with an eGFR\text{MDRD} <95 mL/min/1.73 m².

Funding: Government Support - Non-U.S.

SA-OR080

Predonation Recruitment of Renal Functional Reserve Capacity Is Associated with Early Renal Adaptation after Living Kidney Donation

Marco van Londen, Jessica V. Weijden, Jan-Stephan Sanders, Stefan P. Berger, Stephan J. Bakker, Martin H. De Borst, Gerjan Navis. University Medical Center Groningen, Groningen, Netherlands.

Background: Early renal adaptation after kidney donation results in a GFR above the threshold is 114 mL/min/1.73 m². Recruitment of Renal Reserve Capacity (RRC) assessed by the renal response to dopamine infusion (RRC) is considered to reflect functional reserve capacity, but it is unknown whether it predicts short- or long-term renal adaptation or both. In this study we investigate the association between pre-donation RRC and GFR changes after donation.

Methods: To assess RRC and GFR changes after donation we used linear regression, Receiver Operating Characteristic curves, and Bayesian statistics to test the performance of eGFR equations.

Results: Mean donor age was 51±11 years, 48% of donors were male. Predonation mGFR was 102±16 mL/min/1.73 m², stimulated mGFR was 110±18 mL/min/1.73 m², eGFR\text{MDRD} was 88±14 mL/min/1.73 m², eGFR\text{CKD-EPI} was 93±19 mL/min/1.73 m², and eGFR\text{CG} was 86±16 mL/min/1.73 m². Predonation mGFR and the results of the three eGFR formulas were positively associated with postdonation mGFR (mGFR R²=0.49, dopamine stimulated mGFR R²=0.34, eGFR\text{MDRD} R²=0.21, eGFR\text{CKD-EPI} R²=0.22, eGFR\text{CG} R²=0.14). A predonation eGFR\text{CG} >102 mL/min/1.73 m² (present in 16% of donors) excludes a postdonation mGFR <60 mL/min/1.73 m² with a specificity of 100% (AUC 0.74), for predonation eGFR\text{MDRD} this threshold is 114 mL/min/1.73 m² (AUC 0.78) and for eGFR\text{CKD-EPI} 114 mL/min/1.73 m² (AUC 0.70). A predonation eGFR\text{MDRD} >95 mL/min/1.73 m² (present in 30% of donors) excludes a postdonation mGFR of <50 mL/min/1.73 m² with 100% specificity (AUC 0.78), for predonation eGFR\text{CG} this threshold is 105 mL/min/1.73 m² (AUC 0.82) and for eGFR\text{CG} >97 mL/min/1.73 m² (AUC 0.74).

Conclusions: We provide cut-off values for predonation donor eGFR to select donors with a high probability of good renal function postdonation without requiring mGFR measurement. In order to avoid incorrect exclusion of a large proportion of donors, additional renal function tests such as measured GFR are warranted in donors with an eGFR\text{MDRD} <95 mL/min/1.73 m².

Funding: Government Support - Non-U.S.
Methods: In 750 living kidney donors between 1984 and 2017, we prospectively measured mGFR (U+V-lobe evaluation) and RCC and RCC. We performed multivariable linear regression analysis with short-term postdonation mGFR as dependent variable. In a subgroup with 5 year follow-up after donation we observed the association with long-term mGFR.

Results: Mean donor age was 52±11 years, 48% were male. Mean predonation mGFR was 107±28 ml/min, mGFR_intra was 115±30 ml/min, resulting in a 9±10 ml/min. Three months postdonation, mGFR was 73±15 ml/min and mGFR_intra was 76±15 ml/min, indicating that donors still had RRC (2.7±5.8 ml/min, p<0.001). Proteinuria was associated with mGFR, preservation, independent of age, mGFR, blood pressure and BMI (st. β 0.12, p=0.001, final model R²=0.63). In the subgroup of donors of whom 5-year follow-up data was available, RCC was neither associated with absolute mGFR at 5 years postdonation (st. β 0.02, p=0.78), nor with compensatory mGFR increase between 3 months and 5 year after donation (st. β 0.03, p=0.67).

Conclusions: Donor recovery reserve capacity is independently associated with preservation of mGFR early after donation, but not with long-term mGFR. This indicates that RC_intra is a marker of early, hemodynamic-driven, adaptation to kidney donation rather than long-term mGFR changes. More long-term follow-up data is needed to provide conclusive results about the use of dopamine in living kidney donors.

Funding: Government Support - Non-U.S.

SA-OR081
Role of COUP-TFI in Pericyte Activation and Kidney Fibrosis Li Li, Xiaoyan Xiao, Takaharu Ichimura, Julia Willfingseder, Joseph V. Bonventre. Brigham & Women’s Hospital/Harvard Medical School, Boston, MA.

Background: Genetic fate mapping studies suggest that the pericytes are the main source of myofibroblasts enriched in injury-induce kidney fibrosis. The transcriptional network that controls the pericyte-myofibroblast transdifferentiation is poorly understood. COUP-TFI (Caudal type homeobox-1 promoter transcription factor II) is a zinc-finger transcription factor critical to the kidney development. It is broadly detected in the mesenchyme of developing organs and has a profound impact on organogenesis and cell fate determination.

Methods: We measured COUP-TFI mRNA by quantitative real-time PCR (qRT-PCR) and protein by Western Blot from normal C57BL/6 mice kidneys and at different times after unilateral ureteral obstruction (UUO). To assess the origin of COUP-TFI+ cells, we crossed Forkhead Box D3 (Foxd1)-Cre driver mice to U2O tumor reporter mice to genetically label the Foxd1-derived stromal cells. In vitro, knockdown of COUP-TFI was attained by transfecting a small interfering RNA (siRNA) into CH310T1/2 (pericyte-like cells). COUP-TFI and c-SMA expression was evaluated in tissue by immunostaining and in siRNA-transfected CH310T1/2 by RT-PCR.

Results: In non-injured kidney, expression of COUP-TFI is sparsely distributed in interstitial cells, Bowman’s capsule and a lesser extent in tubules. Cells expressing COUP-TFI are PDGFRα+ (pericytes/fibroblasts) and are adjacent to CD31+ (endothelial) cells. Most COUP-TFI+ cells are localized in the region of Foxd1-derived stromal cells. Upon injury, COUP-TFI expression is significantly increased in e-CaMKIIα+ cells (myofibroblasts) localized within the fibrotic region. COUP-TFI expression did not overlap with F4/80 (macrophages) staining. Both mRNA and protein levels of COUP-TFI increased at 5, 7 and 10 days after UUO and are associated with increased expression of αSMA. At the same time point, in vitro, knockdown of COUP-TFI by siRNA results in decreased c-SMA expression in pericyte-like cells.

Conclusions: COUP-TFI is expressed at basal levels in non-injured kidney in Foxd1-derived stromal cells. Upon injury, COUP-TFI expression increased in e-CaMKIIα+ cells located within the fibrotic region. Expression of COUP-TFI transfection is associated with reduced expression of c-SMA in pericyte-like cells. These data suggest that COUP-TFI may play a role in the regulation of pericyte-myofibroblast transdifferentiation in injury-induce kidney fibrosis.

Funding: Other NIH Support - National Institute of Biomedical Imaging and Bioengineering (NIBIB), Organ Design and Engineering Training Grant 1T32EB016652-01A1

SA-OR082
The Breast Cancer Type 1 Susceptibility Protein (BRCA1) Mediates Fibrotic Kidney Disease Akinwande A. Akinfolarin, Amenda K. Ajayi, Venkata Sabbisetti, Joseph V. Bonventre. Brigham and Women’s Hospital, Boston, MA.

Background: Repetitive tubular injury leads to chronic fibrotic kidney disease (CD). Chemical, ischemic and obstructive kidney injuries lead to replication fork arrest (RFA) and double strand DNA breaks (DSB), triggering the DNA damage response. BRCA1 is a breast tumor suppressor gene with a role in homologous recombination (HR) and maintenance of genome integrity by DNA repair. Here we deplete BRCA1 in the adult mouse proximal tubule (PT) to examine its effect on the development of interstitial fibrosis.

Methods: SLC34A1 Cre mice were crossed to mice with floxed Brca1 exon 1 allele yielding models of inducible Pt Brca1 gene deletion. After Tamoxifen-induced Cre activation, we subjected mice to bilateral ischemia/reperfusion (IR), unilateral ureteric obstruction (UUO), or aristolochic acid (AA)-induced injury. Kidney extracts were evaluated by western blot, real time PCR and Masson’s trichrome (MT) and Picrosirius Red (PS) staining for markers of interstitial fibrosis. Markers of DNA damage, cell cycle arrest and senescence were examined by immunofluorescence. BRCA1 was also down regulated in murine cells using short hairpin RNA against BRCA1 and cells were treated with AA and cisplatin to explore the relationship between injury and cell cycle stage, apoptosis and secretory senescence.

Results: There was reduced kidney fibrosis in mice heterozygous (Brca1+/-) and homozygous (Brca1-/-) mice after BRCA1 (1p13.3) deletion. Cisplatin and IR treatment of BRCA1 deficient (Brca1-/-) mice caused an increase in apoptosis among Brca1+/- and Brca1-/- mice when compared to WT mice. These marine data were supported in vitro experiments with AA and Cisplatin and depletion BRCA1 in PT cells which caused less G2 cell cycle arrest and secretion of fewer fibrogenic factors compared to BRCA1 deficient (Brca1-/-) mice. BRCA1 facilitates interstitial fibrosis following renal tubular injury in mice through its role in DNA damage response and induction of senescence. We have thus identified a novel role of BRCA1 in non malignant pathobiology.

Funding: NIDDK Support, Private Foundation Support

SA-OR083
Bone Marrow Stromal Cell Antigen-1 Identified by RNA-Seq and ChiP-Seq is Important for Inducing Renal Ischemia-Reperfusion Injury and Fibrosis Tsuyoshi Inoue,1 Liping Huang,2 Diane L. Rosin,2 Katsukiko Ishihara,3 Youichiro Wada,3 Mark Okusa,1 University of Tokyo, Tokyo, Japan;2University of Virginia, Charlottesville, VA;3Kawasaki Medical School, Kashiwagi, Japan.

Background: Sphingosine kinase 2-deficient mice (SphK2KO) develop less fibrosis after mouse kidney ischemia-reperfusion injury (IRI). Sphingosine-1-phosphate (S1P) produced by Sphk2 inhibits histone deacetylase (HDAC) and changes in histone acetylation status, which can lead to an altered target gene expression. The aim of this study is to elucidate new mechanisms of kidney fibrosis through epigenetic changes.

Methods: RNA-seq and ChiP-seq of H3K9ac and H3K27ac using primary renal fibroblasts from WT, Sphk1KO and Sphk2KO mice were performed. Flow cytometry was used to identify bone marrow stromal cell antigen-1 (BST-1/CD157) expression in hematopoietic cells. In addition, bone marrow chimeric mice were created to evaluate the role of BST-1 in bone marrow-derived cells. Unilateral IRI was used as a renal fibrosis model and bilateral IRI was used as an acute kidney injury (AKI) model.

Results: The combination of RNA-seq and ChiP-seq analysis yielded 30 candidate genes that might be regulated by Sphk2 through epigenetic change. We applied Sphk2 knock down to WT fibroblasts and overexpression to fibroblasts from Sphk2KO to determine if the selected genes are regulated by Sphk2. Gene expression was evaluated using an in vivo fibrosis model. Bst1 was identified as a gene that is regulated by Sphk2 through a change in histone acetylation level. Bst1-deficient mice (Bst1KO) developed less fibrosis after renal unilateral IRI and were protected against renal bilateral IRI in the AKI model. Bone marrow chimeric experiments further revealed that BST-1 expression on hematopoietic, but not parenchymal cells, is responsible for inducing renal IRI and fibrosis. BST-1 was found mainly in B cells and neutrophils by flow cytometry of spleen and bone marrow. The migration of neutrophils from Bst1/KO was suppressed, and adoptive transfer of neutrophils from Bst1WT mice abolished the renal protective effect in Bst1/KO mice.

Conclusions: Bst1 is a gene that is regulated by Sphk2 through epigenetic change and is critical in kidney injury and fibrosis. Bst1/KO mice are protected against renal IRI and have less fibrosis. Further, Bst1 expression in fibroblasts plays an important role in inducing renal ischemia-reperfusion injury and fibrosis.

Funding: NIDDK Support

SA-OR084
BET Protein Family Member BRD4 Promotes Transcription through Super-Enhancer Activation in Kidney Repair and Progression of Fibrosis Julia Willfingseder,1,2 Michaela Willi,1 Chaochen Wang,2 Hannes Olason,1,a Takaharu Ichimura,3 M. Todd Valerius,3 Lothar Hennighausen,2 Joseph V. Bonventre.1 Renal Division, Brigham & Women’s Hospital/Harvard Medical School, Boston, MA;2Laboratory of Genetics and Physiology, NIDDK/NIH, Bethesda, MD;3Division of Renal Medicine, Karolinska Institutet, Stockholm, Sweden.

Background: The mammalian kidney can repair after acute kidney injury (AKI) through robust proliferation of tubular epithelial cells. Maladaptive repair can however lead to kidney fibrosis and chronic kidney disease (CKD). There is currently limited understanding of which transcriptional regulators activate these repair programs and how transcriptional deregulation leads to CKD. Here we investigate the existence of enhancer regulatory elements occupied by BRD4 that are activated in regenerating mouse kidney.

Methods: RNA-Seq and ChiP-Seq (H3K27ac, H3K4me3, BRD4, MED1, POL2) were performed on samples from repairing kidney cortex day 2 after ischemia reperfusion injury (IRI) to identify super-enhancers, enhancer-like cells and super-enhancers associated with kidney repair. Further we investigated the role of super-enhancer activation in kidney repair through pharmacological BET inhibition via the small chemical compound JQ1 in vitro and in three kidney injury models in vivo.

Results: We first establish the enhancer and super-enhancer landscape associated with kidney injury and repair. Furthermore, we identify key transcription factors, which cooperate with BRD4 and MED1 at enhancer sites, likely activating repair programs in tubular epithelial cells. Loss of BRD4 function by systematic administration of the
BET inhibitor JQ1 (50μg/kg/d) before IRI leads to impaired recovery after AKI and increases mortality at 3 and 7 days after injury. By contrast, β-catenin, inhibition of prolonged transcriptional responses during repair, through blockade of BRD4 at enhancer sites via JQ1 starting at day 2 and day 7 after injury, ameliorates interstitial fibrosis in UUO, unilateral IRI and aristolochic acid (AA) kidney injury models at day 10 and day 21, respectively.

Conclusions: These results are the first demonstration of BRD4 enhancer and super-enhancer function in the repairing kidney, providing a critical link between AKI and CKD. In addition, our data call attention to potential caveats for use of small molecule inhibitors of BET and BRD4. These results highlight the potential therapeutic utility of BET inhibition for AKI patients who already benefit from therapeutic trials in patient care at risk for AKI. Our comprehensive analysis of epigenetic changes after kidney injury in vivo has the potential to identify new targets for therapeutic intervention.

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

SA-OR087

GliI+ Pericytes Are Required for AKI Recovery and Regulate Renal Function Flavia G. Machado,1 Eughainn O hAinmhire,1 Benjamin D. Humphreys,2 Lasagni, Paola Romagnani.1 Center of Excellence DENOthe, Department of Biomedical Experimental and Clinical Sciences, University of Florence, Florence, Italy.

Background: GliI+ pericytes are required for renal repair after AKI. More specifically in renal proximal tubule epithelial cells (RPTC) or their wild type littermates (WT) were subjected to ischemia-reperfusion injury (IRI). We also determined the effects specifically in renal proximal tubule epithelial cells (RPTC) or their wild type littermates (WT) were subjected to ischemia-reperfusion injury (IRI).

Methods: We evaluated distribution and density of GliI+ pericytes after bilateral IRI (bIRI) using Gli1-nLacZ reporter mice. We tested whether the Gli1+ population is fixed or dynamic using Gli1-nLacZ, Gli1CreERT2;R26-tdTomato transgenic mice. We asked whether GliI+ pericytes are required for AKI repair by ablation them and measuring GFR, by FTTC-sinistrin, then performing bIRI. We also tested the effect of pharmacologic blockade of hedgehog signaling on bIRI recovery with the smoothed inhibitor LDE225.

Results: GliI+ cells expand in the cortex and outer medulla during AKI recovery. These results are the first demonstration of BRD4 enhancer and super-enhancer function in the repairing kidney, providing a critical link between AKI and CKD. In addition, our data call attention to potential caveats for use of small molecule inhibitors of BET and BRD4. These results highlight the potential therapeutic utility of BET inhibition for AKI patients who already benefit from therapeutic trials in patient care at risk for AKI. Our comprehensive analysis of epigenetic changes after kidney injury in vivo has the potential to identify new targets for therapeutic intervention.

Funding: NIDDK Support, Veterans Affairs Support

SA-OR085

Endocytode-Mediated Hypertrophy and Progenitor Proliferation as Central Mechanisms of Response to AKI Elena Lazzeri, Maria Lucia Angelotti, Anna J. Peired, Carolina Conte, Laura Lasagni, Paola Romagnani. Center of Excellence DENOthe, Department of Biomedical Experimental and Clinical Sciences, University of Florence, Florence, Italy.

Background: Acute kidney injury (AKI) is considered a reversible disease because of the capacity of all tubular cells to proliferate as demonstrated by proliferation markers. As AKI can be followed by chronic kidney disease (CKD), we questioned the high intrinsic regenerative capacity of tubules.

Methods: To investigate the proliferative capacity of tubules after AKI, we developed 2 conditional transgenic mouse models: 1. Pax8+nRtαTetO;Cre;R26;FucciC2α2R (Pax8+ Fucci+), to track all tubular cells; 2. Pax2+nRtαTetO;Cre;R26;FucciC2α2R (Pax2+ FucciC2α2R) to track a putative scattered tubular progenitor population. After doxycycline administration, we investigated the reporter expression in Pax8 and Pax2 cells (cells in G1 phase are mCherry+, in S/G2/M phase are mVenus+) in healthy and at 30 days after unilateral IRI (unilateral IRI and aristolochic acid (AA) kidney injury models at day 10 and day 21, respectively).

Results: Confocal analysis of Pax8+/FucciC2α2R mice demonstrated that immunostaining for proliferation markers (Ki67, PCNA and p-H3) didn’t mirror exactly cell-cycle phase as indicated by FucciC2α2R reporter. This suggests that cell-cycle markers indicate cell-cycle activation but not cell division after IRI. We, therefore, explored aberrant cell-cycles such as endocycle, where G1 and S proceed repeatedly without mitosis, generating cells arrested in G1 phase with a doubled DNA content and an increased size. To detect these cells, we combined FucciC2α2R expression and DNA content assessment by flow-cytometry. This analysis revealed that 11.5±0.8% of Pax8+/ tubular cells underwent endocycles at day 30 after IRI. Most of endocycling cells were in S1-S2 segments of the cortex with a higher cell surface area in comparison to cells in G1 phase. Accordingly, tubular cell hypertrophy via endocycle is the dominant feature in the cortex of human biopsies with CKD after AKI. By contrast, Pax2+ tubular cells didn’t undergo endocycle but rather complete mitosis at day 30 after IRI. Automatic quantification analysis by flow-cytometry demonstrated that while Pax8+/ tubular cells are irreversibly lost, Pax2+ tubular cells are the only proliferating cells, generating new tubular cells after AKI.

Conclusions: These results demonstrate that, although limited regeneration occurs via Pax2 cell proliferation, persistent tubular cell loss and tubular cell hypertrophy via endocycle are the dominant features after AKI.

SA-OR086

YAP, Not TAZ, Mediates EGF Receptor Dependent Renal Recovery from AKI Jianchun Chen, Raymond C. Harris. Vanderbilt University Medical Center, Nashville, TN.

Background: Both EGFGR and the Hippo signaling pathway are implicated in cell proliferation and differentiation. Our previous studies have shown that activation of EGFGR in renal proximal tubule epithelial cells (RPTC) plays a critical role in functional and structural recovery from Ischemia-reperfusion injury (IRI). YAP, TAZ, and TAZ, two downstream effectors of Hippo pathway, are activators for multiple gene transcriptional factors in the nucleus. The goal of these studies was to determine whether YAP and/or TAZ play a role in mediating EGFGR’s effects in AKI.

Methods: We performed deletion of EGFGR receptor (EGFGRf/f), inducible SLc34a1Cre mediated Yap/Taz double deletion (Yapf/f;Tazf/f) or Taz single deletion (Tazf/f) specifically in renal proximal tubule epithelial cells (RPTC) or their wild type littermates (WT) were subjected to ischemia-reperfusion injury (IRI). We also determined the effects of silencing EGFGR, AKT1 and YAP gene expression by specific siRNAs in a human renal proximal tubule epithelial cell line (IRI). Yap and Taz, two key downstream effectors of Hippo pathway, are activators for multiple gene transcriptional factors in the nucleus. The goal of these studies was to determine whether YAP and/or TAZ play a role in mediating EGFGR’s effects in AKI.

Results: Deletion of EGFGR specifically in RPTC or administration of an EGFGR tyrosine kinase inhibitor, Erlotinib, markedly inhibited EGFGR expression and nuclear translocation and the Yap downstream target gene, amphiregulin, in response to IRI Deletion in renal proximal tubule of both Yap and Taz but not Taz alone delayed renal recovery from IRI. BUN remained elevated in Yapf/f;Tazf/f mice at day 7 (64 ± 2.5 mg/dl, n=3, P<0.05), while decreasing to 39 ± 3.8 mg/dl or 32 ± 2.5 mg/dl in the Tazf/f mice or the WT mice after IRI. Upregulation of amphiregulin and cyclin D and phosphorylation of retinoblastoma protein (Rh) in response to IRI were inhibited in EGFGRf/f and the Yapf/f; Tazf/f mice. Exposure of the IRR to hypoxia followed by reoxygenation increased YAP nuclear translocation, cyclin D expression and Rh phosphorylation, which were inhibited by an EGFGR tyrosine kinase or PKD inhibitor treatments or transfection of EGFR, AKT1 or YAP specific siRNAs.

Conclusions: This study demonstrates that EGFR-P38-Akt dependent YAP activation plays an essential role in mediating epithelial cell regeneration during kidney recovery from AKI. Funding: NIDDK Support, Government Support - Non-U.S.

SA-OR088

Myeloid Mineralocorticoid Receptor Controls Inflammatory and Fibrotic Responses after Renal Ischemic Injury via Macrophage Interleukin-1β Receptor Jhonathan Barreca-Chimal,1 Sebastian M. Lechner,1 Soumaya El moghrabi,1 Peter Kolkhof,2 Frederic Jaisser.1 INSERM U1130, Centre de Recherche des Cordeliers, Paris, France; 2BAYER AG, Wuppertal, Germany; 3Instituto de Investigaciones Biomédicas, UNAM, ---Mexico City, Mexico.

Background: Pharmacological mineralocorticoid receptor (MR) antagonism is useful to prevent chronic kidney disease (CKD) after an episode of acute ischemic kidney injury (AKI) in the rat. We aimed to test the involvement of myeloid MR in the development of kidney fibrosis after an ischemic AKI episode.

Methods: We included 18 male C57/B6 mice that were divided in: sham, renal ischemia for 22.5 min and IR plus treatment with the non-steroidal MR antagonist finerenone (10 mg/kg) at -48, -24 and -1 h before IR. MR inactivation in myeloid cells (MR−/−) was achieved by crossing mice with the MR-/-flanked by loxP sites (MR−/−) with mice expressing the Cre recombinase under the Lyso3 promoter activity. In MR−/− and MR+/− mice we induced renal IR of 22.5 min or sham surgery. The mice were followed-up during 4 weeks to test for AKI to CKD transition. In another set of mice, the macrophages were sorted from kidneys after 24 h of reperfusion for flow cytometry analysis or mRNA extraction. Thymoglobulin elicited peritoneal macrophages were used for in vitro studies.

Results: The progression of AKI to CKD after 4 weeks of renal ischemia in the untreated C57/B6 and MR−/− mice was characterized by a 50% increase in plasma creatinine, a 2.5-fold increase in the mRNA levels of TGF-b and fibronectin as well as by severe tubule-interstitial fibrosis. The mice that received finerenone or MR−/− mice were protected against these alterations. Increased expression of M2-anti-inflammatory markers in kidney-isolated macrophages from finerenone-treated or MR−/− mice was observed. Pharmacological ablation of Gli1+ pericytes spontaneously reduced GFR of 242±95 ml/min/100gBW 3-fold by two weeks after IRI. By contrast, nLacZ single positive cells increased 7-fold.

Conclusions: MR antagonism or myeloid MR deficiency facilitates macrophage polarization to an M2, anti-inflammatory phenotype after kidney IR, preventing maladaptive repair and chronic kidney fibrosis. MR inhibition acts through the modulation of IL-4 receptor signaling to facilitate macrophage phenotype switching.

Funding: Government Support - Non-U.S.
SA-OR089
Biodistribution and Homing of Human Endothelial Colony Forming Cell-Derived Exosomes in Ischemia-Reperfusion AKI Jose L. Vinas,1 Matthew Spence,1 William A. Knoll,2 Alex Gusot,4 Dylan Berger,2 David Allan,2 Kevin D. Burns,1,2 Kidney Research Centre, Ottawa, ON, Canada; 1Ottawa Hospital Research Institute, Ottawa, ON, Canada; 2Medicine, Ottawa Hospital Research Institute, Ottawa, ON, Canada; 3University of Ottawa, Ottawa, ON, Canada.

Background: Infusion of human cord blood endothelial colony forming cell (ECFC)-derived exosomes prevents ischemia/reperfusion acute kidney injury (AKI) in mice, via the transfer of microRNA (miR)-486-5p, which is highly enriched within these exosomes. Whether exosomes selectively home to the kidneys, and possibly targeting mechanisms, are unclear.

Methods: Exosomes were isolated from ECFC conditioned media by serial centrifugation. Ischemia-reperfusion injury was induced in mice by bilateral renal vascular clamp (30 min), with i.v. infusion of DiR-labeled ECFC exosomes at the time of reperfusion, followed by optical imaging. miR-486-5p levels were measured by qPCR in various tissues. Cy3-labeled pre-miR-486-5p was used to study the transfer of exosomal miR-486-5p from ECFCs to cultured human umbilical vein endothelial cells (HUVECs). The potential role of the chemokine SDF-1α and its receptor CXCR4 in exosome homing was studied in HUVECs using a blocking antibody to SDF-1α.

Results: In mice, i.v. infusion of exosomes at the time of reperfusion increased kidney miR-486-5p levels after 30 min (p<0.01 vs AKI alone, n=3), with no significant change in miR-486-5p levels in liver, spleen, or heart. After 24 hrs, a further significant increase in miR-486-5p levels was observed only within kidneys (p<0.01, n=3). Compared with control, Cy3-labeled exosomes selective homed to the kidneys 30 min after reperfusion (p<0.01, n=4). Conditioned media from ECFCs transfected with Cy3-pre-miR-486-5p induced an increase in cytoplasmic fluorescence within HUVECs, which was blocked when ECFCs were first treated with the exosome release inhibitor GW4869 or when ECFC exosomes were co-cultured with the inhibitor of pinocytosis, ethylenediamine propylamine chloride (p<0.01, n=5). By immunoblot, ECFC exosomes expressed CXCR4, and incubation of HUVECs with blocking antibody to SDF-1α prevented exosome uptake (n=5).

Conclusions: ECFC exosomes selectively home to the kidneys after infusion in mice with ischemia/reperfusion injury, and are associated with selective increased miR-486-5p levels of miR-486-5p. Endothelial cells are targeted by exosomes, possibly via interaction of CXCR4 with SDF-1α, leading to transfer of miR-486-5p. The results suggest that ECFC exosomes may have therapeutic potential in human AKI due to selective kidney targeting.

Funding: Private Foundation Support

SA-OR090
Role of Cyclin G1 in Maladaptive Repair and Kidney Fibrosis Adam W. Scott,1,2 Craig R. Brooks,3 Takaharu Ichimura,1 Joseph V. Bonventre1,2,3 Boston Children’s Hospital, Boston, MA; 4Maimonides Medical Center, Brooklyn, NY; 1Brigham & Women’s Hospital/Harvard Medical School, Boston, MA.

Background: Survivors of acute kidney injury (AKI) have an increased risk for the development of chronic kidney disease (CKD). Previous work from our lab has demonstrated that G2/M cell cycle arrest is an important driver for the maladaptive repair process that leads to renal fibrosis. Using unbiased gene expression profiling, one of the major pathways deregulated following injury is the mTORC1, ERK1/2 and eNOS signaling pathways in EC, which may explain its strong effect on EC injury. Moreover, miR-142-3p and miR-451 upregulated following injury in vivo and in vitro. The consequences of this miRNA transfer were analyzed using an overexpression approach in microvascular EC.

Methods: We performed bilateral IRI to evaluate the effect of cyclin G1 on AKI. Animals were transfected with the mouse (mCG1) or human form of cyclin G1 (hCG1), and analyzed cell cycle markers as well as inflammatory cytokines.

Results: Cyclin G1 overexpression leads to an increase in the number of cells in the G2/M phase of the cell cycle, and suggests a role for cyclin G1 in promoting maladaptive repair following AKI that leads to renal fibrosis.

Funding: NIDDK Support, Other NIH Support - Adam W. Scott is supported by NIH T32 Ruth L. Kirschstein National Research Service Awards

SA-OR091
Neutrophils Induce Endothelial Cell Injury through the Release of Extracellular Vesicles Containing miRNA in ANCA-Associated Renal Vasculitis Alexandre Glemain,1,2 Melanie Néel,1,2 Rozenn Le Blouz,1,2 Fadi Fakhoury,1,2 Sarah Bruneau,1,2 Centre de Recherche en Transplantation et Immunologie UMR1064, INSERM, Université de Nantes, Nantes, France; 1Centre de Transplantation Urologie Néphrologie (ITUN), CHU Nantes, Nantes, France.

Background: To date, the pathophysiological mechanisms by which neutrophils cause endothelial damage in anti-neutrophil cytoplasm antibodies (ANCA)-associated renal vasculitis (AARV) are not fully elucidated. Some data suggest that neutrophil-derived extracellular vesicles (EV) may contribute to endothelial cell (EC) activation, but the mechanisms by which these EV can induce EC damage in the context of AARV, and the role of miRNA they may contain have not been studied.

Methods: In these studies, we used TaqMan Low Density Arrays to identify miRNA released in EV by ANCA-activated neutrophils that are internalized by microvascular EC in vitro. The consequences of this miRNA transfer were analyzed using an overexpression approach in microvascular EC.

Results: We identified three particular miRNA transferred from ANCA-activated neutrophils to microvascular EC in vitro: miR-223, miR-142-3p and miR-451. The overexpression of miR-142-3p and/or of miR-451 in EC led to profound cell damage, especially in inflammatory conditions (TNFα). This was characterized by the induction of EC apoptosis by miR-142-3p (8, P<0.01), the inhibition of EC proliferation by miR-451 (n=8, P<0.05) and as a result, a impairment of EC repair and angiogenesis by these two miRNA as observed in wound-healing (n=6, P<0.05) and tube formation (n=7, P<0.05) assays. Using phosphokinase protein arrays, we found that miR-142-3p inhibits the mTORC1, ERK1/2 and eNOS signaling pathways in EC, which may explain its strong effect on EC injury. Moreover, miR-142-3p and miR-451 overexpression in EC resulted in marked activation responses, characterized by induced expression of the leukocyte chemoattractant CCL22 and the chemokines CXCL10 (2- to 5-fold), CXCL11 (2- to 3-fold) and IL8 (6-fold), as well as the proinflammatory cytokine IL6 (4-fold), as assessed by mRNA expression arrays. In contrast, miR-223 overexpression had no significant impact on EC responses in our studies.

Conclusions: Collectively, these findings identify miR-142-3p and miR-451 as critical mediators of neutrophil-induced endothelial damage in the course of AARV, and suggest that specific targeting of these miRNA in EC may have implications for the prevention of microvascular injury in AARV patients.

Funding: Private Foundation Support, Government Support - Non-U.S.
SA-OR093

Genetic Risk for Scleroderma Renal Crisis in RNA-Polymerase III Antibody Positive Patients Edward Stern,1,2 Sandra G. Guerra,2 Mark Harber,1 Aine Burns,1 Carmen Fonseca,2 Christopher P. Denton.1 1Centre for Nephrology, UCL, London, United Kingdom; 2Centre for Rheumatology and Connective Tissue Diseases, UCL, London, United Kingdom.

Background: Scleroderma renal crisis (SRC), characterised by accelerated hypertension and AKI, is a life-threatening complication of systemic sclerosis (SSc). Most SSc cases have a disease-specific circulating antibody, including the anti-Scl-70 anti-centromere or anti RNA polymerase III (ARA) antibodies. Previous studies confirm ARA as a powerful serological predictor of SRC, and cases of SRC more than 5 years after the diagnosis of SSc are rare. We developed an innovative approach to identify genetic susceptibility loci for SRC, comparing ARA positive patients with and without the occurrence of SRC.

Methods: From a well-characterised SSc cohort (n=415), we selected 100 ARA+ patients with more than 5 years of follow-up data. 50 had a history of SRC and 50 had not developed SRC. Cases were genotyped using the Illumina Human Omni-express chip. Quality control checks were performed in PLINK (Hardy-Weinberg equilibrium p < 0.001; genotyping rate >90%). Based on the results of logistic regression analysis, ten SNPs were put forward for validation in a separate US cohort of 256 ARA+ patients (40 SRC+), using ThermoFisher TaqMan genotyping probes. Immunohistochemistry (IHC) was performed on SRC biopsy samples to identify proteins associated with our genes of interest.

Results: After quality control checks, 641,489 SNPs were analysed in the first cohort. In logistic regression analysis of our initial cohort, the SNPs within genes and gene regions most strongly associated with SRC were for POU2F1 (p=4.12 x 10^-5), CTNND2 (p=2.92 x 10^-5), HECD2 (p=2.71 x 10^-5), GRIA3 (p=2.16 x 10^-5) and GPATCH2L (p=2.06 x 10^-5). The SNP within the GPATCH2L region was also significantly associated with SRC in the validation cohort (p=0.025). GPATCH2L polymorphisms have been associated with arterial hypertension in previous GWAS analyses. Polymorphisms in the CTNND2 gene have been demonstrated to be associated with pulmonary arterial hypertension, another vasculopathic complication of SSc, in previous studies. We performed IHC for this protein, and confirmed altered staining of mesangial cells in SRC biopsy samples compared with controls.

Conclusions: A novel autoantibody-based extreme phenotype method identifies risk alleles for SRC within a rare disease cohort. In particular we identify CTNND2 and GPATCH2L as candidates for investigation of SRC aetiotopathogenesis.

Funding: Government Support - Non-U.S.

SA-OR094

Upregulation of Lysyl Oxidase Activity in Vascular Smooth Muscle Underlies Increased Vascular Stiffness in CKD Rajesh Mohandas,1,2 Brandon To,1 William W. Hahn,1 Philip Ferns,1 Cody Kilari,1 Mark S. Segal.1,3 1University of Florida, Melbourne, FL; 2University of Florida, Gainesville, FL; 3Renal Section, North Florida/South Georgia Veterans Health System, Gainesville, FL.

Background: Introduction: Individuals with chronic kidney disease (CKD) have increased vascular stiffness which correlates with adverse cardiovascular outcomes and mortality. This increase in stiffness is thought to be a consequence of the metabolic derangements of CKD. However, our data shows that vascular smooth muscle dysfunction occurs early in CKD and is not completely explained by endothelial dysfunction. Lysyl oxidase is an amine oxidase that crosslinks collagen and elastin and contributes to stiffness of extracellular matrix. LOX is upregulated by reactive oxygen species, which is increased in CKD.

Methods: Method: In vitro: Aortic smooth muscle cells were treated with serum from uremic patients or healthy controls. Lysyl oxidase mRNA and activity was measured by a colorimetric assay. In vivo: 6-8 month old C57BL/6 mice were subject to a bilateral nephrectomy model of CKD or sham surgery. 6 weeks later mice were sacrificed. Serum levels of lysyl oxidase were assessed. Mesenteric arteries were mounted in an arteriograph chamber and demuded of endothelium. Passive compliance was determined by measuring changes in luminal diameter to stepwise increments in luminal pressure. Aortic smooth muscle lysates were assayed for lysyl oxidase activity.

Results: Results: Treatment with uremic serum resulted in an upregulation of lysyl oxidase in cell culture supernatant 22.5 vs 15.58 (p=6.0 x 0.001). Mice subjected to the CKD model demonstrated increased vascular stiffness. Aortic smooth muscle lysates demonstrated increased lysyl oxidase activity in CKD mice as compared to sham surgical controls [15.67 vs. 12.75 (n=5, p=0.02)]. There was no change in serum lysyl oxidase activity.

Conclusions: Conclusion: Upregulation of lysyl oxidase in vascular smooth muscle cells occurs early in CKD and may be a key mediator of increased vascular stiffness. Lysyl oxidase is a potential novel therapeutic target for CV disease in CKD.

Funding: Other NIH Support - NHLBI

SA-OR095


Background: The metabolic syndrome (MetS) induces intra-renal microvascular disease, which may involve mitochondrial injury. The mitochondrial cardiolipin-targeting peptide elamipretide (ELAM) improves the microcirculation in post-stenotic kidneys, but its potential for attenuating MetS-induced microvascular dysfunction is unknown. We hypothesized that chronic treatment with ELAM would decrease vascular remodeling and dysfunction in swine MetS.

Methods: Pigs were studied after 16 weeks of diet-induced MetS. MetS after 4 weeks of ELAM treatment (0.1mg/kg SC q.d), and Lean controls (n=6 each). Vascular endothelial cell (EC) mitochondrial density (electron microscopy) and cardiolipin content (10N-nonyl acridine orange staining) were assessed in situ. The density of peritubular capillaries (PTC; H&E staining) and renal microvesseels (20-50um, 3D micro-CT), and the function of renal arteries were measured using organ (organ, endothelial nitric oxide (eNOS) expression) were characterized.

Results: MetS pigs developed obesity, hypertension, hyperlipidemia, and insulin resistance. Mitochondrial density and cardiolipin content in EC were diminished in MetS, but improved in ELAM-treated pigs. Furthermore, ELAM improved PTC and microvascular density, and restored eNOS expression and endothelial-dependent relaxation of renal artery segments.

Conclusions: MetS-induced microvascular alterations might contribute to renal PTC, and microvascular loss, and impair renal artery endothelial function in pigs. These observations suggest a potential role for mitoprotection in preserving the renal microvasculature in MetS.

Funding: NIDDK Support, Commercial Support - Stealth BioTherapeutics, Inc.

SA-OR096

Targeting STUB1-Tissue Factor Axis Normalizes the Hyperthrombotic Uremic Phenotype without Increasing Bleeding Risk Moshe Shashar,1 Mostafa Belgasem,2 Shinobu Matsuura,2 Faisal F. Alousi,1 Keshab Rijal,1 Vijaya B. Kolachalam,3 Joel M. Henderson,4 Amitabh Gattam,4 Jean M. Francis,2 Katty Ravd,3 Vipul C. Chitalia,3 1Boston Medical Center, Boston, MA; 2Boston University, Boston, MA; 3Boston University Medical Center, West Roxbury, MA; 4Boston University School of Medicine, Boston, MA.

Background: Atherothrombosis remains one of the major complications in CKD patients despite their treatment with antithrombotic/antiplatelet therapies. Though associations of uremic solutes (e.g. indollic solutes) and vascular wall protein, such as

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
tissue factor (TF) and Atrial Hydrocarbon Receptor (AHR) have been defined, the specific mechanisms that drive the thrombotic and bleeding risks have not been fully understood, nor means by which they might be therapeutically manipulated. We further probed the uricemic solute-AHR-TF axis for its role in uricemic hyperthrombogenesis.

Methods: TF expression and activity and half-life were examined. Indoxyl sulfate was measured in CSMS approach. Additionally, induced CKD models using dietary novel uricemic-solute injected mice were generated. Customized object-level intensity estimation algorithms were developed to quantify TF and carboxy terminus Hsc70 interacting protein (CHIP/STUB1) expressions in human arterioserous fistulae (AVF) explants.

Results: We demonstrate that indolic solutes mediate the hyperthrombogenic phenotype across all CKD stages in AHR- and TF-dependent manners in both the animal models of CKD without prolonging the bleeding time. This finding is in stark contrast to Heparin, the standard-of-care antithrombotic in CKD patients.

Conclusions: Our data implicate indolic solutes as bonafide mediators of the hyperthrombogenic uremic milieu. Importantly, targeting the STUB1-TF axis reverses the thrombotic risk to the non-CKD range, importantly, without altering the hemostatic balance. Overall, we have significantly expanded the understanding of the interconnected relationships of thrombosis and hemostasis that drive the fragile thrombotic state in CKD.

Funding: Other NHI Support - NATIONAL HEART, LUNG, AND BLOOD INSTITUTE, Private Foundation Support

SA-OR097

Renin Cell Precursors Require B1 Integrin for Normal Vascular Development and Renal Function

Tahagod Mohamed, Rajwinderjit Kaur, Roberto Ariel Gomez, Maria Luisa S. Sequeira Lopez. University of Virginia, Charlottesville, VA.

Background: Integrins are the largest family of cell adhesion molecules that mediate cell-to-cell and cell-to-matrix interactions. β1-Integrin (Itgb1) is the most abundantly expressed integrin subunit and is present in almost every cell type. Previous studies show that Itgb1 is required for normal development of the ureteric bud and podocytes and for the function of the proximal tubule. However, its role in the kidney vasculature has not been explored. Renin cells are crucial for blood pressure homeostasis and for normal nephrogenic vasculogenesis. The mechanisms involved in their morphogenetic functions are not well understood. We found that Itgb1 is highly expressed in renin expressing cells throughout development.

Methods: To study the role of Itgb1 in renin cells we generated a conditional deletion (cKO) of Itgb1 in each of the renin lineage by crossing floxed Itgb1 mice with mice expressing Cre recombinase driven by the renin locus.

Results: Itgb1 cKO mice were smaller in size (20.32 ± 4.5 g vs 29.35 ± 7.39 g, p=0.01), had smaller kidney to body weight ratio (0.92 ± 0.30 vs 1.31 ± 0.30, p=0.017), hypotension (MAP 82.33 ± 4.00 mmHg vs 92.55 ± 7.72 mmHg, p=0.02), anemia (hemoglobin 11.25 ± 1.48 g/dl vs 15.07 ± 1.31 g/dl, p=0.003), hematocrit 40.39 ± 5.48% vs 53.8 ± 4.21%, p=0.002), renal failure (BUN 71.44 ± 32.81 mg/dL vs 29.4 ± 7.76 mg/dL, p=0.004), and lower plasma renin levels (6664.58 ± 43357.09 vs 15.07 ± 4.35 g/dL, p<0.02). Mutants also developed hyperlipidemia (artery oxidomethylglycerol 452 ± 138.98 mmOsm/kg vs 1460.5 ± 482.09 mmOsm/kg, p<0.02). Histological analysis revealed excessive collagen deposition in the interstitium and peri-glomerular areas; fibrocytic glomeruli; tubular dilatation and protein casts in the tubules. Immunostaining for renin and α-smooth muscle actin showed a marked decrease in renin protein expression and abundant α-smooth muscle actin expression in the interstitium. Microdissection of the renal arterial tree combined with renin immunostaining confirmed the decrease in renin and evidenced the overall vascular abnormalities including fewer and shorter arterial and arteriolar branches.

Conclusions: Overall, this study shows that β1-Integrin in cells of the renin lineage is crucial for renin expression, morphogenesis of the renal vasculature and maintenance of the normal kidney architecture and function.

Funding: NIDDK Support

SA-OR098

Liraglutide Treatment Improves Renal Vascular Function in Zucker Rats as Visualized by Microangiography


Background: Metabolic syndrome is a cluster of conditions that synergistically increase the risk of cardiovascular disease, type 2 diabetes, and premature mortality. In this present study, we investigated whether chronic liraglutide (LIRA) treatment affects the metabolic profile and renal vascular function in Zucker rats on a high-salt diet (6%/NaCl).

Methods: Eight-week old Zucker lean and Zucker obese (fa/fa) rats were treated with vehicle (n=8) or LIRA (0.1mg/kg/day) for 8 weeks. Eight-week old Zucker obese (fa/fa) rats were treated with vehicle or LIRA (0.1mg/kg/day) for 8 weeks. Glomerular filtration rate (GFR) was measured at 0 and 8 weeks by using fluorescein isothiocyanate (FITC)-sinistrin method in conscious rats. Further, we used X-ray microangiography to measure the renal arterial diameter (70-350 µm) and vessel number in the anastomised vessels. Renal protein expression of inflammatory molecules IL-1β, MCP-1 and transforming growth factor (TGF)-β1 were detected by Western blotting.

Results: After 8 weeks of high-salt diet, systolic blood pressure was significantly increased, renal function and structure were impaired, and collagen deposition was absent in the overall tissues of vehicle-treated Zucker fa/fa rats. We found that in comparison to the untreated Zucker fa/fa rats, rats treated chronically with LIRA showed improved GFR and nitric oxide-mediated vasodilation in response to acetylcholine in small artery and arterioles (<200 µm diameter). Further, vessel internal diameter and visible vessel number (%) were greater in LIRAtreated fa/fa rats compared to vehicle-treated rats (Figure 1). Moreover, LIRA treatment decreased the protein expression of nitrotyrosine and TGF-β1 compared to those of vehicle-treated rats.

Conclusions: These results suggest that LIRA treatment improved renal vascular function through dilatation of small intrarenal arteries and arterioles.

SA-OR099

Indoxyl sulfate Promotes Macrophage Activation via Novel Crosstalk between OATP2B1 and Dll4-Notch Signaling

Toshiaki Nakano,3 Julius D. Decano,2 Shunsuke Katsuki,2 Mario S. Boff,2 Whitney S. Irvin,2 Hideyuki Higashi,2 Sasha Singh,2 Elena Akaiwa,1 Masanori Aikawa,1 Brigham and Women’s Hospital, Harvard Medical School, Boston, MA; Brigham and Women’s Hospital, Harvard Medical School, Boston, MA.

Background: CKD increases cardiovascular risk, however, its underlying mechanisms remain obscure. We previously reported the role of the Notch signaling ligand Delta-like 4 (Dll4) in macrophages. We tested the novel hypothesis that Dll4-Notch mediates macrophage activation stimulated by indoxyl sulfate.

Methods: We examined the effects of indoxyl sulfate (0.25–1.0 mM) on pro-inflammatory responses and Notch signaling in macrophages and the roles of organic anion transporters (OATs/OATPs). To determine the contribution of OATP2B1 to pro-inflammatory activation of macrophages in vivo, we used macrophage-targeted lipid nanoparticles to deliver siRNA to mice. To address the role of Dll4 in in vitro, we used macrophage-deficient mice, 5/6 nephrectomy and Dll4 neutralizing antibody in mice. These lines of in vitro and in vivo evidence suggest that crosstalk between OATP2B1 and Dll4-Notch signaling mediates indoxyl sulfate-induced macrophage activation. We identified previously unreported 9 OATs/OATPs -Secretase inhibitor, Dll4 siRNA or Dll4 antibody indeed suppressed indoxyl sulfate-induced macrophage activation. We identified previously unreported 9 OATs/OATPs.

Results: [In vitro] In human primary macrophages, indoxyl sulfate induced pro-inflammatory molecules IL-1β, TNFα, and MCP-1 and Notch signaling components Dll4, Notch1 and Hes1. Decreased degradation by ubiquitin-proteasome pathway appears to promote rapid induction of Dll4 <1 hour by indoxyl sulfate (FACS, Western blotting, immunofluorescence), which in turn triggers Notch signaling. Notch inhibition with the γ-Secretase inhibitor, Dll4 siRNA or Dll4 antibody indeed suppressed indoxyl sulfate-induced macrophage activation. We identified previously unreported 9 OATs/OATPs in macrophages, among which human and mouse commonly expressed OATP2B1. To determine the contribution of OATP2B1 to pro-inflammatory activation of macrophages in vivo, we used macrophage-targeted lipid nanoparticles to deliver siRNA to mice. To address the role of Dll4 in in vitro, we used macrophage-deficient mice, 5/6 nephrectomy and Dll4 neutralizing antibody in mice. These lines of in vitro and in vivo evidence suggest that crosstalk between OATP2B1 and Dll4-Notch signaling mediates indoxyl sulfate-induced macrophage activation and vascular disease.
Autologous Mesenchymal Stem Cells Decrease Blood Pressure and Kidney Injury in Human Renovascular Disease

Herrmann, LaTonya J. Hickson, James Gocklock, Allan B. Dietz, Lilach O. Lerman, Stephen C. Textor. Mayo Clinic, Rochester, MN.

Background: Atherosclerotic renovascular disease (RVD) reduces blood flow (RBF), glomerular filtration rate (GFR) and accelerates both systemic hypertension and post-stenotic kidney (SK) tissue injury. Preclinical studies indicate that MSCs stimulate angiogenesis and modify immune function in experimental RVD. We assessed the safety and clinical effects of intrarenal autologous MSCs in a phase 1/2A study of human subjects with RVD.

Methods: Adipose tissue-derived MSCs were collected from 21 RVD patients (age 57.7 ± 4.3; 13 male and 8 females). Inpatient studies were performed during fixed Na+ intake and ACE/ARB Rx before and from 3 months after unilateral intra-arterial single infusion of MSC of either 1.0, 2.5 or 5 x 10^5 cells/kg into the SK (n=7 each). SK cortical/medullary perfusion and RBF were measured using multidector CT, GFR by iothalamate clearance, Injury markers including NGAL and VEGF-C were measured in the renal veins and renal tissue oxygenation was assessed by BOLD-MRI at 3T.

Results: Intra-arterial MSC infusions were tolerated without adverse effects. Tissue perfusion and RBF increased after 3 months (p<0.05 vs. baseline), and fractional hypoxia (%R2*>30 sec-1) decreased in the treated kidneys. Renal vein levels of NGAL and VEGF-C decreased (Table). Systolic blood pressure fell (P<0.05) and iothalamate-GFR marginally increased (P=0.053) 3 months after MSC (Table). These changes were of similar magnitude among the 3 doses.

Conclusions: In this “first-in-human” dose escalation study in 21 patients with atherosclerotic RVD, a single intraarterial infusion of autologous adipose tissue-derived MSCs into the SK decreased systolic blood pressure and increased RBF after three months. These were associated with a reduction in tissue hypoxia and renal injury cytokines, while GFR tended to improve. Our results demonstrate the capability of intrarenal MSC to increase tissue oxygenation and RBF in the human kidney, and support a potential role for MSC in the management of ischemic renal disease.

Funding: NIDDK Support

SA-OR102

Ultrasoundography-Based Volume Status Assessment Unveils Misclassification of AKI in Cirrhotics as Hepatorenal Syndrome

Carlos O. Velez,7 Nithin Karakala,7 John T. Huggins,7 Alan S. Go,2 Alan J. Fish,1 Tim M. Schrier,6 Carlos Q. Velez,7 Alan S. Go,2 Alan J. Fish,1 Tim M. Schrier,6 1Institute for Clinical Evaluative Sciences, London, ON, Canada; 2Division of Pulmonary and Critical Care, Medical University of South Carolina, Charleston, SC; 3Division of Nephrology, University of Arkansas for Medical Sciences, Little Rock, AR; 4Department of Nephrology, Ochsner Clinic Foundation, New Orleans, LA.

Background: The International Ascites Club criteria for the diagnosis of hepatorenal syndrome (HRS) requires documentation of failure to respond to 2 days of intravenous (IV) volume expansion and/or diuretic withdrawal. We hypothesized that ultrasoundography (US)-based bedside techniques to assess volume status may provide clinically significant information to ascertain or disprove the clinical diagnosis of HRS.

Methods: A pilot prospective study was conducted to determine the feasibility and clinical utility of US examination of inferior vena cava (IVC) diameter and collapsibility and echocardiographic measurement of velocity time integral (VTI) to assess intravascular volume status in hospitalized adult patients with cirrhosis and acute kidney injury (AKI) who had been deemed adequately volume resuscitated and assigned a clinical diagnosis of HRS.

Results: A total of 52 patients completed the study (mean age 56.2 years, 48% women, 88% white). Mean serum creatinine (sCr) at the time of volume status assessment (29.8, 95% CI 14.99, 15.85). In addition to older age and nursing home residence, factors most strongly associated with one-year mortality were cancer (hazard ratio [HR] 1.62, 95% CI 1.58-1.65) and inpatient chemotherapy (2.03, 95% CI 1.90-2.17). In a parallel cohort study from 4 centers between 2009-2015 and completed an outpatient baseline visit within 3 months of discharge. Potential hospitalized HF events associated were adjudicated through February 2017 using medical records and standardized criteria. Demographics, clinical characteristics and kidney function were obtained at baseline. Multivariable Cox proportional hazards regression was used to examine the association of AKI with HF events, overall and stratified by AKI severity and by pre-existing chronic kidney disease (CKD) status.

Conclusions: Utilization of bedside US-based assessment of volume status in cirrhotic individuals with AKI may reduce the likelihood of incorrectly assigning a diagnosis of HRS. Further exploration of the clinical applicability of this approach is warranted.

Funding: NIDDK Support

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

99
SA-OR105

Defining Renal Recovery Following Postoperative AKI

Thorir E. Long,1,2 Sólveig Helgadóttir,1 Dadi Helgason,1,2 Runolfur Palsson,1,2 Tomas Gudbjartsson,1,2 Gislí H. Sigurdsson,1,2 Martin I. Sigurdsson,1 Olafur S. Indridsson,1 Lándspitali - The National University Hospital of Iceland, Reykjavík, Iceland; 2Faculty of Medicine, University of Iceland, Reykjavík, Iceland; 3Duke University, Durham, NC; 4Akademiska Hospital, Uppsala University, Uppsala, Sweden.

Background: Consensus on the definition of renal recovery after acute kidney injury (AKI) is lacking. The aim of this study was to examine the association of different definitions of renal recovery with survival among individuals with AKI following surgical procedures.

Methods: This was a retrospective study of all adult patients who underwent abdominal, thoracic, vascular or orthopedic surgery at the University Hospital in Reykjavik in 1998-2015. Clinical data was extracted from electronic medical records. AKI was diagnosed according to the serum creatinine (SCr) part of the KDIGO criteria. Association between 1-year survival and renal recovery of varying degree (SCr reduction to less than 1.5, 1.25 and 1.1 x baseline SCr) and at various time points (10, 20 and 30 days following AKI) was examined by logistic regression. We excluded patients with baseline SCr <15 mL/min/1.73 m², those who died during the index admission, and recurrent AKI episodes.

Results: A total of 2,410 patients had AKI. All recovery definitions, namely SCr <1.5, 1.25 or 1.10 x baseline SCr at 10, 20 or 30 days after surgery, were significantly associated with 1-year survival. Reaching SCr <1.5 x baseline within 30 days had the strongest relationship with 1-year survival (OR 0.37; 95% CI, 0.29-0.48; p<0.001) in a multivariable logistic model adjusting for age, AKI stage, year of the AKI episode, previous diagnoses of congestive heart failure, chronic pulmonary disease or neoplasm, preoperative eGFR<60 mL/min/1.73 m² and type of surgery. Increased odds of 1-year mortality was observed for those who had persistent SCr 1.5 x baseline following AKI compared with patients whose SCr returned to <1.1 x baseline (Table).

Conclusions: Among patients with postoperative AKI surviving to hospital discharge, achieving SCr <1.5 x baseline within 30 days had the strongest association with 1-year survival. This might therefore be a useful definition of renal recovery after AKI.

Funding: Government Support - Non-U.S.

Odds ratio for one-year mortality according to renal recovery at 30 days

<table>
<thead>
<tr>
<th>Recovery at 30 days</th>
<th>Unadj. OR</th>
<th>p-value</th>
<th>Adj. OR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCr&lt;1.1xbaseline</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>SCr&lt;1.25xbaseline</td>
<td>0.7</td>
<td>0.06</td>
<td>0.8</td>
<td>0.11</td>
</tr>
<tr>
<td>SCr&lt;1.5xbaseline</td>
<td>0.5</td>
<td>0.01</td>
<td>0.5</td>
<td>0.02</td>
</tr>
<tr>
<td>SCr&lt;1.25xbaseline</td>
<td>0.1</td>
<td>0.01</td>
<td>0.1</td>
<td>0.03</td>
</tr>
<tr>
<td>SCr&lt;1.5xbaseline</td>
<td>0.09</td>
<td>&lt;0.001</td>
<td>0.09</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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

Underline represents presenting author.
SA-OR107

The Epidemiology and Impact of Fluid Balance on Outcomes in Critically Ill Preterm Neonates: A Report from the AWARE Study

David T. Selewski,1' Ayse Akan Arikan,1 Elizabeth Bonachea,2 Katja M. Gist,3 Stuart Goldstein,3 Mina Hanna,1 Katherine Joseph,1 John D. Mahan,4 Arwa Nada,4 Amy Nathan,5 Kimberly J. Reidy,5 Amy Staples,5 Pia Winternier,5 Louis J. Bookhauer,5 Russell Griffin,3 David J. Askenazi,4 Ronnie Sullivan,5 Rajiv Kovesdy,1 Joy B. Babin,9 Baylor College of Medicine, Houston, TX; Children’s of Alabama, Hoover, AL; Children’s Hospital at Monte Leroi; Albert Einstein College of Medicine, Bronxville, NY; Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; LeBonheur Children’s Hospital, Memphis, TN; McGill University, Montreal, QC, Canada; Nationwide Children’s Hospital, Columbus, OH; Nationwide Children’s Hospital, Columbus, OH; University of Alabama at Birmingham, Birmingham, AL; University of Alabama at Birmingham, Birmingham, AL; University of California, Children’s Hospital Colorado, Aurora, CO; University of Kentucky, Lexington, KY; University of Michigan, Ann Arbor, MI; University of New Mexico, Albuquerque, NM; University of Rochester, Rochester, NY.

Background: Critically ill preterm neonates are at risk of AKI and disorders of fluid balance (FB). Very little data exist on the association between FB and outcomes in this population. We aim to evaluate the epidemiology of FB over the first week of life and impact on outcomes in a multicenter neonatal cohort.

Methods: The Assessment of Worldwide Acute Kidney injury Epidemiology in Neonates (AWARE) study included neonatal ICU admissions at 24 institutions from 1/14-3/14. Inclusion criteria: intravenous fluids for ≥ 48 hrs. Exclusion criteria: congenital heart disease repair at ≤7 days of life (DOL), lethal chromosomal anomaly or death ≥48 hrs. This analysis includes infants <36 weeks gestational age admitted by DOL 7. FB during the first week of life was defined by percent change in weight from birthweight in 510 (44.8%), 0-5% in 458 (40.2%), 5-10% in 83 (7.3%), 10-15% in 36 (3.1%) and >15% in 51 (4.9%). 155 (13.6%) were on MV at DOL 7 and 46 (4%) died.

Results: 1136 preterm neonates were enrolled. Median peak FB was 0% (IQR -2.9, 1.9) at median DOL 2 (IQR 1.5). The pattern of peak FB over the first week included: <birthweight in 510 (44.8%), 0-5% in 458 (40.2%), 5-10% in 83 (7.3%), 10-15% in 36 (3.1%) and >15% in 51 (4.9%). 155 (13.6%) were on MV at DOL 7 and 46 (4%) died. Table 1 describes the association of variables, including FB, with MV at DOL 7. Peak FB was higher in non-survivors (0% [IQR -2.9, 1.7]) vs. non-survivors [9.3, p<0.002].

Conclusions: The AWARE study describes the impact of FB in the first week of life on outcomes in preterm infants. Over half of the cohort had a positive peak FB in the first week of life. Peak FB was associated with MV at DOL 7 and mortality in this cohort.

SA-OR108

Development and Validation of a Risk Prediction Model for AKI Following the First Course of Cisplatin

Shivita S. Motwani,1 Geardoid M. McMahon,1 Benjamin D. Humphreys,3 Sushrut S. Motwani,2 Gary C. Curhan,1 Brigham and Women’s Hospital, Brookline, MA; Brigham and Women’s Hospital and Massachusetts General Hospital, Boston, MA; Channing Division of Network Medicine, Brigham and Women’s Hospital, Boston, MA; Washington University School of Medicine, Clayton, MO.

Background: Cisplatin-associated acute kidney injury (C-AKI) remains a frequent problem occurring in up to 30% of patients who have received cisplatin (Cis). Candidate for Cis has largely been determined by renal function alone. We sought to develop and validate a predictive model for C-AKI for patients who received Cis.

Methods: Clinical and demographic data were collected on patients who received Cis between 2000-2016 at two large independent cancer centers in Boston. C-AKI was defined as a 0.3mg/dl rise in creatinine from baseline to peak measurement within 14 days of the first course of Cis. Multivariable (MV) logistic regression models using C-AKI as the primary outcome were created and a scoring model was developed using one cohort (C). The score-based model was then tested in the validation Ct.

Results: C-AKI occurred in 13.2% of 2049 patients and 11.6% of 2362 patients after the first course of Cis in the development and validation Cts respectively. The following factors were associated with C-AKI in the development Ct: age ≥67 years (OR=1.72, 95% CI 1.26, 2.32; p=0.0007) and age 71-90 years (OR=3.21, 95% CI 2.21, 4.66, p<0.0001) when compared with age ≤60 years; Cis dose 101-150mg (OR=1.62, 95% CI 1.16, 2.27; p=0.005) and >150mg (OR=3.77; 95% CI 2.69, 5.30; p<0.0001) when compared with ≤100mg; history of hypertension (OR= 2.24; 95% CI 1.67, 3.01; p=0.0001) when compared with no hypertension; serum albumin 2.0-3.5 g/dl (OR=1.95; 95% CI 1.39, 2.73; p=0.0001) when compared with serum albumin ≥3.5 g/dl; and low blood pressure within 14 days of Cis (OR=1.47; 95% CI 1.07, 2.05; p=0.02) when compared with those without low blood pressure during that interval. The c-statistics of the score-based model in the development Ct and validation Ct were 0.73 and 0.70, respectively.

Conclusions: A score-based model using the patient’s age, Cis dose, history of hypertension, serum albumin, and low blood pressure after infusion is predictive of cisplatin-associated acute kidney injury.

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

Underline represents presenting author.
SA-OR110

Kidney Tubular Dysfunction among HIV-Negative Persons Receiving Tenoviral-Based Pre-Exposure Prophylaxis

Vasantham Ijamoti,1 Rebecca Scherzer,2 David V. Gildden,3 Steven G. Coca,1 Chirag R. Parikh,2 Robert M. Grant,1 Michael Shlipak,1 1Icahn School of Medicine at Mount Sinai, New York, NY; 2Yale University and VAMC, New Haven, CT, San Francisco V4 Medical Center, San Francisco, CA; 3UCSF, San Francisco, CA

Background: Pre-exposure prophylaxis (PrEP) with once-daily tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) has been adopted by the World Health Organization and the United States Centers for Disease Control as a global strategy for HIV prevention. Tenofovir can cause proximal tubular damage and chronic kidney disease in HIV-infected persons, but little is known regarding its nephrotoxicity in persons without HIV. We evaluated the effects of PrEP on kidney health using a panel of urinary biomarkers.

Methods: Biomarker levels were measured in urine specimens collected before and after PrEP initiation in 109 HIV seronegative participants of the iPrEx-OLE study, a longitudinal cohort of former PrEP trial participants who received open-label TDF/FTC. Cross-sectional correlations of hair drug concentrations with post-TDF urine biomarker levels were evaluated.

Results: After 24 weeks on PrEP, we observed statistically significant increases in proteinuria and α1-microglobulin, a marker of proximal tubule dysfunction, whereas monocyte chemotactic protein-1 (MCP-1), a marker of renal repair, and eGFR declined (112 ml/min/1.73m2 pre-TDF vs 108 ml/min/1.73m2 post-TDF). Higher tenofovir concentrations, measured in hair, were associated with lower concentrations of urinary MCP-1 (r=−0.404, p<0.001), a protein secreted by healthy tubular cells.

Conclusions: PrEP with TDF/FTC was associated with changes in renal tubular health, captured by urine biomarker levels. Urine biomarkers may be useful indicators of nephrotoxicity in PrEP users.

Funding: NIDDK Support, Other NIH Support - NIAID - University of California San Francisco-Gladeストン Center for AIDS Research

Biomarkers levels before and after initiation of PrEP

| Biomarker                  | Pre-TDF Mean (IQR) | Post-TDF Mean (IQR) | Relative change | P-value
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria</td>
<td>176 (144, 211)</td>
<td>176 (144, 211)</td>
<td>0%</td>
<td>0.992</td>
</tr>
<tr>
<td>α1-microglobulin (mg/dL)</td>
<td>0.5 (0.3, 1.0)</td>
<td>0.45 (0.3, 1.0)</td>
<td>10%</td>
<td>0.002</td>
</tr>
<tr>
<td>MCP-1 (ng/mL)</td>
<td>112 (80, 160)</td>
<td>108 (80, 160)</td>
<td>4%</td>
<td>0.017</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m2)</td>
<td>112 (100, 124)</td>
<td>108 (100, 124)</td>
<td>3%</td>
<td>0.016</td>
</tr>
</tbody>
</table>

P-values from Wilcoxon Signed-Rank test.

SA-OR111

Complement System and Rapid Renal Function Decline in Type 1 (T1D) and Type 2 Diabetes (T2D) – Application of Novel SOMAscan-Based Proteomic Technology

John J. Tsai,1 Adam Smiles,2 Stephanie E. Croall,3 Joseph V. Bonventre,1 Andrzej S. Krolewski,1 Monika A. Niewczas,2,4 Brigham and Women’s Hospital, Boston, MA; 3Joslin Diabetes Center, Boston, MA; 4Veterans Affairs Administration, West Roxbury, MA; 5Harvard Medical School, Boston, MA

Background: We aimed to investigate inflammatory protein signatures in the urine associated with rapid renal function loss in subjects with diabetes.

Methods: In a case-control study of 60 subjects nested within the Joslin Kidney Study cohort of subjects with T1D, proteinuria and CKD 3 (diabetes panel), we performed urinary baseline measurements of 194 inflammatory proteins using the SOMAscan platform. Subjects with a Rapid Renal Function Decline (eGFR loss >40% over 5 years; n=24) and those with normal eGFR (n=36) were defined as cases (n=29). Eighteen out of 20 subjects developed ESRD within this time period. Further, we performed urinary protein measurements in the validation panel of T2D patients. The 2a nested case-control study group consisted of 26 T2D subjects with eGFR loss >40% within 5 years (cases); 11 of these progressed to ESRD, and 26 controls remained alive with preserved renal function during the follow-up.

Results: Six major inflammatory classes of proteins were measured within the array. We identified 26 proteins that were concordantly associated with rapid eGFR loss in the discovery panel (Bonferroni corrected nominal p-value) and in the validation panel (nominal p-value < 0.05). Candidate inflammatory proteins were particularly enriched for proteins from the complement system (χ2 = 21.5; p=0.0001). Complements C3a, C5a and C3c factor H were among the top proteins associated with an increased renal risk.

Conclusions: In our study we identified a robust inflammatory signature enriched for proteins of the complement system that are associated with rapid renal function decline in both types of diabetes. Our findings suggest that local kidney disturbances of the complement pathway are etiologically linked to the development of kidney complications in diabetes.

Funding: NIDDK Support, Private Foundation Support

<table>
<thead>
<tr>
<th>Inflammatory Classes</th>
<th>Total N</th>
<th>Proteins Associated with Increased Renal Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complement System</td>
<td>26</td>
<td>12.6±2.6*</td>
</tr>
<tr>
<td>Interleukin</td>
<td>2</td>
<td>0.6±0.6*</td>
</tr>
<tr>
<td>Lipopolysaccharide</td>
<td>80</td>
<td>3±0.7±0</td>
</tr>
<tr>
<td>Tumor Necrosis Factor</td>
<td>41</td>
<td>1.4±0.7±</td>
</tr>
<tr>
<td>Others</td>
<td>194</td>
<td>4±1.7±</td>
</tr>
<tr>
<td>Total</td>
<td>26±14±4*</td>
<td></td>
</tr>
</tbody>
</table>

*Denotes statistical significance (p<0.05).

SA-OR112

Systemic Methylation Analysis Identifies CTCF-Regulated Pathways in Disease Progression to Diabetic Nephropathy

Jari Khanum,1 Mark E. Cooper,1 Per Henrik Groop,2 Assaam El-Osta,3 Department of Diabetes, Central Clinical School, Monash University, Melbourne, VIC, Australia; 4University of Helsinki and Helsinki University Hospital, Helsinki, Finland. Group/Team: Finnish Diabetic Nephropathy study

Background: Despite extensive GWAS by multiple groups and consortia, including the The Finnish Diabetic Nephropathy Study (FinnDiane), only a few genes that explain <5% of susceptibility to nephropathy in type 1 diabetes (T1D) have been identified. With increased awareness of epigenetics as it pertains to human disease, there remains scepticism whether the signalling pathways in diabetes are an association or represent a direct pathogenic state. Therefore, we used a global approach to characterize methylation-mediated function in clinical samples combined with integrative molecular studies to define mechanisms implicated in hyperglycemia and diabetic nephropathy. The current group included 25 participants with T1D characterized into three groups, normalalbuminuria (Normo), microalbuminuria (Macro) and end stage renal disease (ESRD). The control group consisted of 14 non-diabetic participants with no proteinuria.

We show for the first time DNA methylation sequence changes derived from leukocytes for genes important in insulin signaling, integrin interactions and lipid metabolism. Methylation sequencing identified mechanistic target of rapamycin (mTOR) gene regulation was subject to differential CpG methylation in the genebody at CTCF binding sites. Ex vivo cell experiments confirm transitive from normal to high glucose conditions reduced DNA methylation and increased mTOR gene expression. The significance of DNA methylation on mTOR was also validated using the DNA methylation inhibitor, 5-aza-2’-deoxycytidine (5adC). We show exon-specific mTOR expression is DNA methylation dependent and hypothesize alternative splicing of mTOR is mediated by Pol II passing countered by DNA methylation. CTCF binding is dependent on DNA methylation and regulates mTOR in primary cells stimulated by hyperglycemia and, Squeze

Conclusions: These results highlight glucose-derived changes to CTCF binding sites are sensitive to loss-of-methylation with gain-of-function of mTOR in diabetes strengthens the evidence base against DNA methylation changes just being an epiphenomenon.

Funding: Government Support - Non-U.S.

SA-OR113

Fasting Plasma Trimethylamine-N-Oxide as a Risk Marker of Poor Renal Outcomes, Cardiovascular Disease, and Mortality in Patients with Type 1 Diabetes with Diabetic Nephropathy

Signe Abitz Winther,1 Jens C. Ollgaard,2 Hans-Henrik Parving,1 Stanley L. Hazen,3 Oluf Pedersen,4 Peter Rossing,6 1Center for Cardiovascular Diagnostics and Prevention, Copenhagen, OH; None, Kege, Denmark; 2Novo Nordisk Foundation Center for Basic Metabolic Research, Köbenhavn Ø, Denmark; 3Steno Diabetes Center Copenhagen, Gentofte, Denmark; 4National Hospital, Copenhagen, Denmark; 5Novo Nordic A/S, Maaløv, Denmark; 6University of Copenhagen, Copenhagen, Denmark.

Background: Trimethylamine-N-Oxide (TMAO) is a metabolite of phosphatidylcholine, choline and carnitine produced by the gut microbiota from ingested animal foods. It has been suggested as an independent gut-derived risk factor for renal and cardiovascular disease (CVD). Patients with type 1 diabetes are at increased risk of renal and cardiovascular disease and early mortality. We investigated associations between fasting plasma TMAO and outcomes in a prospective study.

Methods: TMAO was measured at baseline in 384 patients with type 1 diabetes with diabetic nephropathy (u-AER > 300 mg/g, 61% were male, mean age was 42 years and eGFR 66 ml/min/1.73m2). Fasting plasma levels of TMAO were measured using stable isotope dilution tandem mass-spectrometry. Endpoints included mean yearly decline in eGFR (follow-up (FU) up to 12 years), ESRD (n=65; mean FU: 7.2 years), fatal and non-fatal CVD (n=154; mean FU: 7.5 years) and all-cause mortality (n=134; mean FU: 9.0 years). Associations between TMAO and the endpoints were tested using linear regression or Cox proportional hazard regression in uni- and multivariate analyses adjusting for conventional risk factors at baseline.

Results: Plasma TMAO was inversely associated with baseline eGFR (R² = 0.42; p<0.001). In univariate analysis higher TMAO was associated with all endpoints (p=0.002). All endpoints remained significant associated with higher TMAO after adjustment for baseline age, diabetes duration, sex, smoking, systolic blood pressure, cholesterol, HbA1c and u-AER (p<0.014). After further adjustment for baseline eGFR

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
significant loss for all endpoints, except for CVD events (HR per doubling: 1.22, 1.05-1.41; p=0.010). Conclusions: In type 1 diabetes patients with diabetic nephropathy, higher fasting plasma TMAT level was predictive of poor renal outcomes, CVD events and mortality independent of conventional risk factors. Only the relation to CVD events remained after further adjustment for baseline eGFR. This elucidated the close relationship between TMAT and renal function.

Funding: Private Foundation Support

SA-OR114

Identification of Novel Biomarkers for Predicting the Renal Prognosis in Patients with Type 2 Diabetes by Glyceran Profiling in a Multicenter Cohort Study: U-CARE Study

1Koki Misio, Hitoshi Sugiyama, Haruhiyo A. Uchida, Jun Wada,
2Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan; 3Department of Human Resource Development of Dialysis Therapy for Kidney Disease, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan; 4Department of Chronic Kidney Disease and Cardiovascular Disease, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.

Background: Recent studies have demonstrated that alterations of glycosylation are critically involved in the development of diabetes and in the progression of diabetic nephropathy (DN). However, the association between changes of glycosylation and the renal prognosis of DN patients remains unclear because of difficulty in quantifying glycans due to their complex structures.

Methods: A total of 680 patients with type 2 diabetes admitted to 8 affiliated hospitals in Okayama during 2012 were enrolled in this study. At baseline, we measured urinary levels of C3-labeled glycans that bound to 45 lectins with different specificities. The endpoint was a decrease of the estimated glomerular filtration rate (eGFR) by a 30% from baseline or commencement of dialysis for end-stage renal disease (ESRD).

Results: During a median follow-up period of 4.0 years (IQR: 3.9-4.0), the primary endpoint was reached in 60 patients. Baseline mean eGFR was 71.0 ± 17.7 ml/min/1.73 m² and 594 patients (87%) showed either normoalbuminuria (63%) or microalbuminuria (24%). A log-log linear time trend for known indicators of DN, including baseline eGFR and albuminuria, the urine levels of glycans binding to some lectins (including SNA, SSA, ABA, ACA, and MPA) were significantly associated with the primary endpoint (+1SD for log[glycan signal intensity/urinary creatinine concentration], HR for SNA: 1.43 [95% CI: 1.07-1.90], HR for ABA: 1.39 [1.05-1.80], HR for ACA: 1.37 [1.03-1.81], and HR for MPA: 1.33 [1.01-1.76], respectively). The glycan Sia2-6GalGalNAc was reported to bind with SSA and SNA, while Galβ1-3GalNAcSia2-6Gal/GalNAc was reported to bind with SSA, SNA, ABA, ACA, and MPA.


Funding: Private Foundation Support

SA-OR115

ACE Inhibitor, ARB, or Combined Therapy in Patients with Diabetes and Microalbuminuria: The Long-term Impact of RAS Inhibition on Cardiorenal Outcomes (LIRICO) Randomized Clinical Trial

Giovanni F. Strippoli, Suetonia Palmer, Bozena Krolewski, Andrea S. Begin, Xuefang Ma, Lilach Skupien, heater volunteers (HV).

Background: Combination ACE inhibitor/ARB therapy may be a viable option for the treatment of DKD. However, patient-related factors, including hyperglycemia and hypertension, are important contributors to the progression of diabetes and kidney disease.

Methods: The LIRICO trial was a phase III, prospective, randomized, open-label, non-inferiority clinical trial to evaluate the efficacy and safety of combined ACE inhibitor/ARB therapy versus monotherapy on cardiovascular and renal outcomes in patients with diabetes and microalbuminuria. The long-term impact of RAS inhibition on cardiorenal outcomes (LIRICO) randomized clinical trial evaluated the comparative efficacy of combined ACE inhibitor/ARB therapy versus monotherapy on cardiovascular endpoints.

Conclusions: Patients with microalbuminuria (ACR ≥30mg/g) or macroalbuminuria and diabetes were randomly assigned to an ACEi (n=427), ARB (n=428) or combination (n=432) titrated to full doses. Non-randomized antihypertensive therapy was administered to achieve blood pressure <140/90. The primary outcome was all-cause mortality. Secondary outcomes were cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for cardiovascular causes, end-stage kidney disease, and surrogate renal outcomes (doubling serum creatinine, chronic kidney disease [eGFR<60 ml/min/1.73 m²], development of macroalbuminuria, or normoalbuminuria).

Results: During a median follow-up of 2.8-3.0 years, the number of all-cause mortality events was similar between groups (15 deaths [3.6%] in the ACEi group; hazard ratio 0.84 versus combination group, 0.42-1.67, 20 [4.8%] in the ARB group (HR 1.11, 0.59-2.12), and 18 [4.3%] in the combination group). The secondary outcome of end-stage kidney disease was similar between groups (6 events [1.5%, HR 1.53, 0.43-5.44], 7 events [1.7%, HR 0.50, 0.09-2.76] and 4 events [1.0%, respectively]. There was no difference between groups for cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or renal outcomes.

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

SA-OR116

Biomarkers Protective against ESRD in Advanced Diabetic Nephropathy

Adam Smiles, Monika A. Niewczas, Jan Skupien, Bozena Krolewski, Andrzej S. Krolewski, Joslin Diabetes Center, Boston, AL.

Background: A population of patients with type 1 diabetes, persistent proteinuria and CKD stage 3 was followed for progression to End Stage Renal Disease (ESRD). From the group of 219 subjects, 119 were identified as cases, based on their progression to ESRD within 10 years. The control group was the remaining 100 subjects who did not progress to ESRD.

Methods: Baseline plasma from these subjects was assayed on the SOMAscan platform. Relative concentrations were measured for 568 proteins. A protein fold change was calculated as the ratio of mean protein concentration for cases divided by concentration in controls. 16 potentially protective proteins were identified by having a fold change < 1 and a p<0.001. This list was reduced to 12 proteins that also had nominal significance in a similar cohort of Type 2 patients.

Results: In Yamanouchi et al. (KI 2017) we have shown that plasma level of TNFR1 is the primary predictor of ESRD and accounts for most of the traditional risk factors. As such, we performed a Cox proportional hazards model for each protein, adjusting for TNFR1 concentration. Hazard Ratios and p values are reported in the table below.

Conclusions: Clusters of protective proteins might have similar physiological relevance, be part of common or related pathways or be under the same genetic regulation. Identification of proteins that protect patients from ESRD in the face of such advanced diabetic nephropathy may be useful targets for the development of therapeutics for preventing or delaying the onset of ESRD.

Funding: NIDDK Support, Private Foundation Support

SA-OR117

Diabetic Kidney Disease (DKD) Alters the Transcriptome in Adipose Tissue-Derived Mesenchymal Stromal/Stem Cells (MSC)


Background: Cellular therapy applying autologous MSC may be a viable option for the treatment of DKD. However, patient-related factors, including hyperglycemia and uremia, may alter their reparative capacity. To explore the effect of these biological factors on MSC, we characterized the MSC transcriptome and compared to a set of healthy volunteers (HV).

Methods: MSCs were harvested from subcutaneous abdominal adipose tissue of DKD (n=21) and HV (n=8 kidney donors) subjects. Next-generation sequencing (RNA-seq) of MSC (3rd passage) and functional annotation analysis (DAVID 6.8 database) were then performed to identify differentially expressed mRNAs and rank the primary gene ontology categories.

Results: DKD subjects were older, had higher body mass indices, and lower glomerular filtration rates compared to HV (Table). RNA-seq generated reads for 13,182 mRNAs, of which 180 were differentially expressed in DKD-MSC vs. HV-MSC (False Discovery Rate <5% and log2 fold change ≥2 or ≤-2) (Figure). Functional analysis identified extracellular matrix remodeling and inflammation as the most prominent categories (enrichment score >10), followed by genes capable of modulating cellular pathways linked to tissue repair.

Conclusions: DKD and associated comorbidity modulate the expression of genes involved in inflammation, matrix remodeling, and tissue repair in adipose tissue-derived MSC. These alterations may impact the endogenous repair capacity of MSC and may have clinical implications for the capacity of exogenous autologous MSC delivery to repair DKD.

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

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

Underline represents presenting author.
SA-OR119

SGLT2 Inhibitors Induce Local Mitochondrial Unfolded Protein Responses in the Proximal Tubules by Suppressing Mitoribosome Proliferation and Influencing Mitonuclear Imbalance in Diabetic Nephropathy  
Hirovuki Umino, Kazuhiro Hasegawa, Shu Wakinou, Hiroshi Itoh. Keio University School of Medicine, Tokyo, Japan.

Background: We have previously reported a molecular mechanism by which SGLT2 inhibitors maintain the anti-aging gene SIRT1. The findings that mitoribosome blockade causes mitonuclear imbalance and induces mitochondrial unfolded protein responses (UPRs) are reportedly linked to longevity. These changes also underlie the elongation occurring from modulation of NAD metabolism and SIRT1. In this study, we analyzed whether SGLT2 inhibition and SIRT1 retention would produce this effect in the proximal tubules.

Methods: Canagliflozin (Cana), a SGLT2 inhibitor, was administered to 8-week-old db/db and db/db mice, and the following parameters were evaluated at 16 weeks of age: (1) SGLT2 and SIRT1 expression; (2) mitoribosome and cytoplasmic ribosome (cytoribosome) numbers on electron microscopy; and (3) COX1, representing mitoribosome function, which is encoded by mitochondrial DNA and translated in mitoribosomes, and ATP5A, a marker protein reflecting cytoribosome function, which is encoded by nuclear DNA and translated in cytoribosomes.

Results: In db/db mice, SGLT2 expression was elevated and SIRT1 expression was decreased; these changes were suppressed in db/db mice treated with Cana. In db/db mice, an elevated mitobosomal number was observed despite no marked change in the cytoribosomal number in the proximal tubules observed on electron microscopy. Consistent with mitobosomal proliferation, a significant increase in COX1 was detected in db/db, whereas ATP5A was not changed. The elevation in mitobosomal number and function was suppressed in db/db + Cana. Such specific inhibition of mitoribosome protein expression can lead to mitonuclear protein imbalance and associated UPR.

One of the marker proteins induced by UPR is heat shock protein 60 (HSP60). Indeed, elevation of HSP60 was detected in db/db + Cana.

Conclusions: A mitoribosome synthesizes the enzyme complexes of the electron transport system in the inner membrane (Complexes I–IV). Its increase suggests excessive ATP and ROS production and is a sign of metabolic regulation failure. However, a SGLT2 inhibitor induces an ast stress response caused by UPR. This newly identified organelle change occurs in early-stage diabetic nephropathy, and the mitoribosome may serve as a novel therapeutic target.

SA-OR120

Genetic Deletion of Myo-Inositol Oxygenase (MIOX) Rescues ob/ob Mice from the Progression of Tubulo-Interstitial Injury  
Isha Sharma, Yashpal S. Kanwar, 1NORTHWESTERN UNIVERSITY, CHICAGO, IL; 2Northwestern University Medical School, Chicago, IL.

Background: MIOX, a proximal tubular enzyme, is up-regulated in diabetic state and is involved in the pathogenesis of tubulo-interstitial injury. Previously, we reported that MIOX over-expressing mice with STZ-induced diabetes have remarkable tubulo-interstitial changes. These changes were largely attributed to excessive generation of ROS leading to increased activity of fibrogenic cytokines, especially in the tubulo-interstitial compartment. Such phenotypic changes were not observed in MIOX-/- mice.

Methods: Aim of this study was to assess if genetic ablation of MIOX ameliorates the progression of tubulo-interstitial injury in ob/ob mice by reducing the oxidant stress in proximal tubules. MIOX-/- mice were cross bred with ob/ob mice to generate mice with double mutation (MIOX-/-ob/ob). Animals were sacrificed at age of 20 weeks and kidneys were harvested for various studies. Prior to sacrifice blood and urine samples were obtained.

Results: The MIOX-/-ob/ob mice had improved levels of serum creatinine, urea and insulin compared to ob/ob mice. No change was observed in blood glucose levels. The double mutants had decreased urinary excretion of high molecular weight proteins. The MIOX expression was highly accentuated in kidneys of ob/ob mice compared to WT, and it was absent in MIOX-/- mice and with double mutation. The renal interstitial compartment had notable decreased staining of fibronectin, collagen I and III in mice with double mutation compared to ob/ob mice. The generation of ROS in the kidney tissues notably less in MIOX-/-ob/ob mice compared ob/ob mice, as indicated by decreased DHE staining. Analyses of various metabolic sensors revealed revival of the expression of SIRT1, AMPK, YY-1, and of the master regulator of mitochondrial biogenesis, i.e., PGC-1alpha. In vitro, HK-2 cells treated palmitate-BSA had decreased expression of various metabolic sensors with increased ROS generation, and these aberrant parameters of metabolic sensors were normalized with the treatment of MIOX-siRNA.

Conclusions: In conclusion, these findings suggest that ablation of MIOX gene ameliorates the progression of tubulo-interstitial injury in the settings of diabetic nephropathy by reducing the oxidant stress and improving the status of various metabolic sensors.

Funding: NIDDK Support
Renal Crisis in Sclerodema: A Renal Complementopathy?

Background: Complement, in particular C5a, is the major player of ischemia Reparation injury. Renal Proximal Tubular Epithelial Cells (RPTEC) express the C5aR, however the underlying mechanisms of C5a-C5ar interaction remain poorly understood. We aimed to investigate the impact of C5a exposition on DNA methylation profile in RPTEC.

Methods: Genome-wide array-based DNA methylation levels were measured in several RPTEC lots stimulated with C5a for 24h by the Illumina 450 BeadChips. The analysis was performed on site and region level considering the difference in mean methylation levels both in gene centric regions (promoter, 5UTR, first exon, gene body, and 3UTR) and in Cpg island regions (Cpg islands and CpG island shore and shelves). Gene Ontology tools were used to determine genes interaction. qPCR, WB, SA-β-Gal staining and MTT were performed for validation analysis.

Results: Compared to basal, 144 sites were hypomethylated and 24 sites were hypermethylated by C5a. Several sites differentially methylated were located in CpG island regions and promoters of genes involved in DNA damage checkpoints in response to genotoxic events, in cell cycle regulation, apoptosis, Hedgehog, Wnt and p53 pathways. The most representative protein classes were: nucleic acid binding proteins (DNA topoisomerase), enzyme modulators, transcription factors and cytoskeletal protein (classification analysis: 21.9%, 9.40%, 7.80% and 7.70% respectively), qPCR and Bonferroni confirmed that the hypermethylated genes were downregulated and hypomethylated genes were upregulated. Interestingly, among these genes we found several effectors involved in aquaporin expression of a SAPS (Semenass-Associated Secretory Phenotype). In accordance, 3h of exposure of RPTEC to C5a induced cellular senescence as observed by up-regulating SA-β-Gal and by cell proliferation reduction (p<0.05). Moreover, senescent RPTEC showed a significant increase in p53 and p21 protein level, as sign of cell cycle arrest (p<0.05).

Conclusions: These results suggest a role of complement in inducing tubular senescence affecting epigenetic programs, in particular the DNA methylation profile. Targeting epigenetic mechanisms may represent a strategy to protect tubular cells from aging.

Abnormalities of Alternative Pathway of Complement in C3 Glomerulopathy Aishwarya Ravindran, Fernando C. Fervenza, Sanjeev Sethi. Mayo Clinic, Rochester, MN.

Background: CG3, comprising C3 glomerulonephritis (C3GN) and dense deposit disease (DDD), is characterized by glomerular accumulation of complement components due to abnormal regulation of the alternative pathway (AP) of complement. Large scale studies describing genetic and acquired abnormalities of AP associated with C3G are lacking. We describe our institutional experience of the abnormalities of AP associated with C3G.

Methods: Of the 114 C3G patients seen at the Mayo Clinic, 76 (66.7%) patients (65 C3GN/11 DDD) were evaluated for abnormalities of the AP of complement during the period 2007-2016. Results: C3 levels were low in only 44.6% patients, while 11.8% patients also had low C4 levels. Overall, 29 (43.9%) were positive for mutations of complement factors and/or regulatory proteins, the most common (15.2%) was a heterozygous mutation in C3 related factor (CFHR3- CHFR1) deletions were the most frequent (8 patients each; 6%); 9 (13.5%) had MCP2CD46 mutations (DV2A G = A) with C3G. Patients with homozygous mutations had a trend towards presentation at a younger age (mean 35 vs 50 years; p=0.1) compared with those with heterozygous mutations.

Conclusions: In this single-center analysis of 15 consecutive aHUS patients, we reported that a large majority (87%) had complement gene mutations. This might represent increasing knowledge of identifiable mutations in the contemporary era. A large majority of patients had an excellent response to C5 blockade. Patients being evaluated for kidney transplants with a history of unexplained TMA should be screened for aHUS.
Most of the reports on C3G are based on individual cases or small series of C3GN/DPG patients.

Methods: We provide a comprehensive evaluation of 114 patients seen at Mayo Clinic during a 10-year period (2007-2016), of which 102 (89.5%) had C3GN and 12 (10.5%) had DPG.

Results: The median age at diagnosis of C3G was 42 years; C3G patients were older (median age 42 years) while DPG patients were younger (median age 23.5 years). The median serum creatinine and proteinuria at presentation was a 1.6 mg/dL and 2605 mg/24 hours. Hematia was present in 100 (87.7%) patients, C3 levels were low in only 44 (40%) patients. Monoclonal gammopathy was present in 37.9% patients; 66% of the patient’s s 50% had a monoclonal Ig. 28.9% patients had a history of infection and 23.7% patients had an associated autoimmune abnormality. Mutations in complement regulating proteins including CFI, C3 nephritic factor, and other autoantibodies (anti-CFH and CFB) were detected in 43.9%, 43.9% and 10.9% patients, respectively. All patients tested carried C3G risk-associated polymorphisms, the most common being CFH allele variants. Membrano- and mesangial proliferative glomerulonephritis were most common patterns of injury on kidney biopsy. Most patients received steroids and other immunosuppressive drugs. After a median follow-up of 34 months, the median serum creatinine changed by 1.4 mg/dL and the median proteinuria was 689 mg/24 hours. Eighteen patients (15.8%) progressed to ESRD. The predictors of ESRD on univariate analysis were serum creatinine >1.5 mg/dL and the median proteinuria was 809 mg/24 hours. Eighteen patients (15.8%) progressed to ESRD. The predictors of ESRD on univariate analysis were serum creatinine >1.5 mg/dL, proteinuria >3 g/24 hours at diagnosis, severity of glomerular sclerosis and the extent of tubular atrophy and interstitial fibrosis.

Conclusions: C3G is a heterogeneous disease entity that affects both children and adults. In younger patients, both mutations and autoantibodies to complement regulating proteins are present, while in older patients, a monoclonal Ig, which presumably acts as an autoantibody to complement regulating proteins, is most frequently identified.

TH-PO006
Disregulation of the Alternative Complement Pathway in C3GN and IgAN


Background: Dysregulation of the alternative pathway plays an important role in glomerular disease, including IgA nephropathy (IgAN) and C3 Glomerulopathy (C3G). These disorders share some clinical manifestations, such as microscopic hematuria and episodes of syphangphritic flares. Both are characterized by variable mesangial deposits of C3.

Methods: In this cross-sectional study, we collected plasma from 55 participants with IgAN, 105 diagnosed with C3G, as well as from 62 unrelated healthy controls. All cases of IgAN and C3G were diagnosed by biopsy. Major components of the alternative pathway, including C3, CFH and CFB levels, were measured by ELISA.

Results: Compared to controls, plasma CFD levels were higher in IgAN and C3G groups. When compared to the IgAN group, the C3G group has a significantly lower level of plasma C3 and CFH levels.

Conclusions: These data demonstrate dysregulation of the alternative complement pathway in both IgAN and C3G. Lower C3 and CFH levels are characteristic of C3G and differentiate it from IgAN. Analysis of larger cohorts during both active and inactive stages of the disease will better clarify shared and distinct complement profiles between these disorders.

TH-PO007
The Complement System and Hemodialysis: Activity of the Lectin Pathway

Philip De Javu,1 Katrine Pilelye,3 Peter Garred,4 Bo Nilsson,2 Bengt C. Fellsstrom,1 Inga Soveri.1 1Department of Medical Sciences, Uppsala university, Uppsala, Sweden; 2Department of Immunology, Genetics and Pathology, Uppsala university, Uppsala, Sweden; 3Department of Clinical Immunology, Rigshospitalet, Copenhagen, Denmark.

Background: Complement activation occurring during hemodialysis (HD) has been put forward as a driving force for inflammation in HD patients, but the importance of the lectin complement pathway in HD is largely unknown. Aim: To quantify level of plasma C3 and CFH levels.

Methods: Blood was sampled from 20 consecutive HD-patients before, at 30, 60, 120, 180 and 240 minutes and after the prescribed HD-session using either polysulphone or polysulphone based dialyzers. Plasma concentration of the lectin pathway initiator molecules, ficolin-1, -2, -3, manose-binding lectin (MBL), lectin pathway regulator MAP-1 and enzyme MASP-3 as well as the soluble form of the terminal complement complex, sC5b-9.

Results: Plasma concentrations of ficolin-2, MASP-1 and MASP-3 decreased significantly after 30 minutes and remained low for the rest of the HD session. MBL.

Complement Your Knowledge of Kidney Disease
Poster/Thursday

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Increased Expression of Complement Receptor C5aR1 in Macrophages Contributes to Kidney Fibrosis

Ranjit K. Sahu,1 Sandhya Xavier,1 Susan G. Landes,2 Ronald P. Taylor,3 Joerg Megyesi,2 Susan J. Portilla,4 Joerg Megyesi,2
1University of Virginia Health System, Charlottesville, VA; 2Department of Veterans Affairs, Salem Veterans Affairs Medical Center, Salem, VA; 3University of Liebeck, Liebeck, Germany; 4Division ofImmunobiology, Cincinnati Children’s Hospital Medical centre, Cincinnati, OH.

Background: We recently demonstrated increased expression and activation of the complement system with increased expression of C5 and C5aR1 in whole kidney tissue homogenates of mice subjected to folic acid and Unilateral ureteral obstruction (UUO) injury. Given the central role of complement activation product C5a in the development of the inflammatory response through interaction with C5aR1, in the present studies we examined the cellular localization of C5aR1 during injury, and the potential mechanism(s) by which its activation contributes to kidney fibrosis.

Methods: C5aR1 expression was studied by immunohistochemistry, flow cytometry, qPCR, and by western blot analysis of wild type, GFP-C5aR1-floxed, and C5−/− mice subjected to UUO or the UUO model RAW264.7 cells were used as an in vitro model to study how increased C5aR1 expression on macrophages was linked to the process of fibrosis.

Results: Immunohistochemistry studies localized expression of C5aR1 to proximal tubules in sham mice but increased expression was seen mostly in interstitial cells after UUO. C5aR1 mRNA levels were increased in CD45+ cells isolated from UUO mice. Flow cytometry analysis using GFP/C5aR1-Floxed mice demonstrated a 75-fold increase in CD68+/GFP+ macrophages after UUO. Reduced staining of CD68+/C5aR1+ Prominin-1+ cells by flow suggests loss of renal tubular epithelial cells during UUO. C5aR1 expression as well as kidney fibrosis were significantly reduced in C1r−/− mice when compared to wild type mice subjected to UUO. Our studies suggest that increased C5aR1 expression on macrophages during UUO is associated with increased kidney fibrosis. In vitro studies using RAW 264.7 cells treated with LPS showed increased C5aR1 expression correlated with increased production of IL-1β and IL-6, as well as inflammasome activation, all indicative of an increased inflammatory response.

Conclusions: Our results are the first to report that increased expression of C5aR1 on CD11b+ F4/80+ Ly6c− macrophages correlates with the advent of kidney fibrosis. Increased cytokine production and inflammasome activation represent cellular mechanisms by which increased C5aR1 expression contributes to kidney fibrosis.

Funding: NIDDK Support, Veterans Affairs Support

TH-0011

Role of Complement C1r and C1s Serine Proteases in Kidney Fibrosis

Sandhya Xavier,1 Ranjit K. Sahu,1 Susan G. Landes,1 Judit Megyesi,2 Jing Yu1, Ronald P. Taylor,1 Didier Portilla,41 University of Virginia Health System, Charlottesville, VA; 2University of Arkansas for Medical Science, Little Rock, AR; 3University of Virginia, Charlottesville, VA; 4Salem Veteran Affairs Medical Center, Salem, VA.

Background: Complement C1 complex consists of C1q, and proteases C1r and C1s. Our previous studies of UUO (Unilateral Ureteral Obstruction) demonstrated complement activation with increased expression of C1q, C1r and C1s in whole kidney tissue homogenates. To better understand the cellular processes leading to increased classical complement activation we examined the cellular localization and potential mechanisms leading to increased expression of C1r and C1s in kidney cells.

Methods: We performed real time-PCR, immunohistochemistry, in situ hybridization in wild type and in C1r−/− mice subjected to sham or UUO injury. Cultured RAW 264.7 macrophages were treated with interferon gamma to induce C1r/C1s expression.

Results: We showed increased synthesis of C1q in pericytes and CD45 positive cells, but C1r/C1s was only increased in CD45 positive and PDGFR-β negative cells during UUO. In situ hybridization and immunohistochemistry showed that C1s is induced following UUO injury in cortical thick ascending loops (cTALs) and distal collecting ducts (CDs). C1r immunostaining was increased in cTALs, distal tubules and dilated CDs. Cultured RAW 264.7 macrophages treated with Interferon gamma had increased expression of C1r and C1s mRNA due to activation of the IFN--regulatory factor-1 (IRF-1) binding site present in the C1r promoter. Expression of C1r mRNA was absent in kidney tissue from C1r−/− mice as compared to wildtype littermates. The ablation of C1r also leads to reduced expression of C1s mRNA in kidney tissue from C1r−/− mice. Preliminary studies in these mice suggest that protection against kidney fibrosis is dependent on the expression levels of C1s and C3, and this needs to be further investigated.

Conclusions: The results support the role of complement activation with de novo increased synthesis of C1r/C1s expression by tubular epithelial and immune cells as an important mechanism leading to tubulointerstitial fibrosis.

Funding: NIDDK Support, Veterans Affairs Support

TH-0012

The Relationship between Renal Atherosclerotic Lesions in CKD and the Serum Levels of Complement C3 and C4 and Proteinuria

Chiisato Fukuhara,1 Ryo Zamami,1 Kentaro Kohagura,1 Yusuke Ohya,2 Kunitoshi Inoki,3 1University of the Ryukyus, Okinawa, Japan; 2Tomishiro Central Hospital, Okinawa, Japan.

Background: We previously reported that hyperuricemia (HUA) was related to renal arteriosclerosis in patients with chronic kidney disease (CKD). Serum complement C3 (C3), which is also an apolipoprotein, has also been suggested to be related to renal arteriosclerosis. Here we examined the significance of concurrent occurrence of HUA and elevated C3 levels in renal arteriosclerosis.

Methods: This study involved 172 CKD patients whose biopsies were taken at our department. Of these patients, we excluded those who were receiving corticosteroids or calcineurin inhibitors, those with hypocoomplementation, and patients affected by disease which could cause morphological change in the renal arteries. Arteriosclerosis was analyzed in renal pathological specimens obtained from renal biopsy using arteriolar hyalinization grade, which represents the mean grade obtained following semiquantitative assessment of the degree of hyalinization. Scores equal to or higher than the C3 median were classified into a high (HC3) group. The definition of HUA was determined as those taking antihyperuricemic drugs or those with serum uric acid levels at ≥7 mg/dL for men and ≥6 mg/dL for women. The subjects were divided into four subgroups of HC3−/HUA−, HC3−/HUA+, HC3+/HUA− and HC3+/HUA+ by the presence or absence of HCU and HUA and we then compared their arteriolar hyalinization grades.

Results: The mean arteriolar hyalinization grade after HC3/HUA subgrouping, and proteinuria (mg/dl) as an independent factor is shown in the table below. Arteriolar hyalinization grade after HC3−/HUA− subgrouping was significantly lower than that of HC3+/HUA+. A significant difference was observed with that for HC3−/HUA−. However, the differences between the HC3+/HUA− and HC3+/HUA+ or HC3−/HUA− subgroup were relatively small. We performed multivariate analysis of the determination factors of high arteriolar hyalinization (median grade (higher) including age, pulse pressure, Hba1c, LDL cholesterol level, and HC3/HUA subgroups (Ref: HC3−/HUA−). We found that HC3+/HUA+ (OR, 4.3; 95%CI, 1.2–15.9) was a significant factor. Furthermore, in comparison to the HC3−/HUA− subgroup, the flow-mediated dilation (%FMD) in the HC3+/HUA− subgroup was significantly decreased.

Conclusions: In CKD patients, the relationship between HUA and renal arteriosclerosis may become more notable in patients with high levels of serum complement C3.

TH-0013

An Association of Renal Arteriopathy with Combination of Hypertriglyceridemia and Increased Serum Component C3 in CKD

Chisato Fukuhara,1 Ryo Zamami, Tsuyoshi Miyagi, Masanobu Yamazato, Akio Ishida, Kentaro Kohagura, Yusuke Ohya.1 University of the Ryukyus, Nishihara-cho, Japan.

Background: Metabolic syndrome, which is characterized by adiposity, is a risk factor for progression of chronic kidney disease (CKD). Complement component 3 (C3), one of apolipoproteins correlated with serum triglyceride (TG) levels. We previously reported that combination of hypertriglyceridemia (hTG) and increased serum C3 related to proteinuria via unknown mechanism. Arteriolar hyalinization may relate to proteinuria via disrupted autoregulation of glomerular hemodynamics. In the present study, we examined the association between this combination and renal arteriopathy, oxidative stress and inflammation in patients with CKD.

Methods: A total of 139 patients with non-nephrotic CKD who underwent renal biopsy were enrolled in this study. Renal arteriolar hyalinization was semi-quantitatively assessed via arteriole grading. Oxidative stress and inflammation was assessed by measuring serum C3, triglyceride, high-density lipoprotein cholesterol and C-reactive protein (hs-CRP), respectively. We assessed via arteriole grading. Oxidative stress and inflammation was assessed by measuring serum C3, triglyceride, high-density lipoprotein cholesterol and C-reactive protein (hs-CRP), respectively. We examined the association between this combination and renal arteriolopathy, oxidative stress and inflammation in patients with CKD.

Results: The mean values for age, estimated glomerular filtration rate (eGFR), serum TG and C3 were as follows: 44 years, 74 ml/min/1.73m2, 169 mg/dl and 106. Serum TG, but not C3 was significantly correlated with arteriolar hyalinization index. Subgroup analysis showed that hTG+/ hC3+ group was characterized by higher levels of body mass index, proteinuria, hs-CRP and dROMs. In multivariate regression analysis, hTG+/hC3+ as well as systolic blood pressure and Hba1c was positively associated with arteriolar hyalinization.

Conclusions: These findings suggest that coexistence of hTG and hC3 may relate enhanced oxidative stress and inflammation, which may cause proteinuria in association with arteriosclerosis.

TH-0014

Association of Renal Artery Sclerosis with Serum Component C3 and C4, Proteinuric Glucose Index in CKD

Chiisato Fukuhara,1 Tsuyoshi Miyagi, Ryo Zamami, Masanobu Yamazato, Akio Ishida, Kentaro Kohagura, Yusuke Ohya.1 University of the Ryukyus, Nishihara-cho, Japan.

Background: An association between serum complement C3 (C3) and renal artery sclerosis has been suggested to be related to renal arteriosclerosis. We investigated the influence of the C4-kidney-glucose index (TyG), a marker of insulin resistance, in regard to this association.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Arteriosclerosis was semiquantitatively evaluated by hyalinized arteriolar area of pathological specimens obtained from kidney biopsies, and average score (grading of arteriolar hyalinization) was calculated. Patients with median or higher C3 levels were classified as the high-C3 (HC3) group. TyG was calculated as fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2, and patients with median or higher TyG value were classified as the high-TyG (HTyG) group. Patients were then divided into subgroups based on the presence or absence of HC3 and HTyG (HC3–HTyG−, HC3+HTyG−, HC3+HTyG+, and HC3–HTyG+).

Results: The average score for arteriolar hyalinization grading after applying a subgroup-specific logarithmic transformation was significantly higher in the HC3+/HTyG+ group than in the other groups. A multivariate analysis was conducted with an age, sex, systolic blood pressure, serum uric acid levels, presence or absence of diabetes, and HC3/HTyG subgroup (HC3–HTyG−, HC3+HTyG−, HC3+HTyG+, and HC3–HTyG+) as explanatory variables. Results indicated that HC3+HTyG+ was significant but HC3+HTyG− was non-significant. The HC3+HTyG+ group also had the lowest percent flow-mediated dilatation.

Conclusions: An association between C3 and renal artery sclerosis in patients with chronic kidney disease may be prominent in terms of endothelial dysfunction under conditions of high insulin resistance.

TH-PO015

Complement C5a Moderates Renal Lipid Metabolism and Fibrosis in Diabetic Nephropathy

Wai Han Yu1, Ruixi Li, Dickson W. Wong, Haojia Wu, Kam wa Chan, Loverta Y.Y. Chan, Joseph C. K. Leung,1 Kaiz Neng Lai,1 Steven H. Sacks,2 Wuding Zhou,3 Sydney C. Tang.4 Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong, China; Medical Research Council Centre for Transplantation, King’s College London, Guy’s Hospital, London, United Kingdom.

Background: Complement C5 activation has been implicated in tubulointerstitial injury with increased levels of tubular C5a in renal biopsies from patients with diabetic nephropathy. We investigated whether administration of a C5a inhibitor would confer protection against the progression of diabetic nephropathy in an animal model of type 2 diabetes.

Methods: Urate-accelerated diabetic db/db mice were administrated with novel C5a inhibitor, NOX-D21 (10 mg/kg, a kind gift from NOXXON) or an equal volume of saline for a total of 12 weeks. Non-diabetic db/m mice were used as control.

Results: In db/db mice, treatment with NOX-D21 for 12 days did not affect hyperglycemia, but significantly prevented the increase in serum creatinine and BUN levels. NOX-D21-treated mice had reduced glomerulosclerosis and tubular damage compared to the vehicle-treated diabetic mice. In addition, blockade of C5 signaling reduced the overexpression of TGF-β1, activation of Akt signaling and interstitial expression of fibronectin and collagen type I in the diabetic kidney. NOX-D21 also ameliorated lipid abnormalities in db/db mice, and resulted in significant decrease in serum triglycerides and expression of lipid metabolism-related genes (DAGT1 and SREBP1c) in the diabetic kidney.

Conclusions: Our findings suggest a pathogenic role of C5a in diabetic nephropathy, especially in regulating TGF-β1-mediated renal fibrosis. Inhibition of C5a signaling partially improves renal function and ameliorates dyslipidemia in diabetic animals. Funding: Hong Kong Society of Nephrology and Hong Kong Kidney Foundation Research Grant (2016).

TH-PO016

C-Terminal Oligomerization of Podocin Can Mediate Interallelic Complementation Exspter Balogh,1,4 Pal Straner,4 Gusztáv Schay,1,4 Cristelle Arrondel,5 Anila Begaj,6,7 Gerda Laume,6,8 Alexandre Benmerah,9 Andreas Perczel,10 Dora K. Menyhárd,11 Corinne Antignac,12 Geraldine Molié,13 Karlovich13 R.286Tfs*17 podocin lacking the C-terminal tail (CTT) and other podocin variants encoded by other CTT. Podocin variants containing the first helix (H1) of the CTT (273-313) dimerized, and those also containing the 332-348 region, oligomerized. Truncated podocin variants with an intact H1 were not dimerized or oligomerized. Dominant negative influence was exerted through the FDL344_346LTY amino acid changes encoded by the frameshift sequence.

Conclusions: Oligomerization of podocin is mediated exclusively by the CTT. Though oligomerization is not prerequisite for membrane-targeting, it may mediate not only a dominant negative effect between podocin variants, but also normalization of the localization, i.e. interallelic complementation. Such a complementation can also modify the pathogenicity of NPDR2 alleles.

Funding: Other NIH Support - MTA-SE Ladendult Research Grant (LP2015-11/2015) of the Hungarian Academy of Sciences, OTKA K109718, MedinProt Synergy grant (DKM, SP and TK), Eotvos Scholarship of the Hungarian State (KT) and by the French-Hungarian bilateral project (PHC 3401SM Balaton, Hungarian Grant No. TET_14_1-2015-0020).

TH-PO017

Complement Activation Is Not Required for MPO-ANCA Induced Pulmonary Granulomatosis in Mice

Hong Xiao, Peiqi Hu, Marco A. Alba, Ronald J. Falk, J. Charles Jennette, University of North Carolina at Chapel Hill, Chapel Hill, NC.

Background: We previously developed a animal model of human pauci-immune crescentic glomerulonephritis (CGN) caused by myeloperoxidase (MPO) specific antineutrophil cytoplasmic autoantibodies (MPO-ANCA) by i.v. injection of mice with antibodies specific for mouse MPO. The induction of CGN by injection of anti-MPO IgG required activation of the alternative complement pathway, and was prevented in deficient in complement factor B (CFB) or C5. We now have developed a model of ANCA pulmonary granulomatosis is caused by i.v. injection of anti-MPO IgG after intratracheal spray of lipopolysaccharide (LPS).

Methods: 9-11 wk-old B6 WT, CFB/- and C5-/- mice were treated with an intratracheal spray of LPS (5ug) at day 0, plus two doses of anti-MPO IgG, i.v. (75ug/g BW) at day 7 and day 14. Mice were sacrificed at day 7. Kidney and lung tissues were obtained for pathologic examination.

Results: With this regimen, all B6 WT mice (n=5) developed CGN (mean 20% glomeruli with crescents) and pulmonary necrotizing granulomatous lesions (mean scores = 2.6 out of 3). All CFB/- (n=3) and C5-/- (n=4) mice developed pulmonary necrotizing granulomatous lesions (mean scores = 3) but none developed CGN. Negative control WT mice that received LPS alone (n=6), and MPO-/- mice that received LPS and anti-MPO (n=3) did not develop no CGN or pulmonary granulomatosis.

Conclusions: Absence of CFB or C5 protects from anti-MPO induced CGN but not anti-MPO induced pulmonary granulomatosis, indicating complement activation is not required for ANCA induced pulmonary granulomatosis in mice. These interesting and potentially impactful observations suggest that although both necrotizing CGN and necrotizing pulmonary granulomatosis are caused by MPO-ANCA, the mediators are different, and, thus optimum therapy for the kidney disease may differ from optimum therapy for the lung disease. For example, although blockade of alternative pathway activation may be effective adjunct therapy for ANCA CGN, it may have no effect on ANCA pulmonary granulomatosis.

Funding: NIDDK Support

TH-PO018

The Role of Complement C9 as a Marker for Therapeutic C5 Blockade in Lupus Nephritis

Hannah R. Wilson,1 Alyssa C. Gilmore,2 Nicholas R. Medjeral-Thomas,2 Pritesh Trivedi,2 Kathleen I. Seyb,2 Ramin Farzaneh-Far,1 Tom Cairns,2 Liz Lightstone,2 Matthew C. Pickering,2 H. Terence Cook.2 1Ra Pharmaceuticals, Inc., Cambridge, MA; 2Imperial College Lupus Centre, Imperial College Healthcare NHS Trust, London, United Kingdom.

Background: Complement plays an important role in the pathogenesis of lupus nephritis (LN) and there are reports of therapeutic benefit with eculizumab, a C5 inhibitor. How LN can also develop in complement-deficient individuals. With the emergence of therapeutic C5 inhibition, there is a need to identify patients in whom complement-driven inflammation, attributable to C5a, C5b-9, or both, is a major cause of kidney injury in LN.

Methods: Clinical and histopathological data from 54 patients with class III, IV and V LN were obtained retrospectively. Staining for C9, C5b-9, C3c and CD68 was performed and intensity assessed. Response was defined using urine protein-creatinine ratio and estimated glomerular filtration rate.

Results: Staining for C9 was significantly different between C9 staining was detected in the mesangium of both active and chronic proliferative (class III and IV) LN in the majority of patients and in the capillary wall of class V LN in all patients. C9 staining intensity in the tubular basement membrane correlated with creatinine levels at the time of biopsy and with markers of tubulo-interstitial damage. C9 staining intensity did not correlate with C3c staining intensity or glomerular CD68 count. C9 staining also did not correlate with serological markers of activity, however C3c and CD68 staining did. Although not statistically significant, a low C9 staining intensity appears to indicate a greater chance of complete remission in active disease.

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

Underline represents presenting author.
Decay Accelerating Factor (DAF), Local Complement Inhibitor, Protects from Adriamycin (ADR)-Induced FSGS

Methods: We injected 20mg/kg Adr into B6 WT, and congenic DAF-/-, DAF-/-C3aR-/-, DAF-/-C3aR-/-, DAF-/-C3-/-, DAF-/-C3ar mice and DAF-/-C3-/-, DAF-/-C3ar mice, mechanistically implicating DAF-dependent restraint on complement activation and ensuing C3a/C3ar signaling in the disease process (Fig 1B). Using newly developed DAF conditional KOs, absent DAF from podocytes (DAF activation and ensuing C3a/C3aR signaling in the disease process (Fig 1A), DAF-deficiency-induced proteinuria correlated with higher histological scores (Fig 1C) and IF.

Results: A DAF-/-C3ar mice, mechanistically implicating DAF-dependent restraint on complement activation and ensuing C3a/C3ar signaling in the disease process (Fig 1B). Using newly developed DAF conditional KOs, absent DAF from podocytes (DAF activation and ensuing C3a/C3aR signaling in the disease process (Fig 1A), DAF-deficiency-induced proteinuria correlated with higher histological scores (Fig 1C) and IF.

Conclusions: Podocyte-expressed DAF mediates resistance to Adr-induced glomerular injury in B6 mice. In the absence of DAF, Adr-induced kidney injury is propagated by local C3a/C3ar signaling that likely contributes to PEC recruitment and glomerulosclerosis. Studies addressing a role for DAF/complement in human FSGS and related diseases are warranted.

An In Vitro Model of Idiopathic Membranous Nephropathy Reveals PLA2R- and Complement-Dependent Pathways of Podocyte Injury

Methods: PLA2R expression levels in conditionally immortalized human podocytes were modulated by infection with a lentivirus vector carrying FLAG-tagged full length human PLA2R or by siRNA-mediated knock down. These cells were then pretreated with sera from PLA2R-positive iMN patients or control sera and subsequently, human complement was added. Cell lysates were collected and analyzed by qPCR, Western blot, and IF.

Results: Podocytes overexpressing PLA2R treated with a high-titer (1:1000) PLA2R antibody positive sera and complement in sublytic concentration resulted in decrease synaptopodin and NEPH1 expression with a noticeable synaptopodin rearrangement. The complement sublytic effect on podocytes is likely to involve the activation of the lectin pathway and C3aR-I and C5aR-I signaling as knock down of these receptors rescued synaptopodin and NEPH1. Synaptopodin and NEPH1 degradation appeared to occur via two independent pathways involving E3 ligase and apoptosis, respectively.

Conclusions: Podocyte injury by iMN serum and sublytic complement includes synaptopodin and NEPH1 degradation. In addition, we have developed an in vitro assay to specifically assess the complement-dependent podocytopathic effect of iMN sera that will allow to screen for protective compounds.

Calcineurin Inhibitor-Induced Endothelial Cell Injury – A Role for Complement

Results: The sequence of CsA incubation and 50% NHS resulted in a dose and time-dependent enhancement of EC complement deposition and EC death, exacerbated by serum starvation and sensitization with anti-CDS9 antibody. An optimal balance of EC survival and CNI effect was obtained with CsA 10 mcg/ml for 48 hours. CsA led to upregulation of CD46, CD55 and CD59 on EC surface. CsA diminished the EC glycoscalyx with subsequent decreased CFH surface binding and surface cofactor activity. In further support of our in vitro findings, MCP-deficient BOECs exposed to CsA had significantly higher surface complement deposition compared to healthy controls.

Conclusions: Our findings suggest a role for complement-mediated EC injury induced by CsA, with CFH surface dysregulation playing a key role in CsA-induced complement activation on EC surfaces. MCP-deficient BOECs were genetically predisposed to be more susceptible to CsA-induced endothelial complement depletion. CsA-induced abolishment of EC glycoscalyx may be the key mechanism leading to alternative pathway dysregulation, and warrants further studies.

The Rs6677604 in Complement Factor H Is Associated with Long Term Graft Function in Transplant Recipients with IGA Nephropathy

Methods: 128 patients with a biopsy-proven diagnosis of IGA nephropathy (IgAN). IgAN has a negative outcome on renal transplantation. We tested the role of CFHR3-1Δ and CFHR3-2 polymorphisms in African Americans who received a kidney transplant assessing the impact on long-term graft survival.

Results: Of 67 patients, 22 (32.8%) had the rs6677604 AG genotype and 45 (67.2%) the rs6677604 GG genotype. These two groups were comparable in terms of demographic characteristics, donor features and transplant-related factors such as the occurrence of delayed graft function, episodes of acute rejection and therapeutic regimen. No difference was found when we analyzed the progression of the disease before the
transplant. However, we observed a significantly worse outcome of the graft in patients with ACKR1 deficiency compared to by univariate survival analysis (P=5.8E-05) during the follow-up (69 ± 62 months). A multivariate Cox survival analysis revealed that the rs6676704-GG genotype (HR 30.8; 95% CI 3.3-285.5; P=0.003) is the strongest independent predictor for the graft outcome in a model adjusted for age, gender, delayed graft function, acute rejection, HLA match and donor specific antibodies.

Conclusions: Our study suggests a major impact of CFIHR3-1a on long term graft function in kidney transplant recipients with IgAN and that rs6676704 typing can be used to predict the outcome in these patients.

TH-PO024
IL-17C/IL-17 receptor E Signaling in CD4+ T Cells Is Required to Promote TH17 Cell-Driven Glomerular Inflammation
1Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; 2University Hospital Hamburg, Hamburg, Germany; 3University of Hamburg, Hamburg, Germany; 4University Medical Center Hamburg-Eppendorf, Hamburg, Germany; 5University of Hamburg, Hamburg, Germany; 6Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; 7University: Group/Team: Panzer Lab.

Background: The IL-17 cytokine family (IL-17A-F) and their cognate receptors (IL-17RA-RE) play a unique role in organ-specific autoimmunity. So far, most studies focused on the IL-17 founding member, IL-17A, as the critical mediator of diseases. The specific function of the other IL-17 family members in immunity and inflammatory diseases is largely unclear. The aim of our study was to examine the potential role of these cytokines in human and experimental immune-mediated glomerular diseases.

Methods: Serum IL-17A/E/F levels of 70 patients with acute ANCA-associated crescentic GN (biopsy proven) and 20 healthy control subjects were analyzed by multiplex technology (Meso Scale Discovery). The function of IL-17 cytokines and their receptors was assessed in experimental models of glomerulonephritis.

Results: Serum IL-17C levels were significantly elevated in patients with acute ANCA-associated crescentic GN compared to healthy controls (p = 0.001). In contrast, no significant differences in serum IL-17A/E/F levels were detected between patient groups and controls. Using mouse models of crescentic GN (NTN) and pristane induced lupus nephritis, we showed that the lack of IL-17C and its unique receptor IL-17RE significantly ameliorated the course of the GN in terms of renal tissue injury and kidney function. Interventional studies using an anti-IL-17A neutralizing antibody demonstrated that this protective effect was due to a reduced Th17 response in IL-17C and IL-17RE gene-deficient mice. GN induction in bone marrow chimeric mice lacking IL-17C in either hematopoietic or tissue cells revealed that systemic and renal IL-17C is expressed by tissue resident cells and not by lymphocytes. Finally, we demonstrated that IL-17RE was predominantly expressed by CD4+ Th17 cells and that this expression is instrumental for the induction / maintenance of the Th17 responses with subsequent tissue injury in crescentic GN.

Conclusions: Our findings indicate that IL-17C promotes Th17 cell responses and autoimmune kidney disease via IL-17E signaling on CD4+ Th17 cells. Targeting the IL-17C/IL-17RE pathway may present an intriguing therapeutic strategy for Th17 driven autoimmune diseases.

Funding: Government Support - Non-U.S.

TH-PO025
Amphiregulin Aggravates Glomerulonephritis via Recruitment and Activation of Myoid Cells Simon Melderis, Georg R. Herrstadt, Anna Nosko, Gisela Stieg, Oliver M. Steinmetz, III. Medical Clinic, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; Institute of Experimental Immunology and Hepatology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

Background: Amphiregulin (AREG), a member of the epidermal growth factor family, plays a role in development and tumorigenesis. Recently AREG has also emerged as novel player in immune responses. Both, pro- and anti-inflammatory functions have been attributed, leaving the role of AREG in immune disorders widely unclear. In particular, nothing is known about the role of AREG in glomerulonephritis (GN). Given that EGF-receptor directed therapies have recently become available, we aimed to clarify the function of AREG in an experimental model of crescentic GN.

Methods: Nephrotic nephritis (NTN) was induced in AREG-KO mice and wild type controls. Time course and tissue specific AREG expression was assessed. Renal histology, function and leukocyte influx were analyzed. Broad analyses of renal and systemic immune responses were performed.

Results: Renal AREG expression was undetectable under homeostatic conditions. After induction of NTN AREG mRNA levels increased within the first 5 days and peaked at day 7. Expression subsequently decreased to baseline levels at day 20. In contrast, splenic expression remained below detection level at all time points. Importantly, the crescentic GN was significantly attenuated in AREG-KO mice in terms of kidney function, albuminuria and histological damage. In search of a potential mechanism, we found reduced renal expression of the pro-inflammatory cytokine IL-1β, the macrophage attracting chemokine monocyte chemotactic protein 1 (MCP-1), as well as granulocyte activating CXC-chemokine ligand 1 (CXCCL1) and 5 (CXCCL5). As a consequence, renal infiltration of macrophages and neutrophils was significantly impaired in AREG-KO mice. Furthermore, characterization of renal macrophage markers revealed a less inflammatory phenotype in the absence of AREG.

Conclusions: Our data strongly suggest that AREG has pro-inflammatory effects in acute GN. As one mechanism, we hypothesize, that AREG induces renal chemokine expression. This in turn results in enhanced recruitment and activation of inflammatory myeloid cells. AREG is thus a potential new therapeutic target for crescentic GN.

Funding: Government Support - Non-U.S.

TH-PO026
Erythroid ACKR1 Expression Has Profound Impact on the Development of Experimental Glomerulonephritis
1Medical University of Graz, Graz, Austria; 2University of York, York, United Kingdom; 3Queen Elizabeth University Hospital, Glasgow, United Kingdom.

Background: The majority of individuals of West African ancestry carry a polymorphic “erythroid silent” FyB(ES) variant of ACKR1. Individuals with FyB(ES) express ACKR1 on endothelial cells but not on erythroid cells. The FyB(ES) polymorphism is of special interest for understanding human kidney disease as the individuals of West African ancestry have higher incidence of chronic kidney diseases. Moreover, chemokine ligands of ACKR1 are involved in driving the inflammatory pathology in the experimental model of nephrotic serum nephritis (NTS).

Methods: We developed humanized transgenic mouse strains, which do not express mouse ACKR1, but instead either West African Fy(ES) or Caucasian FyB polymorphic ACKR1 variants. These strains as well as ACKR1-deficient and WT mice were subjected to NTS, a murine model of immune complex glomerulonephritis. The parameters of immunopathogenesis and kidney phenotype were evaluated after 14 days.

Results: Albuminuria, PAS and tubular injury scores were significantly increased in FyB(ES)tg and ACKR1-deficient mice as compared to their respective control strains. While monocytes were unchanged in peripheral blood, we found significantly increased numbers of macrophages and neutrophils infiltrating the kidneys of FyB(ES)tg and ACKR1-deficient mice. Interestingly, T cell numbers in the draining lymph nodes were comparable between FyB(ES)tg and ACKR1-deficient mice and their respective controls.

Conclusions: We found that NTS was more severe in ACKR1-deficient and FyB(ES) mice as compared to their respective controls. Our results show that ACKR1 expression in the erythroid compartment has a significant impact on the development of experimental glomerulonephritis. These findings are of special interest for understanding the role of ACKR1 in the immunopathogenesis of glomerulonephritis in individuals of West African ancestry who lack ACKR1 selectively in the erythroid lineage.

TH-PO027
Upregulation of Matrix Metalloproteinase-10 in Glomerular Cells and Macrophages by Inflammation Keisuke Osaki, Yukiko Kato, Naohiro Toda, Akira Ishii, Keita P. Mori, Shoko Ohno, Kiyoshi Mori, Moin Saleem, Taiji Matsusaka, Masashi Mukoyama, Motoko Yanagita, Hideki Yokoi, Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan; 2Kyoto University Graduate School of Medicine, Kyoto, Japan; 3Tokai University, Tokyo, Japan; 4School of Pharmaceut Sci, University of Shizuoka, Shizuoka, Japan; 5Tokai University School of Medicine, Isehara, Japan; 6University of Bristol, Bristol, United Kingdom.

Background: Recently, we and others have unveiled the novel renal function of natriuretic peptide receptor/guanylyl cyclase-A (GC-A) system on antagonizing aldosterone-induced podocyte injury as well as the conventional effects on natriuresis and reducing blood pressure. High salt-fed systemic or podocyte-specific GC-A knockout mice with aldosterone and uninephrectomy showed accelerated glomerular injury with massive albuminuria. However, genes involved in glomerular injury are elusive. We identified matrix metalloproteinase-10 as a key player in the development of glomerular injury.

Methods: We analyzed gene expression in the glomeruli of systemic GC-A knockout mice and wild-type mice with aldosterone and examined gene expression by glomerular cells and macrophages using multiplex technology (Meso Scale Discovery) for an identified protein.

Results: We identified matrix metalloproteinase-10 (MMP-10) in glomeruli of aldosterone-induced podocyte injury as well as the conventional effects on natriuresis and reducing blood pressure. High salt-fed systemic or podocyte-specific GC-A knockout mice with aldosterone and uninephrectomy showed accelerated glomerular injury with massive albuminuria. However, genes involved in glomerular injury are elusive. We performed immunohistochemical analysis for an identified protein.

Results: We identified matrix metalloproteinase-10 (MMP-10) in glomeruli of aldosterone-induced podocyte injury as well as the conventional effects on natriuresis and reducing blood pressure. High salt-fed systemic or podocyte-specific GC-A knockout mice with aldosterone and uninephrectomy showed accelerated glomerular injury with massive albuminuria. However, genes involved in glomerular injury are elusive. We performed immunohistochemical analysis for an identified protein.

Results: We identified matrix metalloproteinase-10 (MMP-10) in glomeruli of aldosterone-induced podocyte injury as well as the conventional effects on natriuresis and reducing blood pressure. High salt-fed systemic or podocyte-specific GC-A knockout mice with aldosterone and uninephrectomy showed accelerated glomerular injury with massive albuminuria. However, genes involved in glomerular injury are elusive. We performed immunohistochemical analysis for an identified protein.

Results: We identified matrix metalloproteinase-10 (MMP-10) in glomeruli of aldosterone-induced podocyte injury as well as the conventional effects on natriuresis and reducing blood pressure. High salt-fed systemic or podocyte-specific GC-A knockout mice with aldosterone and uninephrectomy showed accelerated glomerular injury with massive albuminuria. However, genes involved in glomerular injury are elusive. We performed immunohistochemical analysis for an identified protein.
Absence of RORyt+ Foxp3+ biTregs Aggravates Glomerulonephritis Disease

Methods: MHC II and costimulatory marker expression in wild type (WT) and RORyt knockout (KO) podocytes was characterized at baseline and after stimulation with IFNg using flow cytometry. We compared antigen presentation in WT and RORyt KO podocytes using an in vitro antigen presentation assay. We created a podocyte-specific Foxp3 KO mouse and examined albuminuria, renal pathology, intraglomerular neutrophil accumulation, and C3 deposition after induction of anti-glomerular basement membrane (anti-GBM) nephritis. Fluorescence lifetime imaging (FLIM) was used to examine metabolic changes in the glomeruli of KO and control mice after induction of nephritis.

Results: We found that treatment with IFNg upregulated MHC II expression in both WT and RORyt KO podocytes. At baseline, WT podocytes expressed significantly more CD80 than RORyt KO podocytes and there was no increase in CD80 expression in the KO after treatment with IFNg. Neither WT nor KO podocytes expressed CD86 at baseline or after treatment with IFNg. When treated with immune complexes in an in vitro antigen presentation assay, WT podocytes induced a very modest increase in T-cell IL-2 production whereas KO podocytes did not stimulate T cells at all. There was no difference in BUN, albuminuria, intraglomerular neutrophil infiltration, C3 deposition, glomerulosclerosis score, or percent crescents in control versus podocyte-specific Foxp3 KO mice after induction of anti-GBM disease. FLIM demonstrated a decreased shift in glycosylation in KO mice compared to control after disease induction.

Conclusions: This study demonstrates that podocytes are inefficient antigen presenting cells and podocyte specific KO of Foxp3 does not prevent induction of anti-GBM disease.

Funding: NIDDK Support

Inhibition of the TLR4/NF-κB Axis Attenuated Glomerular Inflammation and Injury in Long Term Experimental Diabetic Kidney Disease

Background: The TLR4/NF-κB pathway regulates the transcription of inflammatory interleukin genes. There is evidence that activation of this innate immune pathway is involved in the development of diabetic kidney disease (DKD). We investigated whether NF-κB inhibition with pyrrolidinedithiocarbamate (PDTC) exerts long term renoprotection in experimental DKD.

Methods: Diabetes (DM) was induced in 27 Munich-Wistar rats by a single streptozocin injection (65 mg/kg). Blood glucose (BG) was kept between 300 and 400 mg/dL with daily NPH insulin. Rats were divided into Groups (untreated) and DM+PDTC (receiving PDTC, 60 mg/kg/day vo). Untreated nondiabetic rats (C, n=12) were also studied. After 12 months, we assessed: urinary albumin/creatinine (AUC) ratio, kidney/body weight (K/BW); glomerular sclerosis (GS, %); glomerular zonula occludens-1 (gZO-1, %); glomerular macrophage infiltration (gMφ, cells/mm²); glomerular TLR4, IL-1β and NLRP3 positive staining (%), renal content of heme oxygenase-1 (HO-1) and nuclear p65 (NF-κB) (fold change).

Results: After 12 months, the untreated DM group exhibited high Ualb/Ucr, renal hypertrophy, high GS, loss of gZO-1, and more intense gMφ. In contrast, treatment with PDTC prevented the increase in AUC, reduced kidney/body weight (K/BW), and preserved glomerular structure, and reduced gZO-1 content.

Conclusions: These findings suggest a specific involvement of the TLR4/NF-κB axis in the pathogenesis of DKD and the possibility that this signaling pathway becomes a therapeutic target.

Funding: CNPq
TH-PO032
Glomerular Mechanical Tension Promotes Activation of the NLRP3 Inflammasome Pathway in Experimental Diabetic Kidney Disease: Role of Podocytes
Simone C. Arias, Mathews T. Yellosa, Viviane D. Faustino, Victor F. Avila, Luciene dos Reis, Denise M. Malheiros, Niels O. Camara, Clarice K. Fujihara, Roberto Zatz. Univ of Sao Paulo, Sao Paulo, Brazil.

Background: We showed previously (ASN 2016) that in the 5/6 ablation the estimated glomerular capillary mechanical tension (GCMT) was increased along with activation of the TLR4/NLRP3/CASP1/IL-1 innate immunity (InIm) axis, helping to explain the link between hemodynamic insult and glomerular inflammation. Here we investigated whether such effect of cell agglutination may mediate in streptozotocin diabetes mellitus (DM), and the possible role of podocytes in this response.

Methods: We analyzed retrospectively, by immunohistochemistry, renal tissue from male Munich-Wistar rats divided into Control (C), Uninephrectomy (UNx) and UNx+DM groups. Mean arterial pressure (MAP, mmHg) was measured 60 days after induction, whereas GCMT (mmHg/gram) was estimated from glomerular pressures and mean glomerular radii. Glomerular infiltration by macrophages (MΦ, cells/mm²) was also assessed. The protein content of TR4, NLRP3, CASP1, and IL-1β was evaluated in DM glomeruli (% area), as well as in cultured murine podocytes in the presence or absence of 15% stretching.

Results: In UNx, MAP was elevated without change in GCMT or InIm components. In UNx+DM, hypertension was associated with increased GCMT, MΦ and InIm components, whereas a positive correlation was observed between NLRP3 and IL-1β mean glomerular radii. Glomerular infiltration by macrophages (MΦ, cells/mm²) was also assessed. The protein content of TR4, NLRP3, CASP1, and IL-1β was evaluated in DM glomeruli (% area), as well as in cultured murine podocytes in the presence or absence of 15% stretching.

Conclusions: In UNx activation may mediate the inflammatory effects of GCMT, thus participating in the initiation and perpetuation of progressive glomerular injury in both diabetic and non-diabetic kidney disease. FAPESP/CNPq.

Funding: Government Support - Non-U.S.

TH-PO033
RNA-Seq Profiling of Microdissected Glomeruli in Clinically Early IgA Nephropathy
Sehoon Kim,2 Yon Su Kim,1 Seung Hee Yang,2 Dong Ki Kim,3 Yon Su Kim,2 Hajeong Lee4. 'National Cancer Center; Seoul, Republic of Korea; 2Seoul National University Boramae Medical Center, Seoul, Republic of Korea; 3Seoul National University College of Medicine, Seoul, Republic of Korea; 4Seoul National University Hospital, Seoul, Republic of Korea.

Background: IgA nephropathy (IgAN) is the most common primary glomerular disease worldwide and also a leading cause of chronic kidney disease and renal failure. Although recent studies have shed light on genetic variants associated with IgAN, transcriptional changes in the glomerulus and their relevance to the pathophysiology of IgAN have been poorly defined. To identify early gene-expression changes in IgAN, we profiled the transcriptome in microdissected human glomeruli using deep sequencing of RNA species (RNA-seq).

Methods: Glomeruli were microdissected from the biopsy specimen obtained from 6 IgAN patients with preserved renal function (eGFR > 60 mL/min/1.73m² and proteinuria < 1 g/d). As negative controls, normal glomeruli were obtained from patients undergoing nephrectomy (n=3). Glomerular mRNAs were captured using oligo-dT primers and made into cDNA libraries for Illumina sequencing. After mapping to the human reference genome (GRCh38/p15 assembly), reads mapping to Ensembl genes were counted. Wald test for a negative binomial model was used to call differentially expressed genes.

Results: Each library produced 29-43 million pairs of reads, more than 70% of which were uniquely aligned to the human genome. Of 17,833 Ensembl genes with >10 reads, 285 were upregulated and 434 downregulated in the IgAN glomeruli. Downregulated genes included transcription factors (FOS, FOSB, ZFP36, EGR1, ATF3, JUNB, NRRAAZ, JUN, SKI, POSUIF1, KLF9, KLF8, KLF4, CTNNB1, DMTF1, and CREBBP), peristin (POSTN), cytoskeletal proteins (MYO15A and TPM2), and C-X-C motif chemokine ligand 2 (CXCL2). Among upregulated genes were integrin subunits (ITGA5, ITGA6, ITGB4, and ITGB5), histone deacetylase (HDAC5), adenylyl cyclase 7 (ADCY7), cyclin D2 (CCND2), homeobox D1 (HOXD1), and interleukin-6 receptor (IL6R). None of the genes positively correlated in the GWAS studies on IgAN have been found to be differentially expressed in our dataset.

Conclusions: In human glomeruli obtained from patients with clinically early IgAN, RNA-seq revealed altered expression of DNA-binding transcription factors, cytoskeletal proteins, and integrin subunits that are potentially important for maintaining the integrity of the glomerular filtration barrier.

TH-PO034
Fecal Microbiome Profiles and Pathogenesis of IgA Nephropathy
Hyunjeong Cho,1 Hajeong Lee,2 Dong Ki Kim,3 Seung Hee Yang,2 Jung Pyo Lee,1 4 Kangwon National University Hospital, Chuncheon-si, Republic of Korea; 2Kidney Research Institute, Seoul National University, Seoul, Republic of Korea; 3Seoul National University Boramae Medical Center, Seoul, Republic of Korea; 4Seoul National University College of Medicine, Seoul, Republic of Korea; 5Seoul National University Hospital, Seoul, Republic of Korea.

Background: Mucosal immune system plays a role in pathogenesis of Immunoglobulin A nephropathy (IgAN); however, little has been known about the relationship between IgAN and the intestinal microbiome.

Methods: We prospectively enrolled 30 biopsy-proven IgAN patients at 3 centers and collected fecal specimens at the time of renal biopsy. Feces from thirty healthy volunteers were used as control. The composition of microbiota was analyzed using extracted metagenomic DNA from the feces by Illumina MiSeq system. Downstream analyses were performed using SPSS, Phylogenetic reconstruction of unobserved states (PICRUSt), and Linear discriminant analysis effect size (LEfSe).

Results: The age, sex, and BMI were comparable between the groups. The fecal microbiota of both IgAN and control group were dominated by two bacterial phyla, Firmicutes and Bacteroidetes. Compared to control group, fecal microbiota of IgAN patients showed significantly lower OTUs and Shannon diversity index. The relative abundances of Firmicutes and Acinetobacteria were higher, whereas those of Bacteroidetes and Proteobacteria were lower in IgAN patients than healthy subjects. At Genus level, the abundances of Blautia were higher and those of Bacteroidetes, Prevotella, and Escherichia were lower in the fecal specimens from IgA nephropathy patients compared to healthy subjects. PICRUSt analysis showed that genes involved in galactose metabolism were enriched in IgAN while those responsible for glycosyltransferases were significantly associated with the controls. By dividing patients on the basis of 3 g/day proteinuria, bacterial diversity was significantly lower in severe group compared to less severe group.

Conclusions: The fecal microbiota of IgAN patients differed from those of control group. We also showed that microbial difference was possibly related to galactose metabolism or glycosyltransferases. Such differences might be related with pathogenesis of IgAN.

TH-PO035
Dysregulation of Mucosal Immune Response in IgA Nephropathy
Toshiaki Kan, Hitoshi Suzuki, Yuko Makita, Yoshito Nihei, Yusuke Suzuki. Nephrology, Juntendo University Faculty of Medicine, Tokyo, Japan.

Background: IgA nephropathy (IgAN) is associated with dysregulation of mucosal immune system, which manifests as mesangial IgA deposition leading renal impairment. However, it is not clear which gut-associated lymphatic tissue (GALT) or nasal-associated lymphoid tissue (NALT) is more involved in the pathogenesis of IgAN. Indeed, the origin of nephritogenic IgA has been obscure. Several studies demonstrated the efficacy of tonsillectomy and corticosteroid therapy, whereas recent NEFIGAN study suggested that the novel targeted-release formulation of budesonide targeting intestinal mucosal immunity reduced proteinuria in IgAN patients. In present study, we focused on the role of GALT in murine IgAN using IgAN-prone “ddY mice”.

Methods: Mesenteric lymph node (MLN) is considered to be a key function of GALT in murine. Levels of aberrantly glycosylated IgA and IgA-IgG immune complexes (IC) in serum and supernatant from cultured MLN and splenocytes were measured using IgAN onset and quiescent ddY mice (each n=15). Level of aberrantly glycosylated IgA was measured by the binding of Sambucus nigra bark lectin and Ricinus communis agglutinin 1.

Results: Serum levels of aberrantly glycosylated IgA and IgA-IgG IC in IgAN onset ddY mice were significantly higher than those in quiescent ddY mice (P<0.01). However, there were no significant differences in the levels of aberrantly glycosylated IgA and IgA-IgG IC produced by MLN between IgAN onset and quiescent mice. Serum levels of aberrantly glycosylated IgA and IgA-IgG IC correlated with those in culture supernatant of splenocytes (P<0.05). However, the sugar component of IgA produced by MLN was different from those in circulation in IgAN onset ddY mice. Furthermore, serum IgA-IgG IC was not associated with those levels produced by cultured MLN.

Conclusions: Serum levels of aberrantly glycosylated IgA and IgA-IgG IC elevated in IgAN onset ddY mice. Glycosylation pattern of circulating IgA was different from those originated from GALT. Therefore, IgA originated from GALT did not form immune complexes with IgG. Present study suggested that the GALT may not be involved in the pathogenesis of murine IgAN.

Funding: Government Support - Non-U.S.
Tonsillar Microbiome in IgA Nephropathy: Methods: We prospectively enrolled 29 biopsy-proven IgAN patients at 3 centers and collected tonsillar swabs at the time of renal biopsy. Tonsillar swabs from 29 healthy volunteers who visited hospital for a medical check-up were used as control. The composition of microbiota was analyzed using extracted metagenomic DNA from the tonsil swabs by Illumina MiSeq system. Downstream analyses were performed using SPSS, Phylogenetic reconstruction of unobserved states (PICRUSt), and Linear discriminant analysis Effect Size (LEfSe).

Results: The mean age was 32.4 and 42.9 in control group and IgAN patients group, respectively. Though the age was significantly different between the groups, there was no trend or clustering according to the age groups. Compared to control group, tonsillar microbiota of IgAN patients showed significantly higher Shannon diversity index. The relative abundances of Firmicutes and Bacteroidetes were higher, whereas those of Proteobacteria were lower in IgAN patients than healthy subjects. At Genus level, relative abundances of Gramicidae were higher, whereas those of Acinetobacter and Veillonella were significantly lower in the tonsil specimens from IgAN patients compared to healthy subjects. PICRUSt analysis showed that genes involved in galactose metabolism were enriched in IgAN. By dividing patients on the basis of 3 g/day proteinuria, we tried to control for confounders, enhanced transcript level of CD71 was significantly associated with a higher transcript level of CD71.

Conclusions: The tonsillar microbiota of IgAN patients differed from those of control group although it was not associated with disease severity. In addition, these differences showed possible relation with galactose metabolism which was involved in pathogenesis of IgAN.

Racial Comparison of IgA1 Hinge-Region O-Glycoryms by High-Resolution Mass Spectrometry: Background: Mucosal immune system plays a role in pathogenesis of Immunoglobulin A nephropathy (IgAN); however, little has been known about the relationship between IgAN and the microbiome reside in tonsil.

Methods: Human serum IgA1 was purified by affinity chromatography. After neuraminidase treatment and trypsin digestion, IgA1 O-glycans were identified by electron transfer dissociation (ETD) tandem MS after selective release of galactoslyated O-glycans.

Results: Serum IgA1 O-glycans were determined in 50 healthy subjects recruited by affinity chromatography. After neuraminidase treatment and trypsin digestion, IgA1 O-glycan HR heterogeneity was analyzed by liquid chromatography-high-resolution mass spectrometry (LC-MS). To increase the throughput of the analysis, we developed an in-house automated program, Glycan Analyzer. The attached site(s) of the Gal-deficient O-glycan chain(s) were identified by electron transfer dissociation (ETD) tandem MS after selective release of galactoslyated O-glycans.

Conclusions: Despite high susceptibility to IgAN in Asians, O-glycans were lower in Asian, including Japanese subjects. His20[Arg18]HR was present in 12 different glycans with 3-6 O-glycans. Approximately 58% of HR O-glycans contained one to three Gal-deficient O-glycans in IgA1 samples from the subjects of all races. ETD tandem MS revealed that Gal-deficient O-glycans were consequently observed at specific site(s), which was dependent on both species and glycans.

IgA Nephropathy Patients B Cells Producing IgA Exhibit High Epstein-Barr Virus Infection Rate in Comparison to Disease and Healthy Controls: Methods: Serum Gd-IgA1 levels were determined in 50 healthy subjects recruited by ELISA using novel monoclonal antibody specific for Gd-IgA1 (35A12, Tomiyama Laboratory Co. Ltd., Tokyo, Japan). Human serum IgA1 was purified by affinity chromatography. After neuraminidase treatment and trypsin digestion, IgA1 O-glycans were identified by electron transfer dissociation (ETD) tandem MS after selective release of galactoslyated O-glycans.

Results: Serum Gd-IgA1 levels were determined in 50 healthy subjects recruited from Africa, Atlantic, Asian, and Japanese. Gd-IgA1 levels were lower in Asians, including Japanese subjects. His20[Arg18]HR was present in 12 different glycans with 3-6 O-glycans. Approximately 58% of HR O-glycans contained one to three Gal-deficient O-glycans in IgA1 samples from the subjects of all races. ETD tandem MS revealed that Gal-deficient O-glycans were consequently observed at specific site(s), which was dependent on both species and glycans.

Conclusions: Despite high susceptibility to IgAN in Asians, Gd-IgA1 levels were lower in Asian, including Japanese subjects. His20[Arg18]HR was present in 12 different glycans with 3-6 O-glycans. Approximately 58% of HR O-glycans contained one to three Gal-deficient O-glycans in IgA1 samples from the subjects of all races. ETD tandem MS revealed that Gal-deficient O-glycans were consequently observed at specific site(s), which was dependent on both species and glycans.

Funding: Government Support - Non-U.S.
Results: We studied peripheral B-cells in 16 IgAN patients, and 15 HC, in the steady state. Increased numbers of IgA plasma cells (88 per 1000 activated B-cells) were detected in the peripheral blood of IgAN patients compared to HC (20 per 1000 activated B-cells), correlating with increased levels of IgA and IgA1 detected in the plasma. Following in vitro stimulation, IgA cells from IgAN patients have a greater proliferative capacity compared to HC. We next asked if the increased number of peripheral IgA B-cells in IgAN patients arose by monoclonal or polyclonal expansion. We used NGS to sequence the immunoglobulin repertoire to determine if there were differences in usage of immunoglobulin heavy chain variable (V), heavy chain joining (J), kappa and lambda germline segments in the heavy chain and kappa light chain genes. These data did not show a monoclonal expansion of IgA B-cells. Future studies will be directed towards identification of intrinsic and extrinsic regulatory factors leading to globally enhanced proliferative potential in IgA plasma cells.

Funding: NIDDK Support

TH-PO041

TLR9 Activation Induces Overproduction of Aberrantly Glycosylated IgA through the APRIL Mediated Pathway in IgA Nephropathy

Yuko Makita,1 Hitoshi Suzuki,1 Yoshihito Nihei,1 Bruce A. Julian,2 Jan Novak,1 Yuji Komatsu,2 Masahiko Ikeda,2 University of Florida, Gainesville, Florida, USA;1 University of Tennessee Health Science Center, Memphis, Tennessee, USA;2 University of Alabama at Birmingham, Birmingham, AL, USA

Background: Involvement of Toll-like receptor 9 (TLR9) that play a key role in the innate immune system has been discussed in the pathogenesis of IgA nephropathy (IgAN). There are increasing evidences that galactose-deficient IgA1 (Gd-IgA1) and Gd-IgA1 containing immune complexes (ICs) have critical roles in the pathogenesis of IgAN. We recently demonstrated that interleukin-6 (IL-6) can enhance the production of Gd-IgA1 by IgA1-producing cells. Moreover, a proliferation-inducing ligand (APRIL) may be involved in the overproduction of the nephritogenic IgA1. However, the mechanisms leading to overproduction of Gd-IgA1 and subsequent formation of Gd-IgA1 containing ICs are still unclear.

Methods: IgAN prone ddY mice were divided into two groups with Cpg-ODN (TLR9 ligand) immunization (n=19) or without (n=19). Cpg-ODN was injected intraperitoneally 3 times a week for 12 weeks. Renal pathology and serum levels of aberrantly glycosylated IgA (Gd-IgA), IgG-IgA ICs, IL-6 and APRIL were evaluated after 12 weeks. We also examined the mechanisms of production of Gd-IgA1 in human IgA1-secreting cells through TLR9 activation and stimulation with IL-6 and APRIL.

Results: Mice immunized with Cpg-ODN, but not non-immunized mice, showed mesangisiproliferative glomerulonephritis accompanied by mesangial deposition of IgA, and C3. Immunization with Cpg-ODN elevated serum levels of Gd-IgA, IgG-IgA IC and APRIL (P<0.05). Serum levels of APRIL significantly correlated with serum level of Gd-IgA and IgG-IgA IC (P<0.05). The activation of TLR9 induced production of IL-6, and IL-6 stimulation induced overexpression of APRIL in splenocytes. Moreover, in human IgA1-secreting cells, TLR9 activation induced Gd-IgA1 production, while overexpressions of IL-6 and APRIL. Production of Gd-IgA1 was reduced by anti-IL-6 and/or siRNA for APRIL. However, anti-IL-6 could not inhibit overproduction of APRIL completely.

Conclusions: TLR9 activation exacerbated murine IgAN by enhancing production of aberrantly glycosylated IgA and nephritogenic ICs. TLR9 activation induced overproduction of IL-6 and APRIL. Present study suggested that TLR9-induced overproduction of both IL-6 and APRIL resulted in enhancing production of Gd-IgA1 and subsequent formation of Gd-IgA1 containing ICs in IgAN.

Funding: Government Support - Non-U.S.

TH-PO042

O-Glycan Profiling of High Molecular Weight Forms of IgA1 in Archival Plasma Samples from IgAN Patients and Controls

Oliver Ludwing,1 Candace D. Henderson, Caroline J. Poulton, Patrick H. Nachman,1 UNC Kidney Center, Chapel Hill, NC, USA

Background: IgA nephropathy (IgAN) is the most common form of glomerulonephritis worldwide. The hallmark of the disease is deposition of IgA1 in the mesangium. These deposited IgA1 are mainly polymeric in nature. Serum polymeric forms of IgA1 are diverse and may include homodimeric IgA1, homodimeric secretory IgA, and heparin-like and heparin-like complexes of IgA1 covalently bound to other plasma proteins. Abnormalities in O-glycosylation of circulating IgA1, resulting in increased Tn antigen, are hypothesized to be involved in IgAN pathogenesis, and O-glycan structures of monomeric and homodimeric form of IgA1 have been described in great detail. However, so far, very little information is available concerning the O-glycosylation patterns of heterodimeric and other polymeric forms of IgA1 present in the circulation of IgAN patients.

Methods: IgAs were affinity purified from serum samples from 16 patients with IgAN and 16 control subjects. Various molecular forms of IgA1 were size-separated by size-exclusion chromatography and then transferred to nitrocellulose membranes for Western blotting. IgA-containing bands were in-gel digested with trypsin, and the released glycopeptides were analyzed by electrospray/tandem mass spectrometry (ESI-MS/MS).

Results: Approximately 25% of IgA1 in archival samples from IgAN patients and controls was found as high molecular mass complexes linked through disulfide bonds. Immunoblots demonstrating similar intensities between IgA1 and albumin, alpha-2-macroglobulin, and C3. Quantitative analysis of O-linked glycosylation showed no significant differences in glycan composition between different types of circulating IgA1 complexes and no significant difference between glycan composition of IgA1 complexes from IgAN patients and from healthy controls.

Conclusions: We demonstrated that naive human IgA1-secreting cells, TLR9 activation enhanced Gd-IgA1 production through IL-6 and APRIL (P<0.05). Serum levels of APRIL significantly correlated with serum level of Gd-IgA1 and C3. Immunization with CpG-ODN elevated serum levels of Gd-IgA, IgG-IgA IC containing immune complexes (ICs) have critical roles in the pathogenesis of IgAN. We recently demonstrated that interleukin-6 (IL-6) can enhance the production of Gd-IgA1 by IgA1-producing cells. Moreover, a proliferation-inducing ligand (APRIL) may be involved in the overproduction of the nephritogenic IgA1. However, the mechanisms leading to overproduction of Gd-IgA1 and subsequent formation of Gd-IgA1 containing ICs are still unclear.
two monomers to effectively neutralize oligomeric APRIL, the biologically relevant form of IgA, and confirmed our rationale for targeting it for the treatment of IgAN.

Results: Treatment of NHP with VIS649 resulted in significantly lower serum levels of IgA (up to 70%) and IgG (~40%), and minimal modulation of serum IgM levels. The VIS649 administration was described with an indirect response model. A population pharmacokinetic/pharmacodynamic (popPK/PD) model was developed. Temporal changes in IgA concentration following VIS649 administration was described with an indirect response model.

Conclusion: Targeting APRIL for the Treatment of IgA Nephropathy

Preclinical Safety Profile of VIS649, a First-in-Class Humanized IgG2 Targeting APRIL for the Treatment of IgA Nephropathy

Methods: Cynomolgus monkeys (NHP; n = 4/group) were administered VIS649 (25 mg/kg) or vehicle alone once weekly for eight weeks by intravenous injection, and were then followed for an additional 3 weeks without treatment. Study endpoints included serum VIS649 and immunoglobulin (Ig) levels. In order to characterize the temporal relationship between circulating VIS649 and IgA, a population pharmacokinetic/pharmacodynamic (popPK/PD) model was developed. Temporal changes in IgA concentration following VIS649 administration was described with an indirect response model.

Results: Treatment of NHP with VIS649 resulted in significantly lower serum levels of IgA (up to 70%) and IgG (~40%), and minimal modulation of serum IgM levels. The visit in IgA levels were not reversed during the week no-dose period, which was attributed to the saturating levels of VIS649 at the dose administered. Analysis of the VIS649 pharmacokinetic data revealed that serum levels of VIS649 accumulated following weekly dose administrations at 25 mg/kg, and estimated the VIS649 half-life in NHP as 15 days. The popPK/PD model fit available PK and PD data well. Simulations were performed over a range of doses to inform dose selection and frequency in a follow-on study that will test lower VIS649 doses. Model predictions suggest that approximately 50% reduction in IgA levels may be achieved with lower dose levels.

Conclusion: VIS649, a humanized IgG2 monoclonal antibody that targets APRIL, reduced serum IgA levels significantly in healthy NHP following 8 weekly doses at 25 mg/kg. The specific targeting of APRIL confirmed its important role in the homeostasis of IgA, and confirmed our rationale for targeting it for the treatment of IgAN.

Funding: Commercial Support - Visterra, Inc.

TH-PO047

Sympathetic Renal Denervation Locally Aggravates Kidney Inflammation in Crescentic Glomerulonephritis

Methods: Renal denervation was performed by application of a mixture of ethanol and cyclic aromatic chemicals to the renal hilus. We induced the nephrotic nephritis by intraperitoneal injection of nephrotoxic serum. Analytic methods included flow-cytometry, ELISA and histology. Furthermore we utilized light sheet microscopy in which we made use of fluorescent tracers, kidney tissue clearing and algorithm-based full kidney reconstruction and measurement.

Results: Unilateral renal denervation caused neither albuminuria nor tubular damage in healthy mice. But already at d3 after NTN initiation, proteinuria was exacerbated. We noted an increased influx of neutrophils, which can directly mediate glomerular damage during the early phase of NTN, into the denervated infiltrated tissue. Furthermore, we detected a differential gene expression in the denervated kidney, which might be causative for the increased PMN influx. Examination of histological sections showed stronger inflammation in the cortex of the denervated kidney. To distinguish effects on the glomerular function in denervated and contralateral kidneys, we performed light sheet microscopy of cleared kidneys after injecting fluorescent tracers. This revealed that proteinuria commenced on d3 in the denervated kidneys, while the contralateral kidney fulfilled its function without noticeable alterations at this time point. Finally, we noted significant swelling of glomeruli in the denervated kidneys.

Conclusion: Neuronal signals locally attenuate inflammation and inflammation in experimental glomerulonephritis. Our findings suggest that renal denervation, for example in the treatment of arterial hypertension, might aggravate preexisting chronic inflammation in nephritis patients.

Funding: Commercial Support - Fresenius Medical Care, Government Support - Non-U.S.

TH-PO048

 Annexin A1 Promotes the Resolution of Inflammation in Murine Crescentic Glomerulonephritis

Methods: We utilized an Annexin A1 deficient (−/−) and wildtype mice (+/+) on a C57BL/6 background as well as rats for imaging experiments. All experiments were performed in accordance with the principles outlined in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. Analysis of gene expression was performed using RNA-Seq and qRT-PCR. All data were assessed via Student’s t-test.

Results: Gene expression analysis revealed an increased number of sclerotic glomeruli and aggravated tubulointerstitial damage in the kidneys of annexin A1 deficient mice as compared to wildtype controls. Knockout of annexin A1 attenuated inflammation and fibrosis in murine crescentic glomerulonephritis.

Conclusion: Annexin A1 is a key regulator of the resolution process in crescentic glomerulonephritis.
CD4+ T Cells Control TH17 Responses in an IL-17 Receptor A-Dependent Manner
Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany.

Background: The characterization of IL-17A producing CD4+ T_{H}17 cells has substantially improved our understanding of organ-specific autoimmunity including crescentic glomerulonephritis. The biological effects of IL-17A are mediated via the IL-17 receptor A. Recent clinical trials targeting the IL-17A signaling pathway by IL-17RA antibodies, have been remarkable effective for the treatment of some autoimmune disorders (psoriasis) but even led to the exacerbation of colitis in patients with inflammatory bowel diseases. The reason for these controversial results are unknown.

Methods: We generated conventional and conditional IL-17RA deficient mice to analyze the effect of IL-17 signaling in models of inflammatory kidney and gut diseases. Cytokine production was analyzed using multi-color flow cytometry.

Results: Using the T_{H}17 dependent model of crescentic GN (nephrotic nephritis), we found that IL-17RA gene-deficiency, as well as IL-17RA antibody treatment, did not ameliorate the clinical course of the GN in terms of glomerular crescent formation, albuminuria, and renal function. Of note, Citrobacter rodentium induced colitis, that triggers a potent T_{H}17 cell response in the gut, was significantly aggravated in IL-17RA-deficient mice. Mechanistically, we identified a deficiency of IL-17A+ T cells in cell immunity in these animals. Production of IL-17A, IL-17F and IL-17RA was highly upregulated in the inflamed organs accompanied by tissue injury in the absence of IL-17A signaling. Competitive adoptive transfer experiments with wildtype and IL-17RA−/− mice revealed that T_{H}17 genes were upregulated in cells lacking the IL-17A. Using IL-17A reporter mice and cell-specific IL-17RA−/− mice we finally demonstrated, that IL-17RA is highly expressed by CD4+ T_{H}17 cells and that this expression is critical for the control of the IL-17A mediated inflammatory processes. γδ T cells in IL-17RA−/− mice showed a high degree of plasticity allowing for a high degree of plasticity in inflammation and tissue injury in the absence of IL-17A.

Conclusions: Our findings indicate that IL-17A expression on CD4 T cells control T_{H}17 immune response and production of IL-22 and GM-CSF via a self-inhibitory loop. This knowledge might help to understand organ specific outcome after anti-IL-17A antibody treatment in autoimmune mediated disorders. In summary, we found that IL-17RA blockade might be ineffective for treatment of RPGN or colitis.

Funding: Government Support - Non-U.S.

Staphylococcus aureus Sepsis Drives a Highly Flexible TH17 Immune Response in the Kidney

Background: CD4+ T cells play an important role in autoimmunity and infections. IL-17A expressing T_{H}17 effector cells are involved in autoimmune diseases and in the immune response to bacterial infections. Plasticity within the CD4+ T cell system seems to be a critical factor for their pathogenicity in autoimmune diseases. T_{H}17 cells have a high degree of plasticity in experimental autoimmune encephalomyelitis (EAE) a mouse model for multiple sclerosis (MS), while renal T_{H}17 cells in crescentic glomerulonephritis (cGN) show a high degree of stability (70% maintain IL-17 expression). However, the knowledge about the T_{H}17 cell immune response and their plasticity in bacterial infections in the kidney is very limited.

Methods: To investigate the CD4+ T cell response in infections, we established a mouse model of Staphylococcus aureus (S.aureus) sepsis induced by intravenous injection of S. aureus SH1000 (2.5x10^8 CFU). Renal tissue was analyzed by histology and flow cytometry. To analyze T cell plasticity, we used fluorescent reporter mice (IL-17A fate reporter and FoxP3−/− IL-10-11-17 acute reporter).

Results: S. aureus were detected in kidneys at day 3-6 after infection, while no live bacteria were found after 10 days. Infection resulted in abscess formation Klinik, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; 1Medizinische Mikrobiologie, Virologie und Hygiene, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany.

Conclusions: We demonstrate a high degree of flexibility of T_{H}17 cells in the kidney in a S. aureus induced model. In contrast, T_{H}17 cells in crescentic GN are rather stable, thus suggesting that T_{H}17 cell plasticity is not specific but might rather depend on the trigger of inflammation. Further understanding of T_{H}17 cell plasticity will allow more specific targeting of beneficial and detrimental T cell populations in settings of autoimmunity and infections.

Funding: Government Support - Non-U.S.

AZIUTHROMYCIN MODULATES GIANT CELL FORMATION IN GRANULOMATOUS DISEASES

TH-PO060

Alkylating Histone Decacytelase Inhibitor Treatment in Animal Models of MPO-ANCA Vasculitis
Debshalee Dooley,1 Eoin O’Brien,1 Barbara Fazekas,2 Charles D. Pusey,1 Fionnuala B. Hickey,1 Thomas Mehrling,1 Peter Heerings,2 Mark A. Little,1 EDO GmbH, Basel, Switzerland; 1Imperial College Kidney and Transplant Institute, London, United Kingdom; 2Imperial College London, London, United Kingdom; 6Trinity College Dublin, Dublin, Ireland; 7University Medical Center Groningen, Groningen, Netherlands.

Background: Anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) is a systemic inflammatory, autoimmune condition that affects the microvasculature. The lungs and kidneys are most frequently affected, leading to lung haemorrhage and glomerulonephritis (GN). When left untreated, AAV has a mortality rate of around 80% in year one and a 25% five-year mortality rate with current conventional treatments consisting of cyclophosphamide and steroids. However, these therapies do not prevent disease relapse and patients often require long-term treatment which is associated with severe morbidity. Recently, histone deacetylase inhibitors (HDACi) were shown to have beneficial effects in inflammatory rodent models and have been found to act synergistically with a diverse range of pharmacological agents including cyclophosphamide.

Methods: EDO-S101, a small molecule compound developed by Mundipharma EDO GmbH, is an alkylating HDACi fusion molecule which combines the strong DNA alkylation effect of bendamustine, with a fully functional pan-HDACi, vornixat. In this study, we investigated the effects of EDO-S101 in 2 well established rodent models of AAV. These consisted of a passive mouse model of anti-myeloperoxidase (MPO) IgG-induced GN and an active rat model of MPO-ANCA microscopic polyangiitis: experimental autoimmune vasculitis (EAV).

Results: Our data indicate that although pre-treatment with EDO-S101 reduced circulating leukocyte populations, it did not affect development of anti-MPO IgG-induced GN in mice. On the other hand, EDO-S101 in EAV significantly reduced the degree of lung haemorrhage, severe/severe almost completely abolished crescent formation. EDO-S101 treatment in EAV also significantly depleted B and T cells compared with vehicle-treated controls, suggesting a selective effect on the adaptive immune response.

Conclusions: Taken together, we have demonstrated that EDO-S101 is a promising novel therapy for treatment of AAV that operates primarily through its effects on the adaptive immune response to the autoantigen MPO.

Funding: Commercial Support - Mundipharma EDO GmbH

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
TH-PO053
Transcriptional Profile Distinguishes Two Groups of ANCA Vasculitis Patients
Independent of Serotype Britta E. Jones,1 Joshua Starmer,3 Caroline J. Poulton,2 J. Charles Jennette,4 Ronald J. Falk,1,3 Dominic J. Ciavatta,4,5 UNC Kidney Center, Chapel Hill, Chapel Hill, NC; 1UNC Kidney Center, Chapel Hill, NC; 2University of North Carolina Hospitals, Chapel Hill, Chapel Hill, NC.

Background: Increased expression of ANCA autoantigen genes myeloperoxidase (MPO) and proteinase 3 (PR3) has been observed in several cell types, but global transcriptional changes are less well defined in ANCA vasculitis patients.

Methods: We isolated neutrophils, CD14+ monocytes and CD4+ T-cells from 30 healthy controls and 75 patients during active disease or remission, including 25 longitudinal patient pairs. Expression of MPO and PR3 in these purified cell populations was determined by quantitative real-time PCR. RNA-seq was performed on the CD4+ enriched cell population from 12 active-remission pairs, 7 MPO-ANCA and 5 PR3-ANCA, to identify differentially expressed genes (DEGs) between active disease and remission.

Results: Expression of the autoantigen genes was elevated in patients with active disease compared to healthy controls in all three cell populations. A non-significant fold change in expression was seen in monocytes while the mean fold-change in expression for MPO and PR3 in these purified cell populations was determined by quantitative real-time PCR. RNA-seq was performed on the CD4+ enriched cell population from 12 active-remission pairs, 7 MPO-ANCA and 5 PR3-ANCA, to identify differentially expressed genes (DEGs) between active disease and remission.

Conclusions: The transcriptional profile that divides ANCA vasculitis patients into two categories suggests a molecular signature can distinguish disease status.

Funding: NIDDK Support

TH-PO054
Monocytes Promote Crescent Formation in Anti-Myeloperoxidase Antibody-Induced Glomerulonephritis Anthony Rousselot,1 Ralph Ketritz,1,5 Adrian Schreiber,1,3 Charles Berlin, Berlin, Germany; EBC, Berlin, Germany; 3Charite, Experimental and Clinical Research Center, Berlin, Germany.

Background: Neutrophils and monocytes express ANCA antigens, and activation of these cells by ANCA is central to ANCA-associated vasculitis (AAV) and necrotizing crescentic glomerulonephritis (NCGN). The importance of neutrophils is established; however, any role of monocytes is less clear. We tested the hypothesis that depletion of CCR2 inflammatory monocytes and their derivatives would abrogate anti-MPO antibody-induced NCGN.

Methods: We used anti-MPO IgG (50 μg/g body weight, BW) transfer to induce NCGN in LPS-challenged wild-type (WT) mice and in mice expressing the CCR2 antagonist (AAV) and necrotizing crescentic glomerulonephritis (NCGN). The importance of neutrophils is established; however, any role of monocytes is less clear. We tested the hypothesis that depletion of CCR2 inflammatory monocytes and their derivatives would abrogate anti-MPO antibody-induced NCGN.

Results: Both mouse strains showed similar circulating Ly6C+ monocytes and neutrophils at baseline. Diphtheria toxin robustly depleted circulating circulating only in CCR2-DTR mice, whereas neutrophil numbers were similar. Anti-MPO antibody transfer resulted in nephritic urine by dipstick and albuminuria by ELISA, and monocyte depletion had no effect. However, monocyte depletion significantly reduced glomerular necrosis and crescent formation (21±0.5% vs. 4.3±2% for crescents and 12.0±1.7% vs. 0.1±0.1% for crescents, p<0.05 for both) and abrogated monocyte-induced crescentic cell increase in the affected kidneys, whereas renal neutrophil numbers were not affected. Soluble CD163 increased in serum, but not in urine with anti-MPO antibody treatment and was completely abolished with monocyte depletion.

Conclusions: Our findings provide novel experimental evidence that monocytes are important disease contributors in ANCA-mediated NCGN. Whereas neutrophils are sufficient to induce nephritic urine abnormalities, albuminuria, and some NCGN, inflammatory monocytes clearly enhanced necrosis and crescent formation.

Funding: Government Support - Non-U.S.

TH-PO055
Detecting Autoreactive Cells and Pathogenic Epitopes in MPO-ANCA Vasculitis Katherine G. Stemmer,2 Jacob Hess,3 Candace D. Henderson,3 Simon Mallal,1 J. Charles Jennette,1 Ronald J. Falk,4 Dominic J. Ciavatta,4 Meghan E. Free3 UNC Kidney Center, Chapel Hill, NC; 3University of North Carolina Chapel Hill, Chapel Hill, NC; 4University of North Carolina at Chapel Hill, Chapel Hill, NC.

Background: Anti-neutrophil cytoplasmic autoantibody (ANCA) vasculitis is an autoimmune disease that damages blood vessels throughout the body, and treatment regimens include immunosuppression. Previous studies demonstrated dysregulation of the adaptive immune system and identified two autotigens: myeloperoxidase (MPO) and proteinase 3 (PR3). GWAS studies found an association between ANCA vasculitis and human leukocyte antigen (HLA). Mouse and human studies identified pathogenic MPO epitopes. Our lab sought to investigate MPO epitopes recognized by autoreactive B and T cells in patients.

Methods: We used an in-house ELISA to test antibody reactivity to a previously identified linear MPO epitope. We HLA sequenced 203 patients to identify disease-associated alleles and used predictive and in vitro binding studies to assess MHC-peptide binding. MHC II tetramers were produced for DPB1*04:01 and DRB4*01:01 containing MPO epitopes and controls. Patient PBMCs were incubated with tetramers, stained with surface markers, and analyzed by flow cytometry day 1 ex vivo.

Results: Our ELISA revealed 35% percent of patients have autoantibodies that bind MPO at site most often at disease onset. Patients carrying HLA of interest demonstrate specific CD4+ T cell recognition of tetramers containing MPO epitopes. The majority of tetramer positive cells are CD25+CD38high cells, and are positive for CD45R0 andCCR7 memory markers. Additionally they secrete IL-17 when stimulated.

Conclusions: Recently, it was shown that MPO epitope-induced tolerance and attenuated disease in a mouse model of anti-MPO ANCA. Patient PBMCs showed reactivity to tetramers carrying the human homolog of this epitope. Ideally, we will use this region of MPO to inform the development of new therapies for patients with ANCA vasculitis.

Funding: NIDDK Support

TH-PO056
Neutrophil-Gelatinase Associated Lipocalin (NGAL) Attenuates ANCA-Induced Glomerulonephritis by Inhibiting Th17 Immunity Adrian Schreiber,1,3 Charlotte Rousselle,2 Ralph Ketritz,1,5 Charles Berlin, Berlin, Germany; EBC, Berlin, Germany; 3None, Hamburg, Germany; 4Universitatsmedizin Berlin, Berlin, Germany; 5Charite, Berlin, Berlin, Germany.

Background: ANCA activate neutrophils and monocytes and thereby participate in vasculitis and necrotizing crescentic glomerulonephritis (NCGN). NGAL is a marker of intrinsic kidney injury and is expressed by neutrophils and renal tubular cells. Whether or not NGAL is merely a diagnostic marker or participates mechanistically in renal damage is not known. We hypothesized that neutrophil NGAL plays a pathogenic role in ANCA-induced NCGN.

Methods: We used an in-house ELISA to test antibody reactivity to a previously identified linear MPO epitope. We HLA sequenced 203 patients to identify disease-associated alleles and used predictive and in vitro binding studies to assess MHC-peptide binding. MHC II tetramers were produced for DPB1*04:01 and DRB4*01:01 containing MPO epitopes and controls. Patient PBMCs were incubated with tetramers, stained with surface markers, and analyzed by flow cytometry day 1 ex vivo.

Results: Our ELISA revealed 35% percent of patients have autoantibodies that bind MPO at site most often at disease onset. Patients carrying HLA of interest demonstrate specific CD4+ T cell recognition of tetramers containing MPO epitopes. The majority of tetramer positive cells are CD25+CD38high cells, and are positive for CD45R0 andCCR7 memory markers. Additionally they secrete IL-17 when stimulated.

Conclusions: Recently, it was shown that MPO epitope-induced tolerance and attenuated disease in a mouse model of anti-MPO ANCA. Patient PBMCs showed reactivity to tetramers carrying the human homolog of this epitope. Ideally, we will use this region of MPO to inform the development of new therapies for patients with ANCA vasculitis.

Funding: NIDDK Support
bivariate analysis, MPTFa adjusted for serum creatinine was still significantly associated (HR=1.21, 95% CI 1.02, 1.45; p=0.04) and serum creatinine (HR=1.29, 95% CI 1.0, 1.66; 95% CI 1.03, 1.33; p=0.02) but not at active disease. Per unit increases of both hs-CRP and anti-Plg during remission was associated with VTE (HR=1.17, MPTFa at remission was also associated with VTE (HR=1.4, 95% CI 1.11, 1.77; p=0.005). For every 10 units increase of MPTFa during active disease, the risk of VTE increased by 60%. This is a significant unit of measure as the threshold for positivity was set at 11%.

Methods: Patients were enrolled during active disease. Twelve patients experienced a VTE (VTE+) and were compared to patients without VTE (VTE−, n=29) and 56 healthy controls (HC). Platelet free plasma and serum samples were assayed for MPTFa and anti-Plg. IL-6 was measured by a commercial ELISA; positivity was defined as 2 standard deviations above the HC mean. D-dimer, high sensitivity CRP (hs-CRP) and serum creatinine were measured by our clinical laboratory. Measures were assessed at active disease and remission. Univariate and bivariate analyses were performed by Cox regression.

Results: Demographics were similar in patients and HC. VTE+ and VTE− patients did not differ in ANCA serotype, titer or BV AS. In univariate analysis, elevated MPTFa during active disease was associated with VTE (HR=1.06, 95% CI 1.01, 1.10; p=0.009). For every 10 units increase of MPTFa during active disease, the risk of VTE increased by 60%. This is a significant unit of measure as the threshold for positivity was set at 11% of the positive control. Assuming remission values before and after VTE are comparable, MPTFa at remission was also associated with VTE (HR=1.4, 95% CI 1.11, 1.77; p=0.005). Similarly, increased anti-Plg during remission was associated with VTE (HR=1.37, 95% CI 1.03, 1.33; p=0.02) but not at active disease. Per unit increases of both hs-CRP (HR=1.21, 95% CI 1.02, 1.45; p=0.04) and serum creatinine (HR=1.29, 95% CI 1.0, 1.66; p=0.05) were associated with VTE. IL-6 and D-dimer were not associated with VTE. In bivariate analysis, MPTFa adjusted for serum creatinine was still significantly associated with VTE (HR=1.05, 95% CI 1.01, 1.10; p=0.01).

Conclusions: Our data suggest that of the variables evaluated, elevated MPTFa provides the best marker of VTE and may identify patients at high risk for VTE in ANCA vasculitis.

Funding: NIDDK Support, Private Foundation Support

TH-PO058

Overexpression of Preeclampsia Induced miR-26a-5p Leads to Proteinuria in Zebrafish Janine Miller-Deile,1 Patricia A. Schroder,2 Jenny C. Nystrom,2 Hermann G. Haller,2 Mario Schiffer,1 Hypertension and nephrology, Hannover medical school, Hannover, Germany; 2Hannover Medical School, Hannover, Germany; 3Mount Desert Island Biological Laboratory, Salisbury Cove, ME; 4University of Gothenburg, Goteborg, Sweden.

Background: So far the pathomechanism of preeclampsia in pregnancy is focused on increased circulating levels of sFLT1 that neutralizes glomerular VEGF-A expression and prevents its signaling at the glomerular endothelium. MiR-26a-5p is upregulated in the preeclamptic placenta.

Methods: We analyzed miR-26a-5p expression in podocytes and microinjected zebrafish eggs with a miR-26a-5p mimic. We analysed protein, proteinuria and ultrastructural changes of the glomerular filtration barrier.

Results: We found that miR-26a-5p targets VEGF-A expression in cultured podocytes and that its overexpression in zebrafish causes proteinuria, edema, glomerular endotheliosis and podocyte foot process effacement. Recombinant zebrafish vegf-Aa protein could rescue glomerular changes induced by miR-26a-5p. Preeclamptic patients with preeclampsia and preeclampsia with preeclampsia identified by podocyturia, expressed significantly more urinary miR-26a-5p compared to controls.

Conclusions: Thus, functional and ultrastructural glomerular changes after miR-26a-5p overexpression can resemble the findings seen in preeclampsia and indicate a potential pathophysiological role of miR-26a-5p in addition to sFLT1 in this disease.

Funding: Poster/Thursday

TH-PO059

Protective Effect of TRPC6 Knockout in Chronic PAN Nephropathy in Sprague-Dawley Rats Stuart E. Dryer, Eunyoung Kim, University of Houston, Houston, TX.

Background: Mutations in TRPC6 channels give rise to rare forms of focal and segmental glomerulosclerosis (FSGS). A possible role of wild-type TRPC6 channels in the progression of acquired forms of FSGS is not firmly established, and it is important to examine this in multiple species. Here we examined the role of TRPC6 channels in chronic puromycin aminonucleoside (PAN) nephropathy in Sprague-Dawley rats. Chronic PAN nephropathy is one of the most extensively studied models of secondary FSGS. A major advantage of this model is that experimental animals get a severe glomerular disease.

Methods: A global constitutive TRPC6+ rat was generated on the Sprague-Dawley background using CRISPR/Cas9 technology. Experiments were carried out using TRPC6+ and TRPC6− littermates. Rats were given two i.p. injections of PAN at 30 day intervals. Renal phenotypes were characterized by standard histological, ultrastructural, and biochemical methods. All experiments were approved by the University of Houston IACUC.

Results: Nephrotic range albuminuria was present 9-10 days after the first PAN injection and there was no difference in 24-hour urine albumin excretion in TRPC6+ and TRPC6− rats at that time. In marked contrast to the acute phase, at 30 and 60 days after the initial PAN injection, TRPC6− rats had biologically and statistically significantly reduced urine albumin excretion, reduced serum cholesterol and triglycerides, and improved BUN compared to TRPC6+− littermates. Glomerulosclerosis was severe during chronic PAN nephropsis in TRPC6− rats, but was markedly reduced in TRPC6−− littermates. TRPC6 knockout rats also had less severe tubulointerstitial fibrosis, and reduced foot process effacement and glomerular basement thickening compared to TRPC6−− controls. TRPC6− rats also had reduced infiltration of monocytes or macrophages into glomeruli, and reduced expression of α-smooth muscle actin in renal cortex compared to TRPC6−−− littermates. Basal TRPC3 abundance in renal cortex was increased in TRPC6− rats compared to TRPC6−− controls. However TRPC3 did not increase further in chronic PAN nephropsis. None of the manipulations in this study affected TRPC5 channels.

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

118
**Conclusions:** TRPC6 mutation results in shorter survival compared to WT. NIDDK Support

**TH-PO060**

**Calpain Activation by TRPC6 in the Podocyte**

**Lisa Krugman,1 John O’Toole,2 Sethed M. Madhavan,3 John F. O’Toole,1,4 and John F. O’Toole,1**

**Division of Nephrology, Washington University School of Medicine, St. Louis, MO; Division of Endocytology, Metabolism, and Lipid Research, Washington University School of Medicine, St. Louis, MO.**

**Background:** Emerging evidence has demonstrated that podocyte endolysosomal reticulum calcium depletion (ER) stress caused by gene mutations contributes to the pathogenesis of nephrotic syndrome (NS). ER stress-mediated calcium efflux from the ER to the cytosol can activate calcium-dependent protease calpain 2, which underlies the development of proteinuria. Here for the first time, we have shown that a novel ER calcium stabilizer can inhibit calpain activation.

**Methods:** We have developed a NS mouse model in which C321R mutation of the glomerular basement membrane constituent laminin β2 (LAMB2), a mutation identified in human patients, leads to podocyte ER stress. We isolated mouse glomeruli and cultured primary podocytes at the early stage of the disease to investigate the functional impact of these mutations on NS.

**Results:** We have developed a NS mouse model in which C321R mutation of the glomerular basement membrane constituent laminin β2 (LAMB2), a mutation identified in human patients, leads to podocyte ER stress. We isolated mouse glomeruli and cultured primary podocytes at the early stage of the disease to investigate the functional impact of these mutations on NS.

**Conclusions:** TRPC6 mediated activation of calpain plays an important role in podocyte motility and detachment. Disease causing mutations in TRPC6 could be playing an important role in the pathogenesis of NS.

**TH-PO061**

**Targeting Podocyte Endolysosomal Reticulum Calcium Depletion to Treat Nephrotic Syndrome**

**Sun-Ji Park,1 Keawon Kim,1 Jeffrey H. Miner,1 Fumihiko Urano,2 Ying M. Chen,2,3 Division of Nephrology, Washington University School of Medicine, St. Louis, MO; Division of Endocytology, Metabolism, and Lipid Research, Washington University School of Medicine, St. Louis, MO.**

**Background:** Emerging evidence has demonstrated that podocyte endolysosomal reticulum (ER) stress caused by gene mutations contributes to the pathogenesis of nephrotic syndrome (NS). ER stress-mediated calcium efflux from the ER to the cytosol can activate calcium-dependent protease calpain 2, which underlies the development of proteinuria. Here for the first time, we have shown that a novel ER calcium stabilizer can inhibit calpain activation.

**Methods:** We have developed a NS mouse model in which C321R mutation of the glomerular basement membrane constituent laminin β2 (LAMB2), a mutation identified in human patients, leads to podocyte ER stress. We isolated mouse glomeruli and cultured primary podocytes at the early stage of the disease to investigate the functional impact of these mutations on NS.

**Results:** We have developed a NS mouse model in which C321R mutation of the glomerular basement membrane constituent laminin β2 (LAMB2), a mutation identified in human patients, leads to podocyte ER stress. We isolated mouse glomeruli and cultured primary podocytes at the early stage of the disease to investigate the functional impact of these mutations on NS.

**Conclusions:** TRPC6 mediated activation of calpain plays an important role in podocyte motility and detachment. Disease causing mutations in TRPC6 could be playing an important role in the pathogenesis of NS.

**TH-PO062**

**TRPM4 Is Expressed at the Apical Surface of Podocyte Just Above Silt Diaphragm, and Its Altered Expression Is Involved in Podocyte Injury**

**Ying Zhang,1 Yoshiyasu Fukusumi,2 Hiroshi Kawachi.1 Department of Cell Biology, Kidney Research Center, Niigata University, Niigata, Japan.**

**Background:** TRPM4, a member of TRP channels is reported to play an important role in regulating the slit diaphragm (SD) function. To explore novel molecules involved in the development of proteinuria, we performed cDNA subtraction assay and RNA-seq analysis on 53 molecules identified to be decreased to less than 20 % in PAN nephropathy. We found transient receptor potential melastatin 4 (TRPM4), another member of TRP channels was clearly downregulated. In this study we examined the expression and localization of TRPM4 in glomeruli and its possible roles in pathogenesis of proteinuria.

**Methods:** The expression and the localization of TRPM4 under the physiological and pathological conditions were analyzed by real-time PCR, dual-labeling immunofluorescence and Western blot. We prepared three rat models, PAN nephropathy, a mimic of MCNS, ADR nephropathy, a mimic of FSGS and anti-nephritis antibody (ANA) induced nephropathy, which is characterized as a silt diaphragm specific dysfunction.

**Results:** The mRNA expression of TRPM4 in glomeruli was more extensive than that in renal cortex and other tissues. The expression of TRPM4 was also detected in cultured murine podocytes. Immunostaining of TRPM4 in renal cortex was restricted to glomeruli, and it was observed to be a discontinuous linear pattern along the glomerular capillary loops. TRPM4 staining was slightly aside from nephrin, an extracellular component of the SD, and some portions of TRPM4 were colocalized with podocyte apical membrane marker podocalyxin. TRPM4 first appeared in the presumptive podocytes in early S-shaped body stage, when nephrin was not detected yet. The mRNA expression of TRPM4 was evidently decreased immediately after disease induction (1h: 10 % in ANA, 31 % in PAN) and the decrease was still detected when proteinuria peaked (42 %, 57 %). The immunostaining of TRPM4 shifted to a discontinuous patchy pattern in PAN nephropathy. The staining intensity of TRPM4 was lowered in ANA nephropathy and ADR nephropathy.

**Conclusions:** TRPM4 is expressed at the apical surface of podocyte just above silt diaphragm and its expression and localization are decreased in the onset of proteinuria. The immunostaining of TRPM4 was altered in proteinuric states. It is conceivable that the altered expression of TRPM4 is involved in initiating the slit diaphragm dysfunction.

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

**TH-PO063**

**Brevin R-SNARES Provide a Cellular Address to Localize APOL1 to Podocyte Endosomal Compartments**

**Sethed M. Madhavan,1 John F. O’Toole,1 and John F. O’Toole,1,2**

**1Division of Nephrology, Washington University School of Medicine, St. Louis, MO; 2Case Western Reserve University, Cleveland, OH.**

**Background:** Genetic variants in APOL1 (G1 and G2) associate with non-diabetic kidney diseases in individuals with African ancestry. Kidney-expressed, but not circulating APOL1 variants, confer risk for CKD. Most subjects with high risk APOL1 genotypes do not develop kidney disease, suggesting a second hit is necessary. Sites of proteinuria in kidney, its subcellular localization and the identity of its cognate binding partners as well as the pathways by which variant APOL1s promote nephropathy remain unclear.

**Methods:** In situ hybridization (ISH) was performed in normal human kidney tissue to detect APOL1 transcripts. APOL1 subcellular localization was examined by immunoelectron (IEM) and confocal immunofluorescence microscopy. Co-immunoprecipitation (Co-IP) experiments to study APOL1-SNARE protein interaction was performed in 293T cells ectopically expressing tagged proteins. Bacterially expressed proteins purified by metal affinity and size-exclusion chromatography were used to study protein interaction by surface plasmon resonance (SPR).

**Results:** ISH demonstrated that APOL1 is synthesized in podocytes of human kidney and less so in tubules. In kidneys of mice transgenic for APOL1 and human nephrectomy samples, IEM localized the protein to double membrane vesicles and endocytic compartments in podocytes. APOL1 did not localize to plasma membrane in podocytes. By immunofluorescence, podocyte APOL1 did not localize with either mitochondrial marker, beta-subunit of ATP synthase or a lysosomal marker, LAMP1. APOL1 interacted with the R-SNARES, VAMP8 and VAMP1 in Co-IP. APOL1 colocalized with VAMP8 in podocytes of normal human kidney and Co-IP and SPR experiments confirmed that APOL1-G1 and -G2 interact with VAMP8 with lower affinity than -G0.

**Conclusions:** Reference APOL1 is expressed in the podocyte, localizes with vesicular structures and directly interacts with VAMP8, consistent with regulation of podocyte vesicular trafficking. APOL1 variants attenuate interaction with VAMP8. We propose that reference APOL1, by interacting with VAMP8 or other R-SNAREs, identifies vesicles containing cargo capable of mediating cellular damage, and activates a cellular response, which mitigates the pathogenic potential of these cargos. Variant APOL1 proteins fail to do so, disrupting vesicular trafficking and permitting kidney disease progression.

**Funding:** NIDDK Support

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

Underline represents presenting author.
The Effects of Mechanical Strain on Adhesion in MYH9- Ablated Podocytes

Keith H. Keller,1,4 Mostafa Belghasem,1 Hui Chen,1 Joel M. Henderson,2,3 BMC, Boston, MA; 2Boston University Medical Center, Boston, MA; 3Boston University School of Medicine, Boston, MA; 4Brigham and Woman’s Hospital, Boston, MA.

Background: Myh9 is a gene that encodes for non-muscle myosin IIA (NM-IIA), an actin cytoskeleton component and protein involved in cell movement and adhesion in multiple organs, including podocytes. Autosomal dominant mutations in NM-IIA have been associated with focal segmental glomerulosclerosis (FSGS). Podocyte specific Myh9 knockout in mice showed that this gene alone was not enough to cause proteinuria or glomerulosclerosis. However, in our own laboratory we have found that when these same mice are exposed to models of glomerular hypertension, glomerular damage is promoted. This damage was preceded by evidence of podocyte loss in urine and tissue. Podocyte loss is a hallmark of kidney disease, and while it is known to occur in vivo, the mechanisms behind this phenomenon are unknown. It is believed that increase in glomerular capillary blood pressure is likely to be a strong contributing factor. Here we investigated the effect of mechanical strain on adhesion and cell morphology in Myh9 ablative podocytes.

Methods: Myh9 was knocked down, using RNAi, in immortalized mouse podocytes cultured on flexible silicone 6-well plates at a density of 6000 cells per well. Cells were mechanically stretched in a step-change fashion for 24hrs then cells were fixed or lysed for protein. Each experiment included three groups with two conditions (stretch/no stretch): WT - lentiviral control; KD - Changes in adhesion were assessed using cell counts, and morphologic changes were evaluated using immunofluorescence and quantified using image analysis.

Results: Transfected cells showed marked decrease in cellular attachment (VCTL: -53%; VCTL-ST: -53%; KD: -50%; KD-ST: -60%), compared to control cells (CTL: -77%; CTL-ST: -120%). Mean focal adhesion area increased with stretch in each experimental condition (KD vs. KD-ST: CTI: 1.41 ± 1.62 µm²; VCTL: 2.12 ± 3.13 µm²; VCTL-ST: 0.54 ± 0.74 µm²; VCTL-ST: 2.77 ± 3.59 µm²; KD-ST: 3.04 ± 2.57 µm²; KD-ST: 2.09 ± 1.13 µm²). KD-ST cells showed large decrease in focal adhesion number compared to all other groups. Mean cell size was drastically larger in the KD groups (CTI: 505.6 ± 377.7 µm²; VCTL: 817.6 ± 1008.5 µm²; VCTL-ST: 1209.6 ± 787 µm²; KD: 3576.5 ± 2694.7 µm²; KD-ST: 5416.7 ± 13456.3 µm²).

Conclusions: Myh9/NM-IIA may be necessary for cells to bolster cell adhesion structures during events of mechanical stress, and its loss may compromise this protective adaptation.

MicroRNA671-5p Mediates Wtβ-Catenin-Triggered Podocyte Injury by Targeting WTCH1-Chungang Wang.1 Wenjuan Zhu,1 Lili Zhou,2 Youhua Liu,2 1Division of Nephrology, Nanfang Hospital, Southern Medical University, Guangzhou, China, 2Department of Pathology, University of Pittsburgh, Pittsburgh, PA.

Background: Podocyte injury is the major pathological feature of many proteinuric kidney diseases. It has been shown that dysregulated activation of Wtβ-catenin signaling in podocytes can lead to podocyte dedifferentiation and mesenchymal transition, causing impaired glomerular filtration and proteinuria. MicroRNAs (miRNAs) are a class of short non-coding RNAs, which regulates specific genes by targeting and fine-tuning their expression. To study whether miRNA is involved in mediating Wtβ-catenin-triggered podocyte injury, we performed a comprehensive miRNA expression profiling and sought to identify the miRNAs that may play a crucial role in this process.

Methods: Results: Mouse podocytes were transiently transfected with expression vector encoding constitutively activated β-catenin (pdel-β-cat) or empty vector (pdeDNA3). The differential expression of miRNAs was identified through a microarray analysis. Among several dozens of miRNAs which expression levels were altered after β-catenin activation, only miR-671-5p was among the top of the list. Subsequent qRT-PCR confirmed that mir-671-5p was upregulated in cultured podocytes after β-catenin activation, as well as in the kidneys of proteinuric CKD. Bioinformatics analysis predicted that miR-671-5p was specifically upregulated in glomerular podocytes, as shown on the level of WT1 mRNA. Inhibition of miRNA671-5p mitigated podocyte injury down-regulation of WT1 protein and promoted podocyte injury, whereas it had no effect in the kidneys of proteinuric CKD. Bioinformatics analysis predicted that miRNA671-5p was upregulated in cultured podocytes after short non-coding RNAs, which regulates specific genes by targeting and fine-tuning their expression. To study whether miRNA is involved in mediating Wtβ-catenin-triggered podocyte injury, we performed a comprehensive miRNA expression profiling and sought to identify the miRNAs that may play a crucial role in this process.

Conclusions: Our results show the discovery of a novel protein ISM-1 specifically expressed in podocyte in normal conditions. This expression is further increased in the progression of nephrotic syndrome. We are currently investigating the pathophysiologic role of this increase.

Isthmine-1, A New Podocyte Protein Involved in the Progression of Nephrotic Syndrome

Jean-Jacques Boffa,1,2 Lu Zhang,1,2 Sahiri V. Marie auve,6 Khalil A. Ghauchem,1 Placier Sandrine,1 Chantal Jouanneau,3 Christos Chatziantoniou,4,5 INSERM U1155, Paris, France; 2Jiangsu Province Hospital of Chinese Medicine, Nanjing, China; 3INSERM UNIT 1155, Paris, Bichat University Hospital, Paris, France; 4Tenon Hospital, AP-HP, Paris, France; 5INSERM U1155 / UPMC, Paris, France; 6INSERM U1155 - UPMC, Paris, France; 7insern, Paris 20, France.

Background: Using differential transcriptomic analysis in renal cortical slices from hypertensive rats with nephrotic level of proteinuria, we identified and studied isthmine-1 (ISM-1), a new player of renal diseases.

Methods: Results: Under control physiological conditions, ISM-1 is strongly expressed and colocalized with nephrin in rodents and humans as well. Immunogold electron microscopy revealed that ISM-1 localizes on podocyte foot processes. Because its two receptors, avb5Integrin and gap78 (Bip) are involved in podocytopathy, we induced nephrotic syndrome in rats by PAN and doxorubicin injection. In both experimental models, we found increased expression of ISM-1 mRNA and protein on isolated glomeruli. Likewise, the expressions of its two receptors were increased and contrasted to the decrease of nephrin protein expression. In addition, ISM-1 expression increased after doxorubicin stimulation in primary cultured podocytes in vitro. To determine the role of ISM-1, ISM-1 antisens ODN were administered in experimental models of nephrotic syndrome in vivo. Although ISM-1 antisens administration blunted ISM-1 expression, no difference was observed in the progression and severity of the disease in PAN rats. Because, ISM-1 has been shown to function to act as a permeability factor during lung sepsis, we are pursuing our studies by examining its role on glomerular membrane permeability.

Conclusions: Our results show the discovery of a novel protein ISM-1 specifically expressed in podocyte in normal conditions. This expression is further increased in the progression of nephrotic syndrome. We are currently investigating the pathophysiologic role of this increase.

Loss of Robo2 Rescues Podocyte Number and Ultrastructure Defects in Adult Ilk Knockout Mice

Richa Sharma, Hila Milo Rasouly, Xueping Fan, Sudhir Kumar, Arielle R. Strzelewicz, Mostafa Belghasem, Joel M. Henderson, David J. Salant, Weining Lu. Boston University School of Medicine, Boston, MA.

Background: Previous studies showed that ROBO2 signaling functions as a negative regulator on podocyte actin polymerization and podocyte adhesion. Our data shows that ROBO2 forms a complex with integrin-linked kinase (ILK) and loss of Robo2 improves the survival of Ilk podocyte-specific knockout (cKO) mice. However, the mechanism of this renoprotective role of Robo2 loss in Ilk-cKO is not clear.

Methods: Loss of Ilk single cKO were crossed to generate Robo2-Ilk double knockout mice (dKO). Glomerular histology, podocyte number, and podocyte ultrastructure of single cKO and double dKO mice were analyzed at 4 weeks and 16 weeks of age. Glomerular histology was evaluated by PAS staining. Podocyte numbers were quantified using WT1 staining. Podocyte ultrastructure was analyzed and quantified by transmission electron microscopy (TEM). Quantitative data were analyzed using SPSS statistics software.

Results: At 4 weeks old, the podocyte number and glomerular sclerotic index are almost the same in both Ilk single cKO and Robo2-Ilk dKO mice. However, analyses of podocyte number, glomerular histology, and TEM in 16 weeks old mice showed a significant improvement in podocyte number (p=0.02), sclerotic index (p=0.006), glomerular basement membrane width (p=0.03), podocyte foot process width (p=0.008) and slit diaphragm diameter (p=0.034) in Robo2-Ilk dKO as compared to Ilk single cKO mice.

Conclusions: Loss of Robo2 improves the survival of Ilk podocyte-specific knockout mice by rescuing podocyte number and podocyte ultrastructure defects in adult mice. Our findings suggest that inhibition of ROBO2 signaling could be beneficial for glomerular disease associated with podocyte loss and be a potential therapeutic target.

Funding: NIDDK Support, Commercial Support - Pfizer Centers for Therapeutic Innovation

In Vivo Characterization of Podocin Variants Based on a CRISPR/ Cas9 Based Genome Editing Approach

Linus Butt,1 Lena K. Ebert,1 Markus M. Rinsch,2 Martin Höhne,3 Branko Zevnik,5 Paul T. Brinkkötter,2 Bernhard Scherner,4 Thomas Benzing,3 1Department II of Internal Medicine and Center for Molecular Medicine, University of Cologne, Cologne, Germany; 2Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases, University of Cologne, Cologne, Germany.

Background: NPHE2 encodes for Podocin, a membrane protein at the inner leaflet of the plasma membrane of podocytes, and is the most frequently mutated gene in patients with Steroid-Resistant Nephrotic Syndrome (SRNS). Analyzing the role of posttranscriptional and -translational regulations of Podocin in the maintenance of the architecture and functional integrity of the slit diaphragm would extend our understanding of the underlying pathomechanisms. In previous studies, we confirmed the expression of a short isoform of Podocin in the human kidney, characterized its

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
biochemical properties in vitro and showed an altered localization of the protein. In addition, we identified two phosphorylation sites within Podocin by analyzing the glomerular phosphoproteome and found evidence for their biological significance, e.g. for Podocin multimerization (p.T234).

Methods: We used different CRISPR/Cas9 based genome editing strategies that enable us to alter monomorphic and elevated retention parameters indicating a loss of kidney function. Histological examinations reveal Focal-Segmental Glomerulosclerosis (FSGS), a hallmark of glomerular disease. Mouse homozygous for the T234I allele do not display an overt phenotype and up to now we did not observe living offspring homozygous for the short isoform allele.

Conclusions: CRISPR/Cas9 technology allows us to create a fast and efficient pipeline to generate mutant alleles mimicking human genetic diseases and our pioneer project already provided novel insights into the pathogenesis of SRNS.

TH-PO069
Par6β Interaction with Ephrin-B1 at the Slit Diaphragm Could Be a Differential Diagnostic Marker of Nephrotic Syndrome: Interaction of the Par-Complex Molecules with Ephrin-B1/Nephrin in Podocyte
Savuri Takamura,1,2 Yoshitsuya Fukusumi,1 Ying Zhang,1 Ichie Narita,1 Hiroshi Kawachih,1 Dept. Cell Biology, Kidney Research Center, Nippon Medical School, Tokyo, Japan; 2Division of Clinical Nephrology and Rheumatology, Niigata University, Niigata, Japan

Background: Par-complex, Par3/Par6/Cdc42/2/3/Par3 is reported to be a component of the slit diaphragm (SD) and to play a role in maintaining the podocyte function. However, the precise differential roles of the Par-complex molecules in podocyte are not fully understood. We have reported that ephrin-B1 is a novel component of the SD. Although ephrin-B1 is reported to control cell-cell junctions of vascular endothelial cells through Par-complex, no studies on the interaction of the Par-complex molecules with ephrin-B1 at the SD have not been analyzed.

Methods: The expressions of the Par-complex molecules in podocyte were analyzed in the normal adult and developing glomeruli and in the rat nephrin models of MCNS and FSGS, respectively. Western blot analyses were performed. The expressions of Par6 and Par6β with ephrin-B1 and nephrin were analyzed by the IP analyses with glomerular lysates and HEK-293 transfected cells. The expressions of the Par-complex molecules in the podocyte-specific ephrin-B1 conditional KO (KO) mouse were analyzed.

Results: mRNA expressions of Par6β and Par3 decreased from the early phase in the MCNS model and the decreases were detected when proteinuria peaked in both models. mRNA of Par6β increased in both models. Western blot analyses showed Par6β decreased in both models and Par3 decreased in the MCNS model. Immunostainings of Par6β and Par6β with ephrin-B1 and nephrin were analyzed by the IP analyses with glomerular lysates and HEK-293 transfected cells. The expressions of the Par-complex molecules in the podocyte-specific ephrin-B1 conditional KO (KO) mouse were analyzed.

Conclusions: Altered expressions of Par6β and Par3 are involved in the pathogenesis of both nephrin models, and these molecules could be differential diagnostic markers of nephrotic syndrome. Not Par3 but Par6β is highly associated with ephrin-B1 at the SD.

TH-PO070
Soluble Form of VCAM-1 Ameliorates Podocyte Phenotypic Change by Suppression PI3K-Akt Signaling in Podocyte
Sayuri Takamura,1,2 Yoshiyasu Kawachih,1 Dept. Cell Biology, Kidney Research Center, Nippon Medical School, Tokyo, Japan; 2Division of Clinical Nephrology and Rheumatology, Niigata University, Niigata, Japan

Background: VCAM-1 is a well-known cell adhesion molecule that forms a complex with a guide gene which selectively binds to DNA and induces double strand breaks. Subsequently, repair mechanisms can either lead to random indel mutations via Non-Homologous End-Joining (NHEJ) or precise mutations via Homology-Directed Repair (HDR). By promolecular injection we generated a mouse line that, in analogy to the human short isoform, lacks the entire exon 5. In an additional approach we eliminated a phosphorylation site within the PHB domain (p.T234I) by integrating a point mutation.

Results: Strikingly, in vivo data of compound-heterozygous animals show a rapid development of podocyte abnormalities and elevated retention parameters indicating a loss of kidney function. Histological examinations reveal Focal-Segmental Glomerulosclerosis (FSGS), a hallmark of glomerular disease. Mouse homozygous for the T234I allele do not display an overt phenotype and up to now we did not observe living offspring homozygous for the short isoform allele.

Conclusions: CRISPR/Cas9 technology allows us to create a fast and efficient pipeline to generate mutant alleles mimicking human genetic diseases and our pioneer project already provided novel insights into the pathogenesis of SRNS.

TH-PO071
Protein or Lysosomal Degradation System Failures Have Different Consequences on Renal Cell Protein Homeostasis
Wiebke Sachs,1,2 Giorgia Giudici,2,3,4 Marina Pohl,5 Catherine Meyer-Schewesinger,6 UKEM, Hamburg, Germany; 2University Medical Center Hamburg-Eppendorf, Hamburg, Germany; 3University of Hamburg, Hamburg, Germany.

Background: Protein degradation plays an important role in protein quality control and contributes to maintain renal cell homeostasis. One different degradation pathways responsible for clearance of defective proteins is the ubiquitin-proteasome system (UPS) and the autophagy-lysosome system (ALS), which are interconnected and influence each other. The aim of this project is to understand the significance of the proteasomal and lysosomal degradation systems for proteinostasis of renal cells such as podocytes.

Methods: In order to dissect the significance of the UPS and ALS for renal cells, Balb/c mice were treated with epoxomicin (proteasomal inhibitor) and leupeptin (lysosomal inhibitor respectively over 4 days. Furthermore, mice with general lysosomal dysfunction due to defective targeting of all newly synthesized lysosomal enzymes Mcoln2−/− were used. The effects on both the UPS and ALS on the renal and lysosomal functions were investigated clinically, morphologically and biochemically.

Results: Epoxomicin treatment resulted in a successful proteasomal inhibition. Mice with Mcoln2−/− showed abnormal protein accumulations in the subepithelial space and in podocytes. The tubulointerstitium was morphologically inconspicuous. Leupeptin treatment successfully reduced lysosomal function. Mice did not develop proteinuria. Morphological analyses were significant for abnormal accumulations in tubular cells and the mesangium of glomeruli. MLIII mice showed severe lysosomal dysfunction in combination with proteasomal dysfunction in glomeruli and tubulointerstitial cells. Clinically, MLIII mice showed slight proteinuria. Morphologically, MLIII mice exhibited accumulations of enlarged lysosomes in interstitial cells, in the mesangium of glomeruli and in podocytes, with abnormal protein accumulations in podocytes.

Conclusions: Based on our results we conclude that the UPS and ALS interplay in renal cells and are compensatory upregulated when the other is inhibited. Failure of the proteostational degradation system has a greater impact on renal cell proteinostasis and renal function that cannot be compensated by the lysosomal degradation system.

TH-PO072
Altered Hydrolysis Function of Ubiquitin C-Terminal Hydrolase L1 (UCH-L1) Regulates Altered Oxidative Modification Affects Protein Homeostasis in Podocytes
Julia Reichel,1 Anna Reinecke,2 Julia M. Felhér,3,4 Marlies Sachs,5 Günther Zahner,6 Catherine Meyer-Schewsing,1 UKEM, Hamburg, Germany; 2University of Hamburg, Hamburg, Germany; 3University Medical Center Hamburg-Eppendorf, Hamburg, Germany; 4University hospital hamburg, Hamburg, Germany; 5Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany.

Background: The ubiquitin proteasome system (UPS) represents the major system for protein degradation and is important for maintenance of protein homeostasis. Ubiquitin C-terminal hydrolase L1 (UCH-L1) regulates the pool of monoubiquitin required for tagging target proteins. The hydrolyse-deficient mutant UCH-L1(ΔN) is highly associated with the development of neurodegenerative disease in humans and structurally resembles oxidative-modified UCH-L1. During podocyte injury UCH-L1 is de novo produced in podocytes and accumulation of polyubiquitinated proteins by unknown mechanisms. Aim of this project is to investigate the toxic gain of function of UCH-L1.

Methods: In order to dissect UCH-L1 hydrolysis versus UCH-L1 hydrolyse-independent mechanisms we take advantage with analogy to UCH-L1 wildtype or an enzymatic-deficient form UCH-L1(ΔN) were generated. The effects of altered degradation were investigated in cultured podocytes and in 5-7 week old naive mice morphologically, clinically and biochemically. By use of PAS key.

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

121
and immunofluorescence stainings for podocyte-specific proteins and by measurement of proteinuria the glomerular integrity was characterized. To analyze the biochemical properties of UCH-L1 (such as expression levels or proteolytic activity) quantitative real-time PCR, Western blot, activity assays and immunohistochemical stainings were executed.

**Results:** In cultured podocytes UCH-L1 expression was induced following oxidative stress. UCH-L1-induced accumulations of polyubiquitinated as well as oxidative modified proteins in cultured podocytes and isolated glomeruli of transgenic mice. This conglomeration resulted from impaired prosurvival protein activity (UCH-L1) and the second was characterized by increased proteasome activity and a dedifferentiated phenotype. This was indicated by decreasing levels of podocyte-specific proteins nephrin and α-actinin-4 induced by declining amount of WT-1 which seems to be regulated by the proteasome.

**Conclusions:** UCH-L1 expression in podocyte injury might mediate two effects: first, dedifferentiation of the podocyte and second, accumulation of polyubiquitinated proteins conditioned by defective enzymatic function.

**TH-PO073**

**Liproteins Modulate Podocyte Damage and Proteinuria**

Yohei Tsuchida,1 Jianyong Zhong,2 Talat Alp Ikizler,3 Agnes B. Fogo,1 Taiji Matsusaka,1 Haichun Yang,1 Valentina Kon,1 Tokai University School of Medicine, Isehara, Japan; 2Vanderbilt University, Nashville, TN; 3Vanderbilt University Medical Center, Nashville, TN.

**Background:** Although high density lipoprotein (HDL) and its main protein, apolipoprotein A1 (apoA1) have established benefits in various cell types, their effects on renal cells remain unclear. We investigated the consequences of exposing normal and damaged podocytes to HDL (HDL-ApoA1), and HDL from patients with established CKD known to have dysfunctional HDL (HDL-D).

**Methods:** In vitro, primary mouse podocytes were injured by puromycin (PAN) and cellular viability, proliferation, migration and cellular production of reactive oxygen species (ROS) assessed. In vivo, transgenic mice expressing human CD25 in podocytes that can be selectively injured by injection of immunotoxin were used as the prometric model. At injury, half the mice received L-4F x 2 wks. Urinary albumin-creatinine ratio (ACR) was measured and expression of podocyte markers, synaptopodin and WT1 assessed.

**Results:** PAN reduced podocyte viability, proliferation, migration and increased ROS production in vitro. Each of these perturbations was significantly lessened by apoA1 and HDL-ApoA1 but not HDL-D (Table). Critically, while maximum proteinuria was similar in treated and untreated mice, L-4F significantly accelerated ACR reduction and preserved podocyte expression of synaptopodin and WT1-positive cell density.

**Conclusions:** The results indicate that normal apoA1 and HDL, but not dysfunctional HDL-D protect against podocyte damage. ApoA1 mimetic provides in vivo benefits to podocytes culminating in reduced albuminuria. We suggest supplemental apoA1 may be a novel candidate to lessen podocyte damage and proteinuria.

**Funding:** Other NIH Support - 1P01HL116263-01A1 NHLBI HDL Function in Human Disease (Project PI)

**TH-PO074**

**Novel Role for Podocyte SIRPα and Pulmonary Surfactants in Minimal Change Disease**

Miguel A. Lanaspa, Ana Andres-hernando, Christina Cicerchi, Richard J. Johnson. University of Colorado Denver; Aurora, CO.

**Background:** Minimal change disease (MCD) is the most common cause of proteinuria in children. In adults, MCD is diagnosed by a constellation of histological and biochemical findings and a strong familial background. Recent studies identified podocyte CD80 as a key deleterious player in MCD. SIRPα is a receptor that regulates cell growth and differentiation by controlling phosphatases like PTPN11. SIRPα agonists include soluble surfactants SP-A and SP-D, produced by alveolar type II cells, which have anti-inflammatory properties.

**Methods:** Serum, renal and urinary levels of surfactants are determined in MCD subjects in relapse and remission and correlated with albumin excretion and urinary CD80. To test the role of surfactants in podocyte activation, podocytes are exposed to surfactants and then subjected to the same treatments as in vivo. The surfactants are added back and SIRPα, PTPN11 activity, nephrin phosphorylation, CD80 expression, actin reorganization and proteinuria is determined in these podocytes and in a mouse model of intranasal exposure to LPS.

**Results:** Human subjects with MCD in relapse but not remission and intranasal exposure to LPS in mice have elevated serum SP-A/D suggesting a crossstalk between lungs and kidneys. The stimulation of SIRPα in cultured podocytes with serum from MCD patients in relapse or by addition back of surfactants to serum of patients in remission selectively upregulates SIRPα to express and dephosphorylate nephrin. This action results in NFKB activation and transcription of CD80 and pro-inflammatory cytokines, Similarly, nephrin loss results in loss of cell polarity that combined with the pro-inflammatory response re-organizes actin structure leading to the podocyte activation.

**Conclusions:** Based on our data and the observation that 70% of the cases of MCD relapses are preceded by respiratory tract infections, we conclude that MCD is associated with the deregulation of podocyte SIRPα signaling leading to its activation characterized by PTPN11-mediated nephrin dephosphorylation, CD80 expression and actin reorganization ultimately causing loss of foot processes, proteinuria and nephrotic syndrome.

**Funding:** NIDDK Support

**TH-PO075**

**Apoptosis Signal-Regulating Kinase 1 (ASK1) Inhibitor GS-444217 Mitigates Progression of HIV-Associated Nephropathy**

Kyung Lee,1 Jin Xu,2 Anqun Chen,2 John T. Liles,2 John C. He.1 ’Icahn School of Medicine at Mount Sinai, New York, NY; ’Gilead Sciences, Inc., Foster City, CA.

**Background:** Renal inflammation is the major pathology in chronic kidney diseases, including HIV-associated nephropathy (HIVAN) that ultimately progresses to end stage renal disease. Activation of apoptosis signal-regulating kinase 1 (ASK1) has been shown to drive renal inflammation, apoptosis, and fibrosis by downstream activation of MAPK kinases p38 and c-Jun N terminal kinase (JNK). Recent studies have shown that a potent selective ASK1 inhibitor substantially reduced renal p38MAPK activation and halted the disease progression in mouse models of diabetic kidney disease. Thus we sought to determine whether the blockade of ASK1 would also attenuate renal injury and impede the progression of HIVAN.

**Methods:** A well-established transgenic model of HIVAN, Tg26 mice on FVB/N background, was used for the study. Tg26 mice typically start to develop proteinuria and mild glomerulosclerosis (GS) at 4 weeks of age, moderate GS and mild tubulointerstitial inflammation (TI) at 12 weeks of age, and advanced GS and tubulointerstitial fibrosis (TIF) at 4 months of age. Tg26 mice received either standard chow or chow supplemented with selective ASK1 inhibitor GS-444217 (0.1% or 0.2% in chow). There were 7 to 10 mice in each group. Urine and blood were collected weekly to assess their kidney functions, and kidneys were harvested for analysis after 6 weeks of treatment.

**Results:** Administration of ASK1 inhibitor GS-444217 at both 0.1% and 0.2% concentrations significantly reduced p38 activation and albuminuria, and improved renal function. In Tg26 mice treated with GS-444217, we observed a marked reduction in GS and tubular damage in mice treated with GS-444217 compared to control Tg26 mice. GS-444217 administration increased the expression of differentiated podocytes markers and significantly curtailed podocyte loss in Tg26 mice. GS-444217 also reduced marker expressions of inflammation and apoptosis. Furthermore, GS-444217 administration resulted in significant reduction in collagen deposition and renal fibrosis.

**Conclusions:** Selective ASK1 inhibitor reduced both glomerular and tubular injury and mitigated the progression of HIVAN in Tg26 mice, suggesting that blockade of ASK1 pathway is a potential therapeutic approach against progression of CKD, including HIVAN.

**Funding:** Commercial Support - Gilead Sciences, Inc., Foster City, CA

**TH-PO076**

**Sox9 Is a Marker for Activated Parietal Epithelial Cells and Potentially Involved in Podocyte Regeneration in a Rat Anti-GBM Nephritis Model**

Christoph Daniel,1 Ania Prochnicki,1 Jeffrey W. Pippin,2 Stuart J. Shankland,1 Kerstin U. Amann,1 ’FAU Erlangen, Erlangen, Germany; ’University Erlangen-Nürnberg, Erlangen, Germany; ’University of Washington, Seattle, WA.

**Background:** In healthy kidneys parietal epithelial cells (PECs) line out the Bowman’s capsule. During renal disease PECs are thought to be involved in crescent formation as well as in podocyte regeneration. However, the activation of PECs during crescent formation and its potential role in scar formation or podocyte regeneration is not well understood. The aim of the study was to investigate a potential role of the transcription factor Sox9 as a marker of activated PECs in renal disease, healthy adults and during anti-GBM nephritis.

**Methods:** Renal Sox9 expression was investigated in different species including mouse, rat, pig and humans using immunohistochemistry. Glomerular Sox9 expression was characterized in more detail in healthy (n=11) and anti-glomerular basement membrane (anti-GBM) nephritic (n=11) rats on days 7 and 14 after model induction as well as in newborn rats (n=3) using immunofluorescence double staining and confocal laser scanning microscopy.

**Results:** In glomeruli from healthy rat kidneys Sox9 expression is restricted to approx. 30% of PECs nuclei. During anti-GBM nephritis the number of glomerular Sox9-positive cells was increased 2-fold on day 7 and about 5-fold on day 14 after disease induction. In nephritic glomeruli Sox9 expression was not restricted to Bowman’s capsule lining but was also found on cells of the glomerular tuft. Nearly all Sox9-positive cells also expressed the parietal epithelial marker Pax8 whereas Otx2-positive mesangial cells, CD11-positive endothelial cells and CD68-positive macrophages lacked Sox9 expression. While in healthy glomeruli only 4% of Sox9-positive cells showed proliferative activity, during anti-GBM nephritis more than 60% on day 7 and about 40% on day 14 of glucocorticoid (GC)-treated Sox9-positive cells were expressed PCNA, an indicator of cell cycle, on day 7.0±0.9 and on day 14 1.9±1.3 cells per glomerular cross-section express both Sox9

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

Underline represents presenting author.
and the podocyte marker podocalyxin. In addition, during glomerulonephritis Sox9 was expressed in parietal epithelial cells as well as podocytes.

Conclusions: Our data are in line with Sox9 being a marker of activated parietal epithelial cells and may further point to a potential role in podocyte regeneration.

Funding: Government Support - Non-U.S.

TH-PO077

Morphometric Quantitation of Parietal Epithelial Cells in Human Kidneys
Christopher L. O'Connor, Mohamed A. Elshayeb, Jeffrey B. Hodgkin, Roger C. Wiggins, Markus Bitzer, University of Michigan, Ann Arbor, MI; University of Michigan Health System, Ann Arbor, MI; Pathology, University of Michigan, Ann Arbor, MI.

Background: Parietal epithelial cells (PECs) play a key role in glomerulosclerosis. We therefore developed a method for quantification of PECs usable in routine FFPE archival histologic sections. Initial data are reported.

Methods: PECs were identified by anatomic position, lining the inner aspect of Bowman's Capsule (BC), and positive immune-peroxidase nuclear staining for PAX8. The morphometric method used principles previously reported for podocyte quantitation in which observed PEC nuclear number per glomerular tuft profile is corrected according to nuclear size, shape and section thickness (Venkatareddy et al. JASN 2014). 600 glomerular profiles were assessed in 12 normal human kidneys obtained at nephrectomy (mean age: 64.9, range: 46-82y). Glomerular and tubule-interstitial parameters were assessed through quantitative computer-assisted image analysis on 50 glomeruli per case. Qualitative glomerular characteristics were assessed in all glomeruli (mean 198 glomeruli per sample, range 71-392). Quantitative morphometric parameters were evaluated in 50 randomly selected glomeruli per sample.

Results: PECs identified as cells lining the inner aspect of BC were >99% PAX8 positive. In contrast <5% of glomerular tufts contained PAX8-positive nuclei. In the normal human kidney sample tested the BC surface area was 159 (range 110-216) x10^2 mm^2. The number of PECs per glomerular tuft (total BC surface area) was 407 (range 70-722). The estimated average PECs per area of BC was 25.3 (range 5.2-43.6) PECS/10^6 µm^2. Average PEC cell area was 578µm^2 (range 247-2103 µm²). PEC density correlated with podocyte nuclear density (p=0.02; r=0.64), mean podocyte volume (p=0.001; r=-0.82) and segmental glomerular sclerosis (p=0.004; r=-0.76), and eGFR (p=0.05; r=0.75).

Conclusions: We report a method for quantitatively evaluating PECs. PEC number per glomerulus, density and estimated cell size varies substantially between individual samples. Furthermore, these PEC parameters significantly correlate with both podocyte parameters and clinical phenotype in the small sample evaluated. Additional samples from our human kidney biobank (>150) will be used to confirm and extend these data.

TH-PO078

Microecological Imbalance of Intestinal Microflora Activates Renal Renin-Angiotensin System to Contribute to the Progression of Early Diabetic Nephropathy
Chenchen Lu, Kun ling Ma, Yang Zhang, Guihua Wang, Zebo Hu, Peipei Chen, Jian Lu. Zhongda Hospital, Southeast University Medical School, Nanjing City, China; Institute of Nephrology, Zhong Da Hospital, Nan Jang City, China.

Background: It is well-known that activated renal rennin-angiotensin (RAS) plays a key role in the development of early diabetic nephropathy (DN). However, the initiating factors and potential mechanisms led to RAS activation have not been fully elucidated. This study aimed to investigate the underlying mechanisms of how abnormal intestinal microenvironment activates RAS to contribute to early injuries of DN.

Methods: Streptozotocin-induced diabetic rat model was randomly divided into three groups: Control group, diabetic group (DM), and diabetic-antibiotics (DM-AB) group. The rats of DM-AB group were fed for 8 weeks with regular chow and antibiotic mixed liquor (ampicillin 1g/L + vancomycin 0.5g/L + neomycin 1g/L + amphotericin B 0.1g/L). Gene sequencing of intestinal microflora was carried out using 16S-rDNA pyrosequencing technique. The morphological changes to the renal pathology and ultra-structures were checked by pathological staining and electron microscopy. The plasma RAS components were determined by radioimmunossay. The protein expressions of RAS components in the kidneys were determined by immunohistochemical staining and Western blot.

Results: Compared with control group, DM group showed with abnormal intestinal microflora, which significantly increase the production of acetate in the plasma. There were increased ACR, thickened glomerular basement membrane, podocyte foot process effacement in the kidneys of DM group compared with the controls. The plasma levels of angiotensin II and the protein levels of angiotensinogen, angiotensin II, renin, angiotensin-converting enzyme, and angiotensin II type 1 receptor in the kidneys of DM group were significantly increased compared to the controls, which were positively associated with kidney injuries of DM group. However, in DM-AB group, after intestinal microflora were completely killed by antibiotics, kidney damage and RAS activation were weakened accordingly compared with the DM group.

Conclusions: These findings suggest that microecological imbalance of intestinal microflora might be a new mechanism for the progression of early DN, which leads to kidney injuries via the RAS activation.

TH-PO079

Glomerular Enhancer of Zeste Homolog-2 (EZH2) Histone Methyltransferase Reduces Glomerular Endothelial Glycocalyx during Diabetic Nephropathy by Regulating Hyaluronan Synthesis
Jielong Qiu, Johan Van der vlag, Jacob van den Born, Benito Yard, Jan-Luk Hillebrands, Jan A. Kamps, Guido Krenning. Dept. of Nephrology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; Dept. of Pathology and Medical Biology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands; Dept. of Nephrology, Endocrinology and Rheumatology, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany; Dept. Internal Medicine, Div. Nephrology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands.

Background: Diabetic nephropathy (DN) is the leading cause of end-stage renal failure worldwide. The glomerular endothelial glycocalyx is the first barrier that prevents leakage of circulating proteins into the extracellular milieu. In the glomerulus, the glycocalyx failure. The polycomb group methyltransferase Enhancer of Zeste Homolog 2 (EZH2) inhibits expression of its target genes through methylation of lysine 27 on histone 3 (H3K27me3). We recently performed a targeted screen for genes involved in glycocalyx turnover, which indicated that EZH2 inhibits glycoalyx synthesis in glomerular endothelial cells. We hypothesized that EZH2 activity is increased in the glomerular endothelium during DN thereby reducing glycoalyx synthesis.

Methods: H3K27me3 was analyzed in glomerular endothelial cells by immunofluorescence in BTBR- ob/ob mice, a mouse model for DN. Glycoalyx in these mice was measured by the binding of fluorescein-labeled wheat germ agglutinin. In glomerular endothelial cells, EZH2 was silenced by RNAi. Gene expression was assessed by Quantitative Real-time PCR.

Results: EZH2 H3K27me3 in glomerular endothelial cells was increased 1.5-fold compared to non-diabetic mice (p=0.026). Albumin-creatinine ratios of BTBR- ob/ob mice correlated with the increase in H3K27me3 (p=0.044; r=0.674). A 2-fold loss of glomerular glycoalyx was observed in BTBR- ob/ob mice (p=0.002). Silencing of EZH2 in glomerular endothelial cells led to a decrease in H3K27me3 and an 8-fold increase in the hyaluronan synthesizing enzyme HAS1 (p=0.001). ENCODE database analysis revealed a binding site for EZH2 in the HAS1 gene, suggesting that HAS1 is a direct target of EZH2. Interestingly, the hyaluronan degrading enzymes, HYAL1 (p=0.002), HYAL2 (p=0.015), and HYAL3 (p=0.014) were all decreased upon knockdown of EZH2.

Conclusions: In our data, we suggest that EZH2-mediated epigenetic changes reduce endothelial glycocalyx via reduction of hyaluronan in DN.

TH-PO080

Depletion of Gprc5a Promotes Development of Diabetic Nephropathy
Jiajuo Patrakka, Mark Lal, Sonia Zambrano Sevilla, Astrazeneca, Gothenburg, Sweden; Karolinska Institutet, Huddinge, Sweden; None, Seville, Spain.

Background: Renal glomeruli are the primary target of injury in diabetic nephropathy (DN). In the glomerulus, damage to podocyte cells plays a critical role in the disease progression. Transforming growth factor beta (TGF-β) signaling is involved in this process but mechanisms regulating this pathway in podocytes are poorly understood. G-protein coupled receptors (GPCRs) have been the most successful protein class for drug discovery as 20-40% of currently clinically approved drugs are targeting them. In this study, we investigated glomerular GPCRs in DN with the aim of identifying novel molecular targets for pharmaceutical intervention.

Methods: Results: We performed high throughput molecular profiling of GPCRs in human glomeruli and identified an orphan GPCR, Gprc5a, as a novel highly podocyte-specific molecule whose expression was significantly down-regulated in patients with DN. Inactivation of Gprc5a in mouse resulted in thickening of the glomerular basement membrane and activation of mesangial cells, which are two hallmark features of DN in humans. Gprc5a-deficient animals were susceptible to diabetic glomerular damage as demonstrated by higher albuminuria and more severe histological changes after induction of diabetes with streptozotocin. Mechanistically, we show that Gprc5a modulates TGF-β signaling pathway in podocytes through activation of epidermal growth factor receptor (EGFR).

Conclusions: We conclude that depletion of Gprc5a promotes the progression of DN. Gprc5a can provide us a possibility to develop pharmaceutical tools to manipulate pathogenic signaling pathways in a podocyte-specific manner.

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

TH-PO081

Palavatorenate, Selective Retinoic Receptor-γ Agonist, Inhibited Both BMP4 and TGF-β Signaling Pathways in Diabetic Nephropathy
Yui Fujita, Tatsuya Tominaga, Masanori Tamaki, Taichi Murakami, Seiji Kishi, Kojiro Nagai, Hideharu Abe, Toshio Doi, Tokushima University, Graduate School of Biomedical Sciences, Tokushima, Japan.

Background: We have reported that the BMP4 / Smad1 signaling pathway play a key role in the development of diabetic nephropathy (DN). In recent year, retinoid receptor
agonists have been focused as therapeutic targets for progressive fibrosis. In this study, we examined the effect of palovarotene, selective retinoic acid receptor agonist, on DN.

**Methods:** 12-15 weeks old ICR mice were rendered diabetic by streptozotocin (STZ). Palovarotene was administered 2 times per week intraperitoneally at 60 µg/kg from 4 weeks after STZ injection. Histological analysis was performed at 12 weeks after administration of palovarotene. BMP4 and TGF-β signaling pathways were analyzed with in vivo mouse mesangial cells to reveal the mechanism of palovarotene treatment.

**Results:** Diabetic mice showed significant extracellular matrix expansion associated with increased expression of phosphorylated β Smad1 and reduced expression of Col4 in mesangial cells. The study has unveiled that palovarotene exerts the suppressive effect for both BMP4 and TGF-β signaling pathways. The findings suggest that the chemicals that targeted a retinoic acid receptor is useful as new therapy for DN.

**Conclusions:** Palovarotene has regulated the downstream molecules of the BMP type I receptors, and inhibited β Smad1 and reduced expression of Col4 in mesangial cells. The study has revealed that palovarotene exerts the suppressive effect for both BMP4 and TGF-β signaling pathways. The findings suggest that the chemicals that targeted a retinoic acid receptor is useful as new therapy for DN.

---

**TH-PO082**

**Plasminogen Activator Inhibitor-1 (PAI-1) Modulates Parietal Epithelial Cell (PEC) Movement and Apoptosis after Podocyte Injury**

**Xin Li,1 Marcus J. Moeller,1 Taji Matsukasa,2 Haichun Yang,4 Agnes B. Fogo,1 The Medicine College of Shanghai JiaoTong University, Shanghai, China; 2Tokai University School of Medicine, Isehara, Japan; 3University of Aachen, RWTH, Aachen, Germany; 4Vanderbilt University Medical Center, Nashville, TN.**

**Background:** Parietal epithelial cells (PECs) can migrate on to the glomerular tuft and serve as either progenitor cells to replace podocytes or proliferative cells to secret matrix in response to injury. Claudin-1 is expressed on all PECs, while CD44 is expressed on activated PECs. PAI-1 affects matrix turnover, cell migration and mediates renal fibrosis. The effect of PAI-1 on PECs after podocyte injury, PAI-1 expression on PECs increases. We aimed to study effects of PAI-1 on PECs migration, activation and transdifferentiation after podocyte injury.

**Methods:** NEP25 mice express human CD25 only on podocyte, and podocyte injury is induced by exogenous immunoxxin (LMB2). By mating NEP25/PDAP1 with PEC-rTGFβ+ mice, we generated inducible PEC specific PAI-1 knockout mice (PAI-1-KD, n=8) and control (WT, n=10). All mice underwent doxycycline induction at 9 weeks old followed by LMB2 injection at 10 weeks, and were sacrificed 10 days later.

**Results:** LMB2 induced similar albuminuria and segmental glomerular sclerosis in WT and PAI-1 KD mice. Podocyte density, measured by WT-1 staining, was similar in the two groups (WT 3.9±0.8 vs PAI-1 KD 3.7±0.3 /10^4/mm²), but synaptopodin expression was higher in PAI-1 KD (18.7±4.4% vs WT 13.0±5.9%, P<0.05). By double staining, we assessed the proportion of PECs expressing nephrin, a podocyte differentiation marker, finding 14.1±5.5% (pNS). CD44+ cells expressing nephrin were also similar in the two groups (WT 17.7±9.2 vs PAI-1 KD 13.0±5.9%, pNS).

**Conclusions:** We conclude that knockdown of PAI-1 increased the presence of activated PEC on the tuft and preserved podocyte differentiation, but does not affect PECs transdifferentiation to podocyte in response to injury.

**Funding:** NIDDK Support

---

**TH-PO083**

**Epigenetics-Induced Down-Regulation of MicroRNA (miR)193a Determines APOL1 Expression in Parietal Epithelial Cells**

**Vinod Kumar,1 Xiqian Lan,1 Seyede Shadafarin Marashi Shoshtari,2 Sheowdell Cheowdhury,1 Manali Bhooplapur,1 Catherine Meyer-Schwesinger,3 Ashwani Malhotra,1 Karl Skorecki,4 Pravin C. Singhal,4 Feinstein Institute for Medical Research, Manhasset, NY; 2University of Pittsburgh, Pittsburgh, PA; 3Feinstein Institute for Medical Research, New York, NY; 4North Shore LIJ Health System, Great Neck, NY.**

**Background:** APOL1 is expressed in kidneys of some primate species, including humans. However, the role of kidney cell, both in vitro and in vivo studies. We hypothesize that VDA is an inducer of APOL1 in PECs and plays an important role in the maintenance of PD homeostasis.

**Methods:** Immortalized human PECs proliferate at 33°C but enter into a transition mode (differentiated to PDs) after incubation in special media and collagen/fibronectin substrate at 37°C. PECs and differentiated PECs molecular phenotype (WT1 and podocalyxin vs. PAX2 and Claudin 1) was characterized. To determine the effect of VDA on the entry of PECs transition at 33°C, PECs were incubated in media containing either buffer or VDA (EB1089, 10 nM) for 48 hours at 33°C (n=4). To evaluate the dose response effect, PECs were incubated in media containing different concentrations of VDA (0, 1, 10, 25, 50 and 100 nM) for 48 hours at 33°C (n=4). To determine the effect of other agonists, PECs were incubated in media containing 100 nM VDA with/without VDA (10 nM) or IFN-γ (10 nm). Proteins and RNAs were extracted. Protein blots were probed for APOL1, DNMT1, 124, podocin, PAX2, Claudin 1, and GAPDH. CDNAs were probed for APOL1, WT1, and podocalyxin. RNAs were assayed for miR193a.

**Results:** VDA induced APOL1 protein expression in PECs in a dose dependent manner. IFN-γ also induced APOL1 expression in PECs. Both VDA and IFN-γ also enhanced (2 to 3 fold) transcription of APOL1 in PECs. VDA-induced APOL1 expression was associated with down regulation of miR193a (2.3 fold), PAX2 (1.8 fold) and enhanced expression of WT1 (2.2 fold), podocalyxin (2.5 fold), and podocin (1.8 fold) (both mRNA and protein levels). However, the effects of VDA were partially reversed both by increasing miR193a or silencing APOL1 expressions.

**Conclusions:** VDA stimulates PECs transition through induction of APOL1 and down regulation of miR193a.

**Funding:** NIDDK Support

---

**TH-PO084**

**VDR Agonist (VDA) Facilitates Transition of Parietal Epithelial Cells (PECs) to Podocytes (PDS)**

**Molecular Phenotype through Induction of APOL1**

**Vinod Kumar,1 Xiqian Lan,1 Seyede Shadafarin Marashi Shoshtari,2 Rukhsana Aslam,2 Kamesh R. Ayasolla,1 Catherine Meyer-Schwesinger,2 Ashwani Malhotra,1 Karl Skorecki,4 Pravin C. Singhal,4 Feinstein Institute for Medical Research, Great Neck, NY; 2Feinstein Institute for medical research, Glenoaks, NY; 3Immunology and Inflammation, Feinstein Institute for Medical Research, New York, NY; 4North Shore LIJ Health System, Great Neck, NY; 6Rambam Health Care Campus, Haifa, Israel; 7The Feinstein Institute for Medical Research, Manhasset, NY; 8University of Hamburg, Hamburg, Germany; 9Immunology and Inflammation, Feinstein Inst.Med research and NSLIJ, Manhasset, NY.**

**Background:** APOL1 is expressed intracellularly and also a minor component of circulating lipids-rich trypanolytic multiprotein complexes in certain primate species including humans. However, the role of kidney cell, both in vitro and in vivo studies. We hypothesize that VDA is an inducer of APOL1 in PECs and plays an important role in the maintenance of PD homeostasis.

**Methods:** Immortalized human PECs proliferate at 33°C but enter into a transition mode (differentiated to PDs) after incubation in special media and collagen/fibronectin substrate at 37°C. PECs and differentiated PECs molecular phenotype (WT1 and podocalyxin vs. PAX2 and Claudin 1) was characterized. To determine the effect of VDA on the entry of PECs transition at 33°C, PECs were incubated in media containing either buffer or VDA (EB1089, 10 nM) for 48 hours at 33°C (n=4). To evaluate the dose response effect, PECs were incubated in media containing different concentrations of VDA (0, 1, 10, 25, 50 and 100 nM) for 48 hours at 33°C (n=4). To determine the effect of other agonists, PECs were incubated in media containing variable concentrations of IFN-γ (0, 5, 10, and 20 nM) for 48 hours at 33°C. To examine a causal relationship, PECs were transfected with either control or miR193a plasmids/siRNA APOL1, followed by treatment with/without VDA (10 nM) or IFN-γ (10 nm). Proteins and RNAs were extracted. Protein blots were probed for APOL1 and reprogrammable cell, podocin, PAX2, Claudin 1, and GAPDHS. cDNAs were probed for APOL1, WT1, and podocalyxin. RNAs were assayed for miR193a.

**Results:** VDA induced APOL1 protein expression in PECs in a dose dependent manner. IFN-γ also induced APOL1 expression in PECs. Both VDA and IFN-γ also enhanced (2 to 3 fold) transcription of APOL1 in PECs. VDA-induced APOL1 expression was associated with down regulation of miR193a (2.3 fold), PAX2 (1.8 fold) and enhanced expression of WT1 (2.2 fold), podocalyxin (2.5 fold), and podocin (1.8 fold) (both mRNA and protein levels). However, the effects of VDA were partially reversed both by increasing miR193a or silencing APOL1 expressions.

**Conclusions:** VDA stimulates PECs transition through induction of APOL1 and down regulation of miR193a.

**Funding:** NIDDK Support

---

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

124
HIV Activates Epithelial Mesenchymal Transition (EMT) and Mammalian Target of Rapamycin (mTOR) Pathways in Parietal Epithelial Cells (PECs) via Down Regulation of MicroRNA193a

Vinod Kumar,1 Xiqian Lan,1 Rukhsana Aslam,2 Ali Hussain,3 Seyched Shadafarin Marashi Shoshtari,1 Manali Bhooplapur,2 Sheetal Chowdhary,1 Catherine Meyer-Schweisinger,1 Ashwani Malhotra,4 Pravin C. Singhal,3 Feinstein Institute for Medical Research, Great Neck, NY; 1Feinstein Institute for medical research, Glenoaks, NY; 2Feinstein Institute of Medical Research, New York, NY; 3Immunology and Inflammation, Feinstein Institute for Medical Research, New York, NY; 4North Shore LIJ Health System, Great Neck, NY; 5The Feinstein Institute for Medical Research, Manhasset, NY; 6University of Hamburg, Hamburg, Germany; 7Immunology and Inflammation, Feinstein Inst.Med research and NSLIJ, Manhasset, NY.

Background: Micro-RNA (miR) 193a has been considered to be a tumor suppressor gene and its down regulation has been reported to stimulate EMT and mTOR pathways in cancer cells. HIV-associated nephropathy is characterized by collapsing variant of focal segmental glomerulosclerosis; in this glomerular phenotype, proliferating cells in Bowman’s space are considered to be of PEC lineage; however, the involved mechanism for PECs proliferation in HIV milieu is not clear. We asked whether HIV was inducing PECs proliferation through down regulation of miR193a.

Methods: Vector (PECV) - and HIV (NL4-3; PECHIV)-transduced human immortalized PECs were growth arrested and then incubated media (containing 1% serum) for 48 hours (n=4). In another set of experiments, PECs were incubated in media containing either buffer (control) or a microRNA193a inhibitor (25 nM) for 48 hours (n=4). To examine a causal relationship, PECV and PECHIV were transfected with either control or miR193a plasmids (n=4). In vivo studies, kidneys were harvested from 4-week old control (FVB/N) and HIV-transgenic (Tg26) mice. Proteins and RNAs were extracted. Protein blots were probed for EMT (α-SMA, SNAIL, and fibronectin), mTOR (p-mTOR, p-7056k, p-4EBP, and p-reef) markers and reprogrammed for actin. RNAs were assayed for miR193a. Renal cortical sections were immunolabeled for α-SMA, SNAIL, and p-mTOR.

Results: PECHIV and renal tissues of HIVAN mice displayed enhanced (P<0.05 vs. PECV/FVB/N) expression of EMT markers including alpha-SMA, fibronectin, and SNAIL. Similarly, PECHIV and renal tissues of HIVAN mice showed enhanced (P<0.05 vs. P<0.001 vs. PECV/FVB/N) of p-eEF, indicating activation of mTOR pathway. PECHIV and renal tissues of HIVAN mice displayed fold decrease in miR193a levels (P<0.05) at baseline, had higher rates of the composite outcome (P<0.005) and lowest rates of remission (P<0.003). Clusters 2 and 3 did not have significantly different demographics, baseline clinical characteristics, or outcomes. Microvillous transformation was not predictive of clusters, but was independently predictive of remission (p<0.001).

Conclusions: The NDPSS descriptor-based assessment of EM uncovered the combination of LCM followed by LC-MS/MS, using PEG-FASP and MAX-SPE for glomerular samples from random kidney sections, as demonstrated by differentially identified proteins and clustering of glomerular and random kidney samples.

Funding: Private Foundation Support

Poster/Thursday

TH-PO086

Ultrastructural Descriptors for Clinically Relevant Categorization of MCD/FSGS NEPTUNE Patients

Amarjeet Kaur,1 L. Qiu,2 A. R. Smith,3 Carmen Avila-Casado,4 Jeffrey B. Hodgkin,5 Lawrence B. Holzman,6 Brenda W. Gillespie,7 L. Barisoni,8 Virginia Royal,9 University of Pennsylvania, Philadelphia, PA; 1University of Toronto, Toronto, ON, Canada; 2An Arbor Research Collaborative for Health, Ann Arbor, MI; 3Univestit de Montreal, Montral, QC, Canada; 4University of Miami, Miami, FL; 5University of Michigan, Ann Arbor, MI.

Background: Ultrastructural features of renal biopsies are rarely used in conventional classification systems, and their reporting is often limited to a few parameters. The aim of this study was to investigate the prognostic value of 12 electron microscopy (EM) descriptors from the NEPTUNE Digital Pathology Scoring System (NDPSS) as a carrier, adapted from previously described methods for microdissected colon tissue.

Methods: Study pathologists scored digital EM images from 172 MCD/FSGS patients using the NDPSS. We performed hierarchical clustering of patients based on EM descriptors. We compared demographics, clinical characteristics, time to proteinuria remission, and time to the composite of 40% reduction in eGFR or ESRD across the clusters. We used penalized multinomial regression with cross-validation to test descriptors driving cluster membership and Cox proportional hazards models to link EM descriptors to clinical outcomes.

Results: Of the 3 clusters found [figure], cluster 1 patients had the most EM damage, were older (p<0.018), had lower eGFR (p<0.001) and higher urine protein creatinine ratio (p=0.029) at baseline, had higher rates of the composite outcome (p<0.005) and lower rates of remission (p=0.033). Clusters 2 and 3 did not have significantly different demographics, baseline clinical characteristics, or outcomes. Microvillous transformation was not predictive of clusters, but was independently predictive of remission (p<0.001).

Conclusions: The NDPSS descriptor-based assessment of EM uncovered the significance of ultrastructural parameters usually under-reported in clinical practice. EM descriptor-based patient clusters predicted remission and progression outcomes, reflecting quantifiable transitional vs. permanent damage.

Funding: NIDDK Support

Poster/Thursday

TH-PO087

Laser Capture Microdissection and Liquid Chromatography Tandem-Mass Spectrometry for Small Amounts of Formalin-Fixed Paraffin Embedded Kidney Tissue

Sophie J. Nagelkerken,1 George Janssen,2 Kimberley Verraar,3 Peter Van veelen,4 H. J. Baelde,4 Jan A. Bruijn,5 Ingeborg M. Bajema,1 Department of Pathology, Leiden University Medical Center, Leiden, Netherlands; 2Center for Proteomics and Metabolomics, Leiden University Medical Center, Leiden, Netherlands.

Background: Liquid chromatography tandem-mass spectrometry (LC-MS/MS) is a sensitive and specific technique for in depth protein identification but diagnostic kidney material is scarce, limiting the number of protein identifications. Only a few studies have used this technique for protein identification in formalin fixed paraffin embedded (FFPE) glomerular material and only one used a practical amount that can be used for diagnostic biopsies. Therefore, we optimized a work-flow of laser capture microdissection (LCM) of glomeruli, followed by LC-MS/MS on FFPE tissue for a minimal amount of tissue with a maximum protein yield.

Methods: One FFPE tissue block of a normal human kidney was utilised. Cross-sections of randomly selected kidney and glomeruli were collected from 6 µm sections, mounted on a 1.0 PEN membrane, using LCM. Protein extraction and digestion was performed using filter aided sample preparation (FASP) with polyethylene glycol (PEG) as a carrier, adapted from previously described methods for microdissected colon tissue. Samples were purified using mixed anion exchange solid phase extraction (MAX-SPE) and analysed using LC-MS/MS.

Results: Using the PEG-FASP protocol, we established the optimum amount of tissue to be 3 µl, based on 605 protein identifications, compared to 216 and 693 identifications in 1 and 10 µl tissue respectively. In a reproduction analysis of 5 experiments, using both random kidney and glomerular tissue, an average of 457 and 228 proteins were identified respectively. The method was able to distinguish glomerular samples from random kidney samples, as demonstrated by differentially identified proteins and clustering of glomerular and random kidney samples.

Conclusions: The relative number of proteins detected was comparable to or higher than reported in previous studies using FFPE glomerular tissue. The presented work-flow expands the potential for novel protein identification in glomerular diseases, while keeping the amount of tissue small enough for diagnostic practicality. Therefore, the combination of LCM followed by LC-MS/MS, using PEG-FASP and MAX-SPE for sample preparation, is a suitable and promising technique for diagnostic applications, especially when specific proteins are overexpressed or abundant within glomeruli.

Funding: Private Foundation Support

Poster/Thursday

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

Underline represents presenting author.

125
Background: Accurate detection and counting of glomeruli in renal biopsies is important to assess biopsy adequacy, and for diagnostic accuracy (for example, the percentage of sclerotic glomeruli). A recent evaluation indicates that traditional methods can under-count glomeruli by ~50% when compared to more labor-intensive annotation methods. In recent years, deep learning has significantly advanced in a variety of tasks including image recognition, classification, and segmentation. To improve the accuracy of glomerular enumeration in renal biopsy evaluation, we are developing a convolutional neural network deep learning model to locate glomeruli.

Methods: Twenty-two biopsy sections stained with hematoxylin and eosin were imaged using whole slide scanners (Aperio and Hamamatsu) for use in training and validation of the model. A custom application was developed to record the position of glomeruli in each biopsy with masks processed as geometries (boundaries stored rather than pixel values). This approach minimized file sizes and supported complex operations. Training and validation was conducted at the NIH high-performance computing facility employing multiple NVidia K20 GPU equipped nodes. The keras software package was utilized to define and train the neural network. Data augmentation and a modestly sized training and validation set (3 convolutional layers, a single hidden fully connected layer and an output layer) were used to optimize performance without overfitting the dataset.

Results: The accuracy of the neural network model was 91%. The model performance was robust to changes in stain intensity and the scanner used for imaging. Importantly, manual review of disagreements revealed errors in annotation (the model correctly identified glomeruli that had been missed by the human annotator).

Conclusions: Deep learning techniques can be utilized to accurately identify glomeruli in renal biopsies and can be scaled to handle the large images generated by whole slide scans. A convolutional neural network model may help to improve the accuracy of glomeruli localization and enumeration, without the need for human intervention. This model could be leveraged for classification of glomerular morphology.

Funding: NIDDK Support

TH-P0091

Serum IgA/C3 Ratio May be a Useful Serologic Marker to Predict Remission and Disease Progression in Patients with Adult Onset IgA Vasculitis
Takeyuki Takamura,1 Fumihiko Furuya,1 Kenichiro Kitamura,2 1University of Yamanashi, Chuo, Japan; 2University of Yamanashi School of Medicine, Chuo, Japan.

Background: In adult cases, IgA vasculitis (IgAV) typically represents severe renal dysfunction. Various clinical and histological parameters have been associated with an increased risk of progressive renal disease in several studies. However, there are no serologic markers that can be employed to assess disease activities or to predict renal outcome in IgAV. On the other hand, recently the serum IgA/C3 ratio has been suggested to serve as a marker for the progression of IgA nephropathy.

Methods: The aim of this study was to examine whether the serum IgA/C3 ratio serves as a marker to predict remission and disease progression in adult onset IgAV. We studied 37 patients with adult onset IgAV (mean follow-up of 34.2±5.3 months) with a mean age of 50.8±3.7 years old. Based on the available medical records, we retrospectively evaluated clinical data, IgA/C3 ratio, and kidney biopsy findings according to the ISKD classification.

Results: The serum IgA/C3 ratio at the renal biopsy was significantly lower in patients with remission (no hematuria and urinary T-UP/C <0.15g/gCr) compared to those with non-remission group (2.52±0.16 vs 3.69±0.52, p<0.05); there were no differences in ISKD classification. In addition, patients with small reduction in eGFR (<25%) showed significantly lower serum IgA/C3 ratio than those with large decline in eGFR (<25%) (2.57±0.18 vs 4.42±0.77, p<0.05).

Conclusions: To our knowledge, this is the first report to demonstrate that the serum IgA/C3 ratio can be a good marker to predict remission and disease progression in patients with adult onset IgAV. However, long-term follow-up and further studies are required to clarify the validity of the serum IgA/C3 ratio.

TH-P0092

Clinical Impact of Modified MESC Classification for Renal Outcome among Japanese IgAN Patients
Ahmad B. Kailan,1 Yoshinari Yasuda,2 Takayuki Katsuno,2 Sawako Kato,2 Takahiro Imaizumi,3 Takaya Ozeki,3 Manabu Hishida,1 Naotaka Tsuboi,2 Shiochi Maruyama,2 1Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan; 2Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan; 3Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan; 4Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan; 5Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan; 6Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan.

Background: Our previous study revealed that MES and crescent (C) in the Oxford classifications could not predict real outcome among adult Japanese IgAN patients, probably because that Japanese IgAN patients were diagnosed in earlier and more active stage. The purpose of this study was to modify the cutoff point of MESC classifications to adequate for Japanese patients with IgAN.

Methods: A total of 86 adult IgAN patients diagnosed from 2001 to 2009 by renal biopsy retrospectively evaluated at Nagoya University Hospital by seven nephrologists. The ROC curve analyses were used to modify the traditional cutoff points for MESC. Then the modified and traditional MESC score was analyzed in association with renal outcome, defined as a 50% increase in serum creatinine.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>DM type</th>
<th>MESC</th>
<th>MESS</th>
<th>Renal biopsy</th>
<th>MESC category</th>
<th>MESS category</th>
<th>eGFR (ml/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 (21-22)</td>
<td>Male</td>
<td>Type 1</td>
<td>I</td>
<td>I</td>
<td>Non-aplicable</td>
<td>I</td>
<td>I</td>
<td>75 (57-102)</td>
</tr>
<tr>
<td>35.1±2.4</td>
<td>Female</td>
<td>Type 1</td>
<td>I</td>
<td>I</td>
<td>Non-aplicable</td>
<td>I</td>
<td>I</td>
<td>65 (40-100)</td>
</tr>
<tr>
<td>35 ± 10</td>
<td>Female</td>
<td>Type 2</td>
<td>II</td>
<td>II</td>
<td>Non-aplicable</td>
<td>II</td>
<td>II</td>
<td>50 (20-75)</td>
</tr>
</tbody>
</table>

Values are depicted as mean ± SD, median [min-max] or as number of patients(%).
Results: Baseline characteristics [median and IQR] of study subjects were: age 36 [24-46] years, female, proteinuria 1.2 [0.7-1.8] g/day, and serum creatinine (eGFR) 0.9 [0.7-1.1] mg/dL. The modified cutoff point for MESC was a 40%, a 10%, a 20%, and a 10% in glomeruli respectively. Number and proportion of traditional vs modified MESC were M1: 24 (27.9%) vs 30 (34.9%), E1: 35 (40.7%) vs 17 (19.8%), S1: 57 (66.3%) vs 20 (23.8%) and C1:45 (52.3%) vs 32 (37.2%). During a median follow-up period of 6.8 years, 13 (15%) patients achieved the renal outcome. In univariate analyses, the traditional MESC was not associated with renal outcome, while in modified cutoff point M (HR 2.99, p= 0.05), E (HR 4.94, p= 0.004), S (HR 3.51, p= 0.03) and C (HR 3.67, p< 0.03) were significantly associated with renal outcome. ROC curve analyses (Fig 1) revealed significant predictive value in modified MESC classification (AUC=0.851).

Conclusions: The modified cutoff points for MESC significantly improved predictive value for renal outcome in Japanese patients with IgAN.

Funding: Other U.S. Government Support

TH-PO093

The GRACE IgA Nephropathy in Indians (IgAN) Study

Succena Alexander,1 Vijayakumar Theophilus-Sunder,1 Vinoi G. David,1 Anjali Mohapatra,1 Anna T. Valson,2 SaniLeah T. Kakede,2 Charles D. Pusey,3 Mohamed R. Daha,3 Jonathan Barratt,3 John Fechally,3 George John,3 Santosh Varughese,1 Christian Medical College, Vellore, India; 2University of Leicester, Leicester, United Kingdom; 3Imperial College London, London, United Kingdom; 4Royal Brisbane and Women’s Hospital, Brisbane, NSW, Australia; 5Leiden University Medical Center, Leiden, Netherlands.

Background: In India, about 30-40% IgAN patients present with nephrotic syndrome and renal dysfunction and progress rapidly.

Methods: Prospective longitudinal single center cohort. Inclusion Criteria: Age ≥18 years. Renal biopsy proven primary IgA nephropathy. CKD EPI eGFR > 10ml/min/1.73m². Treatment naive. Definitions: Rapid Progressor (RP): IgAN patients with ≥5ml/min/1.73m²/year fall in glomerular filtration rate (GFR) as estimated by the CKD EPI equation. Slow/Non Progressor (SNP): IgAN patients with <5ml/min/1.73m²/year fall in CKD EPI eGFR. End of study outcome (EOS): Composite end-point of 50% decline in eGFR with eGFR <10ml/min/1.73m², RRT or death whichever occurs earlier.

Results: 165 patients were included. Refer table for baseline parameters. Average in-center follow up duration of 135 patients was 5.0 ± 4.4 months. There were 82/135 (60.7%) SNPs and 53/135 (39.3%) RPs at follow-up. EOS outcome was reached in 1.2% of SNPs vs. 30.2% of RPs. The significant predictors of EOS outcome for the cohort by Cox Regression analysis are given in the figure.

Conclusions: 28% of patients were RPs at follow-up. Higher hsCRP levels were protective whereas female gender, Hb <10g/L and MEST T2 score were significant risk factors for EOS outcome.

Funding: Government Support - Non-U.S.

Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total (n=165)</th>
<th>Slow/Non Progressor (n=135)</th>
<th>Rapid Progressor (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35.8±10.1</td>
<td>36.5±10.3</td>
<td>34.2±11.1</td>
</tr>
<tr>
<td>Gender M/F</td>
<td>126 (76.4%)</td>
<td>63 (46.9%)</td>
<td>63 (21%)</td>
</tr>
<tr>
<td>Serum albumin (g/dL) &lt;5 SD</td>
<td>4.0±0.3</td>
<td>4.0±0.3</td>
<td>4.5±0.4</td>
</tr>
<tr>
<td>Proteinuria (mg/dL, %) ≥0.5</td>
<td>56 (34.4%)</td>
<td>24/1 (18%)</td>
<td>25/1 (83%)</td>
</tr>
<tr>
<td>Serum CRP (mg/dL, %) ≥5</td>
<td>34/12 (20.9%)</td>
<td>13/4 (10%)</td>
<td>20/8 (67%)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL) ≥1.1</td>
<td>85 (52.3%)</td>
<td>37/8 (27.7%)</td>
<td>48/12 (80%)</td>
</tr>
<tr>
<td>30/90 [(g/dL)] &gt;5</td>
<td>30/10 (18.5%)</td>
<td>13/4 (10%)</td>
<td>17/6 (57%)</td>
</tr>
<tr>
<td>CKD EPI estimate of GFR (mg/dL) ≥7.8 (SD)</td>
<td>46.2±10.1</td>
<td>56.9±27.8</td>
<td>82.2±34.6</td>
</tr>
<tr>
<td>Proteinuria (g/dL) ≥0.5</td>
<td>3.7±1.7</td>
<td>3.7±1.7</td>
<td>3.7±1.7</td>
</tr>
<tr>
<td>MEST T1 (g%)</td>
<td>137 (83.1%)</td>
<td>70 (52%)</td>
<td>67 (22%)</td>
</tr>
<tr>
<td>MEST T2 (g%)</td>
<td>70 (43.4%)</td>
<td>39 (29%)</td>
<td>31 (10%)</td>
</tr>
</tbody>
</table>

135 patients had in-center follow-up till date

Cox Regression Curves

TH-PO095

Thrombotic Microangiopathy Like Lesions in IgA Nephropathy: A Cohort Study Qinghua Cai,1 Sufang Shi,2 Jicheng Lv,3 Hong Zhang,1 1Peking University First Hospital, Beijing, China; 2Peking University, Beijing, China.

Background: Thrombotic microangiopathy (TMA)-like lesion often occurs in IgA nephropathy (IgAN), but its role in disease progression is not well established, and recent Oxford MEST-C score system doesn’t include this lesion. In this study, we aim to investigate TMA-like lesions in IgAN using a prospective IgAN database cohort in Peking University.

Methods: Patients with IgAN from 2003 to 2014 who were followed at least 1 year enrolled in this study. Kidney biopsies from all participants were re-reviewed by two investigators independently blinded to the clinical data. The TMA-like lesions
were graded according to criteria by El Karoui K et al (JASN 2012, 23(1):137) under light microscopy and were categorized as minor, focal, or severe. The percentage of stained tubules was estimated in estimated glomerular filtration rate (eGFR), end-stage kidney disease (ESRD) or death. Multivariable Cox regression model was used to evaluate TMA-like lesions for risk of IgA nephropathy.

Results: Among the 1052 patients, 985(93.6%) patients with IgA nephropathy were included in this study. Overall 194 (19.7%) had TMA-like lesions. Patients with TMA-like lesions presented a higher proportion of malignant hypertension (9.8 vs 1.0%, p<0.001), a higher blood pressure (130±19 vs 122±15 mmHg, p<0.001), severe proteinuria [2.3(1.4-4.1) vs 1.4(0.7-2.8) g/d, p<0.001] and lower eGFR (58.8±26.8 vs 86±23.9 ml/min per 1.73 m², p<0.001) at the time of the biopsy compared to those without TMA-like lesions. After a mean follow-up of 4.1 years, 75(17.8%) patients with TMA-like lesions and 89(11.3%) without TMA-like lesions reached end points (p<0.001). In a multivariable Cox regression model, after taking into account clinical and pathological indices, TMA-like lesions were frequent in IgA nephropathy and associated with high risk of renal failure. Future pathological score of IgA nephropathy should include TMA-like lesions.

Funding: Government Support - Non-U.S.

TH-PO096

IgA Nephropathy to Evaluate Effectiveness of Therapy

Results: Proteinuria, major factor of IgAN, viz., low C3, and light chain staining pattern. Subendothelial deposits, low C3 and C4 levels were common in IgAN-SD patients, whereas in IgAN-NSD, C3 and C4 levels were normal. Subepithelial deposits were noted in 51 cases (11%). Compared to IgAN-NSD, mean C3 levels were significantly lower in IgAN-SD patients (C3: 0.5±0.3, p<0.05). Light chain lambda predominance was lower in IgAN-SD patients (47% vs. 63%; p<0.05).

Conclusions: We found IgAN-SD showed the tendency to display atypical findings compared to typical IgAN features. Complement levels, localization of immunoglobulins, light chain staining pattern, and subepithelial deposits were evaluated, besides typical IgAN features. We hypothesized that glomerular FHR5 deposition at the time of biopsy, TMA-like lesion was an independent risk factor for kidney progression in IgAN (HR 1.88, 95%CI:1.30-2.72, p=0.001). Moreover, the risk for kidney failure rose as the severity of TMA-like lesions increased (mild: HR 1.66, 95%CI:1.12-2.48; moderate: 2.35, 1.49-3.90; severe: 2.99, 1.27-7.04). Other renovascular sclerosis (arterial intimal fibrosis and arteriolar hyalinosis) were not risk factors of the progression of IgAN (HR: 0.84, 95%CI:0.54-1.31, p=0.441).

Conclusions: TMA-like lesions were frequent in IgA nephropathy and were associated with high risk of renal failure. Future pathological score of IgA nephropathy should include TMA-like lesions.

Funding: Government Support - Non-U.S.

TH-PO097

Glomerular FHR5 Associates with Severity in IgA Nephropathy

Methods: Three cases were selected as independent predictors (FHR5, initial proteinuria, and initial eGFR) (p<0.05). For PUR, ST besides HG 3 were selected in group C, even after adjustment by RAS blockade, initial mean arterial pressure (MAP), initial proteinuria, and initial eGFR (p<0.05). Percent of the cases receiving steroid therapy with/without tonsillectomy (ST) and those receiving tonsillectomy with/without ST (Tons) were 79% and 41%, respectively in group A or A/C, whereas ST and Tons were 58% and 31% in group C, respectively. An effectiveness of these therapies of therapy was evaluated by multivariate Cox regression analysis to predict renal functional decline (RFD) for 1.5 years, FHR5 is an effectiveness of therapy. The cases with A or A/C but not C is a target of ST and Tons.

Results: All cases with FHR5 staining showed glomerular C staining. A greater proportion of progressive than stable patients had detectable glomerular FHR5 (18/19 progressive vs 1/17 stable patients, p<0.001). Of the 6 patients with absent FHR5, 5 (83%) had progressive compared to 13/18 stable patients, p=0.09). The average amount of proteinuria at the time of the biopsy was 1.1 g/day. Mean eGFR was 76±29 ml/min/1.73m². Pts were divided into group A or A/C (320 pts), group C (410pts), and group without A, A/C, or C (117 pts). Percent of the cases receiving steroid therapy with/without tonsillectomy (ST) and those receiving tonsillectomy with/without ST (Tons) were 79% and 41%, respectively in group A or A/C, whereas ST and Tons were 58% and 31% in group C, respectively. An effectiveness of these therapies of therapy was evaluated by multivariate Cox regression analysis to predict renal functional decline (RFD) for 1.5 years, FHR5 is an effectiveness of therapy. The cases with A or A/C but not C is a target of ST and Tons.

Conclusions: We present these cases to discuss the differential diagnosis, approach to biopsy, potential mechanisms of injury, treatment considerations and to spread awareness of this unique pattern of renal injury seen after chemotherapy.

Funding: Government Support - Non-U.S.

TH-PO098

Utility of Subgroups of the Japanese Histological Grade Classification of IgA Nephropathy to Evaluate Effectiveness of Therapy

Methods: Clinicopathological findings of IgA Nephropathy with Subepithelial Deposits were compared between patients with IgAN-SD and IgAN with no subepithelial deposits (IgAN-NSD). Complement levels, localization of immunoglobulins, light chain staining pattern, and intramembranous deposits were evaluated, besides typical IgAN features. Renal biopsy with/without tonsillectomy (ST) and those receiving tonsillectomy with/without ST (Tons) were 79% and 41%, respectively in group A or A/C, whereas ST and Tons were 58% and 31% in group C, respectively. An effectiveness of these therapies of therapy was evaluated by multivariate Cox regression analysis to predict renal functional decline (RFD) for 1.5 years, FHR5 is an effectiveness of therapy. The cases with A or A/C but not C is a target of ST and Tons.

Conclusions: We found IgAN-SD showed the tendency to display atypical findings for IgAN, viz., low C3, and light chain staining pattern. Subendothelial deposits, low C3 and C4 levels were common in IgAN-SD patients, whereas in IgAN-NSD, C3 and C4 levels were normal. Subepithelial deposits were noted in 51 cases (11%). Compared to IgAN-NSD, mean C3 levels were significantly lower in IgAN-SD patients (C3: 0.5±0.3, p<0.05). Light chain lambda predominance was lower in IgAN-SD patients (47% vs. 63%; p<0.05). Endothelial hypercellularity (E) (45% vs. 28%; P=0.029), IgA staining in glomerular capillary walls (22% vs. 8.2%; P<0.01) were higher in IgAN-SD patients. The incidence of light chain lambda predominance was lower in IgAN-SD patients (47% vs. 63%; P=0.03).

Conclusions: We found IgAN-SD showed the tendency to display atypical findings for IgAN, viz., low C3, and light chain staining pattern. Subendothelial deposits, low C3
Glomerular Gd-IgA1 was specifically detected by KM 55 mAb in all patients with IgAN and IgA-VN. In patients with IgAN and IgA-VN, Gl-d IgA1 was localized predominantly in the mesangial region as IgA deposition. Gd-IgA1 could not be detected even in patients with lupus nephritis accompanied by glomerular IgA deposition. Furthermore, HCV-related nephropathy with secondary IgA deposition after HCV infection did not show any glomerular Gd-IgA.

Conclusions: This is the first observation to clearly indicate that Gd-IgA1 could be specifically deposited in glomeruli of IgAN and IgA-VN, strongly suggesting the pathophysiological function of Gd-IgA1 in those diseases. Further studies are necessary to clarify the underlying mechanisms of Gd-IgA1 deposition and induction of renal injuries in IgAN and IgA-VN. Monoclonal antibody against Gl-d IgA1 could be a novel powerful tool to distinguish primary IgAN and IgA-VN from other renal diseases with glomerular IgA.

Funding: Government Support - Non-U.S.

TH-PO103

Urinary Biomarkers' Efficacy as a Disease-Activity Parameter for Children with IgA Nephropathy: Takegusu Hama1, Yu Tanaka, Masashi Sato, Hirohito Mukaiyama, Hiroko Tokagawa, Yuko Shimizu, Hiroaki Suzuki, Koji Nakamichi, Norishige Yoshikawa, Yuki Shima, Hiroki Sugita,1 Yuko Hayakawa.

Background: Some kinds of biomarkers from urine of IgAN patients have potential to be IgAN-IRGN, but not get diagnosed as IgAN-IRGN owing to lack of clinical history of infection. Secondary IgA nephropathy, resulting from other etiology of IgAN, could be refractory and therapeutic strategy differs from that for IgAN. Secondary IgA deposition should be considered and careful history and clinical course be monitored if we find atypical findings for IgAN.

Conclusions: This study shows that higher expression level of glomerular GCR is associated with a higher probability of steroid-induced CR and better renal outcome in IgAN.

Funding: Government Support - Non-U.S.
TH-PO104
The Oxford IgA MEST Score Is Associated with Worse Kidney Outcomes in Childhood Onset Henoch Schönlein Purpura Nephritis
Sally A. Kellett,1 Paul S. Thornor,2 Rose Chami,3 Natasha Jawa,2 Rulan S. Parekh,2 Damien G. Noone,2 The Hospital For Sick Children, Toronto, ON, Canada; 3The Hospital for Sick Children, Toronto, ON, Canada

Background: Henoch-Schönlein Purpura (HSP) is one of the commonest forms of systemic small vessel vasculitis in children, with kidney involvement occurring in 40–50% of children. Current pathological classification systems have not proved useful in determining long-term kidney outcomes in children with HSP nephritis. Aim: Determine if Oxford IgA MEST score is associated with long-term outcomes in childhood onset HSP.

Methods: This was a single-center, retrospective cohort study of children aged 0 to 18 years who presented with HSP nephritis between 2002 and 2016. Initial renal biopsies were scored based on the MEST criteria (M=mesangial hypercellularity, E=endocapillary hypercellularity, S=segmental glomerulosclerosis, T=tubular atrophy/intertstitial fibrosis) and also for presence of crescents (C=cellular or crescentic lesions) and level of C3 deposition. Analysis of disease progression, we determined if MEST score was associated with clinical outcomes at last clinical follow-up with a composite outcome of proteinuria (protein:creatinine ratio >20μmol/mmol and or eGFR <90ml/min/1.73m²) controlling for age at presentation and sex.

Results: We identified 44 children (F=63.6%) with biopsy data who were followed for at least 6 months. At presentation, median age was 8.3 yrs (IQR 5.8 – 11.5yrs) median protein:creatinine ratio was 236.9mg/mmol (IQR 151.5 – 608.9 mg/mmol). Median length of follow up was 3 yrs (0.5 to 11yrs). Pathology review determined 34.1% had a crescentic score ≥2, 63.6% had crescents of those, 85.7%, <50% and 61.4% C3 staining ≥1+. A total of 79.5% were treated with steroids and 45.5% with an ACE inhibitor or angiotensin II receptor blocker. Median GFR at first follow up was 107.4ml/ min/1.73m² (IQR 83.6 to 146.2). A MEST score ≥3 had an adjusted odds of 8.3 (95% CI 3.3–22.2) of having a poor kidney outcome when adjusted for age and sex. The presence of crescents gave an adjusted odds of 5.4 (95% CI 1.2–25.5) of reaching the composite outcome. C3 was not significantly associated with the composite outcome with adjusted odds of 1.95 [95% Cl 0.5–7.3].

Conclusions: MEST pathological score of ≥3 and presence of crescents on first biopsy in children with HSP nephritis is associated with a worse outcome by 3 years. This study suggests that Oxford IgA MEST score may be useful for disease prognosis.

TH-PO105
Prognostic Evaluation of Pediatric IgA Nephropathy Using Histological Criteria Including Macrophage Accumulation Yohei Ikekuzi,1 Yui Matsumoto,1 Hiroya Hasegawa,2 Takeshi Yamada,2 David J. Nikolic-Paterson.3 Fujita Health University School of Medicine, Toyoake, Japan; 3Monash Medical Centre, Clayton, VIC, Australia; 3Nigata University Medical and Dental Hospital, Niigata-City, Japan

Background: There is no histological classification to predict disease flare in children with IgA nephropathy (IgAN). As macrophage (MQ) accumulation correlates with histological injury, we investigated new histological criteria to predict disease flare in pediatric IgAN.

Methods: A total of 73 children with biopsy proven IgAN underwent 2 years of steroid treatment followed by a protocol biopsy and then steroid tapering. The non-flare group followed by a protocol biopsy and then steroid tapering. The non-flare group had Biopsy taken at less than 6 months and the flare group had Biopsy taken at 6 months or more. The flare group exhibited increased proteinuria during the taper or cessation of treatment (N=12, 11.6±2.3 years at biopsy, p<0.05). Histological findings were evaluated using Oxford classification. Macrophage number and phenotype was assessed by immunofluorescence.

Results: At first (diagnostic) biopsy, urine findings were comparable between the two groups, but the flare group had a higher isgA level (279±83 vs 214±87 mg/dL; P<0.05). Biopsies revealed no difference in mesangial proliferation (M), endocapillary proliferation (E), glomerulosclerosis (S), tubulointerstitial fibrosis (T), and crescent formation (C), however, the flare group had more total MQ (CD68+ cells) (p=0.05) and M1 MQ (CD68+CD86+ cells) (p=0.05). In addition, M1 MQ correlated with glomerular M, E, S, C lesions (all p<0.01). At second (protocol) biopsy, the flare group had more severe S (p=0.01) and T (p<0.05) lesions, and more glomerular and interstitial M2 MQ (CD68+CD163+ cells) (both p<0.01) vs non-flare group. In addition, M2 MQ correlated with S and T lesions (both p<0.001). ROC analyses revealed glomerular M1 MQ number >2.2 cells at first biopsy could predict disease flare by sensitivity of 83%.

Conclusions: MQ accumulation is a potential marker to predict disease flare in pediatric IgAN. The number of glomerular M1 MQ in active lesions at the first biopsy was related to flare occurrence, while glomerular and interstitial accumulation of M2 MQ in chronic lesions may predict disease flare in pediatric IgAN.

Funding: Government Support - Non-U.S.

TH-PO106
Clinical and Pathological Differences in Patients with IgA Nephropathy with IgG Deposit and Position in Glomeruli Chang Ying Xing, Yanfang Zheng. First Affiliated Hospital of Nanjing Medical University, Nanjing, China.

Background: It is not clear the clinical data, pathological changes in patients with IgAN nephropathy with or without IgG deposit in glomeruli. This paper is to explore the significance of IgG deposit in glomeruli in patients with IgAN nephropathy.

Methods: There were 327 patients with IgA nephropathy diagnosed by renal biopsy in our hospital in the past 2 years. All renal biopsy samples were examined by light microscopy and immunofluorescence. IgA nephropathy patients were divided into two groups: IgA+IgG group (n=82) with IgG deposit in glomeruli, and IgA group (n=245) without IgG deposit. Patients in IgA+IgG group were divided 2 subgroups according to the position of IgG deposit, deposit in mesangial area(10) and on glomerular basement membrane(72).

Results: Patients with IgA Nephropathy in IgA+IgG group had more 24 hours urine protein, higher serum creatinine, uric acid, hypertension and lower complement C4, eGFR compared to those in IgA group(p<0.05). The score of renal tubular atrophy/intertstitial fibrosis (T) was higher IgA+IgG group than that in IgA group (P<0.05). There was no significant difference in proliferation of mesangial cells, mesangial hypercellularity, segmental glomerulosclerosis or adhesion, hyperplasia of endocapillary cell (P<0.05). Patients with IgG deposit along mesangial basement membrane(GBM) subgroup had more numbers, younger age, higher blood pressure than those in patients with IgG deposit in mesangial area subgroup(p<0.05). The eGFR, urea nitrogen and uric acid in IgG along GBM deposit subgroup were lower than those in the IgG1 deposit in mesangial area subgroup (P<0.05). There was no significant difference in the pathological changes between the two subgroups (P>0.05).

Conclusions: The patients with IgA nephropathy with IgG deposition are younger, more 24 hours urine protein, higher serum creatinine, and hypertension. Even the different position of IgG deposit in glomeruli may also have different clinical significance. We should strengthen the understanding of IgA nephropathy with IgG deposition and delay the progress of IgA nephropathy.

TH-PO107
Crescentic Lesions and Renal Outcomes in IgA Nephropathy: Validation of the Updated Oxford Classification in Brazilian Patients Precílio D. Neves,2 Rafaela B. Pinheiro,1 Cristiane B. Dias,1 Luis Yu,1 Leonardo A. Testagrossa,2 Viktoria Woronik,1 Lecticia Jorge,3 None, Salvador, Brazil; 3University of São Paulo, São Paulo, Brazil; 2University of Sao Paolu School of Medicine, Sao Paulo, Brazil; 1University of Sao Paulo, Brazil, São Paulo, Brazil; 1University of São Paulo, São Paulo, Brazil.

Background: Background: IgA Nephropathy (IgAN) is the most common form of primary glomerulonephritis worldwide. The Oxford Classification (OC) of IgAN has been recently updated and crescentic lesions were recognized as histological features related to worst renal outcomes. Objectives: Evaluation of crescentic lesions impact in renal outcomes in IgAN patients and validation of the new Oxford Classification of IgAN (MEST-C) in brazilian patients.

Methods: Methods: Analysis of medical reports database and kidney biopsy of patients with diagnosis of IgAN. Kidney biopsy were classified according new OC (MEST-C). Composite outcome was doubling of baseline serum creatinine concentration or end stage kidney disease. We performed comparative analyses between groups with and without crescentic lesions in kidney biopsy.

Results: Results: In the following image we describe baseline clinical data and kidney biopsy features of patients with IgAN as well comparative analysis of groups with (C1/C2) and without (C0) crescentic lesions in kidney biopsy.

Conclusions: Crescentic lesions were associated with both worst renal function at biopsy and outcomes in brazilian patients. These data ratify previous findings in the literature.
TH-PO108

Urinary Excretion of C5a in Membranous Nephropathy

Isabelle Ayoub,1 Daniel J. Birmingham,1 Jessica M. Nelson,1 Lee A. Hebert,2 Brad H. Rovin,3
1Ohio State University, Columbus, AL; 2Ohio State University Medical Center, Columbus, OH; 3Ohio State University Wexner Medical Center, Columbus, OH;

Background: Using proteomic analysis we previously showed that glomeruli from patients with membranous nephropathy (MN) express increased levels of complement components C3 and C4 and decreased levels of the complement receptor CR1 compared to glomeruli from healthy kidneys. Here we measured complement component C5α in the urine of MN patients as a non-invasive surrogate of intra-renal complement activation.

Methods: Urine samples were collected at the time of first kidney biopsy of patients with active MN (n=13). These patients had primary MN as suggested by dominant (n=5) or co-dominant (n=6) IgG4 glomerular immunofluorescence. Two patients only had IgG1 glomerular immunofluorescence, usually seen in secondary MN, but no underlying etiology was found in either case, so they were treated as primary MN. Urine C5α levels were measured by a sandwich ELISA.

Results: Urine protein to creatinine ratios (uPCR) in this group of MN patients ranged from 2.2-11 g/g with a median of 4 g/g. Urine C5α levels were undetectable in 2 two patients. The median value for the group was 4 ng/mg urine creatinine with a range of 0.11 ng/mg. Patients with Ig4 dominant or co-dominant MN had a higher level of C5α (5.1±3.3 ng/mg) than patients who were IgG1 dominant (1.3±1.8). C5α levels correlated with spot uPCR (r=0.68, p<0.01), however the correlation was mainly driven by those with heaviest proteinuria.

Conclusions: In immunologically active primary MN, C5α is present in the majority of urine samples. In secondary (IgG1-dominant) MN C5α levels were much lower than in primary MN, but this is difficult to interpret due to small sample size. The presence or absence of urinary C5α could be useful in differentiating immunologically active proteinuric patients with an historic diagnosis of MN from proteinuria driven by hemodynamic or other factors, facilitating decisions regarding immunosuppressive therapy without repeating kidney biopsy. The relationship between urinary C5α and anti-PLA2R levels remains to be determined.

TH-PO109

Clinical Impact of Glomerular Mannose-Binding Lectin Deposition in Intrinsic Antigen-Related Membranous Nephropathy

Norihumi Hayashi,1 Yuki Matsu,1 Keiji Fujimoto,2 Hiroki Adachi,3 Hideki Yamaya,1 Hitoshi Yokoyama,1 ‘Kanazawa Medical University, Kanazawa, Japan; 2Kanazawa medical university, Kanazawa, Japan.

Background: The M-type phospholipase A2 receptor (PLA2R) and thrombospondin type 1-domain-containing 7A (THSD7A) were identified as intrinsic antigens in primary membranous nephropathy (MN). Complement activation via the lectin pathway in intrinsic antigen-related MN is still unclear.

Methods: We retrospectively enrolled 60 primary MN patients and detected activated complement pathways by staining complement proteins in glomerular deposition. According to the findings of PLA2R and THSD7A staining in glomeruli, they were classified into intrinsic antigen-related or -unrelated MN. We evaluated clinicopathological characteristics and predictors of clinical outcomes in intrinsic antigen-related MN.

Results: Thirty-nine patients (65%) had PLA2R in glomerular deposits and 2 patients (3.3%) had THSD7A. One of them had both PLA2R and THSD7A (double positive). Forty patients were classified into the intrinsic antigen-related MN. The other 20 patients were negative for both antigens (unrelated group). The prevalence and staining intensity of mannose-binding lectin (MBL) deposits was much higher in the intrinsic antigen-related group (55% vs. 20%, P<0.01, 1.0 [1.0-2.0] vs. 1.0 [0.0-1.0], p=0.01, respectively). The staining intensity of MBL in glomeruli also correlated with the IgG4 staining intensity. In intrinsic antigen-related MN, MBL staining intensity was an unfavorable predictor for remission of proteinuria (HR 0.40, p<0.01) and renal dysfunction (HR 3.81, p=0.01) in Cox proportional hazards analysis. Moreover, the glomerular MBL-positive group showed more severe interstitial fibrosis and worse clinical outcomes.

Conclusions: Intrinsic antigen-related MN was more strongly associated with complement activation by the lectin pathway, and was an unfavorable predictor for clinical outcomes.

TH-PO110

Clinicopathological Characteristics of Thrombospondin Type 1 Domain–Containing 7A-Positive Membranous Nephropathy

Shigeco Haraj,1 Shinichi Nishi,2 Akihiro Yoshimoto,1 ‘Kobe City Medical Center General Hospital, Kobe, Japan; 2Diagnostic Pathology, Kobe University Graduate School of Medicine, Kobe, Japan; 3Nephrology, Kobe University Graduate School of Medicine, Kobe, Japan.

Background: Recent studies suggested the possible association of Thrombospondin type 1 domain-containing 7A (THSD7A)-positive membranous nephropathy (MN) and malignancy; however, the clinicopathological characteristics of THSD7A-positive MN have been still poorly characterized.

Methods: Among 164 consecutive cases of pathologically-proven MN, 7 cases were immunohistologically positive for THSD7A (4.2%) and defined as THSD7A-positive MN. Clinicopathological characteristics including renal function, proteinuria levels, and incidence of specific disease entities such as malignancy and other disorders were obtained from the data base record. IgG subclass profiles were examined in 6 cases using frozen sections. PLA2R immunostaining were evaluated in all cases.

Results: The patient age ranged from 42 to 73 (mean 63.7). Male-female ratio was 5:2. The median levels of serum creatinine and proteinuria were 0.84 mg/dl (range 0.53 – 1.4) and 7.41 g/gcr (0.37 – 16.1), respectively. Two patients had cancer concomitantly at the time of renal biopsy; one had small cell carcinoma in the lung and the other had prostatic adenocarcinoma. THSD7A immunostaining was available in the lung cancer case, which was negative for THSD7A. Two patients had concurrent incidence of inflammatory diseases; one had Kimura’s disease, a chronic eosinophilic inflammatory disorder of unknown etiology, and the other had eosinophilic pneumonia in addition to asthma. Remaining three patients had no specific disease entity at the time of renal biopsy, IgG subclass showed IgG4-dominant or co-dominant phenotype in 5 cases. One case with prostatic cancer had IgG2 and IgG3- dominant distribution. One case showed PLA2R positivity (dual positive for PLA2R and THSD7A).

Conclusions: In contrast to the major distribution of IgG4-dominant/co-dominant phenotype, THSD7A-positive MN tends to be associated with various disease entities.

Funding: Government Support - Non-U.S.

TH-PO111

Urinary Anti-PLA2R Antibody Is a Biomarker for Diagnosis and Activity in Idiopathic Membranous Nephropathy

Bing Li, Department of Nephrology, 2nd Affiliated Hospital of Harbin Medical University, Harbin, China.

Background: Detection of the serum anti-PLA2R antibody (sPLA2R-Ab) and the glomerular PLA2R antigen (gPLA2R) has been widely used as a diagnostic tool for idiopathic membranous nephropathy (IMN) and for the evaluation of IMN activity and severity. Since urine samples more directly reflect kidney damage and alterations than blood samples, we evaluated whether urinary anti-PLA2R antibody (uPLA2R-Ab) could be utilized as a noninvasive biomarker for IMN.

Methods: In this study, we completed a qualitative analysis through indirect immunofluorescence test (IIFT) and measured uPLA2R-Ab and sPLA2R-Ab concentrations by enzyme-linked immunosorbent assay (ELISA) in 28 patients with biopsy-proven IMN and 12 patients with secondary membranous nephropathy (SMN).

Results: Overall, 64.3% (n=18) of patients with IMN had IIFT-positive sPLA2R-Ab, 67.9% (n=19) of patients with IMN had IIFT-positive uPLA2R-Ab IIFT, and none of the SMN patients had IIFT-positive sPLA2R-Ab or uPLA2R-Ab. The titers of the anti-PLA2R antibody from the IMN patients in the urine (10.7±22.24 RU/mmol, presented as uPLA2R-Ab/urine creatinine) or the serum (107.3±140.93 RU/ml) were higher than those from the SMN patients (5.3±10.46 RU/mmol, p=0.001; 0.000±0.029 RU/ml, p<0.001, respectively). Statistical analysis indicated that there were positive correlations between uPLA2R-Ab and gPLA2R, sPLA2R-Ab or urinary protein and negative correlations between uPLA2R-Ab and serum albumin in patients with IMN.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: Our results indicate that uPLA2-R-Ab might serve as a biomarker, like sPLA2-R, for IMN diagnosis and that the antibody titer, as measured by ELISA, might reflect IMN activity and severity. Funding: Government Support - Non-U.S.

TH-PO112

The Exact Time Difference between PLA2R Antibody and Proteinuria in Reflecting Disease Activity Change in Idiopathic Membranous Nephropathy Weifeng Lin,1,2 Hang Li,3,1 Xuemei Li,1 Limeng Chen,1 Xuewang Li,1 1Peking Union Medical College Hospital, Beijing, China; 2Department of Nephrology, Peking University Third Hospital, Beijing, China; 3Peking Union Medical College Hospital, Beijing, China; 4Peking Union Medical College, Chinese Academy of Medicine Sciences & Peking Union Medical College, Beijing, China.

Background: According to most studies, PLA2R antibody was faster than proteinuria in reflecting disease activity in idiopathic membranous nephropathy. However, the exact time difference is still unknown. This study was to reveal the precise time difference between them, which could guide clinical practice.

Methods: A total of 162 patients with IMN proven by kidney biopsy at Peking Union Medical College Hospital from January 1, 2014 to December 31, 2015 were enrolled. An observationally prospective follow-up was conducted monthly to monitor the changes in PLA2R antibody titer and disease activity changes based on proteinuria in IMN. The study end point was clinical remission based on proteinuria or the research deadline.

Results: The average follow-up time was (13.3±3.14) months, with a minimum time of 7 months and a maximum time of 21 months. The overall average time of PLA2R antibody turning negative in clinical remission group based on proteinuria was (3.1±1.2±0.97) months. In subgroups, the average time of antibody turning negative in the complete remission (CR) group (3.1±1.2±0.97) months, the partial remission (PR) group (2.1±1.2±0.68) months and the non-remission (NR) group (3.3±1.3±0.05) months, respectively. Importantly, our study showed that PLA2R antibody was (1.91±2.51) months earlier than proteinuria reaching CR in IMN. Also, there was (6.9±3.33) months earlier for antibody to turn negative than proteinuria to achieve clinical CR. There was (3.09±0.66) months earlier for antibody turning positive again than proteinuria recurrence.

Conclusions: The PLA2R antibody changes was faster than proteinuria in reflecting disease activity changes in IMN, about 2 months ahead of proteinuria PR, about 7 months ahead of proteinuria CR and about 3 months ahead of proteinuria recurrence.

TH-PO113

Plasma C4d Differentiates PLA2R Positive Membranous Nephropathy from Other Primary Glomerular Diseases Congcong Jiao,1 Junjun Luan,1 Guangying Guo,1 Wei Qu,1 Ying Chen,1 Weizhe Kong,1 Yani Zhang,2 Jingji Fu,2 Jingbo Pi,1 Jeffrey B. Kopp,1 Lining Wang,1 Hua Zhou,1 Chinese Medical University, Shenyang, China; 1Department of Nephrology, First Affiliated Hospital of China Medical University, Shenyang, P. R. China; 2Nephrology department, The first hospital of China medical university, Shenyang, China; 3NIDDK, NIH, Bethesda, MD; 4China Medical University, Shenyang, China.

Background: Renal C4d staining is a potential diagnostic biomarker for immune complex-mediated glomerular diseases. Positive M-type phospholipase A2 receptor (PLA2R) staining on kidney biopsy is specific for primary membranous nephropathy (pMN) diagnosis. We aimed to assess whether plasma C4d can differentiate PLA2R positive MN from other primary glomerular diseases and to correlate plasma C4d level with renal PLA2R staining.

Methods: Plasma C4d levels were measured by ELISA in 16 healthy volunteers and 187 untreated patients with biopsy-proven glomerular diseases, including 80 PLA2R positive and 55 PLAR negative MN cases, 20 IgA nephropathy, 18 minimal change disease, and 14 focal segmental glomerulosclerosis cases. There were 123 nephrotic and 26 nephritic cases among subjects with primary glomerular diseases. PLA2R negative MN cases included atypical pMN (n=17), hepatitis B virus (HBV)-associated MN (n=23) and autoimmune-associated MN (n=15).

Results: Plasma C4d levels significantly increased in pMN compared with each of the other groups. C4d differentiated pMN from these three primary glomerular diseases either in nephrotic (AUC=0.7, p<0.0001, n=111) or nephritic diseases (AUC=1.0, p<0.0001, n=21). C4d also distinguished PLA2R positive MN from PLAR negative MN (AUC=0.98, p<0.0001, n=135). Interestingly, C4d was significantly decreased in autoimmune-associated MN (AUC=0.78, p<0.0001, n=14) and non-identified primary cases. Plasma C4d was positively correlated with the extent of renal PLA2R staining (r=0.64, p<0.001, n=135).

Conclusions: Plasma C4d differentiates PLA2R positive MN from other primary glomerular diseases and correlated with renal PLA2R staining. Plasma C4d levels serve as a supplementary biomarker, together with circulating PLA2R antibody, as a measurement panel for diagnosing pMN in patients with a contraindication to renal biopsy.

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

TH-PO114

Clinical Significance of Urinary Podocyte-Derived Microparticle Detection in Idiopathic Membranous Nephropathy Jian Lu, Kun ling Ma, Yang Zhang, Zebo Hu, Zhongda Hospital, Southeast University Medical School, Nanjing City, China.

Background: Microparticles (MPs) are a type of extracellular vesicles (EVs) shed from the outer budding of cytoplasm membranes during cell apoptosis and/or activation. These microvesicles release specific contents (lipids, proteins, microRNAs, etc.) and are active participants in a wide range of both physiological and pathological processes at molecular levels. This study aimed to observe the change of urinary podocyte-derived microparticle level and to explore its potential clinical significance in idiopathic membranous nephropathy (IMN).

Methods: We prospectively enrolled patients with IMN (n = 24) before initial immunosuppressive therapy to study renal tissue pathology using periodic acid-Schiff staining by light microscope and ultrastructural observation by transmission electron microscope. After isolation from urine samples, podosayselin-positive podocyte-derived microparticles were characterized by flow cytometry. Twenty IMN patients were studied again 6 months after Glucocorticoids in combination with tacrolimus intervention. Health Volunteers (n=15) served as controls. The correlation of urinary podocyte microparticles and clinical and pathological factors in IMN patients was analyzed.

Results: Compared with the control group, there were increased serum PLA2R antibody tite and 24-hour urinary protein (all P<0.005). The fraction of podocyte microparticles among urinary microparticles was elevated in IMN compared with health volunteers (P<0.01) and decreased after 6 months therapy and after controlling for clinical parameters.

Conclusions: The excretion of urine podocyte-derived microparticles might reflect podocyte injury and might be closely associated with the progression of IMN.

TH-PO115

Practice Patterns in Management and Outcomes of Primary Membranous Nephropathy: A Single Centre Experience Martin E. Durcan, Mohamed Elsayed, Arvind Ponnusamy. Royal Preston Hospital, Preston, United Kingdom.

Background: Membranous nephropathy is a common glomerular disease. In the last number of years there has been many clinical trials addressing its management. These trials have altered the treatment patterns of this condition by giving the physician more treatment options. The aim of this study was to review the practice patterns in management and outcomes of primary membranous nephropathy at a single U.K centre.

Methods: Clinical demographics, relevant laboratory values and modalities of treatments were collected on all patients with biopsy proven membranous nephropathy between 2004 and 2011. Patients were followed up until November 2016. The following outcomes were of interest; complete remission (proteinuria less than 30mg/mmol and stable renal function), partial remission (at least 50% reduction in proteinuria from baseline and uPCR <300mg/mmol with stable renal function <15% drop in eGFR), relapse (recurrence of proteinuria with a 300mg/mmol) and a composite outcome of the following endpoints; doubling of baseline creatinine, start of renal replacement therapy or death.

Results: 129 incident patients were followed up for a median of 5.56 years. Mean age of patients was 56.5 ± 16.7 years of age, 66.6% of patients were male and remainder were female. Prevalence rate of hypertension was 60.6% while 17.4% had diabetes. Mean baseline eGFR was 62.9 ± 34.6 ml/min/1.73m². Mean PCR and albumin at diagnosis was 769.83 mg/mmol and 27.9 ± 6.0 g/L, respectively. 56 (43.4%) received immunosuppressive therapy overall. 24 (19%) patients were treated with the Ponticelli regimen. 36 (28%) received a calcineurin inhibitor. 12 (9.52%) received mycophenolate mofetial (MMF). Patient and renal survival at last follow up was 71.20%. 51% of study population obtained complete remission. 27% achieved partial remission. 40.17% achieved the composite outcome. Achieving remission (whether partial or complete)
decreases hazards of developing composite outcome by 64%. P=0.0007. Please see figure A, for survival outcomes related to each treatment modality.

Conclusions: Outcomes are comparable and better than what is reported in the literature. Treatment of patients with a calcineurin inhibitor seems to be superior to treatment with other modalities. Further analysis of this finding is needed.

TH-POI16
Clinicopathological Manifestation in Patients of Idiopathic Membranous Nephropathy Assigned to a Heterogeneous Group with Nephrotic Syndrome Shinni Kitaigima,1 Tadashi Toyama,1 Akinari Hara,2 Yasunori Iwata,2 Norihiko Sakai,2 Miho Shimizu,1 Kengo Furuuchi,1 Hitoshi Yokoyama,1 Takahiro Washa,2 Division of Nephrology, Kanazawa University Hospital, Kanazawa, Japan; 2Division of Nephrology, Kanazawa Medical University Hospital, Uchinada, Japan.

Background: The 20-year renal survival of Idiopathic membranous nephropathy (IMN) in Japanese adults with nephrotic syndrome was around 60%. Based on the electron microscopic findings, we reported that there are two distinct types, homogeneous type and heterogeneous type; synchronous electron dense deposits or various phases of dense deposits in basement membrane, respectively. (Kidney International in 2004).

Our previous analysis revealed that the rate of renal death was around 20 times higher in heterogeneous group (heterogeneous group; 25.6%, homogeneous group; 1.3%). In this study, we evaluated the predisposing clinicopathological factors for IMN patients assigned to heterogeneous group with nephrotic syndrome (NS).

Methods: Forty patients of NS 24 males and 16 females; mean age 45.7 years) with heterogeneous type IMN were evaluated in this study who were collected in Kanazawa University Hospital and affiliated hospitals from 1965 to 2013. The patients were followed for more than three years, or until renal or patient death. Clinicopathological factors, which might affect renal death were evaluated.

Results: Renal death was observed 12 out of 40 patients (30%). We divided two groups; renal death group and renal survival group. The renal death group showed lower remission rate (CR or ICR renal death; 16.7%, renal survival group; 60.7%, p<0.001) and mortality rate (renal death group; 10.7%, p=0.006). There was no difference in clinical background at onset between two groups. In renal death group, two patients achieved remission, but relapsed after the remission and became renal death. The median duration to renal death after kidney biopsy was 107 months, and patients of sustained NS had a tendency to shorter duration (NS group; 76.5months, non-NS group; 139.1months, p=0.10).

Conclusions: These findings suggest that electron microscopic findings demonstrating heterogeneous type and no-remission of nephrotic syndrome was susceptible to renal death in patients with nephrotic IMN.

TH-POI17
Serological and Immunohistological Characteristics of Membranous Nephropathy: A Comprehensive Analysis. Comparison of Two Groups: 1. Positive and 2. Negative for PLA1 Antibodies. Comparison with Other (DQ6) Antibodies. Hadi J. Kemper,1 Jun Oh,1 Rolf A. Stahl,1 Elon Hoxha,2,3 Pediatric Nephrology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; 2Department of Pediatric Pathology, Asklepios Nord-Heidberg, Hamburg, Germany; 3Department of Pediatrics, Asklepios Nord-Heidberg, Hamburg, Germany. Group/Team: Pediatric MN Study Group.

Background: In adult patients with membranous nephropathy (MN) phospholipase A1 receptor (PLA1-R) and thrombospondin type 1 domain containing 7A (THSD7A) are the target antigens in 80% and 2-3% of patients, respectively. In children MN is less common and two more antigens are involved in disease development: neutral endopeptidase (NEP) and cationic bovine serum albumin (cBSA). In this study we evaluated sera were evaluated every three months. Immunohistochemical analyses for all antigens and IgG subclasses were performed in five biopsies. The median follow-up time was 24 months.

Results: Six (50%) children had a PLA1-R associated MN. There were no antibodies against THSD7A, NEP or cBSA-Antibodies (Ab). Clinical data and blood samples were evaluated every three months. Immunohistochemical analyses for all antibodies and IgG subclasses were performed in five biopsies. The median follow-up time was 24 months. Results: Six (50%) children had a PLA1-R associated MN. There were no antibodies against THSD7A, NEP or cBSA-Antibodies (Ab). Clinical data and blood samples were evaluated every three months. Immunohistochemical analyses for all antibodies and IgG subclasses were performed in five biopsies. The median follow-up time was 24 months.

Results: Six (50%) children had a PLA1-R associated MN. There were no antibodies against THSD7A, NEP or cBSA-Antibodies (Ab). Clinical data and blood samples were evaluated every three months. Immunohistochemical analyses for all antibodies and IgG subclasses were performed in five biopsies. The median follow-up time was 24 months.

Results: Six (50%) children had a PLA1-R associated MN. There were no antibodies against THSD7A, NEP or cBSA-Antibodies (Ab). Clinical data and blood samples were evaluated every three months. Immunohistochemical analyses for all antibodies and IgG subclasses were performed in five biopsies. The median follow-up time was 24 months.

Results: Six (50%) children had a PLA1-R associated MN. There were no antibodies against THSD7A, NEP or cBSA-Antibodies (Ab). Clinical data and blood samples were evaluated every three months. Immunohistochemical analyses for all antibodies and IgG subclasses were performed in five biopsies. The median follow-up time was 24 months.

Results: Six (50%) children had a PLA1-R associated MN. There were no antibodies against THSD7A, NEP or cBSA-Antibodies (Ab). Clinical data and blood samples were evaluated every three months. Immunohistochemical analyses for all antibodies and IgG subclasses were performed in five biopsies. The median follow-up time was 24 months.

Results: Six (50%) children had a PLA1-R associated MN. There were no antibodies against THSD7A, NEP or cBSA-Antibodies (Ab). Clinical data and blood samples were evaluated every three months. Immunohistochemical analyses for all antibodies and IgG subclasses were performed in five biopsies. The median follow-up time was 24 months.

Results: Six (50%) children had a PLA1-R associated MN. There were no antibodies against THSD7A, NEP or cBSA-Antibodies (Ab). Clinical data and blood samples were evaluated every three months. Immunohistochemical analyses for all antibodies and IgG subclasses were performed in five biopsies. The median follow-up time was 24 months.

Results: Six (50%) children had a PLA1-R associated MN. There were no antibodies against THSD7A, NEP or cBSA-Antibodies (Ab). Clinical data and blood samples were evaluated every three months. Immunohistochemical analyses for all antibodies and IgG subclasses were performed in five biopsies. The median follow-up time was 24 months.
TH-POI20
A Single Center Observation Study on Findings in Indication Biopsies and Autopsies for Stem Cell Transplantation

Methods: Retrospectively analysed indication renal biopsies and autopsies after HSCT of the HSCT patient cohort of the University Hospital of Basel, Switzerland. Data of patients’ characteristics were retrospectively collected from the clinical records. The mean age at the time of kidney biopsy was 71 ± 15 years, and 77% were Caucasian patients. The most common diagnosis was either for the rest. Mortality was 15.7% (8 of 51). No histopathological features were associated with mortality.

Conclusions: This retrospective chart review suggests the status of the primary nephrologist (performing biopsy or not performing a biopsy) impacts which patients get a kidney biopsy. These potential biases should be considered as the decision to perform a biopsy is made. This study is limited by its single center design, retrospective nature, and lack of information about patient outcomes.

Nephrologist Procedural Status Impacting Bx. Findings

Key: ± ≥ 0.01

TH-POI22
Primary Nephrologist Procedural Status Impact on Kidney Biopsy Findings

Methods: We performed a retrospective study of 99 native kidney biopsies performed within the last 10 years at our institution. Our primary hypothesis was the status of the primary nephrologist (performs biopsy or does not perform biopsy) had a significant impact on the kidney biopsy findings as assessed by whether immune based therapy was used in the next 3 months after time of kidney biopsy (yes or no). A chi square test was used to compare the outcome (immune therapy or not) in the two referring nephrology groups. The study was reviewed and approved by the Cooper University Hospital IRB.

Results: A significantly higher rate of immune therapy (65.9 vs 29.3%, p < 0.01) was noted in the group whose primary nephrologist performed biopsies (3 nephrologists) compared to the group whose primary nephrologist did not perform biopsies (6 nephrologists). The groups were similar in terms of their age, serum creatinine, and urine protein to creatinine ratio as presented in Table 1. The patient characteristics reported represent data from 30 and 46 subjects, respectively, in the biopsy/ non biopsy groups.

Conclusions: This retrospective chart review suggests the status of the primary nephrologist (performing biopsy or not performing a biopsy) impacts which patients get a kidney biopsy. These potential biases should be considered as the decision to perform a biopsy is made. This study is limited by its single center design, retrospective nature, and lack of information about patient outcomes.

Nephrologist Procedural Status Impacting Bx. Findings

TH-POI23
Histopathologic Findings and Mortality in Fibrillary Glomerulonephritis

Methods: We reviewed 7,579 kidney biopsies performed at our institution between 2001 and 2015 and identified 51 cases of fibrillary GN. Histopathologic features and clinical variables were recorded from the medical record by a nephrologist. Data is presented as mean (SD). Chi-squared test assessed correlation between histologic and categorical clinical variables.

Results: Fibrillary GN constituted 0.7% of kidney biopsies. Average age at diagnosis was 59.9 (8.8) years. Female to male ratio was 1.4:1 with 77% Caucasian patients. On light microscopy, mesangial proliferative/sclerosis GN was present in 62% of cases. Membranous (MGN), membranoproliferative GN (MPGN), and endocapillary proliferative GN accounted for 10%, 20%, and 8% of cases respectively. Mesangial changes were present in 92% of cases. Crescents were present in 7 cases (14%). Interstitial fibrosis and tubular atrophy IFTA was mild, moderate, and severe in 30%, 45%, and 25% respectively. The mean glomerular obstruction was 36%. Immunofluorescence revealed universal staining for IgG and C3. IgM, IgA, and C1q were positive in 56%, 12%, and 16% respectively. No kappa or lambda restriction was present. The average positivity (0-4) scale for IgG, IgM, IgA, C3, C4 was 2.6, 0.9, 0.1, 2.7, and 0.2 respectively. The pattern was granular in 38% and smudged in 62%. Electron dense deposits were seen in 7 of 51 cases (14%), mostly subepithelial. Podocyte effacement, seen in 100% of the cases, ranging from patchy to widespread. The average fibril diameter was 15.3 ± 3.4 nm [9 – 28]. Fibribs were deposited in both mesangium and GBM in 82% of the cases, and in either for the rest. Mortality was 15.7% (6 of 51). No histopathological features were associated with mortality.

Histopathologic Findings and Mortality in Fibrillary Glomerulonephritis

Ammun Hallal, Ranjani N. Moorhi, JWalant R. Modi, Carrie L. Phillips, Pierre C. Dagher, Michael T. Eason. Indiana University, Indianapolis, IN

Background: Fibrillary glomerulonephritis (GN) is a rare glomerular disease with no paucity of literature. We present a retrospective collection of our single-center fibrillary GN database.

Methods: We reviewed 7,579 kidney biopsies performed at our institution between 2001 and 2015 and identified 51 cases of fibrillary GN. Histopathologic features and clinical variables were recorded from the medical record by a nephrologist. Data is presented as mean (SD). Chi-squared test assessed correlation between histologic and categorical clinical variables.

Results: Fibrillary GN constituted 0.7% of kidney biopsies. Average age at diagnosis was 59.9 (8.8) years. Female to male ratio was 1.4:1 with 77% Caucasian patients. On light microscopy, mesangial proliferative/sclerosis GN was present in 62% of cases. Membranous (MGN), membranoproliferative GN (MPGN), and endocapillary proliferative GN accounted for 10%, 20%, and 8% of cases respectively. Mesangial changes were present in 92% of cases. Crescents were present in 7 cases (14%). Interstitial fibrosis and tubular atrophy IFTA was mild, moderate, and severe in 30%, 45%, and 25% respectively. The mean glomerular obstruction was 36%. Immunofluorescence revealed universal staining for IgG and C3. IgM, IgA, and C1q were positive in 56%, 12%, and 16% respectively. No kappa or lambda restriction was present. The average positivity (0-4) scale for IgG, IgM, IgA, C3, C4 was 2.6, 0.9, 0.1, 2.7, and 0.2 respectively. The pattern was granular in 38% and smudged in 62%. Electron dense deposits were seen in 7 of 51 cases (14%), mostly subepithelial. Podocyte effacement, seen in 100% of the cases, ranging from patchy to widespread. The average fibril diameter was 15.3 ± 3.4 nm [9 – 28]. Fibribs were deposited in both mesangium and GBM in 82% of the cases, and in either for the rest. Mortality was 15.7% (6 of 51). No histopathological features were associated with mortality.
Predictive Factors of Renal Involvement in Cryoglobulinemia: A Retrospective Study of 153 Patients

Background: The course of cryoglobulinemia varies widely, from asymptomatic patients to severe vasculitis. Renal involvement (RI) is a major prognostic factor, and frequently occurs several years after diagnosis. Twenty to 56% of patients will develop RI. Predictive factors of RI have not been studied. The aim of our study was to identify factors associated with RI occurrence in patients with cryoglobulinemia.

Methods: We retrospectively reviewed the clinical charts of a consecutive series of 153 patients positive for cryoglobulinemia (from January 2012 to December 2014) in the University Hospital of Lyon (France). Immunoglobulin (Ig) G, IgM and IgA concentrations as well as rheumatoid factor (RF) activity were assessed in cryoprecipitate. Complement fractions C3 and C4, CH50 activity and RF were simultaneously assayed in sera. RI was defined either histologically, or biologically if cryoglobulinemia was the only possible cause of nephropathy (proteinuria > 0.5 g/24h or hematuria > 10/mm3 or eGFR < 60 ml/min/1.73m2 CKD-EPI).

Results: Among the 153 positive measures (mean age 55 years, male gender 37%), cryoglobulinemia was associated with RI in 45 pts (29.4%). The presence of IgA in cryoprecipitate was very significantly associated with RI (22% in RI group vs 1% in control group, P=0.0001) contrary to IgG or IgM. Type 3 cryoglobulinemia was more frequent in controls than in RI group (35% vs 11%, P=0.006). Regarding etiology, only B-cell lymphoma was statistically associated with antibodies in the serum. There was no difference for hepatitis C virus. RF activity was more frequent (42% vs 24%, P=0.03) and cryoglobulin total Ig concentration was higher (137 mg/l vs 39 mg/l, P=0.001) in case of RI, whereas C3 and C4 were similar. There were more men in RI group (60% vs 27%, P=0.0001), and slightly more patients had cutaneous purpura (38% vs 22%, P=0.048).

Conclusions: Several factors may be associated with the occurrence of RI in cryoglobulinemia (IgA, B-cell lymphoma, purpura), whereas type 3 cryoglobulinemia appears to be protective. In these at risk patients, kidney function monitoring and nephroprevention might be intensified. Further studies are needed to confirm these findings and understand mechanisms of these associations with RI.

OHC: occult HCV infection;

TH-PO126

The Characteristics of Membranoproliferative Glomerulonephritis (MPGN) at a Single Center in Japan

Background: MPGN has been recently proposed new classification, and alternative pathway (AP) mediated MPGN (C3 glomerulopathy), which was defined as isolated C3 deposition and absent of immunoglobulin deposition, has been recognized as a different glomerulonephritis from Immune complex (IC) mediated MPGN. However, there was no report analyzed about the difference of these two nephritides in Japan.

Methods: We reclassified 87 MPGN patients diagnosed between 1977 and 2014 in our institution according to the new classification. The clinical, pathological features and outcomes of patients between IC mediated MPGN and AP mediated MPGN were analyzed.

Results: Among 55 MPGN patients except 32 secondary MPGN, there were 42 IC mediated MPGN patients and 13 AP mediated. In the baseline clinical findings, the estimated glomerular filtration rate similarity were equal between both groups (89.69 vs. 76.19, P=0.2581). The amount of proteinuria (2.34 VS 5.20 d/day, P=0.00063), C3 (39.0 vs. 67.25, P=0.0317), and CH50 (22.4 vs. 36.4, P=0.0404) were significantly lower, and albumin serum was significantly higher (3.40 vs 2.70, P=0.0186) in AP mediated MPGN than IC mediated MPGN. In the pathological findings, there were no significance in light microscopic findings, but all immunofluorescence staining except C3 were significantly higher in IC mediated MPGN. Immunossuppression therapy was used in 92.3% patients in AP mediated MPGN, and 90.5% in IC mediated. The 400 months renal survival rate were similar between both groups (70.0 vs. 74.0%, P=0.445).

Conclusions: We have shown that AP mediated MPGN had similar prognosis in comparison to IC mediated MPGN, though proteinuria at baseline was lower than IC mediated MPGN. Lower serum complements were resulted from higher alternative pathway activation, and this phenomenon might induce the poor prognosis in AP mediated MPGN, though their lower proteinuria.

TH-PO127

Glomerulopathies Secondary to Schistosomiasis: Histological Forms and Follow-Up

Background: Schistosomiasis mansoni is a parasitosis caused by Schistosoma mansoni that is endemic in several Brazilian states. Gastrointestinal involvement is the most frequent, but the kidney can also be injured, especially in the form of glomerulopathies. The aim of this study is to show the MS-related glomerulopathies and evaluation of the long-term follow-up.

Methods: Evaluation of clinical data and renal biopsies of patients diagnosed with MS-related glomerulopathies in the period 1992-2017, in addition to clinical-evolutionary follow-up.

Results: Twenty eight patients, predominantly male (78.5%), white (64.2%), median age 38 (33; 44), all cases from the endemic area, most of them from Bahia (32.2%). The most common form of MS diagnosis was through fecal examination (94%), and 60.7% presented the hematopoetic form of the disease. The most common clinical presentation was mixed syndrome (64.3%), with Cr 1.5 ± 0.77mg/dL, MDRD 69.3 ± 91ml/min / 1.73m2, 24h proteinuria: 6.56 ± 3.5g, serum albumin: 2.35 ± 0.91g/dL, low serum complement in 42.8% of patients. The distribution of the histological diagnoses to renal biopsy was: membranoproliferative glomerulonephritis (MPGN) 60.7%, focal segmental glomerulosclerosis (FSGS) 21.4%, membranous nephropathy 10.7% and proliferative mesangial 7.2%. The patients’ follow-up time was 70 (14-124) months, after which 32.1% of the patients had started dialysis. Comparing the patients with MPGN vs non-MPGN, they differed in proteinuria of 24h (5.19 vs 8.67, P = 0.04) and serum albumin (g/ dL) (2.6 vs 1.0, P = 0.04), frequency of hypertension (%) (70.5 vs 9.0, P = 0.002) and hematuria (%) (94.1 vs 45.4, P = 0.007). Comparing patients that evolved and did not evolve to dialysis, they differed in the initial creatinine (1.99 vs 1.28, P = 0.05), MDRD 55.78 vs P = 0.03), renal response to anti-platelet use (%) (0 vs 7%, P = 0.007) and follow-up time (months) (45.7 vs 9.7, P = 0.03).

We have shown that AP mediated MPGN had similar prognosis in comparison to IC mediated MPGN, though proteinuria at baseline was lower than IC mediated MPGN. Lower serum complements were resulted from higher alternative pathway activation, and this phenomenon might induce the poor prognosis in AP mediated MPGN, though their lower proteinuria.
Conclusions: The glomerulopathies secondary to MS are still a reality in Brazilian daily life. Histological presentation as GNMP did not determine a worse prognosis for the patients in this series, but rather the severity of the initial clinical presentation and non-response to the use of antiparasitics.

TH-PO128
An Automated Immunoassay for High-Throughput Measurement of Symmetric Dimethylarginine (SDMA) in Human Serum Joe M. El-Khoury,1 Parker C. Wilson,2 Shay Toohey,2 Chirag R. Parikh,1 Daniel Patch,3 Maha Yerramilli,1 Giosi Farace,1 Murthy V. Yerramilli,1 IDEXX Laboratories, Westbrook, ME; 2Yale University, New Haven, CT; 3Yale University and VAMC, New Haven, CT.

Background: Symmetric dimethylarginine (SDMA) is a byproduct of protein methylation and degradation that is primarily eliminated by the kidneys. It is freely filtered at the glomerulus, with no active secretion or reabsorption by the renal tubules. As a result, SDMA plasma concentrations are affected by changes in GFR and it is emerging as a kidney function biomarker that has outperformed serum creatinine in several studies. SDMA has traditionally been measured using liquid chromatography tandem mass spectrometry (LC-MS/MS), which is a major limitation for its widespread application as a screening marker for kidney function. The objective of this study is to validate a high throughput automated immunoassay for measuring SDMA in human serum.

Methods: Left-over serum samples were used for this study. SDMA was measured using novel immunoassay reagents manufactured by IDEXX Laboratories (Westbrook, ME) loaded on a Roche c501 analyzer (Indianapolis, IN). The assay was evaluated to establish its analytical measurement range (AMR), imprecision, specificity and accuracy. Method comparison with a separate LC-MS/MS was performed using serum collected from 50 adults with varied kidney function.

Results: The analytical measurement range of the SDMA immunoassay was 4.2 to 100.5 μg/ml. Total coefficient of variation (CV) was less than 13.1% at the three different concentrations tested. Hemolysis did not affect assay performance up to a hemolysis index of 186 and common drugs tested did not interfere. Deming regression analysis of the method comparison with the LC-MS/MS revealed a slope of 1.001, intercept of 1.4 and correlation coefficient of 0.99.

Conclusions: A novel immunoassay for measuring SDMA with comparable performance to LC-MS/MS is now validated for use in humans and better suited for high-throughput clinical laboratory testing. This assay will facilitate further research and widespread clinical adoption of this emerging biomarker.

Funding: Commercial Support - IDEXX

TH-PO129
Factors Influencing Initial Treatment Options for Idiopathic Membranous Nephropathy Huaxia Xie,1 Xin Zhang,1 Zhen Xuewang,1 Peking Union Medical College Hospital, Beijing, China; 2Beijing Friendship Hospital, Capital Medical University, Beijing, China; 3Peking University First Hospital, Beijing, China; 4Peking Union Medical college hospital, Beijing, China; 5Peking University Medical College Hospital, Chinese Academy of Medicine Sciences & Peking Union Medical College, Beijing, China.

Background: This study aimed to analyze factors which may influence the initial therapy option for idiopathic membranous nephropathy (iMN) diagnosed in a tertiary center of China.

Methods: In this retrospective study, we consecutively enrolled 875 iMN patients diagnosed in a single tertiary center between 2004 to 2015. Data on sex, age, body mass index, presence of hypertension and diabetes mellitus, and laboratory tests at renal biopsy and treatment options after diagnosis of iMN were retrospectively retrieved from medical records. We retrospectively classified the initial therapy as glucocorticoids plus cyclophosphamide, calcineurin inhibitors alone or plus corticosteroids, corticosteroids alone or plus other immunosuppressives and supportive treatment. Multinomial multiple logistic regression was employed to analyze the factors influencing the selection of a therapeutic regimen.

Results: The presence of diabetes(OR=5.06, 95%CI:12.90-8.84, P=0.001) and age <50 years was associated with selection of calcineurin inhibitors(OR=1.48, 95% CI:0.90-2.37, P=0.048), whereas a 24 hour urine protein total(24h-UP)>8g and a serum albumin<25g/L were associated with selection of supportive treatment (OR=15.2, 95% CI:3.53-65.1, P=0.001 and OR=21.3, 95% CI:3.50-120.9, respectively) and corticosteroids alone or plus other immunosuppressives(OR=4.93, 95% CI:1.00 and OR=1.69, 95% CI:1.05-2.74, respectively) as opposed to selection of cyclophosphamide. When we restricted the analyses in non-diabetes patients, age <30 years was also associated with selection of calcineurin inhibitors as compared with selection of cyclophosphamide(OR=1.69, 95% CI:1.12-2.54, P=0.012).

Conclusions: Serum albumin level, amount of 24h-UP, presence of diabetes, and age may influence a physician’s decision on initial treatment options for iMN.

TH-PO130
Clinical Advantage of Concomitant Use of Low Dose Mizoribine and Prednisolone on Primary Membranous Nephropathy in the Elderly Hajime Hasegawa,1,2 Tetsuya Mitara,1,2 Yasuhiro Tomino,1 Hiroshi Yokoyama,1 Kunihiro Yamagata,3 Masayuki Iwano,1 Shinichi Akiyama,1 Kaori Takeyagi,1,2 Yuka Hasegawa,1,2 Masakazu Yokouchi,1,2 Shinjiro Koyama,1,2 Study Group for Nephrotic Syndrome in the elderly, Kagawa, Japan; 1Nephrol and Hypertens, Blood Purification Center, Saitama Med Center, Saitama Med Univ, Kagawa, Japan.

Background: Initial therapeutic strategy of membranous nephropathy (MN) in Japan is sole administration of Prednisolone (PSL) of 1 mg/kg for 4 weeks, and then addition of immunosuppressant such as Cyclosporin. However, long-term administration of high dose PSL and immunosuppressant in elderly patients is controversial because of their multiple adverse effects. Here, we show the clinical efficacy of concomitant use of lower dose of Mizoribine (MZB) and PSL in terms of earlier induction to the remission by multicentered prospective cohort study.

Methods: Thirty-six patients diagnosed primary MN showing nephrotic syndrome were enrolled from 24 independent facilities. The patients, being older than 65 of age and preliminary obtained none of therapy, were randomly assigned to two groups, solely administered 30 mg of PSL (P group, n=18), or concomitantly administered 150 mg of MZB (MP group, n=18) and observed for 12 months. Remission rate was evaluated by remission score (RS) as follows: 1: Urine protein-to-Cr ratio (PCR)≤0.3, 2.5-3.5: PCR≤1.0, 3: 1.0-PCR<0.3 and 4: PCR<0.3 g/gCr. In some cases, anti-phospholipase A2 receptor antibody (PLA2R-Ab) titer was qualitatively measured.

Results: Mean ages of MP and P groups were 73.3 and 72.8. PCR at 12M was not different in the two groups. However, %PCR vs baseline and RS at earlier phase of M group was better than P (P<0.05): MP: 3.0 ±0.47% vs 55.5 ±5.07%, 6M: 31.4 ±22.7% vs 19.9 ±33.1%, RS: 3M: 1.24±1.2 vs 1.00±0.93, 6M: 1.96±1.03 vs 1.07±1.00). Those results were confirmed by the logistic analysis showed estimated odds ratio of the high responder in MP group was 1.50 (95%CI:0.33-6.83), suggesting that the concomitant use of MZB might accelerate the remission. Additionally, in cases showing qualitatively negative PLA2R antibody, the odds ratio of high responder cases was 2.67 (95% CI: 0.28-25.64) in MP vs 1.00 in P whereas the odds ratio was 0.33 (MP) and 0.40 (P) in cases showing positive PLA2R-Ab, suggesting that concomitant use of MZB might be more effective in PLA2R-Ab negative cases.

Conclusions: Concomitant use of low dose of MZB and PSL might contribute to save time until remission in elderly patients with MN-based NS.

TH-PO131
Long Term Outcome of Apparent Treatment Resistant Patients with Idiopathic Membranous Nephropathy Coralien Vink- van Setton, Anne-Elis van de Logt, Jack F. Wetzels. Radboud University Medical Center, Nijmegen, Netherlands.

Background: Cyclophosphamide is effective in idiopathic membranous nephropathy (iMN). Still, some patients do not respond timely, and do not develop remission at the end of therapy. We evaluated the outcome of these “apparent treatment resistant” (ATR) patients.

Methods: We selected patients with iMN, treated with cyclophosphamide (6-12 months), persistent proteinuria (PCR >3g/10 mmol) at 12 months after start of therapy, and a minimum follow-up of 24 months. Renal failure was defined as > 50% increase in serum creatinine concentration. Remission was defined as PCR of less than 3.0g/10mmol and stable renal function.

Results: Between 1995 and 2016, we evaluated 518 patients with iMN. 219 high risk MN patients were treated with cyclophosphamide. 110 with outcome data were followed for at least 24 months. At 12 months 84 (76.4%) patients achieved partial remission, one (0.9%) patient developed renal failure and 25 (22.7%) patients fulfilled ATR criteria. Of these 25 patients, 20 were males, mean age was 55 ± 12 years, median serum creatinine was 149 umol/l (108.5-195), median PCR 11g/10mmol (6.7-15.3). During follow-up (median 80 months (34.5-126), 16 patients developed partial or complete remission without additional therapy. A relapse has occurred in 4 patients, necessitating a second course of immunosuppressive therapy. Nine patients had persistent proteinuria. Five of these were treated with a second course of immunosuppressive therapy, which resulted in partial remission in 4. Two patients with persistent proteinuria and no additional immunosuppressive therapy have developed renal failure after 60 and 237 months respectively.

Conclusions: Persistent proteinuria at 12 months after start of cyclophosphamide therapy is evidence of treatment resistance. Most patients will develop remission of proteinuria. Patients with persistent proteinuria respond favourably to a second course of therapy. Risk of end stage renal is low.

Funding: Government Support - Non-U.S.
Role of Rituximab in Primary Membranous Nephropathy Refractory to Modified Ponticelli/Calcineurin Based Treatment

Jasmine Sethi, Harbir S. Kohli, Raja Ramachandran. Post Graduate Institute of Medical Education and Research (PGIMER), CHANDIGARH, India.

Background: Rituximab is emerging as a promising therapeutic agent particularly in the management of refractory primary membranous nephropathy. What should be dosage schedule to avoid toxicity without compromising the efficacy is a matter of concern and data on this is limited. This is a single center prospective study to evaluate the role of B cell titrated protocol of rituximab in adults with PMN who failed treatment with conventional immunosuppressive agents and its possible association with aPLA antibodies.

Methods: 14 patients aged 14-65 years of refractory PMN were given intravenous rituximab at a dose of 375mg/m² in a tertiary center in northern India. Following rituximab injection, CD19 counts were monitored weekly for 4 weeks followed by monthly for 6 months. If CD19 count was >5%/6 (or ≥1%), repeat doses of rituximab were given. The change in laboratory parameters (24 urinary protein, serum albumin and serum creatinine) were recorded at the baseline, and monthly till 6 months after rituximab administration. Serum sample drawn just before rituximab infusion and at the end of 6th month post-infusion were tested for aPLA by ELISA.

Results: End of 6 months, 6 out of 14 patients (42.8%) responded, with 1/14 (7.1%) achieving CR and 5/14 (35.7%) achieving PR. Eight out of 14 (57.1%) patients showed no response to rituximab at the end of the 6 months. Mean proteinuria decreased from 4.6±1.7 g/day at baseline to 3.3±2.1 g/day at 3 months, and 3.2±2.3 g/day at 6 months (p=0.29). Mean serum albumin also increased from 2.4±0.6 g/dl at baseline to 2.8±0.6 g/dl at 3 months, and 3.2±0.6 g/dl at 6 months. (p=0.002). Average time to CD19 reconstitution was 3.1±0.8 (2-4) months. Rituximab dose administered during 6 months period was 1289±720 (600-2800) mg. aPLA antibody testing was done in 13 patients. Among these, all 13 patients presented with high levels of antibodies before the treatment, eight of them experienced a reduction of an aPLA antibody titer, while 5 patients experienced no change after treatment (all five patients continued to have resistant disease).

Conclusions: CD19 titrated rituximab therapy is effective in achieving remission in 42.85% of patients of PMN refractory to prior immunosuppression. Titrated therapy might enhance the safety without compromising the efficacy of the therapy.

Improvement of Clinical Outcomes in Kidney Diseases via the On-line Thai Glomerular Disease Registry: Membranous Nephropathy

Panita Tonsawan, Sakkarn Sangkanmon, Boonyarit Cheunusuchon, Warangkana Pichaientong, Mongkon Charoenpitakchai, Bancha Satirapoj. Medicine, Phramongkutklao Hospital and College of Medicine, Bangkok, Thailand; Pathology, Siriraj hospital, Bangkok, Thailand; Pathology, Khon Kaen University, Khon Kaen, Thailand; Division of Nephrology, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand; Pathology, Phramongkutklao Hospital and College of Medicine, Bangkok, Thailand. Group/Team: Thai Glomerular Disease Collaborative Network (TGCN).

Background: The primary membranous nephropathy (MN) is the common cause of adult onset nephrotic syndrome. The Thai glomerular disease registry was established by Thai Glomerular Disease Collaborative Network (TGCN) to evaluate the prevalence, clinical features and outcomes in Thai glomerular disease patients. This study focused especially on MN.

Methods: We conducted a prospective cohort study in the adults with native kidney biopsy proven glomerular diseases between July 2014 and Mar 2017 from TGCN registry. The clinical features and laboratory parameters at the time of biopsy, pathologic findings, treatment regimens and clinical outcomes were monitored.

Results: MN was presented 111 (7.1%) of total 1,556 patients and 111 (15.5%) of total 742 patients with primary glomerular diseases. Mean age was 52.6±15 years. The clinical features of MN were identified; 86% nephrotic syndrome, 46% hypertension, 5.4% acute kidney injury and 4.5% asymptomatic proteinuria. At the time of renal biopsy, median serum creatinine was 0.98 mg/dl (0.42-7.4), median urine protein creatinine ratio was 3.5 g/g (0.14-21.9), mean serum albumin was 2.5±0.7 g/dl, and median interstitial fibrosis was 5% (5-90). Median time to remission was 5.6 months. At 24 weeks of follow up, complete remission and partial remission were observed in 20.7% and 59%, respectively. The predicting factors for clinical remission were identified as young patients, low serum creatinine, high hemoglobin, and high serum albumin at time of kidney biopsy. After the multivariate analysis, high serum albumin and low serum creatinine were the independent factors for clinical remission. Doubling of serum creatinine was observed in only 1.6 % during this period.

Conclusions: This study suggested that the clinical course and outcomes of Thai MN were favorable with low incidence of end stage renal disease. Baseline serum albumin and renal function were significantly predict the renal remission. Funding: Health Systems Research Institute, and Nephrology Society of Thailand support. Funding: Private Foundation Support.

The Investigative Burden of Membranous Nephropathy in the UK

Fiona Wilson, Patrick Hamilton, Rajkumar Chinnadurai, Malinder Singh, Smeeta Sinha, Durga A. Kanigicherla, Paul E. Brenchley, Central Manchester University Hospitals, Manchester, United Kingdom; Manchester Royal Infirmary, Manchester, United Kingdom; NHS, Manchester; United Kingdom; 2SALFORD ROYAL NHS FOUNDATION TRUST, Manchester, United Kingdom; 3Salford Royal NHS Foundation Trust, Salford, United Kingdom; 4LTHTR, Preston, United Kingdom.

Background: Membranous Nephropathy (MN) represents two distinct disease entities. Primary MN (PMN) is now recognized as an autoimmune condition associated with the anti-PLA2R antibody and secondary MN occurs in tandem with malignancy, infection or drug therapy. Prior to the discovery of anti-PLA2R antibody in 2009 and the development of accessible ELISAs, the diagnosis of MN was a diagnosis of exclusion. We investigated the investigative burden for patients with MN and the diagnostic yield of these tests.

Methods: Patients from 2 UK centres with a diagnosis of MN between 2009 and 2014 were identified. Across the Northwest of England, anti-PLA2R testing became readily available in 2012. Therefore patients were divided into those receiving a diagnosis 2009-2011 (pre-ELISA) and 2012-2014 (post-ELISA). Records were reviewed for the investigations which took place months prior and months following the biopsy date to see if these were normal or identified a secondary cause of MN. Investigations included viral and autoimmune screens, X-rays, CT, MRI, PET scan, ultrasound, upper and lower GI endoscopies and cystoscopies.

Hypothesis: The introduction of anti-PLA2R testing leads to a modification of the investigative pathway for MN patients.

Results: 121 patients were identified, 104 with PMN and 17 with secondary MN. Patients went through an average of 7.38 tests with only 18 of 893 (2.0%) tests proving to be instrumental in helping with the diagnosis of secondary versus primary MN. For patients diagnosed with PMN they had an average of 7.48 tests, all of which were negative. With the introduction of anti-PLA2R testing in 2012 there appears to be a trend towards a reduction in the investigative profile of patients with the average number of tests falling from 7.73 to 7.29. A significant reduction was noted in Hepatitis B and C (p=0.029 for both) and colonoscopies (p=0.012). There was also a reduction in the total cost of investigation per patient with PMN from an average of £533.41 in 2009-2011 to £366.02 in 2012-2014.

Conclusions: Patients with a diagnosis of MN undergo multiple investigations, many of which are negative, at a significant cost to both the healthcare system and patients quality of life. The anti-PLA2R test has the potential to reduce this burden as its use becomes more widespread.

Association of Presence of Diabetes with Failure to Complete Remission in Patients with Primary Membranous Nephropathy

Huaixia Nie, Zhen Wu, Xin Zhang, Yuhong Wen, Jianfang Cai, Hang Li, Xuemei Li, Xuewang Li, Peking Union Medical College Hospital, Beijing, China; Beijing Friendship Hospital, Capital Medical University, Beijing, China; Peking University First Hospital, Beijing, China.

Background: This study aimed to assess whether the presence of diabetes will influence renal outcomes in patients with idiopathic membranous nephropathy (IMN). Methods: In this retrospective study, a total of 875 patients with pathology-proven IMN were consecutively enrolled. Among them, 101 were diagnosed as type 2 diabetes mellitus (T2DM) prior to their diagnosis of IMN. Data on age, sex, body mass index (BMI), presence of hypertension and diabetes mellitus, laboratory tests, and therapeutic regimens were retrospectively retrieved from medical record. Complete remission (CR) was defined as urinary protein excretion<0.3g/d with stable estimated glomerular filtration (eGFR). COX regression was used to analyze risks of failure to CR and renal function deterioration associated with the presence of T2DM.

Results: A total of 810 patients were followed at least once with a median follow-up of 23.6 (IQR 9.9-42) months, of whom 292 achieved CR and 95 developed a 30% decline in eGFR. Presence of T2DM was associated with failure to reach CR or IMN (HR=0.53, 95% CI 0.37-0.77, P =0.001), independently of age, sex, hypertension, renal treatment, serum albumin, proteinuria, and baseline eGFR. The association remained statistically significant when we further excluded 103 patients with corticosteroid-induced diabetes (HR=0.49, 95% CI 0.34-0.71, P<0.001), or restricted the analyses in patients with nephrotic syndrome (HR=0.46, 95% CI 0.28-0.67, P<0.002) or in those using calcineurin inhibitors (HR=0.58, 95% CI 0.37-0.91, P =0.017). However, patients with and without T2DM did not differ in developing a 30% decline in eGFR, adjusting for age, sex, BMI, treatment regimen also with or without eGFR<0.67, 95% CI 0.39-1.16, P =0.156.

Conclusions: Presence of T2DM may be independently associated with failure to remission but not eGFR decline in IMN patients.
Treatment of Membranous Glomerulopathy with Ponticelli’s Modified Scheme and with Cyclosporine Are Comparable after 1 Year Follow-Up: Retrospective Cohort Nathalia C. dos Anjos,6 Luis H. Sette,7 Camila B. Oliveira,8 Denise M. Costa,9 Gisele Vieijal,10 Maria Alina G. Cavalcante,11 Lucila Maria Valente,12 HOSPITAL DAS CLÍNICAS, RECIFE, PE, RECAP, Brazil; 2HOSPITAL DAS CLÍNICAS - UFPE, REICEF, Brazil; 3Hospital das Clinicas - UFPE, Recife, Brazil; 4None, Recife, Brazil; 5UNIVERSIDADE FEDERAL DE PERNAMBUCO, Recife, Brazil; 6NEPHROLOGY, University Federal of Pernambuco, REICEF, Brazil.

Background: The standard treatment recommended by KDIGO in patients with membranous glomerulopathy (MG) is performed with corticosteroids and cyclophosphamide (modified Ponticelli’s scheme). However, there are few studies in the Latin American population about the comparative efficacy of an alternative regimen using oral cyclosporine (CSA). The hypothesis is CSA presents therapeutic equivalence and lower side effects when compared to Ponticelli’s scheme. Therefore, this study sought to evaluate the response of these two therapeutic regimens in patients with MG.

Methods: A retrospective cohort was conducted from 1998 to 2016. Data from patients older than 18 years with idiopathic MG for at least 6 months without previous treatment, were analyzed. In addition to the clinical and epidemiological profile, the response to the treatment was evaluated (CyA and Ponticelli), in a period of 6 months and 1 year after initiation of therapy. Definitions of partial response, complete response, relapse, and therapeutic failure were based on KDIGO.

Results: Thirty patients were evaluated 16 were treated with CSA and 14 with Ponticelli’s scheme. The baseline characteristics of the two groups treated with IMM are described in Table 1. After 6 and 12 months the partial and complete response rate was 50% and 69% in the cyclosporine group and 57% and 50% in the Ponticelli’s group. There was no difference between response rates (complete response and partial response) between groups after 6 months (p = 0.69), 12 months (p = 0.64).

Conclusions: The therapeutic regimens of immunosuppression evaluated showed similar response rates after the 6-month and 12-month follow-up.

HLAG-DR3 Impact on Graft Survival in Membranous Nephropathy: A Tricontinental Registry Study Patrick Hamilton,4 Kay V. Polston,1 Lisa L. Munnford,1 Laura H. Mariani,2 Nathan P. Goodrich,7 Robert Merion,2 Stephen P. McDonald,1 Paul E. Brenchley,2 1ANZDATA Registry, Adelaide, SA, Australia; 2Arbor Research Collaborative for Health, Ann Arbor, MI; 3Manchester Royal Infirmary, Manchester, United Kingdom; 4NH, Manchester, United Kingdom; 5NHS Blood and Transplant, Bristol, United Kingdom; 6University of Michigan, Ann Arbor, MI.

Background: Membranous nephropathy (MN) is a rare disease in which a third of patients will need a kidney transplant. The strong genetic predisposition to MN was associated with HLA-DR3, as patients with HLA-DR3 matched donor kidney. These results become more significant if HLA-DR1, HLA-DR2 or HLA-DR7 is combined with HLA-DR3, suggesting an association with HLA-DQB polymorphisms.

Can THSD7A Be a New Marker for Diagnosing Idiopathic Membranous Nephropathy? A Systematic Review and Meta-Analysis of the Diagnostic Value of THSD7A in IMN Song Ren,5 Changwei Wu,1 Guisun Li,2 Li Wang,3 Daqing Hong,1 Renal Department and Institute of Nephrology, Sichuan Provincial People’s Hospital, Chengdu, China; 2Renal Division and Institute of Nephrology, Sichuan Academy of Medical Sciences and Sichuan Provincial People’s Hospital, Chengdu, China; 3Sichuan Provincial People’s Hospital, CHENGDU, China.

Background: Thrombospondin type 1 domain-containing 7A (THSD7A) is a new target antigen in patients with idiopathic membranous nephropathy. Moreover, malignancies are also found in THSD7A-positive membranous nephropathy patients. We aimed to systematically evaluate prevalence of THSD7A in the IMN patients and malignancies in THSD7A-positive patients.

Methods: We searched English database including MEDLINE, Embase, Cochrane Library and Chinese database including CNKI, VIP and Wanfang database to Jan 4, 2017 with the term “THSD7A” or “thrombospondin type 1 domain-containing 7A”. Meta-analysis was used to explore the positive rate of THSD7A in the patients with idiopathic membranous nephropathy. Subgroup analysis was done according to the race, sample size, and detecting method of THSD7A. The incidence of malignancies in THSD7A positive patients was also summarized.

Results: Ten studies involving 3061 participants were eventually included in this review. The prevalence of THSD7A was 3% (95%CI, 3%-4%). In the anti-phospholipase A2 receptor (PLA2R)-negative patients, the prevalence of THSD7A was 10% (95% CI, 6%-15%). A total of 77 patients were detected for positive circulating antibodies, and the prevalence of THSD7A was lower at 3% (95% CI, 2%-4%). Overall 72 patients were THSD7A-positive detected by renal biopsy with immunohistochemistry, and the prevalence was 3% (95% CI 3%-4%). Subgroup analysis did not show significant differences in the prevalence of THSD7A between races and study sample sizes. Among THSD7A-positive patients, 2/10 studies reported malignancies with the incidence varied from 20% to 25%.

Conclusions: The prevalence of THSD7A is not uncommon in the patients with IMN, but more common in the PLA2R-negative patients. Malignancies should be screened and closely monitored in THSD7A-positive membranous nephropathy patients.
Late Relapses of Membranous Nephropathy (MN) Yotonan A. Peleg,1 Andrew S. Bomback,1 Pietro A. Canettia,1 Gerald B. Appella,1 Woonin Ahn,2 Columbia University, New York, NY; 2 Columbia University College of Physicians and Surgeons, Scarsdale, NY; 3 None, New York, NY; 4 Nephrology, New York Presbyterian-Columbia University Medical Center, New York City, NY.

Background: Most patients (pts) with MN who achieve remission carry a risk of relapse that diminishes over time. Relapse of disease after 5 years of sustained remission is considered a rare event.

Methods: We reviewed 15 idiopathic MN pts, who relapsed after a median time of 11 years of disease remission.

Results: 10/15 pts were male. All were white, and one was Hispanic. Median age at diagnosis was 34 yr (range 3-71). Median baseline eGFR was 79.4 ml/min/1.73m² (range 26.8-110). 9 went into complete remission (CR) and 6 pts went into partial remission (PR). CR was achieved with immunosuppression (IS) in 6 pts. Median age at first relapse was 51 y (range 20-80), representing a gap of 11 y (range 6-36) from initial remission. Relapses presented as nephrotic syndrome in 8, while the other 7 were diagnosed by lab surveillance. 10/15 pts underwent repeat biopsy 12 y (range 8-33) after first biopsy: all showed pattern of primary MN. 12 pts received IS after relapse and 1 died prior to treatment. 8/14 surviving pts had PR after their initial relapse, 3 had CR, and 3 had no remission (NR). CR was not associated with IS use. 5 pts had additional relapse episodes after their first relapse, and all were treated with IS. Experiencing PR vs. CR did not predict risk of subsequent relapse. The results of the most recent relapse for these 5 patients are 1 in CR, 1 in PR, and 3 in NR. Median follow up duration was 19 y (range 5-36). The median most recent eGFR was 60.8 (range 6.8-105.6), and median yearly change in eGFR was -0.32 (range -2.73 to +2.82). None reached ESRD. 10 available biopsies during clinical relapse, 6 were stained for PLA2R with all staining positive. Serum PLA2R Ab was tested in 10 pts, with some serialised with serum titers: 2 had positive titers during relapse, 5 had negative titers during relapse, and 3 had negative values during PR. In all, 8/10 pts were positive for either tissue PLA2R or serum PLA2R Ab while in clinical relapse.

Conclusions: We present 15 MN pts with proteinuric relapse a median time of 11 years after initial remission. Repeat biopsies, even as long as 33 years after complete remission, all showed MN, and 80% of pts were PLA2R positive by tissue or serum testing. Thus repeat biopsy to reestablish a diagnosis of MN may be unnecessary. There was no significant decline in renal function despite relapses and median follow up time of 19 years.

Clinical and Pathological Analysis of Renal Tubulointerstitial Injury in Idiopathic Membranous Nephropathy Zilong Li,1 Yibo Zhang,2 Juan Wang,1 Linlin Liu,1 Jianfei Ma,1 Li Yao,1 Department of Nephrology, The First Affiliated Hospital of China Medical University, Shenyang, P. R. China, Shenyang, China; 2 The First Affiliated Hospital of China Medical University, Shenyang, China; 3 The First Hospital of China Medical University, ShenYang, China; 4 the first affiliated hospital of China Medical University, Shenyang, China.

Background: It has been revealed that renal tubulointerstitial injury (TII) plays important roles in the progression of chronic kidney diseases, while how TII affects idiopathic membranous nephropathy (IMN) remains unclear. Herein, we retrospectively studied the clinical and pathological data of 134 IMN patients, to investigate the characteristics of TII in IMN.

Methods: 134 patients diagnosed as IMN via renal biopsy from January 2014 to December 2015 in our department were enrolled. All the patients didn’t receive IS with either corticosteroid or immunosuppressants before undergoing renal biopsy, and accepted appropriate therapy according to the clinical and pathological features after renal biopsy. The patients were divided into two groups: TII group and non-TII group. Clinical and pathological data were accumulated after 12-month follow-up.

Results: Among the 134 IMN patients, 79 were males (58.96%) and 55 were females(41.04%), age from 14 to 74 years. The pathological results suggested 65 cases (48.51%) existed TII in IMN. Compared to non-TII group, TII group appeared significantly higher levels of 24-hour urinary protein, urinary albumin, urinary β2-microglobulin, urinary creatinine and cystatin C (p<0.05), and significantly declined eGFR (p<0.05). Renal tubulointerstitial injury score was positively associated with serum creatinine(r=0.304, p<0.00), cystatin C(r=0.372, p<0.00), 24-hour urinary protein(r=0.207, p<0.016), urinary β2-microglobulin(r=0.174, p<0.044), β2-microglobulin/creatinine(r=0.246, p<0.048) and urinary albumin/r(0.206, p<0.017), and negatively associated with eGFR(−0.304, p<0.00). After 12-month follow-up, patients in TII group showed higher incidence of eGFR decrease.

Conclusions: TII occurs in IMN patients, which may be prompted by some clinical factors. All the patients didn’t receive IS with either corticosteroid or immunosuppressants before undergoing renal biopsy, and accepted appropriate therapy according to the clinical and pathological features. Therefore, the phenomenon of TII in these patients may be due to the absence of IS. Further studies are needed to elaborate the mechanisms and explore effective therapies.

Initial States of Circulating Anti-Phospholipase A2 Receptor Antibody and Cigarette Smoking Predict a Clinical Outcome in Japanese Patients with Idiopathic Membranous Nephropathy Asaka Hachiya, Shin’ichi Akiyama, Shoichi Maruyama. Nagoya University Graduate School of Medicine, Nagoya, Japan.

Background: Idiopathic membranous nephropathy (IMN) is the leading cause of nephrotic syndrome in adults, the clinical outcomes in IMN is difficult to predict. We reported that the prevalence of anti-PLA2R in Japanese patients with IMN is approximately 50%, which was lower than reports from any other countries (approx. 75%). In addition, we reported that cigarette smoking is a significant and dose-dependent risk factor for progression of Japanese patients with IMN. In this study, we tried to reveal the association of initial states of anti-PLA2R and cigarette smoking to clinical outcomes in Japanese patients with IMN.

Methods: We retrospectively enrolled consecutive 78 biopsy-proven IMN Japanese patients with nephrotic syndrome (# of male, 57; median age, 64 [IQR 60-70] years old; # of Current/Ex-smoker, 34) who admitted our hospitals between January 2003 and December 2012, and followed these patients for at least 3 months (median [IQR], 56 [35-81] months). All patients were not treated with any immunosuppressive therapies at renal biopsy, whose serum were collected at the same time of renal biopsy. Duration of current smoking (CR) and predictors of prolongation of CR were assessed and anti-PLA2R in serum was measured by ELISA.

Results: Anti-PLA2R was positive in 53% (41 of 78) of all patients with IMN. The prevalence of anti-PLA2R in current/ex-smokers (59%, 20 of 34) higher than that in never-smokers (47%, 21 of 44). In the follow-up period, CR was observed in 55 patients (anti-PLA2R positive, 27; negative, 28). In patients with anti-PLA2R positive and/or current smoker, the period to CR tended to prolong. Duration of CR with anti-PLA2R positive and ex/current smoker was significantly longer than that of the other groups (log rank, p < 0.009). Multivariate Cox proportional hazards models revealed anti-PLA2R positive and current/ex-smokers (adjusted hazard ratio, 0.16 [95% confidence interval, 0.05-0.51]) associated with prolongation of CR.

Conclusions: The smoking experience and anti-PLA2R positive at diagnosis are rival factors for renal tubulointerstitial injury. Our data suggested that check the initial states of circulating anti-PLA2R and cigarette smoking is useful and easy method to predict a clinical outcome of patient with IMN.

Low Dose Rituximab Is Non-Inferior to Higher or Multiple Dose Schedules in the Treatment of Steroid Sensitive, Frequently Relapsing Nephrotic Syndrome in Children Ben C. Reynolds,2 Rebecca A. Dalrymple,2 Andrew P. Maxted,2 Denise Chisholm,3 John H. McColl,2 Vincent Tse,1 Martin Christian.1 Great North Children’s Hospital, Newcastle upon Tyne, United Kingdom; 2 Greater Glasgow and Clyde NHS, Glasgow, United Kingdom; 3 NHS, Nottingham, United Kingdom; 4 Royal Hospital for Children, Glasgow, Glasgow, United Kingdom; 5 University of Glasgow, Glasgow, United Kingdom; 6 Pediatric Nephrology, Nottingham Children’s Renal and Urology Unit, Nottingham, United Kingdom.

Background: Rituximab is an effective treatment for children with steroid dependent or frequently relapsing nephrotic syndrome. Dosing schedules vary between centres and are based on anecdotal evidence and non randomised controlled data. We hypothesised that a single low dose of 375mg/m² would be non-inferior to higher or multiple doses, in maintaining remission and time to B-cell reconstitution.

Methods: This was a retrospective, observational cohort study of children from three paediatric nephrology centres in the United Kingdom. Children with steroid sensitive, frequently relapsing nephrotic syndrome who received Rituximab since January 2007 were included. Data were extracted from clinical records on the dates of diagnosis, treatment and relapses; lymphocyte subset profiling pre-and post-rituximab administration; and the use of concomitant immunosuppression. The primary outcome was an absence of clinically confirmed relapse 12 months after Rituximab administration. Secondary outcomes were median time to relapse, probability of being relapse free at 6 and 24 months and time to remission of CD19 B cells (CD 19 B cells >0.2 x10⁹/l).

Results: 60 patients received 143 courses of Rituximab. Patients were grouped according to the dose of Rituximab received; those in group 1 (15 courses) received a higher total dose of 1.5g/m², group 2 (25 doses) received an intermediate dose between 750mg/m² – 1g/m², and group 3 (103 courses) received our current low dose regimen of a single dose of 375mg/m². There was no difference in event-free survival at 6, 12, or 24 months between groups. Of those who relapsed, the median time to relapse was not significantly different between the high and low dose groups, 317 days in group one and 299 days in group three. The median time to reconstitution of B-cells was not significantly different between groups at 175, 226 and 196 days for groups 1, 2 and 3 respectively.

Conclusions: We conclude that usage of a single low dosage of Rituximab in the management of frequently relapsing nephrotic syndrome does not affect the probability of relapse at 6 and 12 months, or the time to B-cell reconstitution in our cohort of patients.
Clinical Glomerular Disorders: FSGS, MN, MCD

TH-PO144

Initial Response to Corticosteroid Therapy and Native Kidney Biopsy Findings Predict Disease Recurrence Following Kidney Transplantation in Childhood Nephrotic Syndrome

Adam R. Bensimhon, Jonathan H. Pellietier, Karan Kumar, Michelle N. Rheaute, Tarak Srivastava, Caroline E. Straatman, Thomas K. Davis, Cynthia J. D’Alessandri-Silva, Scott E. Wenderer, Rachel D. Engels, Keisha L. Gibson, Christoph Licht, David T. Selewski, Larry A. Greenbaum, Rasheed A. Gbadegesin, Pediatrics, Duke University Medical Center, Durham, NC.

Background: Steroid resistant nephrotic syndrome (SRNS) is a leading cause of ESKD in children. Disease recurrence following kidney transplantation is the single most important cause of renal allograft loss in SRNS. Previous studies have not consistently identified risk factors associated with recurrence of disease. This study aims to determine predictors of disease recurrence in children with SRNS after renal transplantation.

Methods: A 10 year multicenter review of kidney transplants performed for SRNS in MWPNC participating centers. Data were collected on patients’ demographics, clinical course, and biopsy findings. Patients with primary SRNS (PSRNS) were defined as those initially resistant to standard steroid therapy. SRNS patients with initial FSGS biopsy had an 80% recurrence rate compared with a 31% recurrence rate in those with focal segmental glomerulosclerosis (FSGS) (p = 0.005). Unadjusted multivariate analysis identified MCD (OR 8.9; 95% CI 1.8-45.3, p = 0.008) and LSRNS (OR 4.3; 95% CI, 1.4-13.7, p = 0.013) as predictors of disease recurrence, but in adjusted analysis, only LSRRN predicted disease recurrence (OR 4.3; 95% CI 1.1-16.1, p = 0.032).

Results: We identified 116 patients (67 with PSRNS, 17 with LSRRN, and 32 with genetic SRNS/undetermined pattern of response). Disease recurrence occurred in 35.8% of patients with PSRNS compared to 70.6% of those with LSRRN (p = 0.001). Age at diagnosis and ESKD, sex, race, and ethnicity were similar in patients with and without recurrence. Age at time of initial change disease histology (MCDD) on initial kidney biopsy had a 80% recurrence rate compared with a 31% recurrence rate in those with focal segmental glomerulosclerosis (FSGS) (p = 0.005). Unadjusted multivariate analysis identified MCD (OR 8.9; 95% CI 1.8-45.3, p = 0.008) and LSRRN (OR 4.3; 95% CI, 1.4-13.7, p = 0.013) as predictors of disease recurrence. High risk of recurrence was seen in MCD and LSRNS, while FSGS was not associated with recurrence.

Conclusion: Patients with LSRRN and MCD histology are at significantly higher risk of disease recurrence following kidney transplantation. These findings may be useful for designing studies to test strategies for preventing recurrence.

Funding: NIDDK Support

TH-PO145

Management of Children With Congenital Nephrotic Syndrome: Challenging Treatment Paradigms

Stephanie Dalek, Elisa Yilten, Agnes Trautmann, Enrico Vidal, Taula M. Holita, Rukshana Shroff, Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom; University Hospital Helsinki, Helsinki, Finland; University-Hospital of Padova, Padova, Italy; Center for Pediatrics and Adolescents Medicine, University Hospital Heidelberg, Heidelberg, Germany. Group/Team: On behalf of ESPN Dialysis Working Group.

Background: Management of children with congenital nephrotic syndrome (CNS) is challenging and ranges from antiproteinuric treatment to uni- or bilateral nephrectomies followed by dialysis and transplantation. Early bilateral nephrectomies followed by dialysis and transplantation is currently practised in most centres, but conservative treatment may also be effective.

Methods: We conducted a 6-year survey across members of the European Society for Pediatric Nephrology (ESPN) Dialysis Working Group to compare management strategies and their outcomes in children with CNS.

Results: 81 children (51% male) across 17 tertiary nephrology units in Europe were included (NPHS n=57; NPHS n=2, WT1 n=10, others n=12; details of mutations were not examined). Antiproteinuric treatment was used in 46 (59%) with an increase in S-albumin (p=0.021) and weekly albumin infusion dose decreased by median 4 (0-7) g/kg/week (p=0.018). The median age at bilateral nephrectomy was 7 (9-15) months. Dialysis was initiated in 53 (65%) at a median age of 9 (5.5-15) months, with PP in 9% of children. Children with NPHS1 mutations and <12 months follow-up were divided into two groups and their outcomes were compared: bilateral nephrectomy (n=26) versus conservative management (no nephrectomy, n = 17). Nephrectomised children presented earlier (3 vs 29 days; p=0.01), with comparable S-albumin (p=0.21) and S-creatinine (p=0.19). There was no difference in the number of septic or thrombotic episodes and growth was comparable. At final follow-up (median age 34 months) 53% children in the conservative group remained without renal replacement therapy, 4 (24%) received a renal transplant and 2 died. Amongst nephrectomised children 21 (81%; p<0.01) were transplanted and 1 died.

Conclusion: An individualised, stepwise approach, with prolonged conservative management, followed by unilateral nephrectomy may be a reasonable alternative to early bilateral nephrectomies in children with CNS and NPHS1 mutation.

TH-PO146

Medication Adherence and Perceived Difficulties in Pediatric Nephrotic Syndrome

Chia- Shi Wang, Jonathan P. Troost, Tarak Srivastava, Darcy K. Weidemann, Larry A. Greenbaum, Emory University, Atlanta, GA; University of Michigan, Ann Arbor, MI; Children’s Mercy Hospital, Kansas City, MO. Group/Team: CureGN Working Group.

Background: In children with nephrotic syndrome (NS), there is limited information on the prevalence of medication nonadherence and the role of perceived barriers in determining nonadherence.

Methods: We surveyed a large cohort of prevalent pediatric NS patients enrolled in an international, prospective study, the Nephrotic Syndrome Study Network (NEPTUNE). Self-reports for patients ages 8-18 years and caregiver-reports for patients ages 6-10 years were administered to prevalent patients between 2015-2016. The surveys contained 2 questions on whether medications were taken/missed and 17 questions on difficulties with medication ingestion, regimen adaptation, and disease frustration. All responses were reported in a 5-item Likert-type scale. Non-adherence was defined as responses of “not sure” or affirmative responses to not taking all medications or having missed medications. Patients were noted to have perceived barriers to medication adherence if an affirmative answer was given to one of the seventeen questions on medication difficulties. Association between perceived barriers and adherence was assessed by Chi-square test.

Results: 129 patients/caregivers completed medication adherence surveys, with 13 respondents to medication difficulties surveys. Median time of study enrollment at time of survey was 521 days (interquartile range = 10-1221 days). 51 (39.5%) of patients were non-adherent to medications by self/caregiver-report. 56 (49.6%) reported difficulties with medication ingestion, regimen adaptation, and 69 (16.1%) with disease frustration. 86 (76.1%) patients reported difficulties within at least one domain. Report of perceived barriers was not significantly associated with medication nonadherence (odds ratio = 1.63, 95% confidence interval = 0.64-4.14).

Conclusion: Self-/caregiver-reported medication nonadherence was common among pediatric NS patients. The majority of patients and caregivers reported experiencing barriers to adherence, including difficulties with medication ingestion, adaptation to medication regimen, or frustration with the disease. Prospective studies are needed to assess the effects of reported difficulties on long-term medication adherence and disease outcome.

Funding: NIDDK Support

TH-PO147

Cardiovascular Disease Risk Factors in Pediatric Glomerular Disease: An Early Analysis of the Cure Glomerulonephropathy (CureGN) Study

Isa Ashoor, Donald J. Weaver, Amy Kogon, Rulan S. Parakh, Tetyana L. Vasylyeva, Aftab S. Chishti, Michelle N. Rheaute, Christine B. Sethna, Michelle M. O’Shaughnessy, Margaret Helmut, Children’s Hospital of New Orleans, New Orleans, LA; Levine Children’s Hospital at Carolinas Medical Center, Charlotte, NC; Nationwide Children’s Hospital, Columbus, OH; The Hospital For Sick Children, Toronto, ON; Texas Tech University Health Sciences Center, Amarillo, TX; University of Kentucky, Lexington, KY; University of Minnesota, Minneapolis, MN; Cohen Children’s Medical Center of NY, New Hyde Park, NY; Stanford University Medical Center, Palo Alto, CA; Arbor Research Collaborative for Health, Ann Arbor, MI. Group/Team: CureGN Study Cardiovascular Working Group.

Background: Chronic kidney disease (CKD) is major risk factor for subsequent development of cardiovascular disease (CVD). We sought to describe the burden of CVD risk factors in pediatric glomerular disease.

Methods: CureGN is a prospective multi-center cohort of biopsy-confirmed primary glomerular diseases (minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), and IgA Nephropathy/Vasculitis (IgAN/ IgAV)). Descriptive statistics are used to assess CVD risk factors (hypertension, obesity, dyslipidemia, prematurity, and second hand tobacco exposure) and management practices among 578 participants under age 18. Data were obtained at enrollment.

Results: The Table summarizes baseline characteristics and prevalence of CVD risk factors overall and by primary glomerular disease. Prevalent cardiac disease was rarely reported. Overall, 20% had a history of hypertension. Enrollment BP’s were hypertensive in 21% and pre-hypertensive in 14% of patients compared to 1.6% and 9.6% of general pediatric population. Among those with hypertension, readings, and those with UPCR>3.5, less than a third received RAAS blockers overall. Obesity was present in 31% and elevated total cholesterol (TC > 200 mg/dL) was present in 30% compared to 17% and 7.4% of general pediatric population. Use of lipid lowering medications in children with TC > 200 was infrequent (7%). Prematurity and second hand smoke exposure were rare in general population.

Conclusion: In this pediatric glomerular disease cohort, prevalence of traditional CVD risk factors is high, particularly hypertension and dyslipidemia. Further study is needed to optimize screening and management of CVD risk factors in this population.

Funding: NIDDK Support
TH-PO148
Pregnancy in Women with Relapsing Minimal Change Disease – Experience of a Tertiary Centre

Background: Recent data suggest even patients with CKD stage 1 have an increased risk of pregnancy complications when compared to the general population. However, data on outcomes specifically in pregnant women with relapsing minimal change disease (MCD) are lacking. We now report the largest series to date.

Methods: Women with MCD were identified from our obstetric renal database from 1996-2016. We report maternal outcomes: relapse, AKI & worsening of renal function. HTN; & obstetric outcomes: number of successful pregnancies, preclampsia, preterm delivery & low birth weight.

Results: Out of 977 pregnancies, we identified 14 in 10 women with MCD. Median maternal age: 35 years (19-40). Two patients had chronic HTN – one with relapsing MCD with IgM deposition for 11 years & 8 years of FK treatment; the other patient had dysmature type and MCD diagnosis made on post-partum biopsy. All women were in remission with no proteinuria at the time of conception & were on in remission with no proteinuria at the time of conception & were on immunosuppression (FK (n-7), CsA (n-2) or steroids (n-2) & one had an unplanned pregnancy diagnosed very soon after maintenance rituximab. None of the women developed worsening renal function. Relapses were seen in 2 pregnancies in women who stopped their maintenance immunosuppression. One hypertensive patient had worsening HTN during pregnancy. The majority of babies (69%, n=9) delivered at term (median gestation 38 weeks (range 28-40)). Preterm (35 & 36 weeks) & very preterm (28 weeks) were seen in 3 & 1 pregnancies respectively. Birth weight was 2923 ± 3.03, 1.8 ± 2.71 kg, p = 0.006). Continuous hematuria was present in 3 & 1 pregnancies respectively. Blood pressure was 124 ± 0.68, 0.23 mg/dl, p = 0.59, eGFR (80.5 ± 26.8, 94.3 ± 43.0 ml/min/1.73m², p = 0.46), systolic blood pressure (156 ± 8.0, 141 ± 17.7 mmHg, p = 0.03).

Conclusions: The patients who have proteinuria in pregnancy with continuous hematuria were suspected kidney disease to need aggressive treatments, and renal biopsies were utility as early diagnoses. HTN & obstetric outcomes: number of successful pregnancies, preclampsia, preterm delivery & low birth weight.

TH-PO149
Utility of Renal Biopsy for Proteinuria in Pregnancy

Background: We are often referred patients who have proteinuria in pregnancy. The patients present various clinical conditions; superimposed preclampsia, normotensive nephrotic syndrome, complicating hematuria. These clinical conditions sometimes become the risk of pregnancy termination. The patients with proteinuria in pregnancy had renal biopsies, and were discussed utility of the biopsies based on histopathological findings and clinical courses.

Methods: 17 patients who had proteinuria in pregnancy had postpartum needle biopsies of their kidneys. Then we analyzed clinical findings to need aggressive treatments, based on histopathological diagnosis and onset of proteinuria.

Results: Before 20 weeks’ gestation, the timing of onset of proteinuria, nine of 11 patients were diagnosed kidney diseases to need treatments. Histopathological diagnoses were IgA nephropathy (n = 6), focal segmental glomerular sclerosis (n = 2), mesangial proliferative nephritis (n = 1). Other 2 patients were thin basement membrane disease and minor abnormality. After 20 weeks’ gestation, two of 6 patients were diagnosed kidney diseases to need treatments, there were IgA nephropathy (n = 1), membranous nephropathy (n = 1). Other 4 patients were histopathological findings of pregnancy induced hypertension (PIH). Compared histopathological PIH with non-PIH about clinical characters, gestational age (PIH; 28.7 ± 2.87, non-PIH; 30.7 ± 4.11 y.o., p = 0.32), maximum proteinuria (9.9 ± 3.03, 1.8 ± 2.71 kg/dl, p = 0.006), continuous hematuria (p = 0.00002), serum creatinine (0.75 ± 0.21, 0.68 ± 0.23 mg/dl, p = 0.59), eGFR (80.5 ± 26.8, 94.3 ± 43.0 ml/min/1.73m², p = 0.46), systolic blood pressure (156 ± 8.0, 141 ± 17.7 mmHg, p = 0.03). Significant clinical character of non-PIH was continuous hematuria.

Conclusions: The patients who have proteinuria in pregnancy with continuous hematuria were suspected kidney disease to need aggressive treatments, and renal biopsies were utility as early diagnoses and treatments.

TH-PO150
Factors Associated with the Initiation of renin-Angiotensin-Aldosterone System Blockade in Patients with Sustained Proteinuria

Background: Renin-angiotensin-aldosterone system (RAAS) blockade plays an important role in the treatment of sustained proteinuria. The goal of this study was to investigate the time from the onset of sustained proteinuria to initiation of RAAS blockade therapy and associated characteristics.

Methods: Electronic health record derived NephCare Accelerating Cures Institute cohort data were used. Patients with primary proteinuric kidney disease and onset of sustained proteinuria, defined as two or more days within 6 months with measurements of UP/C > 1 or dipstick proteinuria ≥ 2, were eligible. Kaplan-Meier analysis was used to evaluate the time to initiation of RAAS blockade from the date of the second qualifying proteinuria measurement.

Results: Of 848 registry patients, 147 patients were excluded due to prior RAAS therapy and 496 due to intermittent proteinuria. 205 patients were eligible for this analysis. 89 (43%) patients were prescribed RAAS blockade, 64 of 110 adults and 25 of 95 children. The median time from onset of sustained proteinuria until initiation of RAAS blockade was 241 days (IQR 35 to 653). Patients with Focal Segmental Glomerulosclerosis (FSGS) or Membranous Nephropathy (MN) were more likely to receive RAAS blockade and receive it earlier than Minimal Change or NS-not biopsied patients (Figure). In a multivariable Cox-proportional hazards model, diagnosis but not age or sex, was a significant factor associated with time to initiation of therapy. Discrimination: Following, onset of sustained proteinuria, RAAS blockade was initiated within a median of 8 months. Patients with a diagnosis of FSGS or MN were more likely to be treated and to be treated earlier. This study highlights opportunities for improvements in health care delivery.

Funding: Private Foundation Support
**TH-PO151**

**Time to Initiation of Anti-Hypertensive Therapy after Onset of Elevated Blood Pressure in Patients with Primary Proteinuric Kidney Disease**

**Susan F. Massengill,**1 Cheryl D. Courtlandt,1 Matthew Elliott,2 Patrick E. Gipson,1 Elaine S. Kamill,1 Anne Penesdon,1 Meg Modes,1 David T. Selewski,2 Gia J. Oh,1 Debbie S. Gipson,1 Richard A. Lafayette,2 Halley Desmord,2 Jonathan P. Troost,1 Lauren Lee,1 Sharon G. Adler,2 Levine Children’s Hospital, Charlotte, NC; 2Harbor-UCLA Medical Center, Torrance, CA; 4Medtonia Nephrology Associates, Charlotte, NC; 5NephCare Kidney International, King of Prussia, PA; 6Patient Advocate, Livonia, MI; 7The Polycenic, Seattle, WA; 8University of Michigan, Ann Arbor, MI; 9Cedars Sinai Medical Center, Los Angeles, CA; 10Stanford University, Stanford, CA.

**Background:** Past research suggested a significant lag between onset of hypertension (HTN) and initiation of anti-hypertensive therapy (AHRx). The aim of this study was to evaluate the time to initiation of AHRx in patients with proteinuric kidney disease identified as hypertensive based on standard guidelines.

**Methods:** Longitudinal outpatient blood pressure (BP) measurements were available on 858 patients, 71% adults and 29% children, in the NephCare Accelerating Cures Institute cohort. Patients were defined as hypertensive either by ICD9/ICD10 diagnosis code or having 3 or more elevated BPs in a 6-month period. Patients already on AHRx at first observation were excluded. Kaplan-Meier and cox-proportional hazards analyses were used to evaluate the time to initiation of AHRx.

**Results:** Of the 858 patients available, 492 had evidence of HTN. 195 of these patients were already on AHRx. Of the 287 remaining patients, 234 (82%) were subsequently started on AHRx. The median time from diagnosis or third qualifying BP until therapy initiation was 92 days (IQR=1 to 535). Adults were more likely to receive AHRx compared to children (87% vs 60%, p<0.001). Patients with membranous nephropathy had a shorter time to therapy initiation than those with other diagnoses (Figure). Patients with HTN by coded diagnosis were more likely to receive therapy compared to those with HTN by BP readings alone (83% vs 33%, p<0.003).

**Conclusions:** Patients with HTN in the setting of primary proteinuric kidney disease are prescribed AHRx a median of 3 months after HTN diagnosis. Having a coded diagnosis of HTN increased the likelihood of AHRx. Overall only 11% of the proteinuric patients in the NACI patient registry have HTN without the benefit of AHRx.

**Funding:** Private Foundation Support

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

---

**TH-PO153**

**Tacrolimus as Monotherapy for Relapsing Minimal Change Disease in the Adult Population**

**Anthony T. Chan,**1 Tom Cairns,2 Jack W. Galliford,2 Charles D. Pusey,3 Megan Griffith. 1Imperial College Renal and Transplant Centre, London, United Kingdom.

**Background:** Minimal change disease (MCD) in adults is usually steroid responsive but the relapse rate is high, and some patients may develop steroid dependent disease. Tacrolimus has been used for relapsing/ steroid dependent MCD, however, the relapse rate during treatment has not been studied in adult population.

**Methods:** This is a retrospective cohort study of 27 patients with relapsing MCD treated with tacrolimus from 2011-2017. 21 males and 6 females with average age of 40.7 years old (Range 16-80 years old). All patients had relapsing disease and 5 of 27 patients were steroid dependent. Prior to treatment with tacrolimus, 16 patients had 1 relapse, 3 patients had 2 relapses and 8 patients had 3 or more relapses. 23 patients had previously been treated with prednisolone alone, 2 patients had cyclophosphamide and prednisolone and 2 patients received cyclosporine and prednisolone.

**Results:** Of 27 patients remained in remission after receiving tacrolimus, with an average treatment time of 28 months (Range 3 to 69 months) and all these patients remain on maintenance therapy. 12 of 27 patients had a further relapse after commencing treatment with tacrolimus, average treatment time of 23.6 months (Range 3-65 months). 5 of 12 patients relapsed while still taking tacrolimus, with an average time to relapse of 21.3 months (Range 5-65 months), but 5 of these 8 patients had sub-therapeutic levels at time of relapse (<5 ng/ml). 4 of 12 patients relapsed after stopping tacrolimus with average time to relapse after stopping of 2.25 months (Range 2-3 months). The average estimated glomerular filtration rate before tacrolimus was 83.9 ml/min/1.73m² (Range 24-90 ml/min/1.73m²) and during treatment was 85.73 ml/min/1.73m² (Range 48-90 ml/ min/1.73m²).

**Conclusions:** Tacrolimus is an effective treatment for relapsing MCD in adult. Patients often require long term maintenance treatment with careful drug level monitoring to avoid relapse. In this cohort all patients who had stopped tacrolimus went on to relapse. Retrospective extension of the study cohort is ongoing to investigate the optimal length of treatment with tacrolimus required to prevent future relapse, to facilitate design of a randomised controlled trial.

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

---

**TH-PO154**

**Initial Therapy of Primary FSGS with Calcineurin Inhibitors Decreases Steroid Exposure without Compromising Renal Response**

**Carlos A. Chvez-Mendoza,**1 Jose A. Nino-Cruz,2 Ricardo Correa-Rotter,**2 M. Mejia-Viter,3 Nephrology and Mineral Metabolism, National Medical Sciences and Nutrition Institute Salvador Zubiran, Mexico City, Mexico.

**Background:** Reduction of corticosteroid exposure has been a relevant focus in the management of glomerular diseases. High-dose glucocorticoid remains first-line therapy in primary FSGS, reserving calcineurin inhibitors (CNI) to patients with resistant disease or contraindication to corticosteroids.

**Methods:** Observational. Sixty-two patients were segregated into 3 groups: high-dose steroid (n=35), initial CNI-low dose steroids (n=11), rescue CNI+steroids (n=16). Groups were compared by survival analysis for complete (CR) and partial remission (PR), time to relapse (TTR), doubling of creatinine (DCr), end-stage renal disease (ESRD). Factors associated with SA-AE outcome were obtained by Cox-regression.

**Results:** Median follow-up was 44 months (IQR 24-69). There were no differences in time to CR/PR between steroid and initial CNI group (p=0.592 and p=0.962). Initial
CNI group had a shorter time to prednisone taper (<10mg and lower cumulative steroids. There were no differences between the groups in TTR, DCR, and renal survival. Although the rescue-CNI represented a steroid-resistant/dependent population, this group had no differences when compared to steroid and initial CNI groups. No differences in hospitalizations for infectious events were between the three groups. The factors associated with lower renal survival were higher baseline creatinine, proteinuria, and chronicity score in the renal biopsy.

**Conclusions:** Treatment of FSGS with CNI as a first-line therapy may reduce exposure to steroids with similar response.

**TH-PO155**

Five Year Outcome of Steroid Resistant Focal Segmental Glomerulosclerosis (FSGS) Treated with Tacrolimus Harbir Singh Kohli,1 Raja Ramachandran,1 Krishan Lal L. Gupta,1 Nehru Hospital, Chandigarh, India; 2Post Graduate Institute of Medical Education and Research (PGIMER), CHANDIGARH, India; 3Postgraduate Institute of Medical Education & Research, Chandigarh, India.

**Background:** Calcineurin inhibitors (CNIs) are recommended for steroid-resistant (SR) nephrotic syndrome (NS) due to focal segmental glomerulosclerosis (FSGS) by KDIGO as the 1st line agents. We reported earlier a remission in 52% at 1year. CNI use is limited by relapse after stopping and nephrotoxicity on prolonged use. The objective of the study was to report the 5 year outcome of patients treated initially with tacrolimus (TAC) for SR-FSGS.

**Methods:** Patients were treated with TAC (trough level 5-10 ng/ml and prednisolone (0.15 mg/kg/d). TAC was discontinued in nonresponders at 24 weeks(TAC resistant). TAC was continued for 48 weeks in responders. After completing the study period, patients were managed as per treating physicians discretion. Patients were followed up further for 4 years or till end stage renal disease (ESRD)/death. Primary outcomes, doubling of serum creatinine, ESRD or death and secondary outcomes remission rate (CR and PR) and persistent NS were studied.

**Results:** Of 44 who received TAC, at 48 weeks, CR and PR were achieved in 17 (38.6%) and 6 (13.6%) respectively, 21 (47.7%) patients were TAC resistant. At end of 5 years of starting therapy, 2 patients were lost to follow up in 1 each group. Of 22 responders (61%) had relapse on stopping TAC, they were restarted on TAC for another year. Four had sustained remission, while 4 became TAC dependent and 6 TAC resistant. Of 4 TAC dependent, 3 responded to rituximab, only 2 of 6 TAC resistant received rituximab of which 1 responded. While others took ACE inhibitors or indigenous drugs.

Kidney biopsy done in 8 patients after 2 years of TAC showed chronicity. Of 20 TAC resistant 2 of 3 who received rituximab responded. At the end of 5 years of starting TAC, in responders CR, PR, persistent NS, CKD, ESRD and death were seen in 5 (13.6%), 3 (59.1%), 5 (22.7%), none, 1 (4.6%) and none respectively, and amongst resistant patients 1 (5%), 2 (10%), 3 (15%), 3 (15%) and 4 (20%). Seventy-four (70%) patients with resistant disease had attained primary outcome compared to 1 (4.5%) in the remission group (p<0.0001).

**Conclusions:** TAC resistance portends poor prognosis with 70% having doubling of serum creatinine, ESRD or death at the end of 5 years. TAC dependency was seen in 60% of the initial TAC responders. Rituximab appears to be promising agent in both TAC dependent and resistant patients.

**TH-PO156**

Repeat Rituximab Dosing Is Often Necessary but Effective in Relapsing Minimal Change Disease in Adults Nikhil L. Wong,1 Tom Cairns,1 Jack W. Galliford,2 Charles D. Pusey,1 Megan Griffith,1 IMPERIAL COLLEGE HEALTHCARE, LONDON, United Kingdom; 2Imperial College Kidney and Transplant Institute, London, United Kingdom; 3Imperial College London, London, United Kingdom.

**Background:** Rituximab (RTX) is increasingly being used for relapsing minimal change disease (MCD) in adults, but data is lacking on the need for and efficacy of multiple dosing regimens.

**Methods:** We retrospectively reviewed 19 patients treated with RTX for relapsing, or steroid resistant MCD between 2006-2017. Median age at treatment was 35 years (20-66), mean time from diagnosis 15 years (1-39), and mean relapse rate was 4.5±3 years. Previous maintenance treatment included steroids (17/19), tacrolimus (19/19), ciclosporin (6/19), mycophenolate (1/19), cyclophosphamide/chlorambucil (8/19) and levensimide (3/19).

**Results:** 19 patients received RTX. 8 patients were nephrotic, and 11 were in complete or partial remission at time of treatment. B-cell depletion was achieved in all patients. 10 patients had more than one RTX course [mean (2 ±1.4)], the mean follow-up was 34 months (1-127). Of 8 patients who were nephrotic at RTX initiation, 6 achieved complete or partial remission and 2 failed to respond. 1/2 was steroid resistant and on subsequent rebiopsy was found to have FSGS, the other was steroid intolerant. Of 17 patients in remission post RTX, 9 had no further relapse at mean follow-up of 17 months (1-60). 3/9 received a second course of RTX after a mean 13 months (9-16). At last follow-up 5/9 patients had persistent NS (0.15 mg/kg/d). TAC was discontinued in nonresponders at 24 weeks (TAC resistant). TAC was continued for 48 weeks in responders. After completing the study period, patients were managed as per treating physicians discretion. Patients were followed up further for 4 years or till end stage renal disease (ESRD)/death. Primary outcomes, doubling of serum creatinine, ESRD or death and secondary outcomes remission rate (CR and PR) and persistent NS were studied.

**Conclusions:** RTX is effective for relapsing MCD in adults, but repeated treatment course may be required. B-cell reconstitution is associated with relapse and may be helpful in guiding prophylactic redosing in some patients. Nonresponse to RTX may suggest underlying FSGS. Further trials are needed to determine which patients will relapse and appropriate dosing regimens for maintenance RTX therapy.

**TH-PO157**


**Background:** Previous retrospective and prospective studies have suggested that rituximab may be an effective therapy for patients (Pts) with MCD and FSGS who have failed other therapies. Most studies have had small numbers of Pts and consisted largely of children.

**Methods:** We reviewed the charts of 58 adults (41 male) evaluated at Columbia University Medical Center between 2014 - 2017 who received rituximab for MCD or FSGS. We analyzed clinical, biopsy, and laboratory data pre-infusion and at follow up (F/U). We categorized Pts as frequently relapsing/steroid dependent (FRSD), infrequently relapsing (IR), steroid resistant (SR), and multi-drug resistant (MDR) based on their clinical course prior to rituximab.

**Results:** Of renal biopsy, 31 Pts had MCD, 22 had FSGS, and 5 had podocytopathy associated with another diagnosis (e.g. IgA Nephropathy with MCD). There were 34 Whites, 13 Latinos, 6 Blacks, and 5 Asians. Disease category included 33 FRSD, 2 IR, 6 SR, and 17 MDR. Three patients (all FRSD) were excluded from further analysis; 2 had relapse (5/9 mo) of MCD and 1 was unable to complete treatment due to infusion reaction. The median number of immunosuppressant (IS) medications used prior to rituximab was 3 (range 1-6). The median number of concurrent IS was 1 (range 0-3) at time of infusion and 0 (range 0-2) at F/U. The median F/U was 15.8 mo (range 1-145). 13 Pts achieved a complete remission (CR, UPC <0.5 g/gCr) or partial remission (PR, UPC 0.5-3.5 g/gCr) during the F/U period; 32 remained in CR or PR and 5 relapsed. 62% (37/55) achieved a complete remission (CR, UPC <0.5 g/gCr) or partial remission (PR, UPC 0.5-3.5 g/gCr) during the F/U period; 32 remained in CR or PR and 5 relapsed. The median number of IS used in remission was 1 (range 1-2). The median number of concurrent IS was 1 (range 0-3) at time of infusion and 0 (range 0-2) at F/U. The median F/U was 15.8 mo (range 1-145). 13 Pts achieved a complete remission (CR, UPC <0.5 g/gCr) or partial remission (PR, UPC 0.5-3.5 g/gCr) during the F/U period; 32 remained in CR or PR and 5 relapsed. Of patients in remission at last F/U, 13/22 Pts in CR and 5/10 Pts in PR were off all other IS. Of 23 Pts not in remission at last F/U, 12 never achieved CR or PR, 5 had relapsed, and 6 had progressed to ESRD. Of 17 MDR Pts, 13 achieved CR or PR after rituximab, 3 achieved CR or PR on other IS, and 11 never achieved CR or PR, with 3 progressing to ESRD. 18 Pts repeated rituximab treatment, 9 prophylactically, and 9 for treatment of relapse with all responding.

**Conclusions:** This is the largest study showing the benefit of rituximab in achieving remission of proteinuria and reduction of immunosuppression in adults with MCD or FSGS. Pts with MDR disease were less likely to respond to rituximab.
TH-PO158
Continuous B Cell Depletion for Resistant, Steroid Dependent, and Relapsing Nephrotic Syndrome in Adults
Frank B. Cortazar, Colleen B. Dunbar, Karen A. Laliberte, John Niles. Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA.

**Background:** The clinical course of minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) can be complicated by resistance to treatment, steroid dependence, and frequent relapses. Treatment options for such patients are limited. We present a retrospective series of patients with these phenotypes treated with rituximab (RTX)-induced continuous B cell depletion.

**Methods:** Patients were included if they had biopsy-proven MCD or FSGS that was resistant, steroid dependent, or relapsing. All patients had a UPCR ≥ 3.5 g/g and were treated with RTX-induced continuous B cell depletion. Resistant disease was defined as failure to achieve a partial remission (PR) with prednisone at 1 mg/kg per day for 3 months or a calcineurin inhibitor or mycophenolate mofetil. Steroid dependence was defined as relapse during or within 2 weeks of steroid tapering. Relapsing disease was defined as at least two prior relapses. PR was defined as a urine protein:creatinine ratio (UPCR) of ≤ 3.5 g/g and a 50% reduction from baseline, while CR was defined as a UPCR of ≤ 0.3 g/g. Relapse after any remission was a UPCR ≥ 3.5 g/g.

**Results:** We identified 11 patients who met the inclusion criteria (Table). Over a median follow-up of 4.5 years (IQR, 2-5), patients received a median of 9 RTX doses (IQR, 8-15) and were in a state of B cell depletion for 3.7 years (IQR, 2-5). All patients entered PR at a median time of 89 (IQR, 34-144) days and 7 patients entered CR at a median of 362 (IQR, 34-1208) days. Prednisone dose was tapered from 60 mg/d (IQR, 15 to 60) at entry to 5 mg/d (IQR, 0.75-4) at 1 year. Three patients sustained a relapse after PR, but all subsequently obtained a remission. No relapses occurred following CR.

**Conclusions:** Continuous B cell depletion is an effective treatment strategy for complicated cases of MCD and FSGS. Additional studies are needed.

**Table:**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Disease Phenotype</th>
<th>Failed Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>MCD</td>
<td>Pred, CsA</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>MCD</td>
<td>Pred, CsA</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>MCD</td>
<td>Pred, CsA</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>MCD</td>
<td>Pred, CsA</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>MCD</td>
<td>Pred, CsA</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>MCD</td>
<td>Pred, CsA</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>35</td>
<td>MCD</td>
<td>Pred, CsA</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>30</td>
<td>MCD</td>
<td>Pred, CsA</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>35</td>
<td>MCD</td>
<td>Pred, CsA</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>30</td>
<td>MCD</td>
<td>Pred, CsA</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>35</td>
<td>MCD</td>
<td>Pred, CsA</td>
<td></td>
</tr>
</tbody>
</table>

CsA, cyclosporine; Cyc, cyclophosphamide; MMF, mycophenolate mofetil; Pred, prednisone; Tac, tacrolimus

---

TH-PO159
High Doses of Rituximab Are Ineffective in Adult Patients with Focal Segmental Glomerulosclerosis
Dario Roccatello,1 Savino Sciascia,2 Roberta Fenoglio.1 Ospedale San Giovanni Bosco, Torino, Italy; 1Center of Research of Immunopathology and Rare Diseases (CIMID), Division of Clinical Immunology, Giovanni Bosco Hospital and University of Turin, Italy.

**Background:** A beneficial effect of rituximab on Focal Segmental Glomerulosclerosis (FSGS) in pediatric patients or in transplant recipients has been reported in isolated cases. However, the use of rituximab in adult patients with idiopathic FSGS needs further investigation.

**Methods:** Eight patients who had biopsy-proven FSGS (63.9 ± 14.0, range 40-81 yr, 4 women, 4 men) with major risk factors precluding corticosteroids or conventional immunosuppression were treated with high dose of rituximab (8 weekly doses of 375mg/m²) and prospectively followed up for at least 2 years (29.1 ± 8.8 mo, range 24 to 42 mo).

**Results:** Rituximab failed to improve proteinuria in seven out of 8 patients, who had persistent nephrotic proteinuria. In one case, a rapidly deteriorating renal function was also observed. Only one patient showed an improvement of renal function and a remarkable proteinuria reduction. There were no differences in clinical or laboratory characteristics or in the CD20 B lymphocyte count after rituximab between the responder and the 7 non responders patients.

**Conclusions:** Only a minority (one of eight) in our series of adult patients with FSGS showed positive effects of high doses of rituximab. Future studies are warranted to investigate more promising therapeutic options in the management of FSGS.

---

TH-PO160
Cetirizine and Montelukast Combination Therapy in Patients with Minimal Change Nephrotic Syndrome Concomitant with Allergic Diseases: A Single Center Study
Yoichi Oshimi,1 Keiichi Sumida,2 Masayuki Yamanouchi,3 Junichi Hoshino,1 Yoshifumi Ubara,1,2 Nephrology Center, Toranomon Hospital, Kawasaki, Japan; 1Okinawa Memorial Institute for Medical Research, Tokyo, Japan.

**Background:** In minimal change nephrotic syndrome (MCNS) glucocorticoid treatment is a major therapeutic option; however glucocorticoid may cause many adverse effects since most patients with MCNS are dependent on glucocorticoid. It is known that MCNS often complicates with allergic diseases. We investigated if anti-allergy therapy with cetirizine and montelukast have therapeutic effect in disease control for MCNS.

**Methods:** We identified 125 patients who were diagnosed as MCNS by renal biopsy in our hospital between 1985 and 2015. As shown in figure 1, 15 patients were included in this study. Patients were evaluated by minimum glucocorticoid maintenance dose.

**Results:** Average age at the time of onset was 33.2 years. Nine out of 15 patients were men (60%). Average number of relapses was 4.2 times. Average duration of corticosteroid treatment before the study was 211.3 months. Complicated allergic disorders were allergic rinitis in ten patients (66.7%), atopic dermatitis in eight (53.3%), sinusitis in five (33.3%), drug allergy in four (26.7%), food allergy in three (20%), and asthma in two (13.3%). Average prednisolone dose at the start of the study was 3.78 (range: 0.5-10) mg/day). Eleven patients (73%) became glucocorticoid free without relapse for more than 28 months, while only three relapsed (20%). After the treatment, minimum prednisolone maintenance dose was 0.038 mg/day compared to 0.858 (range: 0-4 mg/day) before the treatment (p=0.042, Wilcoxon nonparametric paired test).

**Conclusions:** Cetirizine and montelukast therapy may have steroid sparing effect in allergy concomitant relapsing MCNS.

**Funding:** Private Foundation Support

---

TH-PO161
Dyslipidemia and Outcomes in NEPTUNE
Christine B. Sethna,2 Kevin E. Meyers,3 Tammy M. Brady,1 Crystal A. Gadebeka,4 Tarak Srivastava,4 Keisha L. Gibson,4 Matthias Kretzler,4 Laura H. Mariani,7 1Children’s Mercy Hospital, Kansas City, MO; 2Cohen Children’s Medical Center of NY, New Hyde Park, NY; 3Johns Hopkins University, Baltimore, MD; 4Temple University, Philadelphia, PA; 5The Children Hospital of Philadelphia and University of Pennsylvania, Philadelphia, PA; 6University of Michigan, Ann Arbor, MI; 7University of North Carolina Kidney Center, Chapel Hill, NC. Group/Team: NEPTUNE Cardiovascular Working Group.

**Background:** Patients with nephrotic syndrome (NS) have a pronounced alteration in lipoprotein metabolism. Dyslipidemia is a major risk factor for cardiovascular disease and may be associated with progression of renal disease; however, this has not been well characterized in NS.

**Methods:** Baseline lipid studies from the Nephrotic Syndrome Study Network (NEPTUNE) were collected. Dyslipidemia was defined as total cholesterol ≥ 200 mg/dL, LDL ≥ 130 mg/dL, HDL ≤ 40 mg/dL or triglycerides ≥ 150 mg/dL. Cox regression adjusted for age, sex, race, disease, disease duration, baseline eGFR and urine protein:creatinine (UPC) examined the association of lipids (per 10 unit increase) with the Composite Outcome (End Stage Renal Disease or eGFR decline by 40%) and first Complete Remission (UPC ≤ 0.3).

**Results:** 271 adults (45.4±16.1 yr, 62% M) and 123 children (10.2±4.8 yr, 59% M) were evaluated. At baseline, 85% of participants had dyslipidemia (table). In the overall group, lower LDL and greater levels of HDL were associated with better outcomes in the composite outcome (HR 0.91, 95% CI 0.83-0.98, p=0.02 and HR 1.02, 95% CI 1.00-1.04).

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

Underline represents presenting author.

---

144
Funding: NIDDK Support, Other NIH Support - Office of Rare Diseases Research (ORDR), NCATS, Private Foundation Support

Conclusions: In NEPTUNE, dyslipidemia is common and is an independent predictor of renal outcomes.

TH-PO162
Cross Sectional Study on the Clinical Manifestations of Focal Segmental Glomerular Sclerosis (FSGS) in Japan from the Data of the Japan-Renal Biopsy Registry (J-RBR)

Takuya Ozeki,1 Shioichi Maruyama,2 Takehiro Kawaguchi,3 Toshiyuki Imasawa,4 Hiroshi Sato,1 Clinical Pharmacology and Therapeutics, Graduate School of Pharmaceutical Sciences, Tohoku University, Sendai, Japan; 2Nagoya University Graduate School of Medicine, Nagoya, Japan; 3National Fukuoka-Highashi Medical Center, Koga, Fukuoka, Japan; 4National Hospital Organization Chiba-East Hospital, Chiba, Japan.

Background: Even though the clinical manifestations of FSGS varies among the underlying etiology, few reports had described the detail of its features comparing with MCD, J-RBR; Japanese nationwide registry started in 2007 and it has 32870 biopsy cases until December 2016. The aim of this study was to clarify the clinical characteristics of FSGS through analyzing the data of J-RBR.

Methods: A cross sectional study; patients were diagnosed with FSGS or MCD and were registered in J-RBR during 2007-2016. <Analysis 1>Among the 3 groups; Children (<18)/ Adult (18-64)/ Elderly (65+), and clinical parameters were compared between subgroups. <Analysis 2> Compare the clinical features between nephrotic FSGS and MCD, patients who fulfilled the criteria below were selected from the database. Criteria: histopathological diagnosis as FSGS or MCD, clinical diagnosis of nephrotic syndrome and over 18 years old.

Results: <Analysis 1>Among the 3 groups; Children (n=166), Adult (n=904), Elderly (65a), and clinical parameters were compared between subgroups. <Analysis 2> The prevalence of FSGS in our study was 10.9%. NOS was the most common histologic variant. The severity of tubular atrophy was the only significant poor prognostic factor.

Conclusions: These diseases only by initial clinical informations.

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

Underline represents presenting author.

TH-PO163
Improvement of Clinical Outcome in Kidney Diseases via the On-line Thai Glomerular Disease Registry: Focal Segmental Glomerulosclerosis Neeransri Pattanacharoen,1 Suehin Worawichawong,2 Boonkit Cheunuschon,3 Ngeuntra Tantranond,4 Warangkana Pachaiwong,4 Pompen Sangthawan,5 Pathology, Ramathibodi Hospital, Bangkok, Thailand; 2Medicine, Bhumibol Adulyadej hospital, Bangkok, Thailand; 3Medicine, Prince of Songkla University Hospital, Songkhla, Thailand; 4Medicine, RAJAVITHI HOSPITAL, Bangkok, Thailand; 5Pathology, Siriraj hospital, Bangkok, Thailand.

Background: Focal segmental glomerulosclerosis (FSGS) is one of the most common cause of end stage renal disease (ESRD) in adults. FSGS is more common in African-Americans than Asians. In Thailand, the data of FSGS have not been well determined. This study was conducted to investigate the prevalence and outcomes of FSGS via using the data from the on-line registry from Thai Glomerular Disease Collaborative Network (TGDN).

Methods: The data of biopsy-proven FSGS in adults were collected by the on-line registry from July 2014 to March 2017. Patients’ clinical data including histopathological diagnosis at baseline, and clinical outcomes at 24, 48 and every 48 weeks after renal biopsy were analyzed.

Results: FSGS was diagnosed in 170 patients (10.9%) from 1,556 renal biopsy specimens. The time of biopsy, 44.2% of FSGS was male, the mean age was 47±16.9 years, median serum creatinine level was 1.7 mg/dL (0.42-8.33), median urine protein creatinine ratio (UPCR) was 4.36 g/g Cr (0.08-25.3), mean serum albumin (sAlb) was 2.8±0.9 g/dL. Nephrotic syndrome was 73%, whilst nephropatho-nephrotic syndrome was only 2%. Most common histologic variant was not otherwise specified (NOS) 80.7% followed by tip lesion (10.0%), perihilar variant (3.6%), cellular variant (3.6%), and collapsing FSGS (21.2%). At 24-week follow up, 22.9% of patients had complete remission and 62.7% had partial remission. The median time to all remission was 7.5 months. The only factor that was significantly associated with the remission rate was the percentage of tubular atrophy more than 50% with HR 0.24 (95%CI 0.07-0.81, p = 0.021).

Conclusions: The prevalence of FSGS in our study was 10.9%. NOS was the most common histologic variant. The severity of tubular atrophy was the only significant poor prognostic factor.

Funding: Health Systems Research Institute, and Nephrology Society of Thailand support

Funding: Private Foundation Support

TH-PO164
Incidence of Focal Segmental Glomerulosclerosis in Olmsted County Musab S. Hommo,1 An S. De Vriese,2 Mariam P. Alexander,3 Sanjeev Sethi,2 Lisa E. Vaughn,4 Kharmen A. Blahucha,5 Ladain Zand,2 Nicola Lepori,2 Andrew D. Rule,1 Fernando C. Fervenza,6 AZ Simon,7 Bruges, Belgium; 2Mayo Clinic, Rochester, MN; 3Ospedale Brozzi, --Cagliari, Italy.

Background: Focal segmental glomerulosclerosis (FSGS) incidence is increasing. However, previous studies reported trends in relative disease frequencies and presented FSGS as a single disease entity. We now know that FSGS is a histological pattern of injury caused by a variety of conditions. Thus, we evaluated the incidence of primary vs. secondary FSGS in a population-based study.

Methods: Olmsted County residents with native kidney biopsy between 1994 and 2013 that showed FSGS as the only glomerulopathy were identified. Primary FSGS was defined as having nephrotic syndrome (serum albumin ≤3.5g/dL and proteinuria ≥3.5g/24h), foot process effacement ≥80% and no identifiable causes. Age and sex adjusted incidence rate per 100,000 person-years was calculated. Poisson regression models estimated the change in incidence rate over time.

Results: Among 370 adults biopsied during this period, 281 had glomerular disease of which 46 (16%) had FSGS as the only glomerulopathy. (Table 1) Estimated native
kidney biopsy incidence rates were significantly higher in 2004-2013 compared to 1994-2003 (22.9 vs. 14.7 per 100,000 person-years, 17% increase per 5 years, p<0.001). Total FSGS incidence rates also increased over the same time period from 1.4 in 1994-2003 to 3.2 per 100,000 person-years in 2004-2013 (41% increase per 5 years, p=0.02). Secondary FSGS accounted for 9/12 (75%) of cases during 1994-2003 and 25/34 (74%) of cases during 2004-2013.

Conclusions: The majority of cases are secondary FSGS. While the incidence of FSGS has increased over the past two decades, the proportion of primary and secondary FSGS has remained stable. Further studies are needed to understand the causes of this increasing incidence though increasing biopsy rates may be a contributor. Importantly, primary FSGS rate remains low (0.85 per 100,000 person-years).

**TH-PO166**

Health Related Quality of Life (HRQOL) in Primary Glomerular Disease: The Initial CureGN Experience Pietro A. Canetta,1 Sharon M. Bartosh,2 Yi Cai,3 Hilda E. Fernandez,3 Alessia Fornoni,4 Rasheed A. Gbadegesin,5 Emily G. Herrshoff,6 Amy Kogon,7 John D. Mahan,8 Shannon L. Mahoney,9 Patrick H. Nachman,1 David T. Selevoski,7 Tarak Srivastava,7 Katherine R. Tuttle,3 Chia- Shi Wang,3 Jonathan P. Troost,3 Debbie S. Gipson,4 Columbia University, New York, NY; 8University of Wisconsin Children’s Hospital, Madison, WI; 3Helen DeVos Children’s Hospital, Grand Rapids, MI; 2University of Miami, Miami, FL; 7Duke University, Durham, NC; 6University of Michigan, Ann Arbor, MI; 4Nationwide Children’s Hospital, Columbus, OH; 4University of North Carolina, Chapel Hill, NC; 3Children’s Mercy Hospital, Kansas City, MO; 1University of Washington, Spokane, WA; 7Emory University, Atlanta, GA. Group/Team: CureGN Consortium.

Background: There is little published data on HRQOL in patients with primary glomerular diseases.

Methods: We studied HRQOL in subjects enrolled in CureGN, an international cohort of participants with minimal change disease, FSGS, membranous nephropathy, and IgA nephropathy or IgA vasculitis. HRQOL was assessed at enrollment using the Patient Reported Outcomes Measurement Information System (PROMIS) domains. Means measured in adults were: Global Assessment of Physical Health, Mental Health, Fatigue, Sleep, and Anxiety; domains in children were: Global Health, Mobility, Fatigue, and Anxiety. Minimally important differences have been defined as score change of 3 for the pediatric domains and have not been defined for adult domains. Immunosuppression (IS) in the past 60 days was classified as None, Glucocorticoids alone, or Other IS. Differences in HRQOL scores are reported as mean [95% confidence interval]. Multivariable analysis was conducted by linear regression with backwards selection.

Results: Data were available from 349 children and 918 adults. In children, multivariable analyses revealed PROMIS Global Health scores were worse with edema (-3.2 [-5.5 to -0.9] and obesity (-4.5 [-6.9 to -2.1]) but were not significantly different across levels of proteinuria or eGFR. In adults, PROMIS Global Physical Health scores were worse with edema (-6.3 [9.0]) log UPCR (0.02 [-0.5 to -0.1]), eGFR (< 30 ml/min/1.73 m2 [-1.1 [-1.6 to -0.5]), female sex (-1.8 [-3.1 to -0.5]), and obesity (-3.2 [-4.8 to -1.7]). Race, ethnicity, diagnosis, disease duration, hematuria, and IS were not associated with HRQOL. In multivariable analysis, edema was the strongest predictor of HRQOL across both age groups and PROMIS domains (Figure).

Conclusions: Children and adults with glomerular diseases report a range of HRQOL. Edema was a consistent predictor of poor HRQOL across all measured domains of Global Health, Anxiety, Fatigue, Sleep, and Mobility.

Funding: NIDDK Support

**TH-PO167**

Cost Analysis on the Use of Rituximab and Calcineurin Inhibitor in Children and Adolescents with Steroid Dependent Nephrotic Syndrome Oluwatoyin F. Bamgbole,1 Diego H. Aviles,2 Franca M. Iorember,3 1Phoenix Children’s Hospital, Scottsdale, AZ; 2SUNY Downstate Medical Center, Brooklyn, NY; 3Dept. of Pediatrics, Louisiana state university health science center, New Orleans, LA.

Background: To minimize adverse effects, steroid sparing agents are used in steroid dependent nephrotic syndrome (SDNS). Although effective, the main drawback of calcineurin inhibitors (CNI) is the need for therapeutic drug monitoring (TDM). Apart from proven efficacy, Rituximab produces a long lasting remission after 1 or 2 single intravenous doses. To reduce frequency of clinic visits and cost efficiency, we introduced rituximab particularly in patients living remotely from laboratory facilities.

Methods: A retrospective analysis of pediatric patients with SDNS treated with either CNI &/ or Rituximab from Jan 2008 to Dec 2012 at Children’s Hospital of New Orleans, Louisiana. All patients were followed up for a minimum of 12 months. We compared the cost effectiveness, efficacy, and safety profiles of the 2 groups.

Results: 11 patients were treated with Rituximab and 9 received CNI. Baseline data were comparable. Annual cost of treatment was lower with Rituximab ($197,031 vs. $189,856; p > 0.05). Amount expended on Rituximab arm was mostly due to drug cost of outpatient care was more for the CNI ($7534 vs. $4383). There was marginally significant side effect in either group. Retrospective analysis of small sample limited ability to demonstrate significant findings. In addition, study outcome may vary with...
Clinical aspects of Collapsing FSGS patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Baseline</th>
<th>With PO</th>
<th>Without PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>28.3±12.3</td>
<td>24.5±15.9</td>
<td>25.3±19.5</td>
</tr>
<tr>
<td>Male (%)</td>
<td>43.1±11.4</td>
<td>71.6±18.4</td>
<td>13.5±6.6</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.9±0.3-1.6</td>
<td>1.0±0.2-2.2</td>
<td>2.2±1.3-1.7</td>
</tr>
<tr>
<td>Proteinuria (g/d)</td>
<td>5.8±3.0-4.0</td>
<td>8.8±3.0-3.2</td>
<td>3.0±1.7-3.0</td>
</tr>
<tr>
<td>ACR (mg/g)</td>
<td>47.0±16.0</td>
<td>21.6±7.0</td>
<td>26.7±12.1</td>
</tr>
<tr>
<td>Renalrt</td>
<td>34.5±16.0</td>
<td>15.6±6.4</td>
<td>14.5±6.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>44.8±16.0</td>
<td>21.8±7.0</td>
<td>12.1±5.0</td>
</tr>
<tr>
<td>Albuminuria (g/L)</td>
<td>2.26±0.9</td>
<td>2.0±0.8</td>
<td>2.4±0.9</td>
</tr>
<tr>
<td>Bgl (mg/dL)</td>
<td>12.1±2.2</td>
<td>15.1±2.2</td>
<td>11.9±2.2</td>
</tr>
<tr>
<td>Focal (mg/gLO)</td>
<td>5.8±1.5</td>
<td>8.4±3.2</td>
<td>12.0±2.6</td>
</tr>
<tr>
<td>Proteinuria (g/dL)</td>
<td>3.8±1.6</td>
<td>3.4</td>
<td>3.7±1.6</td>
</tr>
<tr>
<td>Follow up (years)</td>
<td>0.8±0.3</td>
<td>1.0±0.3</td>
<td>0.8±0.3</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>30.0±16.0</td>
<td>14.0±6.0</td>
<td>22.7±5.0</td>
</tr>
<tr>
<td>Rituximab (mg/kg)</td>
<td>73.0±5.0</td>
<td>17.5±5.0</td>
<td>27.3±5.0</td>
</tr>
</tbody>
</table>

Data showed as mean (+/-SD) or median (IQR).

* p<0.05 versus without PO
† p<3.5/g/day of proteinuria.

TH-PO117

Intermittent Dosing of Rituximab Induces Long-Term Remission in Children with Steroid Dependent Nephrotic Syndrome

Cheryl P. Sanchez, Rita D. Sheth, Drew C. Cutler, Shobha Sanhey.
Loma Linda University Children's Hospital, Loma Linda, CA.

Background: Rituximab is frequently used as an alternative therapy in pediatric patients with nephrotic syndrome.

Methods: 17 children, aged 10.7 ± 3.4 years old, received rituximab infusion at 375 mg/m² per dose weekly x 4 weeks. Renal biopsy showed minimal change, n=10; IgM nephropathy, n=2; FSGS, n=3; C1Q, n=1; no biopsy n=1. All patients were taking prednisone and prograf at the time of rituximab infusion. Prior to rituximab, five out of 17 patients had 5 relapses per year, 4/17 ± 4 relapses per year, 3/17 ± 3 relapses per year, 5/17 without remission.

Results: After 4 weekly doses of rituximab, 12 patients (70%) had complete remission, 2/17 had partial remission and 3/17 did not respond to rituximab. Five of 12 relapsed within 6-12 months of receiving rituximab, 4/10 relapsed 12 months after rituximab, 3/13 remained in remission. CD20 levels decreased at 3 months after rituximab compared to baseline (10.8%±3% vs 0.3%±0.7%, p<0.05), and started to increase at 6 months, 2.3±3.8%. There was no correlation noted between CD20 levels and proteinuria. Nine out of 12 patients who relapsed received 1.7 ± 0.8 additional doses of rituximab at 12 ± 3.2 months after last relapse, and remained in remission for an additional 6.4 ± 3.4 months. Five out of 9 children were off prednisone and prograf, and 4/9 remained on low dose prograf. One patient who had partial remission developed anaphylaxis to rituximab, but successfully treated with olatumumab. There were no complications associated with repeated rituximab therapy.

Conclusions: Intermittent doses of rituximab can be used to maintain remission in steroid dependent nephrotic syndrome to avoid long term complications associated with prolonged prednisone and calciumbury.

TH-PO117

Enabling Large Observational Comparative Effectiveness Studies in Glomerular Disorders

Rhea Bhargava,a Elizabeth J. Brant,b Jorge L. Castaneda,a David J. Friedman,b Neetika Garg,c Michael J. Germain,d Martin R. Pollak,d Johannes S. Schlondorff,d Tripti Singh,d Nikki Agrawal,e Isaac E. Stillman,e Franco H. Cabesa Rivera,f Ali Poyan-Mehr,g Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA; bUniversity of Mississippi Medical Center, Ridgeland, MS; cDartmouth-Hitchcock Medical Center, Lebanon, NH; dNone, Watertown, MA; eRenal and Transplant Assoc of New England, Hampden, MA; fBeth Israel Deaconess Medical Center, Boston, MA.

Background: The heterogeneous presentation of glomerulopathies contributes to ambiguity in diagnosis and management making large comparative studies difficult.

Methods: We created a network of nephrologists and nephropathologists in private practice and academic institutions, leveraging collective power to enroll patients to conduct comparative effectiveness studies(The Glomerular Disease Study and Trial Consortium).

Results: Major requirements identified for registry A Consensus on treatment standards & disease monitoring while preserving freedom of treatment selection B Standardized follow up laboratory studies and evaluations at predefined intervals C Review of tissue diagnosis by experienced nephropathologists, pathological work up and classification systems D Defining clinically meaningful benchmarks E HIPAA secure system has been created for provider referral or patient self-referral for enrollment. Clinical data will be collected and updated quarterly. De-identified data will be available for research to collaborators. Other opportunities: Quality improvement measure development(e.g. TB surveillance, pregnancy counselling, diabetes, cancer screening) Active surveillance for therapy-related adverse outcomes (e.g. quality of life, osteoporosis, infection, malignancy)

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Clinical Glomerular Disorders: FSGS, MN, MCD

1University of Central Florida College of Medicine, Kissimmee, FL; Infection Glomerulosclerosis during Antiviral Therapy for Hepatitis C Virus Development of Nephrotic Syndrome and Tip-Variant Focal Segmental TH-PO172

DAA therapy.

Physicians should be aware of this newly emerging renal adverse effect associated with within days after starting DAA therapy and a kidney biopsy 5 months later revealed lesions. High-dose steroids were initiated, and his proteinuria markedly improved in 3

electron dense deposits. These findings were consistent with FSGS with glomerular tip lesions. Immunofluorescence revealed negative staining for IgG, IgM, IgA, C3, C1q, CR1, CR2, C4d, C5b-9, and lambda mesangial dominance. C3d was present in mesangial deposition, and C4d was negative.

Caseous necrosis, endocapillary hypercellularity with tubular atrophy, and mild mesangial matrix expansion. The proteinuria did not respond to treatment with immunosuppressive drugs in infancy. 3 pts with major risk factors precluding corticosteroids or conventional immunosuppression received RTX as a first-line treatment. Results: Proteinuria decreased from 8.4 (19.5-4.8) g/24 h to 0.03 g/24 h after 6 months. Creatinine decreased from 1.4 (0.7-3.2) mg/dl to 0.86 (0.7-1.1) mg/dl. 3 pts achieved a complete renal remission, in 1 pt proteinuria decreased by 50%, 1 pt didn’t achieve any response at 10 months; a ri-biopsy showed a focal-segmental-glomerulosclerosis. RTX successfully depleted CD19 lymphocytes in 100% of pts for at least 6 months. The follow-up ranged from 3 months to 24 months. No clinically relevant adverse events have been observed.

Conclusions: Our study shows a remarkable efficacy of RTX in treatment of MCD. RTX can be an attractive alternative as induction therapy or to manage recurrent forms of MCD and may be preferentially used in pts at a high risk of development of adverse effects of corticosteroids and should be considered as an important treatment alternative in patients with recurrent nephrotic syndrome. Randomized controlled trials are needed to confirm our observations.

TH-PO174

IgA Nephropathy in a Patient with Alcoholic Cirrhosis Itunu O. Owoyemi, Negiin Pourafsharp, Julia Iezzoni, Tushar Chopra. University of Virginia, Charlottesville, VA; University of Virginia Health System, Charlottesville, VA.

Background: Impaired removal of IgA-containing complexes in the liver is thought to predispose to IgA deposition in the kidney. Portal hypertension has been implicated in IgA nephropathy in cirrhotic patients through various mechanisms leading to decreasing hepatic processing of IgA Immune complexes. Despite the frequency of glomerular IgA deposits in advanced liver disease, most adults have no clinical signs of glomerular disease. There is a dearth of literature regarding differentiation of primary and secondary IgA nephropathy (IgAN) in cirrhotic patients.

Methods: We report a 52-year-old male with alcoholic liver cirrhosis complicated by portal hypertension who presented with a recent history of fatigue and skin rash for three weeks. The serum creatinine (SCr) had increased from baseline 2.1 mg/dl to 3.2 mg/dl with proteinuria of 6.3 g/g. Measured serum IgA level was elevated at 599.2 mg/dl. The patient was 57 yrs old. He had a M CV score of 17. Uramids was significant for microscopic hematuria. His kidney biopsy revealed a mild increase in mesangial cellularity, lambda mesangial predominance, endocapillary hypercellularity with moderate tubular atrophy and moderate interstitial fibrosis consistent with a diagnosis of IgA nephropathy. Skin rash was in line with psoriasis. The patient was eventually discharged home on conservative management with losartan, and fish oil. On follow-up, his SCr was 3.1 mg/dl, and proteinuria decreased to 2 g/

Results: Conclusions: Our case highlights the inherent difficulty in recognition of primary and secondary IgA nephropathy in the setting of liver cirrhosis which would result in difficulty in decision making regarding proper management. We present a case of primary IgAN with diffuse staining of IgA in the glomeruli, and lambda mesangial dominance. In IgAN, lambda is usually, but not invariably, stronger than kappa. Kappa dominance and focal IgA staining not involving all the glomeruli, slightly favors secondary IgAN. Primary IgAN is rarely associated with nephrotic syndrome. Given his multiple co-morbidities, conservative management of IgA nephropathy was implemented. Cirrhotic Nephropathy is usually a clinically silent disease; however, the diagnosis can be suspected by finding proteinuria or abnormalities of the urine sediment. The pathogenesis may relate to defective hepatic processing and portosystemic shunting of circulating immune complexes.

TH-PO175

A Unique Case of IgA Cryoglobulinemia in the Setting of Staphylococcus aureus Infection Stephen L. Jenkins, Pace Romney, Catreena Mariji, Laith El-Rabadi. University of Utah Hospital, Salt lake, UT.

Background: IgA cryoglobulinemia is a rare entity with scarce literature regarding its pathogenesis and management. Herein, we describe a case of IgA cryoglobulinemia in the setting of Staphylococcus aureus infection.

Methods: A 75-year-old Caucasian man presented to the hospital with a two-week history of progressive weakness, lower extremity edema and decreased urine output. He was in acute renal failure with a serum creatinine of 8 mg/dl and serum potassium of 7

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

148
Does Your Differential for Glomerulonephritis in African Americans Include IgA Nephropathy? Abhilash Koratla, Don H. Espirit, William L. Clapp, Jogiraju V. Tantravahi.1 University of Florida, Gainesville, FL;
North Florida/South Georgia Veterans Health System, Gainesville, FL.

Background: Despite being the commonest primary glomerulonephritis in the world, IgA Nephropathy (IgAN) is rarely reported among African Americans (AAs), who otherwise have high renal disease burden. As nephrologists, we have been taught that IgAN should be considered as the last differential for GN in AAs patients unless they have high blood pressure (BP) or severe proteinuria. This assumption is based on the ‘reported’ rarity of this disease in AAs and the fact that AAs make up more than 50% of the new cases of HIV infection in the US. However, IgAN is being increasingly recognized in the non-HIV AA population. Factors such as level of disease awareness, access to appropriate diagnostic facilities and referral patterns may influence the underdiagnosis of IgAN in AAs. Moreover, there are reports suggesting that these patients may have more severe disease at presentation.

Methods: A 48-year-old woman was seen for IgAN. Her baseline serum creatinine (Scr) of 1.2 mg/dL. She was evaluated at an outside facility 3 months ago, when the Scr was 1.4 mg/dL with a UPCR of 1.7 g/g and 60/hr RBGs in the urine. A month later, her Scr increased to 1.7mg/dL, which prompted a repeat biopsy.

Results: Conclusions: Our case serves as a reminder that IgA nephropathy does occur in AAs and needs to be considered in the differentials when they present with nephritic picture.

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

of crescentic IgAN but the sample was inadequate. ANA, ANCA, HIV and hepatitis serologies were negative and complements normal. In our clinic, BP was 110/78mmHg, Scr 1.35 mg/dL and PCR – 1g/g. We elected to rebiopsy her to confirm the diagnosis of crescentic IgAN in an AA patient and possible treatment with an alkylating agent. It was surprisingly consistent with IgAN [Fig.1]. As there were fibrocellular crescents in only 2 of 11 glomeruli and the Scr remained stable, we chose to manage her conservatively.

Results: Conclusions: Our case serves as a reminder that IgA nephropathy does occur in AAs and needs to be considered in the differentials when they present with nephritic picture.

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

of crescentic IgAN but the sample was inadequate. ANA, ANCA, HIV and hepatitis serologies were negative and complements normal. In our clinic, BP was 110/78mmHg, Scr 1.35 mg/dL and PCR – 1g/g. We elected to rebiopsy her to confirm the diagnosis of crescentic IgAN in an AA patient and possible treatment with an alkylating agent. It was surprisingly consistent with IgAN [Fig.1]. As there were fibrocellular crescents in only 2 of 11 glomeruli and the Scr remained stable, we chose to manage her conservatively.

Results: Conclusions: Our case serves as a reminder that IgA nephropathy does occur in AAs and needs to be considered in the differentials when they present with nephritic picture.
A Case of RPGN with Dual Positive Anti-GBM and PR3-ANCA Antibodies Naswshen Chowdhury, Shayan Shirzadian, Nobuyuki (Bill) Miyawaki, James Drakakis.

Background: Anti-GBM disease and ANCA associated vasculitis are the major differentials for patients presenting with RPGN and pulmonary involvement. We report a case of unusual double positivity of both anti-GBM and PR3-ANCA antibodies, as most of the patients with both ANCA and anti-GBM antibodies are MPO-ANCA positive.

Methods: A 47-year-old female presented to the hospital with fatigue, malaise, and hemoptysis. Imaging of the chest revealed patchy consolidations and cavity lesions. Initial creatinine was 1.1 mg/dL, but during the hospital course she developed rapidly progressive renal failure (peak creatinine of 2.6 mg/dL) in the setting of proteinuria and microscopic hematuria. An anti-GBM antibody titer was 135 units/ml and anti-proteinase 3 (PR3) antibody titers were > 100 units. Anti-myeloperoxidase (MPO) antibody titers were negative. Therapy was initiated with pulse steroids and plasmapheresis. Renal biopsy (done after having already received significant immunosuppression) revealed a focal crescentic glomerulonephritis with cellular crescents involving 29% of glomeruli. The patient received a dose of IV Cyclophosphamide and continued on tapering doses of prednisone. She was discharged with a creatinine of 1.5 mg/dL and negative PR3-ANCA and anti-GBM antibody titers. She completed 4 months of oral Cyclophosphamide and currently has a creatinine of 0.7 mg/dL on Azathioprine.

Results: Conclusions: About 30% of patients with anti-GBM disease will have concurrent ANCA seropositivity, most of which are MPO-ANCA associated (74%). Our patient belonged to a smaller subset of patients with anti-GBM and PR3-ANCA antibodies. The reason for the emergence of dual antibody production is not known, however there have been some pathophysiological hypotheses for how MPO-ANCA may injure the glomerular basement membrane, expose antigens and lead to the development of an anti-GBM antibody. Most of the literature on patient and renal survival in dual positivity involves anti-GBM and MPO-ANCA antibodies. It is not clear that these descriptions of mechanism and outcome also apply to an overlap with PR-3-ANCA and more literature is required to help elucidate the potential clinical implications.

Dual-Positive Anti-Myeloperoxidase and Anti-Glomerular Basement Membrane Antibody Vasculitis Muhammad Azfal, Krishna M. Baradhi.

Background: Vasculitis secondary to the combination of anti-glomerular basement membrane (GBM) antibody and antineutrophil cytoplasmic antibodies (ANCA) is not common occurring up to 14% in patients with primary ANCA vasculitis and in up to 38% of patients with primary ANCA-related disease and moreover ANCA is usually directed against myeloperoxidase (MPO). Histologically, both are characterised by crescentic necrotizing glomerulonephritis. Immunofluorescence in anti-GBM disease reveals linear IgG staining, while ANCA vasculitis is pauci-immune.

Methods: 69 yr-old-male presented with abdominal pain & diarrhea and found to have acute oliguric renal failure. Labs showed BUN of 80 mg/dL and creatinine 3.84 mg/dL with associated hematuria and proteinuria. Serology revealed elevated MPO-ANCA (116.9 AU/ml) as well as anti-GBM antibodies (101 U). Renal biopsy showed diffuse necrotizing and crescentic glomerulonephritis with 1+ linear Ig G staining. Patient was started on plasmapheresis concurrently with hemodialysis and immunosuppressive therapy (cyclophosphamide and pulse steroids). Plasmapheresis was continued until Anti-GBM titers were < 20 U. Unfortunately his renal function did not recover and was discharged on tapering steroids, while continuing hemodialysis.

Results:

Conclusions: This is a unique case of rapidly progressive nephritis due to dual MPO-ANCA antibodies and anti-GBM antibodies (DAV). Clinical presentation of DAV may vary from isolated ANCA-related vasculitis and mortality usually tends to be higher. Renal survival in dual-positive patients is not better than that in anti-GBM-positive patients and is inferior compared to patients with MPO-ANCA only. Relapse with Dual-antibody vasculitis is higher than in anti-GBM disease, hence clinical vigilance is necessary to detect relapse. Treatment of DAV is similar to anti-GBM disease with plasmapheresis, cyclophosphamide, and steroids. Patients with either ANCA-related disease or anti-GBM disease, whether diagnosed serologically or histologically, should be tested for the second antibody. This dual serological approach provides better prognostication and dictates appropriate management, as goal is to limit further immunosuppression in dialysis dependent patients.

ANCA Associated Vasculitis in Scleroderma: A Renal Perspective Sam Kant, Duvuru Geetha.

Background: Overlap syndrome of ANCA associated vasculitis (AAV) and scleroderma (SS) is rare with conflicting data on renal outcomes. We describe the clinical characteristics and treatment outcome of ANCA glomerulonephritis (GN) in SS patients followed at a single center

Methods: We conducted a retrospective study of 3840 patients in our SS database to identify SS patients who subsequently developed AAV with renal involvement. Patient demographics, serology, renal function with renal histology and treatment outcomes were assessed.

Results: Of the 3840 patients, we identified 5 patients who had ANCA GN. The median age at SS diagnosis was 52 years, all 5 patients were female and 4 had diffuse scleroderma. ANA was positive in all, with 3 of them having anti Scl 70 antibodies. Four patients had interstitial lung disease and gastrointestinal dysmotility as a part of the constellation of clinical characteristics of SS. Median time of onset of AAV from time of diagnosis of SS was 12 years and all of 5 patients were MPO positive. All patients had acute kidney injury, with biopsy proven crescentic glomerulonephritis and none requiring dialysis. One patient had sinus involvement while AAV was renal limited in the remaining 4 patients. Two of these patients were treated with cyclophosphamide (CYC) and steroids (GC) and three were treated with rituximab (RTX) and steroids. All patients achieved disease remission. The median follow up was 24 months, The mean GFR at diagnosis was 39 ml/min and at last follow up was 38 ml/min. Of the 5 patients, 2 did not receive maintenance immunosuppression and both experienced relapse. None of the patients reached ESRD. Three patients died and of these 2 experienced relapse with fulminant alveolar hemorrhage.

Conclusions: ANCA GN in SS is rare with disease manifestation and course similar to AAV. This case series demonstrates that disease remission can be achieved with standard induction therapy. However vasculitis relapse is common and associated with high mortality without remission maintenance therapy.

TH-PO182

Renal Biopsy Teaching Case: A Patient with Scleroderma, Hypertension, and Type 2 Diabetes

A 65 year old African-American male, with a history of limited scleroderma for 16 years complicated by severe gastrointestinal dysmotility and interstitial lung disease, presented to the clinic with elevated blood pressure of 190/100 mm Hg, on a background of previously well controlled blood pressure. He was found to have an acute kidney injury with a serum creatinine of 2.5 mg/dL, compared to his baseline of 1.3 mg/dL. Urine studies demonstrated microscopic hematuria, with 3.4 grams of proteinuria. His hemoglobin was 7.4 and he had no evidence of hemolysis and platelet count was normal. Serologies revealed a positive c-ANCA serology with PR3 positivity at 97.4 IU/mL with negative ANA, dsDNA, Scl-70, anti-smith, anti-Ro, Anti-La, and RNP. A renal biopsy was performed which demonstrated arteriolar microangiopathy with fibrointimal necrosis and concentric lamellation with no evidence of ANCA GN (Fig 1). He was treated with ACE inhibitor with improvement of his BP and improved serum creatinine of 1.7 mg/dL.

Methods: Results:

Conclusions: This case of late onset scleroderma renal crisis highlights that atypical presentations of scleroderma renal crisis can exist and ANCA positivity can be misleading in such situations. Therefore, clinical decisions for further management should be predicated on expedient renal biopsy.

AUA-Azathioprine; MMF- Mycophenolate mofetil; DAH- Diffuse alveolar hemorrhage
A Case of Collapsing FSGS Presenting with ANCA Positive Pulmonary Renal Syndrome

**Background:** Most cases of HIV-negative collapsing FSGS are idiopathic. However, a growing list of disorders, including mixed connective tissue diseases such as Sjogren’s syndrome and SLE, are being reported to cause this lesion.

**Methods:** A 51-year-old Puerto Rican man without medical history presented with dyspnea and cough. She complained of chronic nasal congestion, pleurisy, dry mouth and Raynauds. There were basilar rales, facial acne, pale conjunctiva but no edema or arthritis on exam. Serum creatinine was 1.47 mg/dl (0.6-1.0 mg/dl) and was seen in nephrology clinic within 24 hours for evaluation. His sCr notably had risen from 0.7 to 1.0 mg/dl over a 5 month-period, he had normal serum complements, and his random urine protein to creatinine ratio was 280 mg/g. Urine microscopy revealed RBC casts. An urgent renal biopsy was performed and pulse IV steroids initiated for presumed renal involvement of granulomatosis with polyangiitis (GPA).

**Results:** Thin Basement Membrane Nephropathy (TBMN) likely explained his microscopic hematuria and RBC casts. This diagnosis portends a good clinical renal prognosis. However, finding benign pathology, including TBMN, does pose challenges in diagnosing uGPA relapse clinically as the hematuria and RBC casts can be intermittent and from the benign condition. Nevertheless, this case highlights the utility of performing renal biopsy even when there is a high index suspicion of renal involvement from ANCA-associated vasculitis.

**Conclusions:** The patient presented as pulmonary renal syndrome and an active urine sediment with high titer anti-MPO Ab. Suspicion was high for ANCA vasculitis with expected pauci-immune crescentic GN on biopsy. Instead, collapsing glomerulopathy was diagnosed. Collapsing lesions can resemble crescents (pseudocrescents) and our case was reviewed by several renal pathologists to confirm the diagnosis. This challenges the notion that biopsy isn’t necessary when pretest probability for pauci-immune glomerulonephritis is high. We propose that this patient’s collapsing glomerulopathy is due to her collagen vascular disease (Sjogren’s) and is analogous to lupus podocytopathy.

---

**TH-PO184**

A Sheep in Wolf’s Clothing: Hematuria in GPA

**Background:** Performing a renal biopsy in a patient with RBC casts, rising serum creatinine (sCr) and positive ANCA serology is justifiable to evaluate for crescentic glomerulonephritis and determine best management strategies. Nonrenal involvement has a better prognosis in patients with ANCA-vasculitis. Finding underlying unrelated benign pathology in such instances can make future clinical decision-making challenging.

**Methods:** A 51 year-old man visited the rheumatology clinic in May 2017 for ongoing unexplained multisystem symptoms. He had been in good health until 10 months earlier when he started having recurrent bouts of sinustitis, cough, fatigue, otitis media leading to deafness and a 40lbs weight loss. Serology for CANCA was positive [1:40 titer; PR3: 87], this was negative earlier in his clinical course. He was noted to have microscopic hematuria and was seen in nephrology clinic within 24 hours for evaluation. His sCr notably had risen from 0.7 to 1.0 mg/dl over a 5 month-period, he had normal serum complements, and his random urine protein to creatinine ratio was 280 mg/g. Urine microscopy revealed RBC casts. An urgent renal biopsy was performed and pulse IV steroids initiated for presumed renal involvement of granulomatosis with polyangiitis (GPA). On biopsy, the 19 glomeruli sampled were histologically normal on light microscopy and immunofluorescence was unremarkable. Electron microscopy revealed thin basement membrane width of 218nm (Figure-right). Alport’s immunostaining was negative.

**Results:** Conclusion: Thin Basement Membrane Nephropathy (TBMN) likely explained his microscopic hematuria and RBC casts. This diagnosis portends a good clinical renal prognosis. However, finding benign pathology, including TBMN, does pose challenges in diagnosing uGPA relapse clinically as the hematuria and RBC casts can be intermittent and from the benign condition. Nevertheless, this case highlights the utility of performing renal biopsy even when there is a high index suspicion of renal involvement from ANCA-associated vasculitis.

**Conclusions:** The patient presented as pulmonary renal syndrome and an active urine sediment with high titer anti-MPO Ab. Suspension was high for ANCA vasculitis with expected pauci-immune crescentic GN on biopsy. Instead, collapsing glomerulopathy was diagnosed. Collapsing lesions can resemble crescents (pseudocrescents) and our case was reviewed by several renal pathologists to confirm the diagnosis. This challenges the notion that biopsy isn’t necessary when pretest probability for pauci-immune glomerulonephritis is high. We propose that this patient’s collapsing glomerulopathy is due to her collagen vascular disease (Sjogren’s) and is analogous to lupus podocytopathy.
immunosuppressive therapy proved to be effective in eliminating abdominal complaints, decreasing proteinuria and improving renal function. Nonetheless, more evidence-based recommendations are needed to pinpoint which immunosuppressive agent is the choice of therapy for HSPN.

TH-PO186

Unusual Cause of Visceral Infarcts Amar Pandit,1 Aditiya S. Pawaskar,2 Randy A. Goldberg,1,3 New York Medical College, Valhalla, NY; 2Westchester Medical Center, White Plains, NY.

Background: Thrombosis is an increasingly recognized feature of ANCA vasculitis.

Methods: An 18 year old lady with history of celiac disease presented with high grade fever, 10 lb. weight loss, nausea and epigastric tenderness. Physical exam was negative for lymphadenopathy, murmur, adventitious lung sounds, hepatosplenomegaly, joint swelling/tenderness or rash. Labs revealed anemia, elevated ESR and CRP and normal white count, renal and liver function tests. Infectious vs. inflammatory processes were considered and she was started on antibiotics. CT abdomen revealed renal and splenic infarcts. Infective endocarditis was ruled out by negative blood cultures and a normal echocardiogram, following which antibiotics were stopped. Urinalysis showed microscopic hematuria and 2+ proteinuria (Urine protein/ creatinine ratio of 961), consistent with nephritic syndrome, likely due to collagen vascular disease vs. thrombotic disease. ANA and anti-PR3 were positive, and dsDNA, anti-Sm, anti-RNP, C3, C4, cryoglobulins, anti-GBM, anti-SS-A and anti-SS-B were negative. Hypercoagulable workup revealed decreased Protein S activity and negative anti-phospholipid antibodies.

CT chest revealed a hemorrhagic infarct, but no nodules. Renal biopsy confirmed the presence of pauci-immune necrotizing crescentic glomerulonephritis, indicating GPA. She was started on IV methylprednisolone, rituximab and tirofiban with resolution of her symptoms.

Results:

Conclusions: Venous (DVT, PE) and arterial thrombosis are being increasingly recognized in GPA, although arterial involvement has predominantly been described in the coronaries. This predisposition to thrombosis is multifactorial: 1) Activation of neutrophils by antibodies and the interaction of activated neutrophils with the endothelium. There is also release of tissue factor which activates thrombosis. 2) Elevated thrombomodulin levels activate thrombosis and inhibition of conversion of plasminogen to plasmin inhibits fibrinolysis. There are no recommendations on use of anti-platelets or anti-coagulants at present.

TH-PO187

Be Brash: Name That Rash

Amit Kazerouninia, Arka Afral, Natasha N. Dave, Rajeev Raghavan. Baylor College of Medicine, Houston, TX.

Background: Granulomatosis with polyangiitis (GPA), is a relatively rare, potentially fatal anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis.

It is characterized by necrotizing granulomatous inflammation and vasculitis, affecting predominantly small to medium vessels. Here, an uncommon manifestation of vasculitis—livedo racemosa—was not addressed and the patient suffered a stroke.

Methods: A 60-year-old woman with hypothyroidism presented to her PCP for rash, progressive weakness, stocking/glove numbness, and intermittent fevers. The rash was not described or addressed, but EMG was ordered. Within a week, she presented to the ED for the same complaints. She was febrile and studies were notable for leukocytosis, 1+ blood on urinalysis, anemia, and hypoalbuminemia. General medicine diagnosed polynephropathy, began gabapentin, and discharged her from the ED. Shortly thereafter, she re-presented to the ED with a left fronto-temporal hemorrhagic stroke. Renal was consulted for AKI and noticed a purple, lacy-like, reticulated rash on both legs, suggestive of livedo reticularis, but with irregularities within the thickness of the reticulations, more consistent with livedo racemosa. Family noted the rash had been present for several months. Her urine had RBC casts, serum was positive for MPO-ANCA, and kidney biopsy showed interstitial granulomas and focal arterial necrosis, all evincing GPA. Given hemorrhagic stroke at an uncommon site, brain angiography was performed showing subtle luminal irregularities in the bilateral small cerebral vessels consistent with CNS vasculitis. Chest CT and EMG were consistent with pulmonary and PNS GPA, respectively. She was given pulse dose steroids and started weekly rituximab infusions. The patient’s kidney function improved somewhat, but dysarthria continues, with only about 60% of her speech understandable by family members.

Results:

Conclusions: Livedo racemosa is always due to a secondary disorder and warrants further evaluation. Multiple clinicians missed the importance of her rash; any livedo-like rash in the setting of active urinary sediment, non-diabetic polynephropathy, intermittent fevers, leukocytosis, anemia, and hypoalbuminemia should be biopsied allowing for early diagnosis of systemic illnesses such as vasculitis. If identified early, GPA remission is possible with immunosuppressive therapy, and may have prevented this patient’s hemorrhagic stroke.

TH-PO188

From a Complicated Biopsy to an Unexpected Diagnosis

Haris F. Murad,1 Randy L. Luciano,2 Yale School of Medicine, New Haven, CT; 2Yale University School of Medicine, New Haven, CT.

Background: Polyarteritis Nodosa (PAN) is a rare systemic necrotizing vasculitis targeting medium sized arteries and can involve any organ in the body except for the lungs. Arterial inflammation causes tissue ischemia and hemorrhage and may present with a wide spectrum of clinical manifestations ranging from neurorethacies and rashes to renal failure and bowel ischemia. Renal failure is thought to be secondary to ischemia from rupture of microaneurysms. Diagnosis requires an integration of clinical, radiographic and pathological findings, but the presence of medium vessel microaneurysms can suffice in the absence of tissue confirmation. We present a case in which the diagnosis was made in unusual circumstances.

Methods: A 46 year old lady with non-cirrhotic hepatoportal sclerosis presents with a gradually uptrending creatinine over two years reaching 4.1mg/dL, worsening proteinuria up to 5.6gm/day and a urine sediment showing granular casts. Renal ultrasound showed bilateral echogenic kidneys and elevated velocities in renal arteries and the aorta. She underwent a renal biopsy which was challenging and on the second pass she had severe abdominal pain. A color doppler demonstrated a pulsatile jet originating from the lower renal pole. She immediately passed a large amount of blood from her urethra. An emergent angiography showed several aneurysms in the liver, kidney and spleen (see figure) along with two pseudoaneurysms, consistent with a diagnosis of PAN. Unfortunately the biopsy sample was insufficient for interpretation. Subsequent labs showed elevated inflammatory markers, negative rheumatoid factor, cryoglobulins, hepatitis B and C titers.

Results:

Conclusions: This case demonstrates that a complication from a kidney biopsy was able to provide an important, and previously unthought of diagnosis in a patient. In addition it highlights the safety concerns of patients with vasculitis undergoing biopsy.

TH-PO189

Bartonella Endocarditis Mimicking ANCA-Associated Glomerulonephritis (GN)

Joseph Vercellone, Lisa J. Cohen, Saima Mansuri, Ping L. Zhang, Paul S. Kellerman. Oakland University/William Beaumont School of Medicine, Royal Oak, MI.

Background: Bartonella henselae is a fastidious organism causing cat scratch disease, commonly associated with fever and lymphadenopathy. Rarely, B. henselae results in culture-negative endocarditis (IE). Herein, we describe a case of B. henselae IE mimicking ANCA-associated GN.

Methods: A 47-year-old male presented with 2 weeks of flank pain and four days of cola-colored urine. Exam revealed a soft murmur over the left sternal border and severe CVA tenderness, with no fever. Labs showed a Hgb of 7.7 mg/dL, a creatinine of 2.36 mg/dL (up from 0.89 mg/dL), and UA showed 3+ blood, 1+ protein, 51-100 RBC/HPF, 51-100 WBC/HPF, and 10-50 epithelial cells/HPF. A urine culture grew B. henselae. Follow-up echocardiogram performed one week later showed a small vegetation on the aortic valve. Additional workup revealed decreased Protein S activity and negative anti-phospholipid antibodies.

Results:

Conclusions: From a Complicated Biopsy to an Unexpected Diagnosis

Haris F. Murad, Randy L. Luciano, Yale School of Medicine, New Haven, CT; Yale University School of Medicine, New Haven, CT.

Background: Polyarteritis Nodosa (PAN) is a rare systemic necrotizing vasculitis targeting medium sized arteries and can involve any organ in the body except for the lungs. Arterial inflammation causes tissue ischemia and hemorrhage and may present with a wide spectrum of clinical manifestations ranging from neuropathies and rashes to renal failure and bowel ischemia. Renal failure is thought to be secondary to ischemia from rupture of microaneurysms. Diagnosis requires an integration of clinical, radiographic and pathological findings, but the presence of medium vessel microaneurysms can suffice in the absence of tissue confirmation. We present a case in which the diagnosis was made in unusual circumstances.

Methods: A 46 year old lady with non-cirrhotic hepatoportal sclerosis presents with a gradually uptrending creatinine over two years reaching 4.1mg/dL, worsening proteinuria up to 5.6gm/day and a urine sediment showing granular casts. Renal ultrasound showed bilateral echogenic kidneys and elevated velocities in renal arteries and the aorta. She underwent a renal biopsy which was challenging and on the second pass she had severe abdominal pain. A color doppler demonstrated a pulsatile jet originating from the lower renal pole. She immediately passed a large amount of blood from her urethra. An emergent angiography showed several aneurysms in the liver, kidney and spleen (see figure) along with two pseudoaneurysms, consistent with a diagnosis of PAN. Unfortunately the biopsy sample was insufficient for interpretation. Subsequent labs showed elevated inflammatory markers, negative rheumatoid factor, cryoglobulins, hepatitis B and C titers.

Results:

Conclusions: This case demonstrates that a complication from a kidney biopsy was able to provide an important, and previously unthought of diagnosis in a patient. In addition it highlights the safety concerns of patients with vasculitis undergoing biopsy.
0-5 WBC/HPF, and RBC casts. Kidneys were normal on ultrasound, but MRI noted wedge shaped segmental hypoechoic lesions which increased in size on follow-up imaging. The patient was initially pulsed with steroids with no further immunosuppression. Serologies revealed normal C3, C4, ASO, ANA, antidiopetin, IgA, and hepatitis panel. ANCA and anti-MPO were negative, but anti-PR3, CRP and ESR were markedly elevated. On biopsy, light microscopy showed focal proliferative injury with two non-necrotic crescents. Immunofluorescence was positive for IgM, IgA, C3, and C1q. Electron microscopy showed subtle mesangial and subendothelial deposits without "humps." With possible immune complexes on kidney biopsy and a murmur, TEE was performed showing a bicuspid aortic valve with vegetation. A diagnosis of culture-negative endocarditis was initiated and patient continues to require outpatient dialysis.

METHODS: Case 1 A 76-year-old female with history of diabetes mellitus presented with lower extremity edema. Serum creatinine was 1.2 mg/dL. Her total creatinine clearance (CrCl) was 53 mL/min. She was admitted for worsening edema and anasarca. Imaging revealed a large right adrenal lesion, which was concerning for metastatic disease. She was found to have AKI with a serum creatinine of 11.9 mg/dL (baseline 1.1 mg/dL). The lesion was found to be a pancreatic mass. She was treated with concurrent chemoradiotherapy and gemcitabine (GEM) was initiated. A 52-year-old man was diagnosed with hilar cholangiocarcinoma at the age of 46. Following surgery, he was treated with GEM therapy (cumulative dose of 16,600 mg). His serum creatinine level was 1.2 mg/dL. At 17 months, his serum creatinine level decreased to 0.8 mg/dL within 22 months. Proteinuria appeared reaching to 3.5 mg/dL. She was treated with concurrent chemoradiotherapy and GEM was administered. Four months later, cumulative dose of GEM was 23,800 mg and her serum Cr level was 1.4 mg/dL. GEM was discontinued and at a follow-up visit of 6 months, her serum creatinine level decreased to 1.0 mg/dL.

RESULTS: Conclusions: We present a case of likely D+HUS where we were unable to isolate Shiga-like toxin-I A1 subunit. The diagnosis of HUS has been complicated by the lack of a complement regulating gene of unknown significance in aHUS, that has other known associations with disease. CFFR5 is associated with protection of glomerular cells against complement activation, yet mutations in the CFFR5 gene do not necessarily cause HUS as there are also present in patients without clinical manifestations. HUS mutations have been described in association with various nephropathies, particularly in Cypriot patients, but few mention HUS, and none have described an intron mutation or its relationship to HUS. Importantly, CFFR5 mutations described in aHUS patients are in coding regions, not the intron. This CFFR5 intron mutation is not predicted to alter or affect splicing, therefore it is unlikely to play a role in this particular case. Hence, complement inhibition with eculizumab is perhaps not indicated. Long-term monitoring is warranted.

TH-PO192
Complement Factor C4d Staining in Gemicitabine-Induced Thrombotic Microangiopathy: A Case Series
Koji Muro, Hideki Yokoi, Kaoor Sakai, Shuichi Endo, Takeshi Matsubara, Motoko Yanagita. Department of Nephrology, Kyoto University Hospital, Kyoto, Japan.

Background: Complement factor C4d staining is a common finding in thrombotic microangiopathy (TMA), regardless of the underlying clinical condition. However, there are few reports in the literature investigating C4d staining of drug-toxicity-induced TMA, especially of gemcitabine-induced TMA (GCI-TMA). We aim to examine the pattern of C4d staining in renal biopsy specimens from three patients with GCI-TMA.

Methods: Case 1 A 52-year-old man was diagnosed with hilar cholangiocarcinoma at the age of 46. Following surgery, he was treated with GEM therapy (cumulative dose of 16,600 mg). His serum creatinine level was 1.2 mg/dL. At 17 months, his serum creatinine level decreased to 0.8 mg/dL within 22 months. Proteinuria appeared reaching to 3.5 mg/dL. She was treated with concurrent chemoradiotherapy and GEM was administered. Four months later, cumulative dose of GEM was 23,800 mg and her serum Cr level was 1.4 mg/dL. GEM was discontinued and at a follow-up visit of 6 months, her serum creatinine level decreased to 1.0 mg/dL.

Results: Conclusions: We present a case of likely D+HUS where we were unable to isolate Shiga-like toxin-I A1 subunit. The diagnosis of HUS has been complicated by the lack of a complement regulating gene of unknown significance in aHUS, that has other known associations with disease. CFFR5 is associated with protection of glomerular cells against complement activation, yet mutations in the CFFR5 gene do not necessarily cause HUS as there are also present in patients without clinical manifestations. HUS mutations have been described in association with various nephropathies, particularly in Cypriot patients, but few mention HUS, and none have described an intron mutation or its relationship to HUS. Importantly, CFFR5 mutations described in aHUS patients are in coding regions, not the intron. This CFFR5 intron mutation is not predicted to alter or affect splicing, therefore it is unlikely to play a role in this particular case. Hence, complement inhibition with eculizumab is perhaps not indicated. Long-term monitoring is warranted.

TH-PO191
Thrombotic Microangiopathy and AKI Associated with MT-3724 Monotherapy
Mona Shaban, Abhijit V. Krishnaraj, Alexei V. Mikhailov, 1University of North Carolina at Chapel Hill, Chapel Hill, NC; 2Nephrology, University of North Carolina at Chapel Hill, Chapel Hill, NC.

Background: Study drug MT-3724 is a CD20-targeting immunotoxin consisting of a recombinant fusion protein with a CD20 binding variable fragment fused to the enzymatically active Shiga-like toxin-I A1 subunit (SLT-I A1). Upon binding to the surface of CD20, SLT-I A1 leads to MT-3724 internalization, which inactivates cell ribosomes and causes cell death. MT-3724 is currently being studied in relapsed diffuse B cell lymphoma (DLBCL). Here, we report a case of acute kidney injury (AKI) secondary to thrombotic microangiopathy after administration of MT-3724 and leading to dialysis dependence.

Methods: A 70-year-old female with relapsed DLBCL presented with lower extremity edema during the cycle of study drug MT-3724. Each cycle of MT-3724 is 75 mg/kg dosed on days 1,3,5,8,10, and 12. Exam was remarkable for significant peripheral edema. Serum creatinine (Scr) was 3.2 mg/dL from a baseline of 1.0-1.2 mg/dL. Urine protein to creatinine ratio (U/P Cr) was 20 g/g. Urine sediment revealed erythrophagocytosis and dysmorphic red blood cells. Renal biopsy was performed and revealed thrombotic microangiopathy with evidence of fragmented red blood cells in the mesangium and interstitium. Glomeruli had signs of low flow and 1 fibrillar crescent was observed. There was moderate to severe interstitial fibrosis and tubular atrophy. Figure 1, Panel A shows strong GBM-C4d staining in renal biopsy specimen from a patient with GCI-TMA. GBM-C4d duplication was observed, and their renal function did not fully recover. GBM-C4d staining in GCI-TMA might imply relatively poor renal prognosis.

Conclusions: A recent study showed that isolated strong GBM-C4d can highlight architectural glomerular remodeling. In our cases, segmental GBM-C4d and GBM duplication were observed, and their renal function did not fully recover. GBM-C4d staining in GCI-TMA might imply relatively poor renal prognosis.

TH-PO194
An Unexpected Finding of Post Influenza Glomerulonephritis
Ashoor Jie Tang. Div of Kidney Diseases and Hypertension, Brown University, Providence, RI.

Background: Active glomerulonephritis with hypocomplementemia has a limited differential. Here we present an interesting case of acute kidney injury (AKI) with influenza, in which kidney biopsy showed cryoglobulinemic membranoproliferative glomerulonephritis (MPGN) and evidence of post-infectious glomerulonephritis (PIGN).

Methods: A 62-year-old man with history of clinically inactive low-grade B cell lymphoma (LGBL), presented with cough, myalgias, and tested positive for Influenza A. He was found to have a serum creatinine of 1.1 mg/dL (baseline 1.1 mg/dL), sub-nephrotic proteinuria and microscopic hematuria. Serologic studies showed low complements (C3, C4) and a weak monoclonal IgG lambda light chain on serum electrophoresis. All other infectious and rheumatologic work up were negative. Kidney biopsy revealed pattern of MPGN, with prominent sub-endothelial deposits and intra-capillary hynaloid pseudo thrombi, staining predominantly for IgG and lambda light chain on immunofluorescence. By electron microscopy, he also had many sub-epithelial "humps" along with sub-endothelial and mesangial deposits. This was consistent with type 1 cryoglobulinemic glomerulonephritis with superimposed PIGN. In the interim, he was started on a course of steroids and over the next 2-3 weeks his kidney function returned to baseline with resolution of proteinuria and hematuria. He was eventually taken off steroids and his kidney function has remained normal.

Results: Conclusions: This case is unique in several aspects. First of all, although his history of LGBL could explain weak paraproteinemia, our patient showed no clinical evidence of lymphoma on routine monitoring by Hematology. Moreover, we had no compelling evidence in which kidney biopsy showed cryoglobulinemic membranoproliferative glomerulonephritis (MPGN) and evidence of post-infectious glomerulonephritis (PIGN).

TH-PO190
Incidental Finding of CFFR5 Mutation in a Case of Hemolytic Uremic Syndrome
Matthew H. Shapiro, Diego H. Aviles, Isa Ashoor. LSUHSC Pediatrics, New Orleans, LA.

Background: Hemolytic-uremic syndrome (HUS) is a triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal insufficiency. It’s divided into two categories, diarrhea-positive (D+HUS) or typical HUS and diarrhea-negative or atypical HUS (D- HUS).

Methods: A previously healthy 7-year-old boy presented with several days of abdominal pain, emesis and bloody diarrhea. Admission labs were notable for Hgb 13.7 gm/dL, Platelets 485k/mm3 and creatinine 0.5 mg/dL. Stool culture, c. diff and Shiga toxin assays were negative. He subsequently developed oliguria and acute kidney injury. Urine was positive for blood (>3), protein (>3) and granular casts. Hgb and platelets fell to 7.1 gm/dL and 22k/mm3, respectively. Creatinine peaked at 4 mg/dL at which point hemodialysis was started. aHUS was suspected and additional labs were drawn. Complement C3/C4 and ADAMST13 levels were normal. Genetic testing for 11 genes involved in thrombotic microangiopathy identified a mutation of unknown significance in the intron of Complement Factor H Related Protein 5 (CFFR5) gene. Renal function returned to baseline within a week without complement inhibition therapy and remains normal 3 months later.

Results:
TH-PO194

Recurrent Venous Thromboembolism (VTE) in Membranous Nephropathy despite Direct Xa Inhibitor Therapy

Monica L. Reynolds, Vinal K. Derebail. University North Carolina at Chapel Hill, Chapel Hill, NC.

Background: In membranous nephropathy, the risk of VTE is high and increases significantly with a serum albumin of <2.8 g/dl. Apixaban, a direct factor Xa inhibitor, is non-inferior to warfarin for VTE treatment in the general population but has not been studied in the nephrotic syndrome. We report a patient with recurrent VTE while on therapeutic dosing of apixaban.

Methods: A 51-year-old Caucasian male presented with new hypertension and lower extremity edema. Imaging studies demonstrated bilateral pulmonary emboli and acute DVT of the left external iliac, femoral and popliteal vein with extension to the IVC. After mechanical thrombectomy and catheter-directed thrombolytics, he was placed on fondaparinux. At one year, he had no further VTE's and serum albumin was 3.3 g/dl. Apixaban 2.5mg BID. Edema recurred two months later and CT demonstrated extension to the left external iliac, femoral and popliteal vein. He was switched back to fondaparinux. Despite appropriate dosing of apixaban, our patient developed recurrent VTE.

Results: Despite appropriate dosing of apixaban, our patient developed recurrent VTE. A four-hour drug level was below the range reported for healthy volunteers at the same dose. Due to its high protein binding, apixaban may have altered pharmacokinetics and pharmacodynamics in patients with nephrotic syndrome and hypoalbuminemia. More data is needed to determine appropriate use of novel oral anticoagulants in the nephrotic syndrome.

TH-PO195

Spontaneous Cerebral Venous Thrombosis as a Presenting Manifestation of Secondary Membranous Nephropathy

Srijan Gundu, 1 Helbert Rondon Berrios. 1University of Pittsburgh Medical Center, Pittsburgh, PA; 2University of Pittsburgh School of Medicine, Pittsburgh, PA.

Background: Membranous nephropathy is one of the most common causes of nephrotic syndrome in adults and accounts for the glomerulopathy associated with the highest rate of thromboembolic complications. We present a case of an otherwise healthy man who presented with spontaneous cerebral venous thrombosis and ultimately was diagnosed with a form of secondary membranous nephropathy.

Methods: A 40-year-old previously healthy man presented with progressively worsening generalized headache and nausea. He had been taking occasional ibuprofen for headaches for 2 weeks. He was febrile and hemodynamically stable at presentation. On examination, he was in moderate distress due to headaches without neck stiffness, temporal artery tenderness or other focal neurological defect. Laboratory data revealed normal blood counts, chemistry profile and renal function but low serum albumin of 2.3 g/dl, high total cholesterol of 263 mg/dl and high LDL of 191 mg/dl. Urine protein-to-creatinine ratio was elevated at 10 g/g. CT angiography of the brain revealed bilateral transverse venous sinus thrombosis. Patient was initiated on warfarin with heparin bridging since thrombophilia workup could not be performed due to acute thrombosis and warfarin reduce levels of antithrombin, protein C, and protein S. However, antiphospholipid antibodies were negative. Serological workup demonstrated low normal serum complement (C3 95, C4 22) with positive ANA (1:320), anti-ß2GPI, anti-SSA, anti-Smith and anti-dsDNA. Hepatitis screen was negative. Kidney biopsy was performed and histopathology was reported as follows: Light microscopy revealed a diffuse thickening of the glomerular basement membrane with “spikes”. Immunofluorescence studies showed a negative PL2AR staining and a classic “full house” staining pattern (IgG1-4, C3, C1q). Electron microscopy revealed subepithelial, subendothelial and mesangial deposits with tubuloreticular inclusions. Based on the above findings a diagnosis of mixed connective tissue disease with lupus overlap was made and patient was initiated on prednisone and mycophenolate mofetil.

Results: Cerebral venous thrombosis is a rare but potentially fatal complication of nephrotic syndrome. Increased risk of thromboembolism has been classically demonstrated in primary, but is also commonly seen in secondary membranous nephropathy. The risk increases with the level of decline in serum albumin.

TH-PO196

Incidental Thin Basement Membrane Associated with Primary Membranous Nephropathy

Felipe Naranjo Sanchez, Helmut G. Renne, Kelly A. Burdge, Brigham and Women’s Hospital, Boston, MA; North Shore Medical Center, Salem Hospital, Cambridge, MA; Massachusetts General Hospital Danvers, Danvers, MA.

Background: Thin basement membrane nephropathy (TBMN) is a benign recessive genetic condition caused by defects of α3 or α4 type IV collagen, presenting with hematuria. A thin BM can also be found in Alport syndrome, an x-linked disorder associated with α5 type IV collagen, which presents with early renal failure and has poor prognosis.

Methods: 52 yo F, PMHx of HTN, CKD3, GERD and Takauso cardiomyopathy, presented to the ER with severe headache and nausia, there she had one episode of syncope lasting 45 sec, in the setting of PRES. In her workup, a UA demonstrated proteinuria. Thrombophilia work-up was negative for Antithrombin and Protein C/S deficiency. He was 2.1 g/dl and urinalysis showed proteinuria. Urine protein to creatinine ratio was 2 mg/dl (previous 1mg/dl); hypercholesterolemia, hypoalbuminemia; AlbCr 8.583 mg/g; negative serology for HBV, HCV, HIV and RPR; normal C3 and C4, negative ANCA, ANA, SPEP and positive PLA2R antibody; low IgG, normal IgA. Kidney biopsy reported membranous glomerulonephropathy (MGN) stage II. Immunofluorescence microscopy revealed co-dominant reactivity for IgG3 and IgG4, weakly reactive to PLA2r. Electron microscopy revealed diffuse attenuation and fraying of lamina densa and effacement of foot processes of the glomerular basement membrane (GBM); thickness of the GBM could not be measured due to marked distortion of the capillary walls; changes suggestive of TBMN, an inherited abnormality of the GBM, possibly involving collagen IV genes. Findings were consistent with a diagnosis of MGN. He was managed with aminoglycosides, diuretics and antihypertensives and his proteinuria significantly reduced. He was continued on low protein diet, diuretics and antihypertensives and is doing well 2 months later.

Conclusions: Cerebral venous thrombosis is a rare but potentially fatal complication of nephrotic syndrome. Increased risk of thromboembolism has been classically demonstrated in primary, but is also commonly seen in secondary membranous nephropathy. The risk increases with the level of decline in serum albumin.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
diuretics with increasing serum Cr to 4.0 mg/dl and was then started on dialysis. Given presence of rapidly progressive pulmonary and renal failure along with skin tumors, these findings strongly supported the diagnosis of ALHE. Plasma VEGF-A before the initiation of prednisolone therapy was measured to be 109 pg/mL in Case 1 (normal level: 42 ± 15 pg/mL). Eosinophils and plasma VEGF-A levels (57.3 pg/mL) were also positive in Case 2. Flow cytometric analysis of peripheral blood revealed that 2.5% of CD3+ T cells were THSD7A-positive. These findings suggested that THSD7A was presented to the immune system at ALHE foci.

**Results:**

**Conclusions:**

The AKI in this case was likely the combination of contrast, ARB therapy, NSAIDs, and hemodynamic insults in setting of hypobulimia. This case highlights the importance of biopsy in determination of etiology of underlying diagnosis.

**TH-PO198**

Gastric Stimulator Infection Complicated by Post-Infectious Membranous Glomerulonephritis

**Tyler Woodell,** Rupali S. Avasare. Oregon Health & Science University, Portland, OR.

**Background:** Acute poststreptococcal glomerulonephritis, though considered rare among adults in developed countries, remains a serious health concern. In contrast to the typical skin or throat infection preceding acute poststreptococcal glomerulonephritis, here we report to our knowledge the first case of infection-related glomerulonephritis associated with intraabdominal infection after gastric stimulator placement.

**Methods:** A 24-year-old woman with type 1 diabetes mellitus complicated by gastroparesis and proteinuric stage IIIA chronic kidney disease underwent placement of a gastric stimulator after multiple emergency room visits for intractable vomiting. She developed acute abdominal pain on postoperative day 27 and presented to the same emergency room. On physical exam she is febrile to 102.5°F, tachycardic to 135 beats per minute and hypotensive to 80s/40s mmHg. Diagnostic studies are remarkable for a serum creatinine of 2.9 mg/dl (increased from 1.5 mg/dl one month prior), a white blood cell count of 29.1 (19.3% neutrophils) and a CT scan of the abdomen and pelvis that reveals a fluid collection adjacent to the gastric stimulator. Blood cultures are negative. She is started on vancomycin and piperacillin-tazobactam and, on postoperative day 30, diagnostic laparoscopy reveals purulent fluid around the stimulator for which it is removed.

**Results:** Intraoperative cultures grow group A Streptococcus pyogenes. The patient’s antibiotics are narrowed and her clinical status improves. Despite rapid initial improvement in renal function, the patient develops recurrent kidney injury four days after removal of the gastric stimulator characterized by a rise in creatinine from 1.4 mg/dl to 2.9 mg/dl, over the subsequent two weeks and oliguria; C3 is reduced and C4 is normal. She is started on hemodialysis for volume overload. A kidney biopsy is performed and findings show mesangial and subepithelial electron dense deposits. A diagnosis of infection-related glomerulonephritis is established and, after two months of supportive care, she is able to discontinue hemodialysis.

**Results:** Clinicians should maintain suspicion for post-infectious glomerulonephritis in the absence of classic infection and, when appropriate, perform a kidney biopsy for its confirmation.

**Conclusions:**

**TH-PO199**

Possible Contribution of Vascular Endothelial Growth Factor in the Pathogenesis of Membranous Nephropathy (MN)

**Ayumi Matsumoto,** Isao Matsui, Tomoko Namba, Yusuke Sakaguchi, Masayuki Mizui, Takayuki Hamano, Yoshitaka Isuka. Osaka University Graduate School of Medicine, Suita, Japan.

**Background:** Autoantibody against thrombopsonin type-1 domain-containing 7A (THSD7A) is responsible for primary MN, but the mechanisms how is THSD7A expression controlled and how is THSD7A recognized by the immune system remain uncertain.

**Methods:** Two cases of THSD7A-associated MN accompanying subcutaneous tumors were transferred to our hospital. Hypersplenomegaly was evident in both cases. Histological analyses of forehead tumors of Case 1 revealed that the tumors were formed by swollen arteries. The arteries were nearly occluded due to small vessels lined by CD31-positive plump endothelial cells, which were surrounded by eosinophils. These findings indicated that the patient suffered from intraarterial angiolympohyperplasia with eosinophils (ALHE). The right axillary tumor of Case 2 indicated that Case 2 also suffered from ALHE. Plasma VEGF-A before the initiation of prednisolone therapy was elevated to 109 pg/mL in Case 1 (normal level: 42 ± 15 pg/mL). Serum level of IL-5, a cytokine that upregulates VEGF-A production and secretion by eosinophils, was also elevated to 15.5 pg/mL in Case 1 (normal level: < 3.0 pg/mL). These parameters were not measured in Case 2. Flow cytometric analysis of peripheral blood revealed that a subset of number of the circulating eosinophils was positive for VEGF-A in Case 1, and eosinophils infiltrated into the ALHE tumor were also positive for VEGF-A in both cases. Prednisolone therapy dramatically decreased the number of VEGF-positive eosinophils and plasma VEGF-A levels (57.3 pg/mL). We found that plump endothelial cells in ALHE strongly expressed THSD7A in both cases. VEGF-A upregulated THSD7A expression in a dose-dependent manner in cultured human umbilical-vein endothelial cells. Furthermore, double-positive cells for THSD7A and CD83, a molecule involved in antigen-presentation activity, surrounded the proliferated small vessels. These findings suggested that VEGF-A-induced THSD7A was presented to the immune system at ALHE foci.

**Results:**

**Conclusions:** Our study clearly demonstrated that VEGF-A induced THSD7A expression in a dose-dependent manner, and our findings suggested that THSD7A was immunized at ALHE foci. Therefore, VEGF-A-induced THSD7A-expression outside of the kidney plays important roles in MN pathogenesis.

**Funding:** Private Foundation Support

**TH-PO200**

A Refractory Case of Membranous Nephropathy Concurrent with IgG4-Related Kidney Disease

**Hiromitsu Araki,** Ryo Kamimatsu, Naohiro Toda, Keisuke Nishikawa, Shuichi Endo, Takeshi Matsubara, Hideki Yokoi, Motoko Yanagita. Department of Nephrology, Kyoto University Hospital, Kyoto city, Japan; Department of Nephrology, Osaka red cross hospital, Osaka city, Japan.

**Background:** IgG4-related kidney disease (IgG4-RKD) is a recently recognized clinicopathological entity characterized by abundant positive plasma cells containing IgG4, extracellular matrix (ECM) deposition and characteristic storiform fibrosis. Tubulointerstitial nephritis is the most common finding, which responds well to corticosteroid therapy. However, it is uncertain whether the treatment for IgG4-RKD is equally effective for membranous nephropathy (MN), which occasionally coincides with IgG4-RKD. We present a refractory case of IgG4-RKD accompanied with MN, which warrants the combination therapy of prednisone (PSL) and cyclosporine (CyA).

**Methods:** A 58-year-old male was referred to our hospital for recently diagnosed nephrotic syndrome. He had a history of autoimmune pancreatitis (AIP), and was maintained on PSL 10 mg/day. Laboratory results revealed serum albumin 2.2 g/dl, creatinine 0.80 mg/dl, IgG4 473 mg/dl, and urinary protein 13.6 g/gCr. Anti-PLA2R antibody was undetectable. Renal biopsy revealed tubulointerstitial lymphoplasmacytic inflammation and storiform fibrosis with increased ratio of IgG4/IgG positive plasma cells (44.8%), predominant subepithelial granular deposits of IgG and IgG2 in glomeruli, and electron dense deposits in subepithelial and subendothelial regions along glomerular basement membrane. As other causes of secondary MN were excluded, we diagnosed secondary MN concurrent with IgG4-RKD. Although PSL was increased to 35 mg/day, proteinuria did not resolve. CyA was initiated, and urinary protein started decreasing. While serum IgG4 level increased by tapering PSL, urinary protein remained suppressed. After 1 year of follow-up, urinary protein decreased to 0.34 g/gCr and AIP did not recur under PSL 12.5 mg/day.

**Results:**

**Conclusions:** Renal biopsy findings and negative anti-PLA2R antibody argued for secondary MN concurrent with IgG4-RKD. While PSL was effective for the extrarenal lesion of IgG4-RKD, proteinuria was refractory to PSL and the addition of CyA resulted. Generally, CyA responds well to renal lesions. However, in our case, our interest is in that serum IgG4 level did not correlate with proteinuria, indicating that serum IgG4 level does not reflect the activity of MN. These findings suggest that the underlying etiology of secondary MN concurrent with IgG4-RKD is different from other lesion of IgG4-RKD.

**TH-PO201**

Hepatitis C Virus-Associated Membranous Glomerulonephritis Following Successful Direct-Acting Antiviral Therapy

**Bogdan Obreja,* Roxana A. Jurubita,* Vlad T. Bebicar,* Bogdan M. Sorohan,* Andreea Andronesi,* Genis Ismail. 1 Fundeni Clinical Institute, Bucharest, Romania; 2University of Medicine and Pharmacy “Carol Davila”, Bucharest, Romania, Bucharest, Romania.

**Background:** Cryoglobulinemic membrano-proliferative glomerulonephritis (MPGN) is the most frequent type of renal involvement in HCV infection. The newer direct-acting antiviral (DAA) agents have been associated with sustained virological response (SVR) in over 95% of cases. However, the efficacy of this therapy on extrahepatic manifestations of HCV infection is still unknown. We report two cases of persistent and new-onset mixed cryoglobulinemia (MC) after successful eradication of HCV infection.

**Methods:** New onset MC. A 57-year-old male was admitted for purpuric rash and acute nephritic syndrome. His past medical history included psoriatic arthritis diagnosed 35 years ago and cirrhosis due to HCV infection (genotype 1b) for the past 11 years. Six months ago he received the ritonavir-boosted paritaprevir, ombitasvir and dasabuvir regimen and obtained SVR, but with persistence of NS. He underwent a kidney biopsy which revealed membranous nephropathy with subendothelial and subepithelial dense deposits. As other causes of secondary MN were excluded, we diagnosed secondary MN concurrent with IgG4-RKD. Although PSL was increased to 35 mg/day, proteinuria did not resolve. CyA was initiated, and urinary protein started decreasing. While serum IgG4 level increased by tapering PSL, urinary protein remained suppressed. After 1 year of follow-up, urinary protein decreased to 0.34 g/gCr and AIP did not recur under PSL 12.5 mg/day.

**Results:**

**Conclusions:** Renal biopsy findings and negative anti-PLA2R antibody argued for secondary MN concurrent with IgG4-RKD. While PSL was effective for the extrarenal lesion of IgG4-RKD, proteinuria was refractory to PSL and the addition of CyA resulted. Generally, CyA responds well to renal lesions. However, in our case, our interest is in that serum IgG4 level did not correlate with proteinuria, indicating that serum IgG4 level does not reflect the activity of MN. These findings suggest that the underlying etiology of secondary MN concurrent with IgG4-RKD is different from other lesion of IgG4-RKD.

**Funding:** Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Immunosuppressant Daclatasvir Plus Asunaprevir Treatment Ameliorated Proteinuria TH-PO202

Masao Infection

TH-PO203

Dignostic Dilema of a Vasculitic Rash in a Patient with Hepatitis C Infection

M. Masahiro,1,2 Masahiro

Background: The standard therapy of a chronic HCV infection is IFN monotherapy or IFN combined with ribavirin; however, after the introduction of direct-acting antivirals (DAAs), the standard therapy for patients with HCV genotype 1 has dramatically changed. However, the effects of DAAs on extra-hepatic manifestations such as HCV-related nephropathy (HCV-RN), especially in cases with renal dysfunction, are not well elucidated. We report a case of HCV-RN successfully treated by Daclatasvir and Asunaprevir, which are IFN-free DAAs for HCV.

Methods: A 66-year-old man was diagnosed as having chronic hepatitis C. Blood examination revealed a high copy number of HCV-RNA (genotype 1b). He presented with microscopic hematuria and proteinuria at the age of 56. After 7 years from the onset of urinary abnormalities, levels of urinary protein increased up to 5 g/gCr, and kidney biopsy was performed. Pathological findings of kidney biopsy specimens revealed mesangioproliferative glomerulonephritis with IgA deposition, and he was diagnosed as HCV. He developed severe nephrotic syndrome with pleural effusion due to the hypoalbuminemia, therefore, we initiated treatment with oral corticosteroid (PSL). However, liver dysfunction was exacerbated and a copy number of HCV-RNA increased after treatment with PSL. Then, we changed medication from PSL to antiviral treatment with Daclatasvir/Asunaprevir. Clearance of HCV-RNA was obtained by 4 weeks and sustained, and microhematuria turned negative, proteinuria decreased (1.5 g/gCr) by 24 weeks. After 2 years from treatment with Daclatasvir/Asunaprevir, level of proteinuria was 0.8 g/gCr.

Results: Conclusions: Patients with HCV infection have a higher risk of end-stage renal disease. This case offers original evidence for the application of newer generation of IFN-free DAAs in the treatment of HCV-RN.

Funding: Clinical Revenue Support

TH-PO204

HCV-Associated Glomerulopathy and Cryoglobulinemia Despite Sustained Remission of Hepatitis C Viremia after Treatment with Oral Direct-Acting Antiviral Agents

Rabia Akhtar,1 Cory Handelsman,2 John A. Walker,2 Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ; Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ.

Background: Millions of people are infected with chronic hepatitis C worldwide. Acute hepatitis is infrequent, hepatitis C virus infection may be associated with a multitude of extrahepatic complications. These include lymphoproliferative disorders (including essential mixed cryoglobulinemia, monoclonal gammapathies and lymphoma), dermatologic conditions such as lichen planus and porphyria cutanea tarda, and glomerular disease.

Methods: We present a case of a 47-year old woman who developed worsening azotemia, nephrotic-range proteinuria, hypocomplementemia, and mixed cryoglobulinemia nearly one year after demonstrating a sustained remission of hepatitis C (HCV genotype 1a) following treatment with the oral direct-acting antiviral agent Harvoni (ledipasvir/sofosbuvir). Kidney biopsy revealed extensive duplication of the glomerular basement membrane on light microscopy, predominant mesangial and capillary wall IgA deposits on immunofluorescence, and extensive dense subendothelial deposits on electron microscopy, consistent with a histologic diagnosis of a hepatitis C virus associated membranoproliferative glomerulonephritis with immune complex deposition. Hepatitis C RNA PCR was negative at the time of the biopsy.

Results: Conclusions: This case is noteworthy in that our patient developed a hepatitis C virus associated membranoproliferative glomerulonephritis with immune complex deposition in the setting of mixed cryoglobulinemia despite achieving a sustained remission of hepatitis C viremia 1 year earlier. Another intriguing and unusual feature of our case is that in membranoproliferative glomerulonephritis, immune complex depositions typically consist of IgG and C3, whereas in our patient the predominant immunoglobulin present was IgA. This case suggests that the immunostimulatory effects of hepatitis C infection may persist or recur despite a successful course of antiviral therapy, and these effects may be responsible for post-treatment glomerular injury.

Funding: TH-PO205

Response to Intravenous Immunoglobulin in Acute Parvovirus B19-Associated Nephrotic Syndrome from Collapsing Focal Segmental Glomerulosclerosis

Nupur N. Upadhyaya, N. Shah, Hofstra Northwell School of Medicine, Great Neck, NY.

Background: Human parvovirus B19 (HPV B19) has been associated with collapsing focal segmental glomerulosclerosis (c-FSGS). However, the optimal therapy for HPV B19-associated c-FSGS is currently unknown. While intravenous immunoglobulin (IVIG) therapy has been used for treatment of c-FSGS in immunocompromised patients, its role in immunocompetent patients remains unclear. We report the response to IVIG treatment in 2 immunocompetent patients with HPV B19-associated c-FSGS.

Methods: Case 1: 37-year-old African American (AA) female with sickle cell disease was hospitalized and treated for transient aplastic crisis secondary to acute HPV B19 infection. Five days later, patient presented with worsening lower extremity (LE) edema. She was found to have massive proteinuria (spot urine TP/CR 56). A biopsy of the right kidney revealed c-FSGS with a normal glomerular filtration rate (GFR). IVIG (2 g/kg) was administered, and patient showed a dramatic decrease in proteinuria. Kidney biopsy showed c-FSGS. Patient subsequently received trial of 2 doses of IVIG therapy. Despite IVIG treatment, patient did not respond to IVIG therapy and continues to have significant nephrotic syndrome and progressive renal failure.

Results: Conclusions: Optimal therapy for HPV B19-associated c-FSGS is currently unknown. Response to IVIG treatment in immunocompetent patients with acute HPV B19-associated c-FSGS remains unclear. Our patients continued to have elevated HPV B19 viral load and progressive renal failure despite IVIG treatment. Well-designed studies are needed to understand the mechanisms and treatment of this devastating medical condition.

Funding: TH-PO206

Parvovirus Infection Mimicking Atypical Hemolytic Uremic Syndrome in an Immunocompetent Adult

Gerald Shovlin,1 Mark A. Kleiman,1 Joseph Vadakara,2 Syam Prasad Mallampalli,2 Maria Bremuzov.2 Geisinger Health System, Danville, PA; Geisinger Medical Center, Danville, PA.

Background: Human parvovirus B19 (PB19) has been associated with thrombotic microangiopathies (TMA) including hemolytic uremic syndrome (HUS) both in immunocompetent and immunosuppressed individuals. To our knowledge, specific pathophysiologic mechanisms for this association is unclear. We present a case of acute

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

Underline represents presenting author.
PB19 infection presenting as atypical HUS and discuss potential pitfalls in the diagnosis and management of this entity.

Methods: A 20-year-old female presents with anaric AKI, thrombocytopenia, and MAHA (low haptoglobin, presence of schistocytes and high LD 1500). Autoimmune diseases including lupus, antiphospholipid syndrome and cryoglobulinemia were ruled out. Her monospot test, hepatitis panel, and HIV were negative. C3 complement level was low at 78. Bone marrow biopsy showed reactive neutrophilia and occasional RBC fragments. ADAMS13 and alternate complement studies were sent and patient was started on dialysis and plasmapheresis (PLEX) for presumed diagnosis of HUS. Reticulocyte count was inappropriate for normal in which PB19 PCR was checked and found to be > 600,000 copies. ADAMS13 came back normal so the patient was started on Eculizumab (990 mg weekly for 4 doses, then 1200 mg every two weeks) for possible atypical HUS. Alternate complement pathway (TMA functional panel) returned normal, without identifiable mutations disposing the patient to aHUS. She completely recovered, came off dialysis, and Eculizumab was discontinued.

Results: Conclusions: Our patient presented with features of atypical HUS in the setting of acute PB19 infection. Her ADAMS13 and alternate complement pathway were normal making the exact pathophysiological mechanism underlying this association unclear. Prompt search for PB19 as a potential trigger of her clinical picture and rapid initiation of PLEX appeared to favor her rapid improvement. Potential role of Eculizumab remains unclear but likely prudent until alternate pathway studies are available. Further studies to better understand this association and approach to therapy are mandated.

TH-PO207 Cytomegalovirus-Associated Collapsing Glomerulopathy and Tubulointerstitial Nephritis in an African American Patient with T-Cell Lymphoma Edgar Hernandez-Montalvo1, Sixto G. Giusti,2 Agnes B. Fogo,3 Païsit Paueksakon,4 Juan Carlos Q. Velez,5 1Department of Pathology, Vanderbilt University Medical Center, Nashville, TN; 2Department of Nephrology, Ochsner Clinic Foundation, New Orleans, LA.

Background: Collapsing glomerulopathy (CG) may occur in association with human immunodeficiency virus (HIV) and parvovirus B19 (PBV19) infections. However, published reports of CG associated with cytomegalovirus (CMV) infection are sparse.

Methods: We describe a case of a 69 year-old African American woman with T-cell lymphoma who presented with 1-week history of fever, anorexia and delirium. She was admitted for worsening kidney function. Her kidney function deteriorated and hemodialysis was initiated on hospital day 10. A laboratory testing revealed normal C3 and C4 levels, positive tubular CMV immunostaining. Glomeruli (2 out of 3) showed collapse of the glomerular tuft, overlying visceral epithelial cell hyperplasia and diffuse foot process effacement without immune complexes, characteristic of CG. Despite treatment with valgancyclovir, the patient progressed to require permanent hemodialysis.

Results: Laboratory testing showed normal C3 and C4 levels. Immunofluorescence staining revealed positive tubular CMV immunostaining. Glomeruli (2 out of 3) showed collapse of the glomerular tuft, overlying visceral epithelial cell hyperplasia and diffuse foot process effacement without immune complexes, characteristic of CG. Despite treatment with valgancyclovir, the patient progressed to require permanent hemodialysis.

Conclusions: The diagnosis of CMV-associated CG should be considered in HIV-infected patients with significant renal insufficiency. Prompt diagnosis and treatment with antiviral agents may improve renal outcomes in this patient population.

TH-PO209 Crescentic C3 Glomerulonephritis in HIV Disease Muhammad Y. Jan,1 Kwaltan R. Modi,1 Phillips, Tarek M. El-Aitchkar,2 Michael E. Tadon.1 Indiana University School of Medicine, Indianapolis, IN.

Background: Crescentic C3 glomerulonephritis (C3GN), a subtype of C3 glomerulopathy, presents a diagnostic and therapeutic challenge, especially in the setting of HIV infection.

Methods: A 24-year-old African-American male with no past medical history presented with leg swelling, upper respiratory tract symptoms and hematuria of 2 weeks duration. Physical exam showed signs of volume overload and uncontrolled hypertension. Lab showed serum creatinine of 3.01 mg/dl and urine with dysmorphic RBCs and spot proteinuria of 2.4 g/l. He was found to be HIV+ with viral load of 64,000 copies and CD4 count of 355 cells/μl. C3 and C4 levels were within normal limits. Clinical course showed worsening kidney injury and proteinuria. Anti-GBM IgG, ANA, ASO titer, hepatitis B and C, ANCA titers, cryoglobulins were all negative. A kidney biopsy revealed crescentic glomerulonephritis with diffuse mesangial and capillary hypercellularity with patchy foot process effacement. Crescent formation was more predominant than the endocapillary component of C3GN. Immunofluorescence revealed + C3 and +1 IgG. Workup for other infections was negative. Alternate complement pathway analysis showed borderline low level of Factor H, normal C3 nephritic factor and low levels of Factor B and C confirming the diagnosis of C3GN. He was initiated on HIV treatment, pulse steroids, and Cellecept®. This led to stabilization and subsequent improvement of renal function.

Results: Conclusions: Diagnosis of glomerulonephritis with predominant C3 deposits with atypical features of C3GN and HIV immune complex disease (HIVICK). The overlap between these entities and the relevance to disease pathogenesis and management is still unclear. Correlation between isolated strong C3 staining on biopsy and normal C3 complement levels may be more suggestive of C3 glomerulopathy. Testing for abnormalities in the complement pathway is crucial to establish a firm diagnosis. The low levels of Factors B and C in this case suggest inhibited C3 activation, which could be related to HIV disease itself. We report a case of crescentic C3GN with altered factors B and C in a patient with HIV disease. Further investigation is required to determine whether HIV may dysregulate complement and precipitate C3 glomerulopathy.

TH-PO210 Congestive Glomerulopathy: An Uncommon Primary Finding in Nephritic Syndrome Michael D. Donnan,1 Bashpal S. Kanwar,2 Daniel Battle,3 Shubhda K. Ahya.1 1Nephrology, Northwestern University Feinberg School of Medicine, Chicago, IL; 2Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL.

Background: Congestion of the intra-glomerular feeding arteries is a pathologic feature uncommonly reported as a primary finding on renal biopsy. Here we present a case of significant congestion of the intra-glomerular arteries in a man with nephritic syndrome and oliguric renal failure.

Methods: A 42 yo man presented with 2 weeks of weight gain and dyspnea. His symptoms were preceded by arthralgias for which he was taking regular ibuprofen. Exam demonstrated anasarca. Labs showed a rising serum creatinine from 0.9 to 6.4mg/dl. Serum albumin was 1.9g/dl, urinalysis with blood and protein, and 24 hour urine protein collection was 2.8g. Renal biopsy was performed and 3 published cases of CMV-associated CG in the literature, are individuals of African descent. Therefore, we speculate that an interaction between CMV and apolipoprotein L1 risk alleles could trigger cases of CMV-associated CG.

Results: Conclusions: Recent evidences indicate that treatment direct against underlying nematode disorder improves survival in MG-associated C3GN. As we described in our case, ASCIT may potentially be an emerging treatment option for patients with MG-associated C3GN, especially in those with poor response to classical chemotherapy.
motefili. One month after presentation, serum creatinine returned to baseline with <1g proteinuria.

Results:  
Conclusions: Marked intra-glomerular congestion is an atypical pathologic finding whose mechanism and significance is not yet known. It has been reported concurrently with visible micro-occlusions, as in the setting of thrombotic microangiopathy or sickle cell crisis. It rarely has been reported with renal vascular flow limitations, such as states of shock and renal vein thrombosis. In the setting of nephrotic syndrome one may postulate smaller venous thrombembolisms may have been present. While not previously reported, we surmise the possibility that the use of NSAIDs may have contributed to these findings.

Methods: Patient data for three lupus nephritis patients who were treated with rituximab was obtained from retrospective chart review. Student t-test was used for comparison of means. Demographic serological, clinical characteristics and indications for rituximab therapy are presented in Table 1. There was a non-statistically significant improvement between pre-rituximab serum creatinine (sCr) (1.26 ± 0.18 mg/dl) and post-rituximab sCr (1.00 ± 0.3 mg/dl, p=0.153) and pre and post rituximab degree of proteinuria (1664 ± 1278 vs 739 ± 595 mg/g, p=0.18). There was a statistically significant improvement in pre and post rituximab serum complement C3 (66 ± 45 vs 94 ± 42 mg/dl, p<0.003) and serum complement C4 levels (10.7 ± 5.5 vs 22.3 ± 11.2 mg/dl, p=0.04). The average time to treatment response, defined as 50% reduction in proteinuria, and serological increase in complement levels, was 7 months. There were no adverse events reported. There was a clinically significant reduction in immunosuppression and medication side effects as well as tolerance to Table 1.  

Results:  
Conclusions: In conclusion, rituximab as a “rescue” therapy was efficacious and well tolerated in our patients. More research is required to ascertain the clinical and serological characteristics of patients with lupus nephritis who may benefit from rituximab therapy.

Table 1: Demographic, Serological and Clinical characteristics

<table>
<thead>
<tr>
<th>Case</th>
<th>Demographics</th>
<th>Lupus Nephritis Class</th>
<th>Proteinuria</th>
<th>Renin</th>
<th>Treatment</th>
<th>Time to Response</th>
<th>Serology Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27, White, Male</td>
<td>4 Pitocinone 100 mg Nephrotic syndrome</td>
<td>3.2 g/g</td>
<td>Normal</td>
<td>1:80</td>
<td>8</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>54, Black, Male</td>
<td>4 Pitocinone 100 mg Nephrotic syndrome</td>
<td>3.2 g/g</td>
<td>Normal</td>
<td>1:80</td>
<td>10</td>
<td>Normal</td>
</tr>
<tr>
<td>3</td>
<td>25, Black, Male</td>
<td>4+ Pitocinone 100 mg Nephrotic syndrome</td>
<td>3.2 g/g</td>
<td>Normal</td>
<td>1:80</td>
<td>4</td>
<td>Normal</td>
</tr>
</tbody>
</table>

*Intolerance secondary to multiple infections (empyema, pyelonephritis)

**All patients were given rituximab 1 gram IV x 2 doses

TH-PO211
Polycythemia Vera: An Unusual Cause of Proteinuria
Christin M. Giordano,1 Marika Manolopoulou,1 Ed Gould,1 Mark Rusco.2
1Vanderbilt University Medical Center, Nashville, TN; 2Vanderbilt University School of Medicine, Nashville, TN; Medicine, Vanderbilt University Medical Center, Nashville, TN.

Background: Polycythemia vera (PV) is a myeloproliferative disease which is typified by increased red cell mass, rarely it has been associated with renal manifestations, including nephrotic syndrome. Here, we present a case of PV associated with glomerular basement membrane thickening and consequent proteinuria.

Methods: Case Description: Patient is a 46 year-old male with a history of mild hypertension on lisinopril monotherapy who presented to nephrology clinic after hypertension on lisinopril monotherapy who presented to nephrology clinic after episodes of gross hematuria for 2 months followed by persistent asymptomatic microhematuria and proteinuria of 2g/day. In the initial workup she was found to have proteinuria up to 2 grams/day and further autoimmune workup revealed positive anti-myeloperoxidase of 115. She did not have any history of diabetes or hypertension, no edema, serum creatinine of 0.8 mg/dl, urinary 1+ protein microhematuria, no RBC cast, urine total protein/creatinine ratio 2.0 gm, serum albumin 3.9 mg/dl, p=0.18). There was a statistically significant improvement between pre-rituximab serum complement C3 (66 ± 45 vs 94 ± 42 mg/dl, p<0.003) and serum complement C4 levels (10.7 ± 5.5 vs 22.3 ± 11.2 mg/dl, p=0.04). The average time to treatment response, defined as 50% reduction in proteinuria, and serological increase in complement levels, was 7 months. There were no adverse events reported. There was a clinically significant reduction in immunosuppression and medication side effects as well as tolerance to Table 1.

Results:  
Conclusions: In conclusion, rituximab as a “rescue” therapy was efficacious and well tolerated in our patients. More research is required to ascertain the clinical and serological characteristics of patients with lupus nephritis who may benefit from rituximab therapy.

Table 1: Demographic, Serological and Clinical characteristics

<table>
<thead>
<tr>
<th>Case</th>
<th>Demographics</th>
<th>Lupus Nephritis Class</th>
<th>Proteinuria</th>
<th>Renin</th>
<th>Treatment</th>
<th>Time to Response</th>
<th>Serology Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27, White, Female</td>
<td>4 Pitocinone 100 mg Nephrotic syndrome</td>
<td>3.2 g/g</td>
<td>Normal</td>
<td>1:80</td>
<td>8</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>54, Black, Male</td>
<td>4 Pitocinone 100 mg Nephrotic syndrome</td>
<td>3.2 g/g</td>
<td>Normal</td>
<td>1:80</td>
<td>10</td>
<td>Normal</td>
</tr>
<tr>
<td>3</td>
<td>25, Black, Male</td>
<td>4+ Pitocinone 100 mg Nephrotic syndrome</td>
<td>3.2 g/g</td>
<td>Normal</td>
<td>1:80</td>
<td>4</td>
<td>Normal</td>
</tr>
</tbody>
</table>

*Intolerance secondary to multiple infections (empyema, pyelonephritis)

**All patients were given rituximab 1 gram IV x 2 doses

TH-PO213
Unusual Case of Lupus Nephritis with Negative Serology
Eddy J. De Jesus, Bindu Goel, Rabih Nasr. Bronx Lebanon Hospital, Bronx, NY.

Background: Lupus Nephritis (LN) is a common complication of Systemic Lupus Erythematosus (SLE) and occurs in 43-55% of the cases, usually in first year of the disease. It is one of the highest predictors of morbidity and mortality, and thus requires prompt diagnosis and treatment

Methods: We report a case of a 25 year old Hispanic female presenting to the nephrology clinic referred due to episodes of gross hematuria for 2 months followed by persistent asymptomatic microhematuria and proteinuria of 2g/day. In the initial workup she was found to have proteinuria up to 2 grams/day and further autoimmune workup revealed positive anti-myeloperoxidase of 115. She did not have any history of diabetes or hypertension, no edema, serum creatinine of 0.8 mg/dl, urinary 1+ protein microhematuria, no RBC cast, urine total protein/creatinine ratio 2.0 gm, serum albumin 3.6 g/dl, p=0.04). There was a statistically significant improvement between pre-rituximab serum complement C3 (66 ± 45 vs 94 ± 42 mg/dl, p<0.003) and serum complement C4 levels (10.7 ± 5.5 vs 22.3 ± 11.2 mg/dl, p=0.04). The average time to treatment response, defined as 50% reduction in proteinuria, and serological increase in complement levels, was 7 months. There were no adverse events reported. There was a clinically significant reduction in immunosuppression and medication side effects as well as tolerance to Table 1.

Results:  
Conclusions: In conclusion, rituximab as a “rescue” therapy was efficacious and well tolerated in our patients. More research is required to ascertain the clinical and serological characteristics of patients with lupus nephritis who may benefit from rituximab therapy.

Table 1: Demographic, Serological and Clinical characteristics

<table>
<thead>
<tr>
<th>Case</th>
<th>Demographics</th>
<th>Lupus Nephritis Class</th>
<th>Proteinuria</th>
<th>Renin</th>
<th>Treatment</th>
<th>Time to Response</th>
<th>Serology Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27, White, Female</td>
<td>4 Pitocinone 100 mg Nephrotic syndrome</td>
<td>3.2 g/g</td>
<td>Normal</td>
<td>1:80</td>
<td>8</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>54, Black, Male</td>
<td>4 Pitocinone 100 mg Nephrotic syndrome</td>
<td>3.2 g/g</td>
<td>Normal</td>
<td>1:80</td>
<td>10</td>
<td>Normal</td>
</tr>
<tr>
<td>3</td>
<td>25, Black, Male</td>
<td>4+ Pitocinone 100 mg Nephrotic syndrome</td>
<td>3.2 g/g</td>
<td>Normal</td>
<td>1:80</td>
<td>4</td>
<td>Normal</td>
</tr>
</tbody>
</table>

*Intolerance secondary to multiple infections (empyema, pyelonephritis)

**All patients were given rituximab 1 gram IV x 2 doses

TH-PO212
Rituximab as Rescue Therapy for Difficult to Treat Lupus Nephritis: A Case Series
Jaime A. Baynes-Fields,1 Al J. Loc,2 Navneet Kaur,2 Sandeep Aggarwal.31 Drexel University, Philadelphia, PA; 2Drexel University College of Medicine, Philadelphia, PA; 3None, Philadelphia, PA.

Background: Conventional treatment of lupus nephritis with antimitobolites, calcineurin inhibitors, and steroids may be associated with intolerable adverse events or treatment resistance. We present a case series of patient characteristics and treatment response to rituximab therapy in three patients with resistance or intolerance to conventional lupus nephritis therapy at our center.

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

Underline represents presenting author.
TH-PO214

Podocyte Contact with the Mesangial Cells at the Mesangial Interposition in a Case of Human Lupus Nephritis: Three-Dimensional Observation by Serial Block-Face Scanning Electron Microscopy Takashi Takaki, Nobuhiko Ohno, Sei Saitho, Masaki Nagai, Kenseki Toh. Showa University, Tokyo, Japan; Jichi Medical University, Shimotsuke-shi, Japan; National Institute for Physiological Sciences, Okazaki, Japan; Narita Memorial Hospital, Toyohashi-shi, Japan; Tohoku University Graduate School of Medicine, Sendai-city, Japan.

Background: We employed serial block-face scanning electron microscopy (SBF-SEM) to examine the three-dimensional relationships among the cells and extracellular matrix in a case of human lupus nephritis.

Methods: A 25-year-old female, who presented nephrotic syndrome, microscopic hematuria 10-20/high, and hypocomplementemia with C3 47 mg/dl and C4 4 mg/dl. Anti-nuclear antigen titer and anti ds-DNA titer were x640 and 191 mg/dl, respectively. Renal biopsy revealed membranoproliferative glomerulonephritis like lesion of lupus nephritis, Class IV A/C in light microscopy. The detail of ultrastructural morphology was almost similar to that of TEM excepting a thicker staining on the nuclear membrane and thinner staining of immune deposits. Using SBF-SEM, we followed the localization of the cytoplasmic processes of the podocyte, which invaded into the lamina densa of the glomerular basement membrane (GBM) and penetrated finally into the mesangial matrix. On the other hand, mesangial interposition was seen of varying length beneath the lamina densa of the GBM along the glomerular capillary loop. The mesangial cells, which were recognized in the extended mesangial matrix as having dense patch on the cytoplasmic membrane, showed a proliferative change. We followed the cytoplasmic process of the podocyte penetrating into the mesangial matrix and have succeeded toward a manifestation of direct cytoplastic impact of the podocytes with the cytoplasm of the mesangial cells (Figure).

Results: Since a direct contact between podocytes and mesangial cells was found, it is easier to understand an effect of podocytes on the mesangial cells by assuming an intercellular signaling communication, which may result in a proliferation of the mesangial cells and an overproduction of the extracellular matrix. This finding provides a new insight on a mechanism of a progression of glomerular sclerosis via podocyte-mesangial interaction.

Funding: Government Support - Non-U.S.

TH-PO215

Primary Tubulointerstitial Lupus Nephritis Complicated by Diffuse Alveolar Hemorrhage Farhan Oseerd, George P. Bayliss, Sairah Shariq, Albert Medical School, Brown University, Providence, RI; Rhode Island Hospital, Providence, RI.

Background: Lupus nephritis (LN) most often affects the glomerulus. While tubulointerstitial nephritis (TIN) commonly accompanies glomerular lesions, predominant and isolated TIN is extremely rare. Here we describe the case of a woman with systemic lupus erythematosus (SLE) who presented with respiratory failure and acute kidney injury due to isolated TIN.

Methods: A 39 year old Caucasian woman with history of SLE for 7 years without renal involvement was admitted with complaints of abdominal pain, vomiting, diarrhea, fevers up to 103 F for 3 days. She took ibuprofen for symptoms. Physical examination revealed blood pressure 110/57, heart rate 116, temperature 98.6 F. She had right sided basilar crackles and no edema. Lab data showed white blood cell 1.0/µl, platelet 200 x10^9/L, hemoglobin 10.2gm/dl, blood urea nitrogen 58mg/dl, creatinine 3.7mg/dl, elevated titers of anti-ANA (1:10240) and anti-double stranded-DNA antibodies (2560), low C3 and C4. Urine sediment showed granular casts, no dysmorphic red blood cells. She was treated with penicillin for strepococcal bacteremia and received empiric high-dose corticosteroids after undergoing a renal biopsy. On hospital day 4 she developed respiratory distress and hypoxia, requiring intubation and ICU transfer. Diffuse alveolar hemorrhage was suspected on the basis of hemoptysis, and she was started on cyclophosphamide. Creatinine rose to 5.8mg/dl; she required hemodialysis for worsening metabolic acidosis, oliguria. Renal biopsy showed normal glomeruli, patchy interstitial inflammation on light microscopy; tubular basement membranes stained positive for IgG, IgM, C3, kappa and lambda on immunofluorescence. After 4 dialysis sessions, renal function improved to baseline and dialysis was stopped. She was extubated and eventually discharged on prednisone with stable renal function.

Results:

Conclusions: TIN along with glomerular lesions has been reported in SLE in up to 64% of biopsy samples, but isolated TIN LN without glomerular lesions is a rare entity. The pathogenesis may be due to circulating immune complexes or cytotoxic T-cell mediated injury. Patients usually present with subnephrotic-range proteinuria, renal tubular acidosis and hypocomplementemia. Most patients have been treated with corticosteroids with reasonable patterns of renal, mesangial, and TIN improvement. To our knowledge this is the first reported case of SLE-TIN with diffuse alveolar hemorrhage.

Funding: Clinical Revenue Support

TH-PO216

Novel PLG Mutation with Heterozygous CHFR1-R3 Deletion in a Patient with Atypical Hemolytic Uremic Syndrome and Lupus Nephritis Huzair Ali, Taseen A. Syed, Joe Ghata, Pubnesh Abbas, OUHSC, Oklahoma City, OK; University of Oklahoma, Oklahoma City, OK; University of Oklahoma Health Science Center, Oklahoma City, OK; University of Oklahoma College of Medicine, Oklahoma City, OK.

Background: Thrombotic Microangiopathy (TMA) is a disease characterized by intravascular thrombosis, hemolytic anemia, and endothelial cell damage, often contributing to renal failure. Atypical Hemolytic Uremic Syndrome (aHUS) is a complement mediated TMA. Most genetic abnormalities linked to aHUS relate to dysregulation of these complement and coagulation pathways. We describe a case of aHUS with lupus nephritis in a patient with a unique set of mutations, including the plasminogen (PLG) gene, recently linked to aHUS.

Methods: A 39 year male presented with facial swelling, rash and fever for three days. On evaluation, he was in hypertensive emergency (>200/100mmHg), hypopigmented facial lesions with vitiligo on right ear. Labs demonstrated acute renal failure (Creatinine C 7.8mg/dl) requiring emergent hemodialysis. Work up revealed pancarditis, ANA titer 1:320, positive schistocytes, low C3/C4 levels, normal ADAMTS13 activity, and negative infectious work up. Kidney biopsy showed diffuse proliferative glomerulonephritis consistent with Lupus nephritis (Class IV-A). Moreover, TMA affected the afferent arterioles. Renal Failure was refractory to PLEX, Steroids, Cellcept, and Rituximab. Renal Failure and hemolytic anemia only improved after Eculizumab, with Cr nadir to 2mg/dL upon discharge. Genetics later showed: (1) Heterozygous missense mutation of exon 2 & 10 of PLG gene, (2) Two polymorphisms in CHF gene, (3) Heterozygous polymorphism within an intron in MCP/C4D4 (4) Heterozygous for the large CHFR1-CHFR3 deletion.

Results: Mutations in the complement pathway have been described with atypical HUS. Coagulation pathway mutations are being linked with the pathogenesis of aHUS. Our patient developed renal TMA through complement dysregulation (via both classical & alternative pathways) likely through a double hit from Lupus nephritis flare, as well as underlying heterozygous genetic mutations (CHFR, CFH, & MCP/C4D4 genes). In addition, dysregulation of the coagulation pathway through his PLG gene mutation likely contributed to his persistent renal TMA. This case suggests heterozygotes for these mutations may benefit from Eculizumab, especially in refractory cases of aHUS.

TH-PO217

A Unique Case of Sjogren’s Syndrome-Associated Cryoglobulinemic Glomerulonephritis Brad Long, Ryan Morton, Catreena Marie, Monique E. Cho, Al-Kabir B., University of Utah Hospital, Salt lake, UT.

Background: Cryoglobulinemic glomerulonephritis is rare and not well described in the absence of Hepatitis C virus. Sjogren’s syndrome continues to be the second most common cause of mixed cryoglobulinemia after hepatitis C virus (HCV). We present a unique case of Sjogren’s disease and cryoglobulinemic glomerulonephritis requiring Eculizumab.

Methods: Patient is a 65 year old man with patient medical history relevant for Sjogren’s disease and hepatitis C, in remission after treatment with interferon 10 years ago, presented to the outside hospital with a 5-day history of fatigue, headache, facial swelling and lower extremity rash. His physical exam was relevant for petechial rash involving his low extremities. Initial investigation revealed well preserved renal function with creatinine of 1 mg/dL. Urine protein was 1346 mg per gram of creatinine. Urine microscopy showed many non-dysmorphic RBCs with no cellular casts. Further workup showed ANA 1:2560, with positive SSA/SSB. The antibodies for GBM, dsDNA, RNP, ASO, Smith Ab, and ANCA were all negative. Complement 3 and 4 levels were 44 mg/dL and undetectable, respectively. HCV PCR was undetectable. Cryoglobulin from outside hospital was negative. Rheumatoid factor was elevated at 411 IU/mL. Immunoabsorption showed a faint band in the IgM kappa region. Light microscopy showed 15 glomeruli, microscopic foot process effacement with mesangial matrix, and electron microscopic findings of subendothelial and mesangial electron dense deposits with no definite structural organization. Repeat Cryoglobulin done at our hospital was positive. Patient was started on prednisone 60 mg and Azathioprine 100 mg daily. He had complete resolution of proteinuria and hematuria in one month.

Results: Elevated rheumatoid factor, and very low complement 4 level were the key for suspecting cryoglobulinemic glomerulonephritis despite the absence of impaired C4. Cryoglobulinemia in this case is likely related to Sjogren’s syndrome, not hepatitis C, given the undetected Hepatitis C PCR. Early treatment is crucial in preserving renal function.
Cryoglobulinemic Glomerulonephritis in a Patient with Sjögren Syndrome

Background: Sjögren's Syndrome (SS) is a disease characterized by lympho-plasmacytic infiltration of exocrine glands. Interstitial nephritis is the most common form of renal involvement in SS. Glomerular involvement including Membranoproliferative glomerulonephritis (MPGN) is relatively rare.

Methods: Case Description: A 73 yr old Caucasian female with past medical history of uncontrolled hypertension and SS presented with fluid overload. Physical examination revealed pulmonary crackles and peripheral edema. Laboratory analysis was significant for a creatinine of 1.3 mg/dL, an urine protein to creatinine ratio of 2.5 g/g. Urine microscopy revealed dysmorphic red blood cells. Serologies for hepatitis B, C, HIV, cryoglobulins and ANA were negative. Serum complement levels were low. Pathology: Light microscopy revealed 14 glomeruli with the following findings: global sclerosis (1), segmental sclerosis (4), endocapillary proliferation (9), and intracapillary collapse of capillaries (2). Mild tubular atrophy / interstitial fibrosis / inflammation, mild arteriosclerosis and arteriolar onlookin pattern were also present. By immunofluorescence microscopy 12 glomeruli showed granular mesangial and capillary loop staining with IgG/Kappa/Lambda (++)+, IgA and IgM (++), and C1q (+). Electron microscopic findings in 2 glomeruli included thickened glomerular basement membrane, mesangial interposition, subendothelial, subepithelial, and mesangial deposits of cryoglobulins. Cryoglobulinemic GN (secondary MPGN) in the background of SS was diagnosed.

Results: Conclusions: In our patient, glomerular involvement by MPGN, an uncommon pathologic manifestation of SS, was complicated by mixed cryoglobulinemia which was not detected in serum but noted on renal biopsy. This reflects the high incidence of false-negativity of cryoglobulin testing due to suboptimal specimen collection and handling. Our case highlights the importance of SS as a non-HCV-related cause of nephropathy concomitant with FSGS. He had a kidney biopsy which showed diffuse alveolar hemorrhage. Further work-up showed a positive C-ANCA titer and elevated proteinase 3 antibodies. Subsequently kidney biopsy was done which was consistent with pauci-immune necrotizing crescentic glomerulonephritis complicating anti-neutrophil cytoplasmic antibodies (ANCA). He responded very well to plasmapheresis, pulse dose steroid and cyclophosphamide.

Conclusions: Both ANCA –positive CGN and mixed myeloma can present with systemic manifestations of renal failure, peripheral neuropathy and skin lesions. An elevated kappa lambda ratio in this context can often perplex the clinical scenario. Careful history and serologic markers often aid in separating one from another. However, a kidney biopsy remains the gold standard in distinguishing amongst variants of RPGN to guide appropriate and effective immunosuppressive therapy.
A Case of Rapid Remission Proteinuria with Ace Inhibitor Monotherapy in HIV Associated Minimal Change Disease

Background: The use of antiretroviral drugs among HIV patients has been associated with a number of renal toxicities including proteinuria. Minimal-change disease (MCD) with nephrotic syndrome in this population has also been described, though the pathophysiology includes a need for prompt and efficient management since this is linked with increased mortality and poor outcomes. However, there is a higher chance for opportunistic infections with HIV. Here we report an atypical case of HIV associated MCD on Atipila (tenofovir/emtricitabine/efavirenz) with rapid remission of proteinuria on monotherapy with angiotensin converting enzyme (ACE) inhibition.

Methods: A 45-years old man with HIV-1/AIDS (diagnosed 2011) initially presented July 2016 to HIV clinic with three-week bilateral lower extremity edema. Screening labs showed creatinine 0.9 mg/dl, albumin 2.2 mg/dl, proteinuria >500 mg/dl and total cholesterol 274 mg/dl. Antiretroviral therapy with Atipila was switched to Triumeq (abacavir/dolutegravir/lamivudine). He returned September 2016 with temporal resolution of his peripheral edema and nephrotic range proteinuria at 13 g/l. He was hospitalized October 2016 with an unremarkable physical exam, and negative autoimmune workup. Pertinent findings included albumin 1.1 mg/dl and creatinine 0.9 mg/dl. Nephrology was consulted for ongoing nephrotic syndrome and renal biopsy showed podocytes with 90% foot process effacement consistent with MCD. The patient was discharged home with Lisinopril 2.5 mg and Lasix 40 mg daily. On November 2016 labs showed significant improvement of his proteinuria to 0.74 g/l. His Lisinopril was increased to 10 mg daily and he continued with Lasix. Recent follow up documented on April 2017 showed a urinalysis with 100 mg/dl.

Results: In closing, it is important to consider optimization of ACE inhibitors or angiotensin II blockers as alternate therapy to corticosteroids among HIV infected patients with MCD. One isolated case of rapid decline of proteinuria exists in a diabetic patient with no literature seen in HIV. This case illustrates the need for additional research into the use of ACE inhibitors with sole ACE inhibition in lieu of corticosteroids in the treatment of MCD and other glomerular diseases associated with nephrotic proteinuria among this group.

Role of DJ-1(PARK7) in Hepcidin-Mediated Protection of the Kidney

Background: DJ-1 (PARK7) is an anti-oxidant protein that is implicated in Ferroptosis (Iron-mediated cell death). DJ-1 is expressed in most tissues with high metabolic rates, but particularly in the kidney and brain. The expression of DJ-1 is increased during hypoxia, an anti-oxidant response (TNFα, IL-6, IL-10) can further renal damage. Previously we have shown that responses to tubular injury with an uncontrolled pro-inflammatory inflammatory signature was also comparable between the two groups. Hamp + LPS 0.85 ± 0.22. In contrast, inhibition of hepatocellular carcinoma (Hepa1-6) and liver metastasis by targeting DJ-1(Lys42) in mice abrogated Hamp's protective effect.

Methods: Hamp pretreated WT mice were protected against LPS-induced AKI as indicated by significantly lower plasma creatinine (WT +BPS ±LPS 95% ± 0.06 vs BPS ±LPS 95% ± 0.11 ± 0.17 VS Hamp +LPS 0.41 ± 0.03; p < 0.0001), NGAL and KIM-1 levels. Hamp +LPS treated animals also had less infiltrating neutrophils and CD11b positive cells compared to BPS ±LPS treated ones. Hamp + LPS treated mice had significantly lower spleenic IL-6, IL-10 and TNFα. In contrast, AMPK activation after AMPK inhibition in HK2 cells increased AMPK activity.

Conclusion: DJ-1 has a protective role in the kidney, but AMPK-mediated DJ-1 activation is required for this protection as AMPK activation after AMPK inhibition in HK2 cells increased AMPK activity.

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

Underline represents presenting author.

161
TH-PO227
PINK1-Parkin Pathway of Mitophagy Is Activated to Protect against Renal Ischemia/Reperfusion Injury Chengyuan Tang, Fuyou Liu, Zheng Dong, Department of Nephrology, The Second Xiangya Hospital of Central South University, Changsha, China; 2Department of Cellular Biology & Anatomy, Medical college of Georgia at Augusta University and Charlie Norwood VA Medical Center, Augusta, GA.

**Background:** Mitochondrial damage contributes to the pathogenesis of acute and chronic kidney diseases. Damaged or dysfunctional mitochondria are toxic to the cell by producing reactive oxygen species and releasing cell death factors. Therefore, timely removal of these organelles is critical to cellular homeostasis and viability. Mitophagy is the mechanism of selective degradation of mitochondria via autophagy. A major mitophagy pathway in mammalian cells is mediated by PINK1 and Parkin. The significance of mitophagy in kidney diseases, including ischemic acute kidney injury (AKI), has yet to be established, and the involved pathway of mitophagy remains poorly understood. In this study, we examined PINK1- and Parkin-mediated mitophagy in the acute kidney injury (AKI) model of renal ischemia-reperfusion.

**Methods:** PINK1 and Parkin single or double knockout mice were compared to their matched wild-type mice for the response to 30 minutes of bilateral renal ischemia followed by 48 hours of reperfusion. Renal function, histopathology, biochemical analysis and electron microscopy analysis were performed to evaluate the effect of PINK1 and Parkin deletion. In vivo, HK-2 cells were subjected to ATP depletion/repletion treatment with CCCP (mitochondrial uncoupler) to examine the effects of PINK1 and Parkin knockdown.

**Results:** Mitophagy was induced in renal proximal tubular cells in both in vitro and in vivo models of ischemic AKI, as evidenced by: (1) increased autophagy flux, (2) decreased expression of mitochondrial membrane proteins TOM20 and TIM23, and (3) increased formation of mitophagosomes. Mitophagy under these conditions was abrogated by PINK1 and Parkin deficiency, supporting a critical role of the PINK1/Parkin pathway in tubular cell mitophagy. Moreover, ischemic AKI was deteriorated in PINK1 and Parkin single as well as double knockout mice, as indicated by aggravated functional or structural renal damage, and enhanced tubular cell death. Mechanistically, PINK1 and Parkin deficiency enhanced mitophagy damaged, ROS production, and inflammatory response.

**Conclusions:** These results indicate that PINK1/Parkin-mediated mitophagy plays an important role in mitochondrial quality control, tubular cell survival, and renal function during AKI.

TH-PO228

**Background:** Class I histone/protein deacetylases (HDAC) 1 and 2 have reciprocal expression in cell types, but their role in renal ischemia-reperfusion injury (IRI) has not been studied.

**Methods:** Wild-type C57Bl6 (WT) and whole animal-inducible HDAC1- or 2- gene knockout (Hdac1-/-; Hdac2-/-) mice are known to have osteoporosis. In this study, we investigated the effect of HDAC2 deletion on renal IRI injury in both WT and HDAC2-/- mice and returned HDAC2-/- mice to a WT renal IRI phenotype.

**Results:** In nuclear extracts, HDAC1 and 2 deficient RTEC have compensatory enhanced protein expression of the other (Fig 1a). HDAC1 pulldown in HDAC2 deficient RTEC demonstrated enhanced association with CoREST and LSD1 compared to wild type RTEC (Fig 1b). HDAC2 pulldowns in HDAC1 deficient RTECs showed no enhanced association with CoREST. In vivo CoREST inhibition increased vulnerability to renal IRI injury in both WT and HDAC2-/- mice and returned HDAC2-/- mice to a WT renal IRI phenotype (Fig 1c).

**Conclusions:** HDAC2 deletion leads to increased association between HDAC1 and other members of the CoREST complex, indicating increased complex stability. Inhibition of the CoREST complex in vivo reverses the protection seen with HDAC2 deletion.

TH-PO229
Lysophosphatidic Acid Regulates FGF23 via LPAR1 in Response to AKI Petra Simic, Wondong Kim, Paola Divieti Pajevic, Andrew M. Tager, Harald Dzau, Marc N. Wein, Eugene P. Rhee, Boston University, School of Dental Medicine, Boston, MA; 2Harvard Medical School, Boston, MA; 3MGH Endocrine Unit, Boston, MA; 4Massachusetts General Hospital, Brookline, MA.

**Background:** Lysophosphatidic acid (LPA) is one of the simplest phospholipids with a range of signaling actions throughout the body. It has been implicated as an important cofactor for calcitriol’s effect on osteoblast differentiation in vitro, and LPA receptor 1 knock-out (Lpar1-/-) mice are known to have osteoporosis.

**Methods:** As FGF23 is a predominantly bone-derived hormone modulated by calcitriol, we have tested the effect of LPA on FGF23 production in vivo in C57Bl6 and Lpar1-/- mice and in vitro in a conditionally immortalized osteocyte cell line (Ocy454 cells).

**Results:** Exogenous LPA (50 mg/kg i.p. single dose) stimulated intact and C-terminal FGF23 production 2.4 fold in C57Bl6 mice as compared to vehicle treated mice (n=8 per group) at 24 hours (P=0.02). This effect was corroborated in Ocy454 cells, with a 10 fold increase in C-terminal and intact FGF23 protein levels 24 hrs following LPA treatment (P=0.03); this effect was specifically dependent on the LPAR1 receptor, as the effect of LPA on FGF23 was abolished in CRISPR generated Lpar1-/- Ocy454 cells but not in Lpar2-/- cells (the other major LPA receptor expressed in osteocytes). Next, we tested in vivo whether the effect of LPA on FGF23 is dependent on LPAR1, injecting Lpar1-/- mice or WT littermates with a single dose of LPA (50 mg/kg i.p.) or vehicle (n=8 per group). LPA increased serum FGF23 levels in WT, but not in Lpar1-/- mice (1215 ± 200 pg/ml vs. 664 ± 98 pg/ml, respectively, P=0.01) after 24 hrs. Finally, we subjected Lpar1-/- mice or WT littermates (n=8 per group) to AKI by performing 35 minutes of bilateral ischemia reperfusion injury (IRI). Circulating levels of FGF23 were 1.5 fold greater in WT mice as compared to Lpar1-/- mice following IRI (P=0.04).

**Conclusions:** In summary, LPA stimulates FGF23 production in vivo and in vitro via the LPAR1 receptor and the effects of AKI on FGF23 are attenuated in LPAR1 deficient mice.

TH-PO230
Proximal Tubular Epithelial Expression of Kim-1 Causes Progressive Kidney Injury in Mice Wenqiao Yin, M. Todd Valerius, Joseph V. Bonventre, Brigham and Women’s Hospital, Boston, MA.

**Background:** Acute kidney injury (AKI) predisposes to the progression of chronic kidney disease (CKD) and the development of end stage renal failure. Previously, we had reported that early and persistent epithelial expression in nephrons of kidney injury molecule-1 (KIM1) causes murine kidney fibrosis, and zebrafish tubule damage through a mechanism involving mTOR. Since prenatal activation also decreases nephron number we tested the hypothesis that postnatal activation of KIM-1 expression specifically in renal proximal tubular epithelial cells would lead to fibrosis independent of any potential effect on kidney development.

**Methods:** We created proximal tubular cell specific Kim-1 transgenic mice by treating the Slc34a1 Cre-ERT2 mouse with tamoxifen to express KIM-1 in proximal tubules in a postnatal context. The resulting KIM-1 Transgens (and non-KIM1

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Acute kidney injury (AKI) is a recognized risk factor for chronic kidney disease (CKD) development. CKD is associated with cardiovascular alterations and the associated mechanisms remain largely unexplored. CKD patients display reduced nitric oxide (NO) levels. The endothelial nitric oxide synthase (eNOS) is regulated by phosphorylation and by its interaction with proteins such as heat shock protein 90α (Hsp90α). We investigated some modifications in the eNOS activation pathway that occur in the kidney during the AKI to CKD transition.

**Methods:** We included 50 male Wistar rats that were divided into sham surgery (n=25) or rats subjected to bilateral renal ischemia-reperfusion (IR) of 45 min (n=25). The renal function of rats was measured at 2, 3, 4 and 5 months post-surgery. Urinary protein excretion was monitored every month. After each experimental period, plasma creatinine, renal blood flow, mean arterial pressure levels and heart and renal weights were determined. The apical part of the heart was snap frozen for western blot analyses.

**Results:** CKD progression in the IR group was characterized by proteinuria that went from 26.5±8 mg at month 1 to 127.6±24 mg at month 5. The renal dysfunction was only manifested after five months of follow-up as shown by a 50% increase in the plasma creatinine levels and a 30% reduction in the renal blood flow. In contrast, heart hypertrophy was observed since the 4th month after IR, as evidenced by a 24% increase in the heart/body weight ratio. Heart dysfunction and fibrosis were determined by a significant increase in brain natriuretic peptide and collagen I levels, respectively (p<0.05). Moreover, an increase in the phosphorylation of eNOS at threonine 495 (inactivating eNOS) was observed. This effect was associated with reduced eNOS/Hsp90α interaction. eNOS phosphorylation at threonines 495 and 497 was negatively regulated by phosphorylation at threonines 895 and 829. Heart function improved in the 4th month after IR when the eNOS phosphorylation decreased.

**Conclusions:** These results suggest fumarate could have preventive as well as protective actions of eNOS in the heart, which may result in reduced NO bioavailability and endothelial dysfunction. PAPIT: IA201107

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

---

Klotho reduces necroptosis by inhibiting oxidative stress involved in renal ischemic-reperfusion injury

**Background:** Klotho is mainly expressed in kidney, but its functional relevance with AKI remains largely unclear. Although necroptosis has been suggested as a hallmark of the pathological progress of renal IRI, it is currently unknown what triggers this death mode during I/R induced AKI and whether the protective actions of Klotho have any relationship to necroptosis.

**Methods:** Male BALB/c mice were grouped as AKI and sham group. AKI model was generated by bilateral renal pedicle clamping. For the therapeutical investigation, recombinant Klotho protein or nec-1 was intraperitoneal applied at 30 min or 0 min of reperfusion respectively. Besides, TCMK-1 cell was used to hypoxygen/reoxygenation and H2O2 insult for pre-determined time. Recombinant Klotho protein or NAC was pre-applied for 1 h. Klotho levels in serum and urine were determined using ELISA. Expression of Klotho, RIP1, RIP3, II-1 β, 3-nitrotyrosine and SOD2 were assessed by Western Blot or TUNEL. TUNEL, TUNEL and immunohistochemistry for Ki-67 and TUNEL were performed. The release of LDH was measured to assess the membrane integrity. Urinary 8-OHdG, renal MDA levels and SOD activity were determined to detect oxidative injury.

**Results:** Klotho levels were decreased in serum and kidney, but increased in urine post-IR, accompanied by enhancement of oxidative stress and necroptosis. In contrast, Klotho administration ameliorated AKI. Klotho application reduced the expression of RIP1 and RIP3, and attenuated the release of LDH induced by H2O2 or H2O2 insult by dose dependent. These functional effects of Klotho on necroptosis can also be duplicated by NAC application. These indicate a critical role of ROS in triggering necroptosis in tubular epithelial cell, which can be partly abolished by Klotho. In support of this, Klotho protected AKI mice from the levels of 8-OHdG, renal MDA and 3-Nitrotyrosine and upregulating SOD2 expression and total SOD activity in AKI mice. Meanwhile, Klotho also abolished the generation of ROS and increased the expression of SOD2 in TCMK-1 cell when exposed to I/R injury.

**Conclusions:** Klotho protects tubular epithelial cell from I/R-induced necroptosis, which may be attributable to its inhibition of oxidative stress.

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

---

Klotho reduces necroptosis by inhibiting oxidative stress involved in renal ischemic-reperfusion injury

**Background:** Klotho is mainly expressed in kidney, but its functional relevance with AKI remains largely unclear. Although necroptosis has been suggested as a hallmark of the pathological progress of renal IRI, it is currently unknown what triggers this death mode during I/R induced AKI and whether the protective actions of Klotho have any relationship to necroptosis.

**Methods:** Male BALB/c mice were grouped as AKI and sham group. AKI model was generated by bilateral renal pedicle clamping. For the therapeutical investigation, recombinant Klotho protein or nec-1 was intraperitoneal applied at 30 min or 0 min of reperfusion respectively. Besides, TCMK-1 cell was used to hypoxygen/reoxygenation and H2O2 insult for pre-determined time. Recombinant Klotho protein or NAC was pre-applied for 1 h. Klotho levels in serum and urine were determined using ELISA. Expression of Klotho, RIP1, RIP3, II-1 β, 3-nitrotyrosine and SOD2 were assessed by Western Blot or TUNEL. TUNEL, TUNEL and immunohistochemistry for Ki-67 and TUNEL were performed. The release of LDH was measured to assess the membrane integrity. Urinary 8-OHdG, renal MDA levels and SOD activity were determined to detect oxidative injury.

**Results:** Klotho levels were decreased in serum and kidney, but increased in urine post-IR, accompanied by enhancement of oxidative stress and necroptosis. In contrast, Klotho administration ameliorated AKI. Klotho application reduced the expression of RIP1 and RIP3, and attenuated the release of LDH induced by H2O2 or H2O2 insult by dose dependent. These functional effects of Klotho on necroptosis can also be duplicated by NAC application. These indicate a critical role of ROS in triggering necroptosis in tubular epithelial cell, which can be partly abolished by Klotho. In support of this, Klotho protected AKI mice from the levels of 8-OHdG, renal MDA and 3-Nitrotyrosine and upregulating SOD2 expression and total SOD activity in AKI mice. Meanwhile, Klotho also abolished the generation of ROS and increased the expression of SOD2 in TCMK-1 cell when exposed to I/R injury.

**Conclusions:** Klotho protects tubular epithelial cell from I/R-induced necroptosis, which may be attributable to its inhibition of oxidative stress.

**Funding:** Government Support - Non-U.S.
Nucleophosmin (NPM) Phosphorylation Mediates Renal Cell Death: A New Therapeutic Target for Ischemic AKI

**Background:** We hypothesize that renal ischemia alters site-specific NPM phosphorylation, converting NPM from an essential protein and synthesis promoter to a killer Bax chaperone that causes renal cell death and AKI.

**Methods:** To detect site-specific phosphorylation and de-phosphorylation events, NPM was subjected to mass spectrometry before and after ischemic stress in both cell and cortical lysates harvested from: (1) normal vs. ATP-depleted primary mouse and primary human proximal tubule epithelial cells (PTEC), (2) sham vs. ischemic mouse kidneys and (3) two pairs of human donor kidneys rejected for transplantation. One of the paired human kidneys was normally perfused, whereas the other was grossly ischemic due to perfusion pump malfunction. Site-specific NPM phosphorylation events were correlated with NPM alterations that mediate its cell death including: nuclear translocation, de-oligomerization, NPM-Bax complex formation, and mitochondrial complex accumulation. To confirm their biologic significance, NPM mutants with site-specific phospho-changes were generated in lentivirus and introduced into PTEC. Peptides that interfere with NPM phosphorylation were tested for their ability to prevent ischemic PTEC death.

**Results:** Mass spectrometry identified 92% of NPM residues that included all known sites, tyrosine and threonine residues of undergoing phosphorylation or de-phosphorylation. Five serine/threonine phosphorylation and de-phosphorylation events differed between NPM harvested from normal vs. ischemic conditions. NPM phosphorylation events were identical in both murine and human NPM harvested from either primary PTEC or intact renal cortex. Only the NPM phospho-mutant that mimicked phosphorylation events detected during renal ischemia caused cytosolic NPM translocation and de-oligomerization, NPM interaction with conformationally active Bax, mitochondrial complex accumulation, and increased PTEC death. In contrast, 2 distinct NPM peptide designs designed to interfere with NPM phosphorylation protected PTECs against ATP-depletion-induced death.

**Conclusions:** Ischemia-induced NPM phosphorylation regulates Bax-induced cell death and contributes to human AKI. This study identifies a new, modifiable cell death pathway and reveals novel therapeutic approach for preventing and treating ischemic AKI.

**Funding:** NIDDK Support

---

TSA Can Induce Autophagy to Protect against Cisplatin-Induced Apoptosis

**Background:** HDAC inhibitors have protective effects against tubular cell injury and death in acute kidney injury (AKI). However, the underlying mechanism remains elusive. Autophagy is known to be an important protective mechanism in AKI. Whether HDAC inhibitors regulate autophagy and protect renal tubular cells from injury via autophagy is currently unknown.

**Methods:** In vitro, rat proximal tubular cells (RPTCs) were treated with cisplatin to induce apoptosis. In vivo, C57BL/6 mice were injected with cisplatin to induce renal I/R. In RPTC, cisplatin induced autophagy in 8 hours, which decreased at 20 hours of treatment as indicated by the analysis of LC3 II accumulation and autophagic vesicle formation. At 20 hours, cisplatin induced significant apoptosis in RPTC as indicated by cell morphology and caspase activation. TSA treatment increased autophagy at both 8 and 20 hours of cisplatin treatment. TSA also attenuated cell apoptosis. Importantly, the protective effect of TSA in RPTC was suppressed by the autophagy inhibitor chloroquine and also by ATG7 knockdown. In mice, cisplatin induced autophagy and AKI. TSA further increased autophagy in kidneys during cisplatin treatment and protected against AKI. The protective effect of TSA was suppressed by chloroquine. Moreover, the protective effect of TSA was diminished in PT-ATG7-KO mice.

**Conclusions:** TSA induced autophagy in renal tubular cells, which accounts for the protective effect of TSA during cisplatin-induced AKI.

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

---

Extracellular Signal-Regulated Kinase 1/2 Regulates Kidney Injury Molecule-1 Following Renal Injury through STAT3 Phosphorylation

**Background:** Kidney injury molecule-1 (KIM-1) is a transmembrane glycoprotein that is highly upregulated during injury and is a renal injury biomarker. Because KIM-1 transcription is highly induced, we explored the role of extracellular signal-regulated kinase 1/2 (ERK1/2) in KIM-1 expression in cells and in different mouse models of acute kidney injury.

**Methods:** Mouse kidney proximal tubule cells (TK) were treated with varying concentrations of hydroxyurea, hydrogen peroxide, and tert-butyl-hydroperoxide with and without treatment with the MEK1/2 inhibitor trametinib (100 nM) or its vehicle (0.1% DMSO). In mice, trametinib was administered 1 hour prior to I/R injury or LPS (10 mg/kg) exposure to TLR4 KO and WT mice and euthanized 18 hours later, respectively. KIM-1 mRNA was measured by RT-qPCR.

**Results:** Trametinib blocked ERK1/2 phosphorylation in all experiments. Toxicant exposure to TK cells for 24 h upregulated KIM-1 mRNA and was blocked by trametinib. At 3 and 24 h post I/R renal cortical KIM-1 mRNA increased 4- and 600-fold, and pretreatment with trametinib resulted in a 50% and 66% decrease, respectively, in induced KIM-1 mRNA. Transcript also decreased KIM-1 protein 24 h post I/R. ERK1/2 phosphorylated the transcription factor STAT3 at sites Y705 and S727, following I/R and was prevented by trametinib. WT mice pretreated with trametinib before LPS had decreased KIM-1 mRNA and protein. In contrast to TLR4 KO mice injected to I/R, TLR4 KO mice injected with LPS did not exhibit increased KIM-1 mRNA or protein, nor was trametinib ERK1/2 12 h after I/R.

**Conclusions:** We have linked ERK1/2 to KIM-1 transcriptional upregulation in the kidney cortex through STAT3 Y705/S727 phosphorylation following renal injury. In I/R and LPS-induced kidney injury KIM-1 mRNA and protein increased and ERK1/2 inhibition attenuated this increase. However, ERK1/2 mediated KIM-1 upregulation was dependent on TLR4 in LPS treated mice but not mice subjected to I/R. These results demonstrate that ERK1/2 is a key initiator of renal KIM-1 expression and that KIM-1 expression is regulated by different ERK1/2 pathways following renal injury.

**Funding:** NIDDK Support, Other NIH Support - S10GS

---

Hypoxia Induces Tubular Apoptosis by Preventing Oxygen-Dependent Prolyl Hydroxylation and Degradation of Stress-Responsive Transcription Factor FOSJ3

**Background:** Renal hypoxia results in metabolic perturbations and cell stress which likely leads to CKD following AKI. Autophagy is an evolutionarily conserved cellular response to stress. Recent finding in our lab has shown that the stress-responsive transcription factor, FOSX3, can activate renal epithelial autophagy.

**Methods:** We used the autophagy reporter line (CREL mouse), which expresses a tandem RFP and EGFP fused with LC3 protein, to study molecular regulation of autophagy during the AKI to CKD transition.

**Results:** At 2-4 weeks following left renal ischemic injury for 35 min and right nephrectomy, we found progressive increases in proximal tubular autophagy in areas of low capillary density and thus hypoxia. Concomitantly, FoxO3 was activated with a 4-fold increase in nuclear expression over controls in the hypoxic tubules. To test whether hypoxia is an upstream activator for FoxO3 leading to autophagy, we exposed primary cultures of proximal tubular cells to 1%O2, and found an increase in FoxO3 protein levels (50% increase at 30 min and 115% increase at 60 min), as well as its prominent nuclear localization. In renal tubular cells isolated from CREL mice, hypoxia or nutrient deprivation (a potent stimulator for autophagy) led to a time-dependent increase in autophagic dots and increased conversion of LC3 to LC3II proteins. How could hypoxia activate FoxO3? We found that FoxO3, like Hif proteins, is prolyl hydroxylated, which leads to its degradation. Immunoprecipitation with FoxO3 antibody followed by immunoblot analyses with pan-prolyl hydroxylase antibody showed that LT and ET hypoxic conditions increased the amount of hypoxic prolyl hydroxylated FoxO3. Treating tubular epithelial cells grown in normal conditions with a prolyl hydroxylase (Phd) inhibitor, dimethylfumaric acid (DMOG), caused a 60% reduction in HO-FoxO3 and a 39% increase in FoxO3 protein abundance. Conversely, treating starved cells with DMKG, a cell permeable analogue of α-ketoglutarate, the Phd substrate, resulted in a 57% decrease in FoxO3 protein abundance.

**Conclusions:** Taken together, our results indicate that FoxO3 can be regulated by the O2- and α-ketoglutarate-dependent Phd enzymes in the kidney. Hypoxia and metabolic perturbations inactivate Phd enzymes to inhibit FoxO3 degradation, thus allowing it to induce tubular autophagy.

**Funding:** NIDDK Support

---

Flow Cytometric Detection of Urinary Renal Tubular Epithelial Cells Directly Reflects Kidney Damage and Predicts Recovery from AKI

**Background:** Acute kidney injury (AKI) is one of the most frequent causes for renal damage and associated with significant increase of morbidity and mortality. Renal tubular epithelial cells (TEC) are arguably the main target cell of AKI. The objective of our study was to establish flow cytometry based detection of different TECs in the urine and assess these cells as a biomarker for AKI.

**Methods:** Urine samples of 28 patients with AKI and 5 healthy controls were collected. Flow cytometry was performed on the BD-FC500 flow cytometer. The FCM analysis was performed using a standard 7-color human TEC panel, including TEC (distal TECs) and EPCAM (distal TECs). The amount of TECs per 100ml urine was correlated to AKIN stadium and subsequent recovery/non-recovery from AKI.

**Results:** Urine samples of 28 patients with AKI and 5 healthy controls were collected. Flow cytometry was performed on the BD-FC500 flow cytometer. The FCM analysis was performed using a standard 7-color human TEC panel, including TEC (distal TECs) and EPCAM (distal TECs). The amount of TECs per 100ml urine was correlated to AKIN stadium and subsequent recovery/non-recovery from AKI.

**Conclusions:** Flow cytometry of urine can be used as a direct method to assess renal damage and recovery from AKI.

**Funding:** NIDDK Support, Other NIH Support - S10GS

---

Poster TH-PO235

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

Underline represents presenting author.
Results: Urinary numbers of TECs were increased upon kidney injury and only slowly increased during recovery. TEC counts correlated with AKIN stage of the patients (p=0.0006, r=0.57 proximal and p<0.0001, r=0.67, for distal TECs, Spearman). TEC numbers were significantly higher in patients with AKI than in healthy donors and enabled to distinguish between different AKIN stadia. Importantly, the amount of distal TECs (Cytokeratine+EPCAM+) upon AKI was able to predict subsequent recovery/non-recovery from AKI. Applying a cut-off of 200,000 cells/100ml urine separated patients with and without recovery (Cytokertine1/EPCAM1, p<0.0068). Conclusions: Urinary cell counts of renal epithelial cells directly reflect the amount of damaged TECs. Our findings suggest proximal and distal TECs as biomarkers to diagnose and estimate the severity of kidney damage and to predict the outcome of patients with AKI. Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO240

Genetic Screening Reveals Potential Therapeutic Targets in Gentamicin-Induced AKI Chinaemere Igwuebuïke,1 Zhiyong Wang,1 Andrea Havasi,2 Michael Y. Sherman,3 Julia Yaglom,4 Yongmei Wang,5 John H. Schwartz,5 Steven C. Borkan.6 1BOSTON MEDICAL CENTER, BOSTON, MA; 2Boston Medical Center, Biomedical Center, Boston, MA; 3Boston Medical Center, Boston, MA; 4Boston University School of Medicine, Boston, MA; 5Boston University Medical Center, Boston, MA; 6Boston University School of Medicine, Boston, MA.

Background: Gentamicin is a highly effective, nephrotoxic antibiotic that accounts for 15% of AKI in the US and has a high mortality rate of 72%. Western blots of cortical samples showed the following effects of IR on class I HDACs compared to sham: HDAC1 was increased 2.5-fold by 48 h, HDAC2 was not affected, HDAC3 initially increased 50% but returned to sham levels by 48 h, and HDAC8 was significantly reduced 48% over the study period. The class II HDAC4 was significantly increased 4-fold over the study period. To determine if the increase in HDAC promoted renal damage and fibrosis, we delivered a class I inhibitor (MS275, 20 mg/kg/day) or a class II inhibitor (trichostatin A, TSA, 1 mg/kg/day) by i.p. osmotic minipump to mice exposed to gentamicin. In the MS275 and TSA mice, creatinine was not increased, indicating that inhibition of HDACs during IR results in a worsening of renal function. Histological analyses revealed reduced fibrosis in the MS275 and TSA mice, however there was an increase in protein casts in these groups. In vitro studies in primary and immortalized proximal tubular (PT) cells determined that class I HDACs may promote fibrosis, while class II HDACs, likely HDAC4, are critical for PT proliferation and repair.

Funding: NIDDK Support

TH-PO241

Endogenous Fructose Production and Fructokinase Activation Mediate Rhabdomyolysis-Induced AKI Yuka Sato, Carlos A. Roncal-jimenez, Ana Andres-hernando, Thomas Jensen, Masanari Kuwabara, Richard J. Johnson, Miguel A. Lanasa. Renal Disease and Hypertension, University of Colorado Denver, Aurora, CO.

Background: Acute kidney injury (AKI) is associated with high mortality. Treatment of AKI is limited to supportive care, and no interventions to improve recovery from AKI have yet been developed. The cause of AKI is diverse including ischemia, nephrotoxic agents and rhabdomyolysis. Endogenous fructose production from glucose by the polyol pathway, and its metabolism by fructokinase (KHK) leads to ATP depletion, oxidative stress and inflammation. We have reported that the metabolism of endogenous fructose is a key deleterious step in the pathogenesis of ischemic AKI, and KHK blockade protected mice from injury. Using genetic screening to identify potential therapeutic targets in rhabdomyolysis-induced AKI, we tested the hypothesis that the endogenous fructose production and metabolism contributed to rhabdomyolysis related AKI.

Methods: To establish the rhabdomyolysis-induce AKI, male wild-type mice (WT) and KHK-deficient mice (KHK-KO) were injected with 50%w/v glyceral or saline (for control) of 6 ml/kg body weight to the two hind limbs intramuscularly. Mice were sacrificed at 24 hours after glyceral injection, and blood, urine, kidney and muscle collected for histological and biochemical analyses.

Results: Serum creatine elevation was significantly suppressed in KHK-KO mice. (WT sham: 0.23mg/dL, KHK-KO sham: 0.10mg/dL, WT glyceral (Gly): 2.03 mg/dL, KHK-KO Gly: 1.47 mg/dL, p<0.01; WT sham vs WT Gly, p<0.01; WT Gly vs KHK-KO Gly). Serum creatine phosphokinase (CPK) levels were similar between WT and KHK-KO mice on saline (WT vs KHK-KO Gly, 270.7 IU/L) suggesting equivalent muscle injury and the protective effect for rhabdomyolysis-induced AKI in KHK-KO was mediated locally at kidney. Consistently, renal endogenous fructose production and metabolism was activated in the kidney of WT Gly compared to WT sham animals. We also identified up-regulation of aldose reductase and KHK.

Conclusions: Endogenous fructose production in kidney by activation of polyol pathway had a deteriorative role for rhabdomyolysis-induced AKI. The blockade of KHK could be the target for preventive and recovery for AKI.

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

TH-PO242

Temporal Changes in Histone Deacetylations after Renal Ischemia/Reperfusion Injury Kelly A. Hyndman, Malgorzata Kasztan. University of Alabama at Birmingham, Birmingham, AL.

Background: Histone deacetylases (HDACs) are epigenetic regulators of transcription through deacetylation of histone lysines. Increased HDAC activity causes uncontroled proliferation, inflammation, and/or fibrosis. Moderate ischemia/reperfusion (IR) of the kidney results in an immediate decline of renal function and injury including fibrosis followed by a stage of repair and improvement of renal function. The aim of this study was to determine if renal HDACs are dysfunctional during injury and repair after IR.

Methods: Male and female 10 week old mice underwent sham or bilateral ischemia for 27 minutes, followed by reperfusion for 1, 24, 48 or 72 h. Results: Abnormal tubular morphology and reduced nuclear number were evident as early as 24 h. Western blots showed by significant reduction by 24-48 h, and reappearance of larger nuclear morphology by 72 h. Western blots of cortical samples showed the following effects of IR on class I HDACs compared to sham: HDAC1 was increased 2.5-fold by 48 h, HDAC2 was not affected, HDAC3 initially increased 50% but returned to sham levels by 48 h, and HDAC8 was significantly reduced 48% over the study period. The class II HDAC4 was significantly increased 4-fold over the study period. To determine if the increase in HDAC promoted renal damage and fibrosis, we delivered a class I inhibitor (MS275, 20 mg/kg/day) or a class II inhibitor (trichostatin A, TSA, 1 mg/kg/day) by i.p. osmotic minipump to mice exposed to gentamicin. In the MS275 and TSA mice, creatinine was not increased, indicating that inhibition of HDACs during IR results in a worsening of renal function. Histological analyses revealed reduced fibrosis in the MS275 and TSA mice, however there was an increase in protein casts in these groups. In vitro studies in primary and immortalized proximal tubular (PT) cells determined that only class II inhibitors led to reduced proliferation. Overexpression of HDAC4, but not HDAC1, resulted in 55% greater PT proliferation.

Conclusions: From this study, we conclude that class I and II HDACs are significantly affected during IR and display different specific expression patterns. Our data suggest that class I HDACs may promote fibrosis, while class II HDACs, likely HDAC4, are critical for PT proliferation and repair.

Funding: NIDDK Support

TH-PO243

Modulation of PPARγ with MTB-2 Post-Reperfusion Attenuates IR-Induced AKI Injury Biomarkers and Histopathology in Rats Christina Bracken, Katelyn Pulito, Effie Tozzo. Mitobridge, Cambridge, MA.

Background: Ischemic acute kidney injury (AKI) is characterized by persistent proximal tubule mitochondrial dysfunction. Due to their highly oxidative metabolism, proximal tubule cells utilize fatty acids to generate the energy required for PT proliferation and repair. We hypothesized that enhancing fatty acid oxidation with a PPARγ modulator will restore mitochondrial function, offering a potential therapeutic treatment for AKI.

Methods: Sprague-Dawley (SD) rats underwent a 45 minute bilateral ischemia-reperfusion (IR) AKI. Following reperfusion rats were treated with 2 IV doses of selective PPARγ modulator MTB-2 at doses varying from 0.3 to 10 mg/kg or vehicle. Plasma and urinary kidney injury biomarkers were measured at 10h, 24h and 48h post reperfusion. Histology assessment of kidney cortex was done 48h post AKI.

Results: MTB-2 treatment resulted in significantly lower plasma creatinine (up to 69% reduction), BUN (up to 60% reduction) and cystatin C (up to 69% reduction) levels at 24 and 48 hours post AKI compared to vehicle animals. Importantly, this translated to an improvement of renal function marked by increased creatinine clearance (up to 80%) and normalization of fractional excretion of Na+ (FENa) (up to 90%) suggesting improved tubular function. Modulation of PPARγ after AKI also led to significantly reduced urinary levels of [TIMP-2*][IGFBP-7], FABP-1 and NGAL. Assessment of kidney histopathology at 48 hours post reperfusion confirmed that MTB-2 reduced tubular injury and normalized renal tubular architecture, resulting in improvement of histopathology scores.

Conclusions: Our data demonstrates that selective PPARγ modulation after an ischemic AKI event in rats is sufficient to recover renal and tubular function, reduce clinically relevant urinary and plasma injury biomarkers and improve kidney histopathology.

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

165
TH-PO244
Identification of Urinary Activin A as a Novel Biomarker for AKI
Shunsuke Takahashi,1 Yoshihiro Takei,4 Masao Nakasatomi,1 Toru Sakairi,2 Hidekazu Ikeuchi,1 Yoriaki Kaneko,1 Keiji Hiromura,2 Yoshihisa Nojima,2 Akito Maeshima,2 Gunma University, Maebashi, Japan; 3Gunma University Graduate School of Medicine, Maebashi, Japan, 4Gunma University Graduate School of Medicine, Maebashi, Japan; 5Gunma university graduate school of medicine, Maebashi, Japan.

Background: Activin A, a member of TGF-beta superfamily, is known to regulate cell growth and differentiation in various tissues. We previously reported that activin A, which is absent in normal kidney, was increased in the ischemic rat kidney and negatively regulates the repair process of the kidney after injury (Maeshima et al. J Am Soc Nephrol 2001). To further investigate the role of activin A in acute kidney injury (AKI), we examined whether activin A can be detected in the urine of mice and humans with AKI.

Methods: Ischemia-reperfusion injury (I/R) was induced in C57BL/6 mice. At the indicated periods after operation, the kidneys and urine were collected for analysis. Expression and localization of activin A in ischemic kidneys (real-time PCR, immunostaining, and in situ hybridization) and urinary activin A (ELISA) were examined. Urine samples were also collected from fifteen patients with AKI as well as from eight healthy volunteers. Correlations of urinary activin A with other parameters were analyzed.

Results: Expression of activin A was markedly increased in the ischemic mouse kidney and peaked at 24 hours after I/R. Immunoreactive activin A was detected in proximal tubular cells of the outer medulla in ischemic kidneys, but not in normal kidneys. In addition to the ischemic kidney, activin A was detectable in the urine of normal mice. In contrast, activin A was undetectable in the urine of normal mice and bimodal peak (3 hours and 48 hours after I/R) was observed. In situ hybridization demonstrated that activin mRNA was expressed in tubular cells of the ischemic kidney, but was not in normal kidneys. Interestingly, urinary activin A level became higher according to the ischemic periods. Urinary activin A was almost undetectable in healthy volunteers, but was significantly increased in patients with renal AKI (7.2±2.6 vs. 48.6±15.3 pg/ml, p<0.05). Interestingly, urinary activin A was absent in the urine from patients with pre-renal AKI due to dehydration. There was a significant correlation between urinary level with urinary creatinine level (activin antagonist), but not with urinary KIM-1, urinary protein and serum creatinine.

Conclusions: Urinary activin A can be detected in mice and humans with AKI and might be a useful biomarker reflecting the severity of AKI.

Funding: Commercial Support - Astellas Pharm Inc.

TH-PO245
Mapping the Spatiotemporal Transcriptional Landscape of the Collecting Duct During Ischemic Injury Using Non-Invasive Optical Guidance
Neel A. Paragas,1 Tomomi Miyazaki,2 Yun-Wei A. Hsu,3 Sina Gharib.
University of Washington, Seattle, WA.

Background: Collecting duct (CD) cells are sensitive to acute kidney injury (AKI) before an appreciable rise in serum creatinine. CD cells are mitochondrial rich and sensitive to oxidative stress (OS), so we specifically targeted them to monitor H2O2 generation along with changes in gene expression.

Methods: To interrogate genetic changes at the peak of OS, we non-invasively monitored H2O2 generation to identify the most relevant mitochondrial points time acquisition for CD specific RNA-seq. We created a CD, HoxB7-luciferase (CD-Luc) bioluminescent reporter animal, to monitor OS. CD-Luc cell-specific reporter mice were injured by 30 min ischemia and reperfusion (I/R) was observed. In situ hybridization demonstrated that activin mRNA was expressed in proximal tubular cells of the outer medulla in ischemic kidneys, but not in normal kidneys. Activin A, which was absent in normal kidney, was increased in the ischemic rat kidney and negatively regulates the repair process of the kidney after injury (Maeshima et al. J Am Soc Nephrol 2001).

Results: We pretreated CD-Luc before IRI with a targeted mitochondrial antioxidant and were able to reverse the CD OS in vivo.

Conclusions: In sum, using our novel integrative approach we: (i) non-invasively and longitudinally imaged the peak time point of OS in the CD; (ii) used ip to isolate CD RNAs at that time point; (iii) successfully carried out RNA sequencing; (iv) performed differential gene expression and pathway analysis to reveal mitochondrial OS as a potential target pathway; (v) revealed the acute OS state with a targeted mitochondrial antioxidant with reduced lipid peroxidation in the kidney; and (vi) validated the reversal of mitochondrial dysfunction in ROS reporter animal model and correlated with the suppression of strong inflammatory stimulus of IRI.

Funding: NIDDK Support

TH-PO246
Iron Deficiency Sensitizes the Kidney to Acute Injuries Xueqiao Wang,1 Wenyun Shang,2 Xiaoping Zheng,2 Zhiqiang Wang,2 Juanlian Zhang,2 Jushan Zhang,2 Jing Nie,3 Jonathan M. Barash,1 Andong Qiu,1,2 Columbia Presbyterian, New York, NY; 3Zhengzhou University, Zhengzhou, China; School of Life science and technology, Tongji University, Shanghai, China; School of Life science and technology, Tongji University, Shanghai, China.

Background: Iron deficiency is the most common micronutrient deficiency in both developing and developed countries and it causes slower development of organogenesis in embryos. However, it remains unknown whether iron deficiency impacts acute kidney injuries (AKI) during postnatal life. Here we studied the effects of iron deficiency on AKI in murine models.

Methods: Mice were fed either iron deficient (22ppm), moderate iron deficiency (60ppm) or iron-replete (260ppm) diets for 3 weeks, and then subject to cisplatin or rhodamineoyls AKI. SCR and BUN were analyzed three days after ip injection of cisplatin and one day after muscular injection of glycolerol. Pro-oxidant and antioxidant, cell death and iron proteins and inflammatory factors were analyzed by q-PCR, western blot or immunofluorescence and CBA.

Results: We found that iron deficiency markedly exacerbate cisplatin- and rhodamineoyls-induced AKI when compared with iron-replete control, and even moderate iron deficiency had similar impacts. Nox4 and inflammatory factors were largely upregulated while catalase was markedly downregulated in the cisplatin-injured kidneys of iron-deficient mice when compared with iron-replete control. Further studies showed that the exacerbation of cisplatin-induced injuries in iron deficient mice could be reversed by Fer-1, a ferroportin inhibitor, demonstrating that the increased iron levels play a role in aggravation of cisplatin kidney injury. Although we were unable to rescue the exacerbation of AKI induced by rhodamineoyls, indicating the existence of a different mechanism for the impacts of iron deficiency on kidney injuries in this model.

Conclusions: Iron deficiency and even moderate iron deficiency markedly exacerbate AKI induced by either cisplatin or rhodamineoyls, and increased ferroportin represented a major mechanism of the exacerbation of kidney injuries in iron deficient cisplatin-induced AKI model.

Funding: Government Support - Non-U.S.

TH-PO247
Omega-3 Fatty Acids Attenuate Cisplatin Nephrotoxicity via Enhancement of Autophagy Flux Youngrok Ham,1 Jin young Jeong,2 Hong jin Bae,3 Chang hun Song,1 Kiyoung Na,1 Kang Wook Lee,1 Jwajin Kim,1 Jwion M. Lee,1 Ee Dan Lee,3 Integrative Nephrology, School of Medicine, Chungnam National University, Daejeon, Republic of Korea; 1Department of Medical Science, Chungnam National University, Daejeon, Republic of Korea; 2Anatomy, School of Medicine, Chungnam national university, Daejeon, Republic of Korea; 3Pediatrics, School of Medicine, Chungnam National University, Daejeon, Republic of Korea.

Background: Various studies demonstrated that omega-3 polysaturated fatty acids (PUFAs) attenuate kidney injuries through anti-antipotic and antioxidative properties. Recently, several studies showed that omega-3 PUFAs enhance induction of autophagy and evaluated whether the administration of omega-3 PUFAs may prevent autophagy in cisplatin nephrotoxicity, and investigated the role of autophagy in attenuating cisplatin nephrotoxicity by ω-3 PUFAs.

Methods: 10-week- old male C57BL/6 mice were divided into 4 groups; control, untreated cisplatin, 3,1 ω-3 PUFAs, 1,3 ω-3 PUFAs. Mice were injected with ω-3 PUFAs in a single dose of cisplatin (16 mg/kg body weight) intraperitoneally. Omega 3 and Vehicle were administered orally using an NG tube (Omega 32,000 μg/kg/day) from pre-injection day to 3 days after injection of cisplatin. Mice were sacrificed at 4 days after administration of cisplatin and kidney tissue were collected. Real time PCR, western blot and immunohistochemistry for molecular study and H&E stain and PAS stain for histologic examination were performed.

Results: Omega 3 treated cisplatin-mice showed improvement of renal cell survival, renal function, and pathologic damage compared to vehicle treated cisplatin-mice. Omega 3 treatment also reduced the renal expression of MCP-1 (Monocyte chemotactic protein-1) and OPN (Osteopontin) in cisplatin-treated kidney. Cisplatin-mice kidney showed that higher amounts of LC3, Beclin-1 and p62 compared to sham mice. Omega 3 treatment showed the decrease of albuminuria, blood urea nitrogen, creatinine, and urea compared to vehicle treated cisplatin-mice. Moreover, renal caspase D and ATP6E were also increased in omega 3 treated cisplatin-mice compared to vehicle treated cisplatin-mice.

Conclusions: Omega 3 fatty acids attenuate renal injury in cisplatin nephrotoxicity by stimulating autophagy flux

TH-PO248
Shroom3 Contributes to a More Severe AKI after Ischemia Reperfusion Darren Bridgewater, Thomas A. Dreadsley, McMaster University, Hamilton, ON, Canada.

Background: Acute kidney injury (AKI) is a severe complication of ischemia reperfusion injury. Individuals who survive AKI have an increased risk of developing chronic kidney disease, end stage renal disease, and death. While several clinical risk factors are associated with AKI, the genetic contributions are limited. Genome-wide

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
association studies (GWAS) identified 53 novel single nucleotide polymorphisms (SNPs) robustly associated with variations in kidney function. Shroom3 is the second most significant gene identified in these studies. Shroom3 is an actin-associated protein that regulates tissue morphogenesis by regulating epithelial cell shape. In the kidney, Shroom3 is expressed in the parietal and visceral epithelial cells, in some tubular epithelial cells, and distal collecting ducts. While Shroom3-heterozygous mice develop chronic kidney disease at 1 year, the role of Shroom3 in AKI is not known.

**Methods:**

- **Basal renal ischemia/reperfusion (I/R) procedure was performed in Shroom3 heterozygous mutant (Shroom3<sup>+/−</sup>) and wild type (WT) mice at 12 weeks to mimic the I/R renal with reactions during transplanted and cardiac surgery.
- **Kidneys were collected 48 hours and 10 days after I/R the procedure to compare the creatinine and urine protein at baseline, days 1, 2, 3, 5, 7, and 10 were measured.**
- **Kiddies were collected 48 hours and 10 days after I/R demonstrating worse histopathology as measured by tubular changes and cell death. Ten days after I/R, the serum creatinine in Shroom3<sup>−/−</sup> mice returned to baseline levels.**
- **However, the histopathological changes in Shroom3<sup>−/−</sup> mice were markedly worse when compared to WT mice.**

**Conclusions:** Our results demonstrate that genetic anomalies or aberrant expression of Shroom3 could lead to worse renal outcomes in patients after an I/R injury.

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

---

**TH-PO249**

**Paricalcitol Ameliorates Radiocontrast-Induced Nephropathy by Regulating Mitophagy**

*Gyeongsang National University Hospital and Gyeongsang National University, Jinju-si, Republic of Korea; 2Gyeongsang national university National University Hospital and Gyeongsang National University, Jinju-si, Republic of Korea; 3Gyeongsang National University Hospital and Gyeongsang National University, Jinju-si, Republic of Korea; 4Institute of Health Science, Gyeongsang National University, Jinju-si, Republic of Korea; 5Gyeongsang National Univ. Hospital, Jinju-si, Republic of Korea.*

**Background:** Radiocontrast-induced nephropathy (RCIN) is an important problem in clinical settings. However, strategies to prevent RCIN have been suboptimal. Paricalcitol was recently found to be effective in a variety of renal animal models, so it was hypothesized that paricalcitol would prevent RCIN by increasing the expression of the radiocontrast medium. It is a known intervention in rats by increasing the serum creatinine and urinary protein levels at baseline. Twenty-four hours after I/R, Shroom3<sup>−/−</sup> mice had a 1.5 fold (P<0.038) increase of serum creatinine from baseline (Fold Mean±SD, 3.89±1.35, N=10) compared to WT mice (Fold Mean±SD, 2.58±1.01, N=8). The Shroom3<sup>−/−</sup> mice demonstrated worse histopathology as measured by tubular changes and cell death. Ten days after I/R, the serum creatinine in Shroom3<sup>−/−</sup> mice returned to baseline levels. However, the histopathological changes in Shroom3<sup>−/−</sup> mice were markedly worse when compared to WT mice.

**Results:** Our results demonstrate that genetic anomalies or aberrant expression of Shroom3 could lead to worse renal outcomes in patients after an I/R injury.

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

---

**TH-PO250**

**Histone Deacetylase 6 Inhibition Protects Against Cisplatin-Induced AKI**

*Ningfa Shi,<sup>1</sup> Na Liu,<sup>1</sup> Linia Xu,<sup>1</sup> Jinhua Tang,<sup>1</sup> Shougang Zhuang,<sup>1</sup> 1Department of Nephrology, Shantou East Hospital, Tongji University School of Medicine, Shanghai, China; 2Department of Nephrology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China; 3Rhode Island Hospital, Alpert Medical School of Brown University, Providence, RI; 4Department of Nephrology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China.*

**Background:** The function of histone deacetylase 6 (HDAC6) has been demonstrated in various pathophysiological events, including cancer, neurodegenerative disorders and inflammatory diseases. Its role in cisplatin-induced acute kidney injury (AKI) is still unclear.

**Methods:** We used a murine model to investigate the role and mechanism of HDAC6 in cisplatin-induced AKI.

**Results:** HDAC6 expression levels were markedly increased in the kidneys of cisplatin-treated mice. Blocking HDAC6 activity with tubastatin A (TA), a high selective inhibitor, protects against cisplatin-induced AKI as demonstrated by improved renal function, attenuated renal pathological changes, reduced expression of AKI biomarkers after I/R, the serum creatinine in Shroom3<sup>−/−</sup> and WT mice returned to baseline levels. However, the histopathological changes in Shroom3<sup>−/−</sup> mice were markedly worse when compared to WT mice.

**Conclusions:** Our results demonstrate that genetic anomalies or aberrant expression of Shroom3 could lead to worse renal outcomes in patients after an I/R injury.

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

---

**TH-PO251**

**Involvement of Sirtuins 1 and 3 during the Acute Phase of Aristolochic Acid Nephropathy**

*Inés Jado,<sup>1</sup> Pauline F. Mossery,<sup>2</sup> Blanche Martin,<sup>3</sup> Olivia Botton,<sup>4</sup> Joelle L. Nortier,<sup>5</sup> Anne-Emilie Decleves,<sup>6</sup> Thierry Arnold,<sup>6</sup> Nathalie Caron.<sup>6</sup> 1Hospital Erasme, Brussels, Belgium; 2Laboratory of Molecular Biology, University of Mons, Belgium, NIMY (MONS), Belgium; 3Molecular Physiology Research Unit (URPHYM), University of Namur, Namur, Belgium; 4Laboratory of Biochemistry and Cell Biology (URBC), University of Namur, Namur, Belgium.*

**Background:** Aristolochic acid (AA) nephropathy (AAN) is a rapidly progressive tubulointerstitial nephritis induced by intoxication with AA is associated with end-stage renal disease and urethral malignancy. While the carcinogenic mechanisms of AA have been well documented, the mechanisms by which AA exert cytotoxic effects on proximal tubular epithelial cells, AAs primary target, are poorly characterized. Since oxidative stress and mitochondrial damage are known to be drivers of acute kidney injury, the goal of this study is to characterize oxidative stress and mitochondrial dysregulation with a particular emphasis on sirtuins (SIRT) during the acute phase of experimental AAN. Indeed, SIRT1 and SIRT3 have been previously described to be protective in different models of kidney disease. In this study, we focus on the first time the involvement of SIRT1 and SIRT3 in the pathophysiology of AAN.

**Methods:** C57BL/6J male mice were randomly subjected to daily i.p. injection of AA (3.5mg/kg) for 4 days. Mice were euthanized 24 hours, 5 days and 10 days after the nephrotoxic insult with AA intoxication.

**Results:** Polypuria and proteinuria were observed 5 days after AA intoxication as well as an increase in plasma creatinine and in blood urea nitrogen confirming renal failure. Histological analysis revealed early alterations of proximal tubules 24 hours after AA injection. By day 5, necrosis together with cellular desquamation were observed thereafter evolving at day 10 to atrophic tubules. Tubular injury was confirmed by upregulation of relative mRNA expression of NGAL. Along with renal failure, inflammation developed with upregulation of mRNA of inflammatory cytokines (MCP1, IL1β, IL6, TNFα, IFNγ, TGFβ and IL10) and with macrophage infiltration. Antioxidant pathways were also downregulated as attested by decrease in mRNA expression of NRF2 and SOD2 at day 5 and day 10. Finally, relative mRNA expression of SIRT1 and SIRT3 was found to be downregulated from day 5 until day 10, the protein expression of SIRT3 being also reduced at the same time-points.

**Conclusions:** The downregulation of SIRT1 and SIRT3 observed in the acute phase of AAN could constitute a key event in AAN pathogenesis. Therefore, this observation could lead to a new potential strategy for improving outcomes of AAN.

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

---

**TH-PO252**

**Characterization of the Metabolome and Renal Tubular Cisplatin Disposition in Cisplatin Induced AKI**

*Aygın Jın (Jins) Lim,<sup>1</sup> Emily D. Hartjes,<sup>1</sup> Brad Uqurqait,<sup>1</sup> Physiological and Pharmacological, Schulich School of Medicine & Dentistry, University of Western Ontario, London, ON, Canada; 2Department of Medicine, Division of Nephrology, University of Western Ontario, London, ON, Canada.*

**Background:** Cisplatin induces acute kidney injury (AKI) in approximately 1/3 of patients. It is currently unknown why some patients develop AKI and others do not. Cisplatin AKI is diagnosed by increases in serum creatinine (SCR), but nephrotoxicity develops before rises in SCR can be detected. Novel diagnostic/predictive markers of AKI may help determine why some cisplatin patients get AKI while others are resistant. FVB mice have greater susceptibility to cisplatin AKI than C57BL/6 mice. These two mouse strains were used to model the variability of cisplatin response observed in humans. We aim to: 1) Determine the effects of AKI on expression of renal transporters and enzymes involved in cisplatin disposition; 2) Investigate metabolic differences between FVB and C57BL/6 mice using metabolomics, with the goal of biomarker discovery.

**Methods:** FVB and C57BL/6 strains were treated with 15 mg/kg cisplatin or saline by intraperitoneal injection. Mice were sacrificed 1 and 3 days following treatment, and blood, urine and kidneys were collected. Gene expression was assessed using RT-PCR. Liquid chromatography-mass spectrometry was used for untargeted metabolomics.

**Results:** In FVB mice, expression of renal uptake transporter Oct2 and metabolizing enzyme Ggt1 were 51% and 66% lower 3 days following cisplatin treatment compared to saline (p<0.01, p<0.01 respectively). Oct1 trended towards lower expression in day 3 cisplatin-treated FVB mice. Principle component analysis (PCA) of untreated FVB and C57BL/6 plasma samples showed clustering based on mouse strain. PCA of day 3 plasma samples clearly separated cisplatin and saline groups for both mouse strains. Multivariate

---

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
analysis revealed indoxyl sulfate and p-cresyl sulfate to be two metabolites associated with cisplatin AKI.

**Conclusions:** mRNA expression results suggest that cisplatin alters expression of drug disposition genes in FVB, but not C57BL/6 mice. PCA clustering of baseline mice indicates metabolic differences between the strains, while separation by treatment groups suggests that cisplatin administration alters the metabolic profile of the mice. Our preliminary data suggests possible mechanisms why FVB mice show increased susceptibility to cisplatin AKI compared to the C57BL/6 mice. Further work will be to identify additional metabolic changes associated with cisplatin AKI.

**TH-PO253**

Blockade of Sonic Hedgehog Signaling in Fibroblasts Protects against AKI

**Authors:** Dong Zhou,1 Haiyan Fu,2 Yuan Tian,1 Hongyang Mo,1 Youhua Liu,1

1Department of Pathology, University of Pittsburgh, Pittsburgh, PA; 2Division of Nephrology, Southern Medical University, Guangzhou, China.

**Background:** Sonic Hedgehog (Shh), an evolutionarily conserved, secreted and extracellular signal protein, is an inducible, tubule-derived growth factor specifically promoting fibroblast proliferation and expansion through its receptor by the so-called canonical pathway in chronic kidney disease. However, whether activation of Shh signaling in fibroblast plays any role in acute kidney injury (AKI) remains to be defined.

**Methods:** Here we show that Shh, Smoighthed (Smo) and fibroblasts were coincidentally activated after ischemic AKI. To investigate the potential role of activation of fibroblast-specific Shh signaling in AKI, we generated conditional knockout mice, designated as FC-Smo-/-, in which the Smo gene was specifically disrupted in renal fibroblasts. The Cre-loxP system. The FC-Smo-/- mice phenotypically normal and displayed no appreciable defects in kidney morphology and function. However, in AKI induced by ischemia reperfusion injury (IRI), loss of fibroblasts Smo substantially ameliorated renal dysfunction and lesions. Compared with controls, FC-Smo-/- mice displayed lower serum creatinine and reduced morphologic injury. Fibroblast-specific ablation of Smo significantly blocked the expression of pro-inflammatory cytokines including TNF-α and MCP-1, and retarded renal infiltration of inflammatory cells such as CD3+ T cells and F4/80+ macrophages after AKI. Less apoptosis was detected in FC-Smo-/- kidneys, accompanied by a decreased expression of Bax and Bax-associated protein with death domain (FADD). Interestingly, loss of Smo in fibroblast in turn caused an increased expression of Shh in tubules by feedback control. Shh then promoted activation of canonical Wnt signaling pathway including upregulation of the majority of 19 Wnt family members after AKI which is strongly associated with AKI severity.

**Conclusions:** Collectively, these results suggest that loss of fibroblast-specific Shh receptor, Smo, is crucial in conferring renal protection after AKI, primarily via a reduced renal inflammation, as well as activation of Wnt signaling through cell-cell communication.

**Funding:** NIDDK Support

**TH-PO254**

Sex Differences in Renal Toxicity of the Neurotoxin Domoic Acid

**Authors:** Robert G. Thompson,1 Hernan E. Grenett,1 Lan He,2 P. Darwin Bell,2

1University of Alabama at Birmingham, Birmingham, AL; 2University of Alabama at Birmingham, Birmingham, AL; 3University of Alabama at Birmingham, Birmingham, AL.

**Background:** The algae-derived neurotoxin, domoic acid (DA), is an isotoxic receptor agonist and is currently considered an increasing threat to mammals and other species. Intraperitoneal administration (IP) of 4-5 mg/Kg/BW in mice has been found to cause neurological symptoms/damage. However, we recently reported (Funk, JASN 2014) that the kidney was 100 times more susceptible to injury with DA compared to brain. With IP injection, the kidney has a 4-fold higher concentration of DA compared to brain and other targets/tissues mediated through signaling of CD36 (pro-inflammatory) and CD47 (anti-inflammatory) ligands. Microparticles (MP’s) are released in response to stress or injury from various cells and can serve as markers of type and state of cell activation. Whether TP-1 induced inflammatory ligands can be detected as MP’s, and could play a role in organ cross-talk in models of AKI is unknown.

**Methods:** By studying in vitro models of AKI using immobilized human renal proximal tubular epithelial cell (RPTEC) line, we incubated cells with and without TP-1 (1 µg/ml for 24 hours) (N = 3 sets). MP’s were isolated and evaluated by flow cytometry techniques and with CD36 and CD47 fluorescent antibodies. Analyses of microparticles was performed using flow-jo software and levels of MP’s was expressed as mean and standard deviation times 10^6 Unpaired t-tests were used for comparison.

**Results:** Morphological assessment of TP-1 treated cells confirmed characteristics associated with apoptosis. CD36 MP’s were significantly higher in TP-1 treated cells vs controls (92.66 +/- 11.06 vs 229 +/-69.77; p = 0.007). CD47 MP’s were statistically similar in TP-1 and control cells (715.33 +/- 248 vs 759.6 +/- 220; p = 0.88). CD10 and CD13 MP’s, as putative markers of RPTEC were also detected in response to TP-1 exposure.

**Conclusions:** Our results show that MP’s containing CD36 and CD47 are released from RPTEC upon exposure to TP-1. CD36 MP’s are significantly increased after TP-1 exposure, whereas CD47 MP’s are statistically similar. It is known that CD-36 serves as a pro-inflammatory ligand for various inflammatory proteins including TP-1; thus raising the possibility that TP-1 exposure could initiate a cross-talk between renal epithelium and other targets/tissues mediated through TP-1 ligand interactions. This is the first report that demonstrates the release of CD36 and CD47 postive MP’s in response to TP-1 exposure. We propose that MP’s originating from kidney under pathological conditions could release pro-inflammatory signals to other remote organs.

**Funding:** Clinical Revenue Support

**TH-PO255**

Thrombospondin-1 (TSP-1) and Microparticles in AKI

**Authors:** Beegoa Campos,2 Brittany N. Gleich,2 Sonam S. Singh,2 Karen M. Domenico,1 Charuhas V. Thakar,2,1 Shriners Hospitals for Children, Cincinnati, OH; 2University of Cincinnati, Cincinnati, OH; 3Cincinnati VAMC, Cincinnati, OH.

**Background:** We have previously shown (Thakar et al, JCI, 2005) that TSP-1 is up-regulated and mediates kidney damage (AKI) in murine ischemia reperfusion injury. TSP-1 exposure to renal epithelial cells is also known to induce apoptosis/necrosis. TSP-1 exerts its inflammatory modulating effects through signaling of CD36 (pro-inflammatory) and CD47 (anti-inflammatory) ligands. Microparticles (MP’s) are released in response to stress or injury from various cells and can serve as markers of type and state of cell activation. Whether TSP-1 induced inflammatory ligands can be detected as MP’s, and could play a role in organ cross-talk in models of AKI is unknown.

**Methods:** By studying in vitro models of AKI using immobilized human renal proximal tubular epithelial cell (RPTEC) line, we incubated cells with and without TSP-1 (1 µg/ml for 24 hours) (N = 3 sets). MP’s were isolated and evaluated by flow cytometry techniques and with CD36 and CD47 fluorescent antibodies. Analyses of microparticles was performed using flow-jo software and levels of MP’s was expressed as mean and standard deviation times 10^6 Unpaired t-tests were used for comparison.

**Results:** Morphological assessment of TSP-1 treated cells confirmed characteristics associated with apoptosis. CD36 MP’s were significantly higher in TSP-1 treated cells vs controls (92.66 +/- 11.06 vs 229 +/-69.77; p = 0.007). CD47 MP’s were statistically similar in TSP-1 and control cells (715.33 +/- 248 vs 759.6 +/- 220; p = 0.88). CD10 and CD13 MP’s, as putative markers of RPTEC were also detected in response to TSP-1 exposure.

**Conclusions:** Our results show that MP’s containing CD36 and CD47 are released from RPTEC upon exposure to TSP-1. CD36 MP’s are significantly increased after TSP-1 exposure, whereas CD47 MP’s are statistically similar. It is known that CD-36 serves as a pro-inflammatory ligand for various inflammatory proteins including TSP-1; thus raising the possibility that TSP-1 exposure could initiate a cross-talk between renal epithelium and other targets/tissues mediated through TSP-1 ligand interactions. This is the first report that demonstrates the release of CD36 and CD47 postive MP’s in response to TSP-1 exposure. We propose that MP’s originating from kidney under pathological conditions could release pro-inflammatory signals to other remote organs.

**Funding:** Clinical Revenue Support

**TH-PO256**

HIF-1-Mediated Production of Exosomes during Hypoxia Is Protective in Renal Tubular Cells

**Authors:** Wei Zhang,6 Xianguan Zhou,1 Hao Zhang,4 Jin Wen,2 Zheng Dong,1 Georgia Regents University, Augusta, GA; 2Sichuan University, Augustia, GA; 3Taihe Hospital, Hubei University of Medicine, ---Shian, China; 4The Third Xiangya Hospital of Central South University, Changsha, China; 5Cellular Biology, Augustia University, Augustia, GA; 6Nephrology Department, the Third Xiangya Hospital, Central South University, Changsha, China.

**Background:** Exosomes are nano-sized vesicles produced and secreted by cells to mediate intercellular communication. The production and function of exosomes in kidney tissues and cells remain largely unclear. Hypoxia is a common patho-physiological condition in kidneys. This study was designed to characterize exosome production during hypoxia in murine renal proximal tubular cells (RPTC), investigate the regulation by hypoxia-inducible factor-1 (HIF-1), and determine the effect of the exosomes on ATP-depletion induced tubular cell injury.

**Methods:** RPTCs were treated with or without hypoxia. Exosomes were isolated by ultracentrifugation. Transmission electron microscopy and Nanoparticle Tracking Analysis (Zeta View) and Nanoparticle Tracking Analysis (ETX) were used to qualify and quantify exosomes. HIF-1α inducer DMOG and its inhibitor YC-1 were used for HIF-1α induction or inhibition. A stable HIF-1α knockout MEF cell line and HIF-1α siRNA induced knockdown RPTCs cells were used to verify the role of HIF-1α in exosomes production. Conditioned exosomes were administrated as a pretreatment before Azide induced ATP-depletion injury in RPTCs. Hoechst staining, morphology images and caspase-3 expression by immunoblot were conducted to evaluate the death and survival rate of the cells.

**Results:** The average size of exosome secreted in hypoxia condition was comparable to the normal condition by the NTA measurement. Hypoxia significantly increased exosome production in a time-dependent manner. HIF-1α induction by DMOG also slightly promoted exosomes secretion. Pharmacal or genomic inhibition of HIF-1α and hypoxia precondition increased exosome production under hypoxia condition; Pretreatment with hypoxia exosomes from tubular cells attenuated the apoptosis of RPTCs after Azide induced ATP-depletion. Exosomes form HIF-1α knock down cells failed to decrease cell apoptosis rate and caspase-3 expression.

**Conclusions:** Hypoxia stimulates exosome production and secretion in renal tubular cells. The exosomes from hypoxia cells are protective against renal tubular cell injury. HIF-1 mediates exosome production during hypoxia and contributes to the cytoprotective effect of the exosomes.

**Funding:** NIDDK Support
**TH-PO257**

**Non-Classical MHC Class I Molecules Regulate Development and Maintenance of Kidney Double Negative CD4 T Cells**

*Mohanad Sadasivam, Sanjeev Noel, Sul A Lee, Abdel Hamad, Hamid Rabb, Johns Hopkins University School of Medicine, Baltimore, MD.*

**Background:** Despite strong evidence that immune cells mediate early injury and repair from ischemic acute kidney injury (AKI), the underlying mechanisms are poorly understood. A recently characterized subset of CD4 T cells that is double negative (DN) for both CD4 and CD8 is present in significant numbers in normal mouse and human kidney. Unlike CD4+ and CD8+ T cells, DN T cells divide actively in the steady state and rapidly increase in response to AKI. In addition, kidney DN T cells secrete anti-inflammatory cytokines IL-10 and IL-27, possess an in vitro and in vivo regulatory function and ameliorate AKI in mice. However, the exact MHC restriction element(s) required for homeostatic DN T cells development and maintenance is not known.

**Methods:**

- **C57BL/6J (WT), B6.129P2-B2m tm1Wjk (B2m KO), B6.129P2-H2-K1 tm1Bpe (MHC II KO) and B6.129P2-H2-D1 tm1Bpe (MHC II KO) and H2-K1 tm1Bpe H2-D1 tm1Bpe (Qa2 KO) mice were used for the analyses.**
- **Rictor -/- or Rictor +/− CD11c-specific Raptor -/- or Rictor -/- CD11c-specific Raptor -/- or Rictor -/- DC simultaneously adoptively transferred into B6 mice at the time of renal IRI.**
- **Renal Rictor -/- or Rictor +/− DC migrating to the injured kidney.**
- **Conclusions:**
  - Our data demonstrate that loss of β2m, but not classical MHC class Iα or class II molecule significantly reduces the frequency (WT, 28.8±3 vs. B2m KO, 9.5±2 vs. MHC II KO, 32.3±2.8 vs. MHC II KO, 32.3±2.8 P<0.05) and the absolute number (WT, 3,355±1.077 vs. B2m KO, 1,016±47 vs. MHC II KO, 1,538±639 P<0.05) of kidney DN T cells. Subsequent studies show the reduction is due to impaired activation (P<0.001) and proliferation (P<0.05) and increased apoptosis (P<0.05) by kidney DN T cell. Further, most of the defects were restored by adoptive transfer of CD8 T cell from wild type mice, leading to activation and expansion (P<0.001) of endogenous DN T cells in B2m KO mice.

**Funding:** NIDDK Support

---

**TH-PO258**

**Loss of the Stress-Responsive Transcription Factor FoxO3 Accelerates AKI to CKD Transition**

*Fangming Li,1 Catherine Ha, Julia D. Liu, Qais Al-Awqati, Fangming Lin, Columbia University College of Physicians & Surgeons, New York, NY.*

**Background:** AKI increases the risk for developing or worsening CKD. Capillary drop out and hypoxia occurs in kidneys transitioning from AKI to CKD. We recently found that hypoxia activated a stress-responsive transcription factor FoxO3 in mouse kidneys by the mechanism of preventing its oxygen-dependent degradation.

**Methods:** To test the function of FoxO3 activation during the AKI to CKD transition, we specifically deleted FoxO3 with high efficiency in tubular epithelial cells using Pax8-Rta-Tet-D3-e cre; FoxO3 +/− mice.

**Results:**

- **Ischemia-reperfusion injury (IRI) of a 35 min duration to the left kidney and right nephrectomy was performed.**
- **One week after, FoxO3 was deleted by giving mice doxycycline in the drinking water to study its role after the acute injury and recovery phase.**
- **Deletion of FoxO3 aggravated renal damage 4 weeks post IRI indicated by significant increase of higher scores of border loss in proximal tubules, renal tubular atrophy, and tubular cast formation (22.9±3.5% vs. 22.2±3.6 in mild type, n=5).**
- **Furthermore, FoxO3 deleted mice had more prominent tubular cell apoptosis. However, neither interstitial fibrosis and inflammation nor microvascular density were significantly different compared with FoxO3 wild type mice.**
- **Mice with FoxO3 deletion also had higher urinary albumin creatinine (53.2±8.3 mg/g vs. 18.4±4.6 mg/g in mild type, n=5) indicating that worse morphology was associated with functional decline.**

**Conclusions:** In summary, our results indicate that FoxO3 activation induces renal autophagy as a stress response, which attenuates CKD development and progression.

**Funding:** NIDDK Support

---

**TH-PO259**

**Optogenetic Stimulation of Specific Neural Circuits in the Neuroimmune Reflex Control of Inflammation in AKI**

*Shinji Tanaka,1 Tsuyoshi Inoue,2 Diane L. Rosin,2 Patrice G. Guynet,2 Mark D. Okusa.1 1Div of Nephrology and Center for Immunology, Inflammation and Regenerative Medicine, Dept of Medicine, University of Virginia, Charlottesville, VA; 2Dept of Pharmacology, University of Virginia, Charlottesville, VA.*

**Background:** We recently reported that electrical vagus nerve stimulation (VNS) protects mice kidneys from ischemia-reperfusion injury (IRI) by activating the cholinergic anti-inflammatory pathway by the transcriptional control of this pathway. Optogenetic stimulation of both the efferent and afferent vagus fibers we ve used optogenetics to begin to distinguish the specific functions of vagus efferent and afferent fibers within the vagus nerve bundle in controlling inflammation by the CAP. Optogenetic stimulation involves the expression of light-reactive ion channels, such as channelrhodopsin-2 (ChR2), in relevant neurons using the Cre/loxP system. When light of a specific wavelength is applied to the target nerve, the ion channels open, resulting in selective activation of the neurons.

**Methods:** We crossed lox-STOP-lox ChR2-eYFP mice with choline acetyltransferase (Chat)-cre and vesicular glutamate transporter 2 (Vglut2)-cre mice to generate Chat-ChR2 and Vglut2-ChR2 mice expressing ChR2 in vagal efferent and afferent fibers, respectively.

**Results:**

- **ChR2 expression was confirmed by direct observation of the eYFP signal in the cervical vagus nerve.** When blue laser (wavelength 473 nm, 50 Hz) was applied to the cervical vagus nerve of Chat-ChR2 mice, heart rate decreased markedly (300–180 beats/minute without change in respiratory rate). Blue laser application to the vagus nerve or the central end of the cut vagus nerve of Vglut2-ChR2 mice completely paused breathing by activation of Hering-Breuer inflation reflex, while application to the distal end of the cut vagus nerve did not affect the respiratory rate, which reflects the effects that Hering-Breuer inflation reflex needsafferent vagal input to the brain. In a preliminary experiment, optogenetic VNS (5 Hz to minimize the effect on respiration) in Vglut2-ChR2 mice protected kidneys from IRI.

**Conclusions:** We have successfully created transgenic mice expressing ChR2 in vagus efferent (Chat-ChR2) and afferent fibers (Vglut2-ChR2) and validated their expression and functional effect following optogenetic stimulation. Our preliminary data showed that selective stimulation of the vagus afferent fibers was protective against kidney IRI. Optogenetics will be useful in identifying selective neural circuits of the CAP that control systemic inflammation and other neural circuits of the kidney.

**Funding:** NIDDK Support

---

**TH-PO260**

**Dendritic Cell Expression of Rектор, but not Raptor, Protects Against AKI**

*Sanjeev M. Rogenski,1 Helong Dai,2 Daniel Fantus,3 Alicia Watson,2 Angela W. Thomson.2 1Comprehensive Transplant Center, Northwestern University, Chicago, IL; 2University of Pittsburgh, Pittsburgh, PA; 3Westmead Institute for Medical Research, Sydney, NSW, Australia.*

**Background:** Dendritic cells (DC) are critical to innate immunity in the kidney and orchestrate inflammation fundamental to the pathophysiology of acute kidney injury (AKI). The mechanistic target of rapamycin (mTOR) functions as 2 independent complexes: Raptor and Rector. The role of mTOR in AKI pathophysiology has been poorly characterized, and the influence of DC-based alterations in mTOR signalling has not been investigated.

**Methods:** CD11c-specific Rector− or Raptor− mice were generated by crossing respective floxed mice with mice expressing CD11c-Cre. Age- and gender-matched DC-2m KO mice were isolated using known markers, bone marrow chimera and adoptive transfer in the steady state and ischemic AKI.

**Results:**

- **CD11c-specific Raptor− or Rector− mice were generated by crossing respective floxed mice with mice expressing CD11c-Cre. Age- and gender-matched DC-2m KO mice were isolated and assessed ex vivo.**

- **We have successfully created transgenic mice expressing ChR2 in vagus efferent (Chat-ChR2) and afferent fibers (Vglut2-ChR2) and validated their expression and functional effect following optogenetic stimulation. Our preliminary data showed that selective stimulation of the vagus afferent fibers was protective against kidney IRI. Optogenetics will be useful in identifying selective neural circuits of the CAP that control systemic inflammation and other neural circuits of the kidney.**

**Funding:** NIDDK Support

---

**TH-PO261**

**Activation of the Cholinergic Anti-Inflammatory Pathway by GABA-A Agonists Cisplatin Induced AKI**

*Prodyg K. Chatterjee,1 Michael M. Yeboba,2 Malvika H. Solanki,2 Gopal Kumar,4 Xiaoying Xue,1 Valentin A. Pavlov,3 Yousef Al-Abed,2 Christine N. Metz,2 1The Center for Biomedical Sciences, Feinstein Institute for Medical Research, Manhasset, NY; 2The Department of Pathology and Laboratory Medicine, Medical College of Wisconsin, Milwaukee, WI; 3Dept. Division of Nephrology, Medical College of Wisconsin, Milwaukee, WI; 4Elmezzi Graduate School of Molecular Medicine, Northwell Health, Manhasset, NY; 5The Center for Molecular Innovation, Feinstein Institute for Medical Research, Manhasset, NY.*

**Background:** Acute kidney injury (AKI) is the most common side effect of cisplatin, a widely used chemotherapeutic agent. Although AKI occurs in up to 1/3 of patients treated with cisplatin, effective protective strategies are lacking. Cisplatin targets renal proximal tubular epithelial cells leading to the production of reactive oxygen species.
(ROS), inflammation, tubular cell injury, and eventually cell death. The cholinergic anti-inflammatory pathway is a vague nerve-mediated physiological mechanism that suppresses inflammation via α7nicotinic acetylcholine receptors (α7nAChRs). Our previous studies demonstrated the renoprotective effects of α7nAChR agonists (e.g. GTS-21) in murine renal ischemia reperfusion injury and sepsis-induced AKI. Therefore, we examined the effect of GTS-21 on cisplatin-Induced AKI.

Methods: Male C57BL/6 mice were treated with saline or GTS-21 (4mg/kg, i.p.) twice daily for 4 days before cisplatin (20mg/kg, i.p.); 72 hrs later mice were euthanized and their plasma and kidneys were analyzed for markers of renal injury, renal inflammation, renal cisplatin accumulation and the expression of cisplatin influx and efflux transporters.

Results: GTS-21 significantly reduced cisplatin-induced renal dysfunction and injury. GTS-21 significantly attenuated renal Pgr2/COX-2, IL-6, IL-1β, and CXCL1 expression, as well as neutrophil infiltration and renal inflammation activity after cisplatin. GTS-21 blunted cisplatin-induced ERK1/2 activation, oxidative stress, as well as renal ATP depletion and apoptosis (p<0.05). GTS-21 suppressed cisplatin influx transporter CTR1 expression and enhanced the expression of cisplatin efflux transporters MRPs, MRP4, and MRP9 (p<0.05). Using cancer cell lines we showed that GTS-21 did not inhibit cisplatin’s tumor killing activity.

Conclusions: GTS-21 protects against cisplatin-AKI by attenuating renal cytokine-chemokine expression, ROS, and mitochondrial dysfunction, as well as by decreasing renal cisplatin influx and increasing efflux. GTS-21 does not impair cisplatin-mediated tumor cell killing. Our results support further exploring the cholinergic anti-inflammatory pathway for preventing cisplatin-induced AKI.

Funding: Private Foundation Support

TH-PO262
Implications of Short-Term Cocssackievirus Infection in Non-Obese Diabetic Mouse Kidneys

Background: End stage renal disease (ESRD) can result from four primary diagnoses, diabetes, hypertension, glomerulonephritis and cystic kidney disease, all of which have viruses implicated as causative agents. Enteroviruses, like cocssackievirus (CV), is a common genus of viruses that have been implicated in both diabetes and cystic kidney disease, however, little is known about early CV infection in the kidney and how that infection may contribute to ESRD. This study, therefore, evaluates short-term CV infection in the kidneys of non-obese diabetic (NOD) mice; a strain of mice with a genetic predisposition to develop type 1 diabetes mellitus (the most common primary ESRD diagnosis), a condition which can be accelerated by CV infection in these mice. Characterizing the short-term effects of CV on the kidneys will define our understanding of how “innocent” viruses like CV may have a more significant impact on chronic kidney disease than previously described.

Methods: Eight-week-old NOD mice were infected with CV and euthanized 3, 7, 10 and 14 days post infection. Kidneys were collected and processed for histological and gene expression analyses.

Results: CV RNA in the kidney peaked 3 days post infection and was identified in both the glomerulus and tubulointerstitial regions. Virus was no longer detectible by real-time RT-PCR or in situ hybridization 14 days post infection. Percent kidney weight and urinary albumin creatinine ratio, hallmarks of kidney injury, did not demonstrate significant alterations. NOD mouse kidneys at these timespont. Histological evaluation of PAS and H&E stained tissue did not reveal any significant pathological changes between infected and non-infected kidneys at any time point. However, gene expression of TLR3 and its signaling products TNFα, IL-6 and CXCL10 were found to be unaltered 3 days post CV infection, indicating a potential kidney cell response to virus infection. Further evaluation will be performed to determine in which cells of the kidney TLR3 is upregulated.

Conclusions: Together, these data will help identify initial kidney gene expression changes in response to virus infection that may play a role in later ESRD.

TH-PO263
Natural IgM and TLR Agonists Switch Murine Splenic Pan-B to Regulatory* Cells That Suppress Immune Induced Inflammation
Oleksandr I. Lohb, KaiHo H. Schneller, Amandeep Bajwa, Mark D. Okusa. University of Virginia, Charlottesville, VA.

Background: Innate inflammation after reperfusion of ischemic organ has a significant role in ischemia-reperfusion injury (IRI). In prior studies, we showed that natural IgM anti-leucocyte autoantibodies (IgM-ALA) inhibit inflammation. Here we show that Pan-B cells are switched to regulatory cells when pretreated ex-vivo with either IgM or CpG.

Methods: C57BL/6 mice were i.v. infused with 0.5X10^6 B cells that were cultured for 48h with either IgM or CpG and 24h later these mice underwent bilateral renal ischemia. Plasma creatinine and other studies were performed 24h after ischemia.

Results: Pre-treatment with regulatory pan-B cells (IgM or CpG treated) protected kidney function and gene expression of inflammation in naive NK1.1+ cells which implies the innate immune response to DAMPS released after ischemia. Such ex-vivo induced regulatory pan-B cells express low CD1d and inhibit inflammation by regulating in-vivo NK1.1 cells in the context of low lipid antigen presentation and by a mechanism that involves either reduced (CD1d) and/or reduced regulatory B cells, but not IgM-induced regulatory B cells, also require IL10 for their regulatory activity. LPS, unlike CpG, fails to down-regulate CD1d and switch pan-B to regulatory cells that inhibit ischemia induced AKI despite increased IL10 production.

Conclusions: Ex-vivo induced regulatory pan-B cells could have therapeutic relevance as these easily available cells can be pre-empitively infused to prevent AKI that can occur during open heart surgery or in transplant recipients receiving deceased donor organs.

Funding: NIDDK Support

TH-PO264
Genetic and Pharmacologic Blockade of Prostaglandin Transporter Attenuates Cisplatin Nephrotoxicity

Background: Cisplatin (CP) is used to treat a variety of malignancies but nephrotoxicity limits its use. CP nephrotoxicity is characterized by renal vasocostriction and proximal tubular damage. Underlying molecular mechanisms include inflammation, reactive oxygen species, and apoptotic pathways. Prostaglandins have been shown to be cytoprotective in many tissues including the kidney. Prostaglandins are metabolized by the prostaglandin transporter, PGT. We have developed a PGT knockout mouse and a high-affinity PGT inhibitor, PV20767 (“PV”). Both have been shown to raise endogenous levels of PGE2, and may be useful therapeutically. We hypothesized that genetic and pharmacologic blockade of PGT would prevent CP nephrotoxicity.

Methods: PGT wildtype and knockout mice were given a single dose of CP 20mg/kg intravenously (IP). C57BL/6 wildtype mice were given vehicle or PV 20mg/kg IP 24 hour and 1 hour prior to CP, and 24 and 48 hours after, one dose of CP 20mg/kg IP. All mice were sacrificed 72 hours after CP. Renal function was evaluated by serum creatinine, cystatin C, Kim-1 immunohistochemistry, and tissue histology by tubular injury score. Quantitative polymerase chain reaction (Q-PCR) and serum cytokine dot-blot assay were used to identify differences in the expression of inflammatory, oxidative stress, and apoptotic genes. TUNEL assay was performed to assess for cell apoptosis. Urine PGE2 levels were measured by ELISA.

Results: Urine PGE2 excretion was increased in KO and PV-treated mice, confirming blockade of PGE2 metabolism. KO mice had reduced serum creatinine after CP. Pharmacologic blockade of PGT with PV significantly attenuated CP nephrotoxicity as assessed by serum biomarkers of renal injury (creatinine, cystatin C) and histologic measurements of tubular injury and cell apoptosis (Kim-1, tubular injury score, TUNEL assay). Serum biomarkers (TNF-α and renal gene expression studies (IL-6, IL-1β, β2, SOD-1, SOD-2) revealed decreased inflammation, apoptosis, and oxidative stress in CP mice given PV.

Conclusions: Genetic and pharmacologic blockade of PGT attenuates cisplatin nephrotoxicity. We hypothesize the mechanism involves PGE2-mediated vasodilatation and/or cytoprotection through reduction of inflammation, oxidative stress, and apoptosis. Pharmacologic blockade of PGT may be a novel renoprotective strategy for cisplatin nephrotoxicity.

Funding: Other NHLI Support - T32 Research Training Grant

TH-PO265
A Distinct Kindney CD45NotCD11bNotF4/80+N HeidiNot1-6-C Macrophage Population in Mice and Humans
Sul A. Lee, Sanjeew Noel, Mohanjn Sadasaivan, Abel Hamad, Hamid Rabb. Johns Hopkins University School of Medicine, Baltimore, MD.

Background: Kidney mononuclear phagocytes cells (MPCs) play important roles in the pathogenesis of acute kidney injury (AKI) and other inflammatory diseases. However, renal MPCs are incompletely understood. We hypothesized that renal monocytes in acute kidney injury (AKI) differ from conventional renal macrophages in many key aspects.

Methods: We isolated from different lymphoid and non-lymphoid organs of C57BL6 male mice at baseline or following ischemic AKI and analyzed for the frequency and phenotype markers. Macrophage ablation was performed by intraperitoneal injection of liposomal clodronate. MPCs in human kidney were analyzed in normal tissue from nephrectomies for renal cell carcinoma.

Results: While focusing on renal lineage markers, we identified a cell population that binds only to CD11b and CD80 antibodies but not to CD86 antibody. Further studies using CD11b and CD80 antibodies displayed this population was a renal macrophage subset which was different from conventional macrophages by its intermediate (int) expression of CD11b.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Analysis of MP's was performed using FlowJo software. MP levels were expressed as

Conclusions: Our data suggest that CD45+CD11b+ F4/80+ MHCII+Ly6c+ macrophages are found in kidney and have distinct patterns of membrane receptors and response to ischemic AKI compared to traditional macrophages. We are currently studying functional characteristics of this population by analyzing their phagocytosis functions, cytokines, and role in kidney diseases.

**Funding:** NIDDK Support

---

**TH-PO266**

**Antisense Oligonucleotide Mediated Inhibition of NLRP3 Expression Attenuates Aristolochic Acid Induced Kidney Injury**

**Aaron Donner,1 Thomas Bell,2 Michael Scanlon,3 William Breitkreutz,4 Robert W. Spellman,5 Michael J. Silverman,6 Karen M. Domenico,7 Charuhas Campos,8 Brittany Scott,9 Adam K. Kiltie,10 Jonathan A. Capen,10 Emily A. Johnston,11 Jeff Stenmark,12 Rosanne Crooke,3 Thomas Saunders,2,3 Thaddeus Saum,2,3

**AKI Basic: Inflammation and Transcription**

**Background:** In addition to its role in innate immunity, there is increasing evidence that the interferon pathway is a crucial driver of pathology in immune, metabolic, and renal diseases. Genetic and pharmacologic inhibition of components of the NLRP3-containing inflammasome (NLRP3, ASC and Caspase-1) or its downstream effectors (IL-1b, IL-18) has been shown to provide therapeutic benefit in animal models of disease. We have sought to target the upstream node, the inflammasome, using ASOs directed against NLRP3 in a mouse model of acute kidney disease. We demonstrated the ability to prevent aristolochic acid 1 induced acute kidney injury (AAI AKI) with prior administration of an ASO targeting NLRP3, a key component of the inflammasome. The NLRP3 ASO attenuated disease both on plasma and urinary biomarkers, and expression of inflammatory and pro-fibrotic mRNA markers and histological changes. Disease-induced increases in plasma creatinine and BUN and urinary increases in protein:creatinine ratios were reduced by prior administration of NLRP3 ASO. AAI induced induction of renal inflammation (intCD11b+) and pro-fibrotic (MMP-1, Mmp2, colla1) mRNAs was also reduced by the NLRP3 ASO. Histologically, the NLRP3 ASO protected from AAI induced morphological changes throughout the nephron. Based on our findings, ASO mediated inhibition of NLRP3 expression could provide therapeutic benefit for those suffering from kidney disease.

**Methods:**

**Results:**

**Conclusions:**

**Funding:** NIDDK Support

---

**TH-PO267**

**Microparticles in Oxidative Stress and Inflammatory Models of Kidney Injury**

**Begoña Campos,1 Brittany N. Gleich,2 Keith L. Saum,3 Karen M. Domenico,1 Charuhas Campos,8 Shriners Hospitals for Children, Cincinnati, OH; 2University of Cincinnati, Cincinnati, OH; 3Cincinnati VAMC, Cincinnati, OH.

**Background:** Acute kidney injury (AKI) is associated with significant morbidity, including remote organ dysfunction. In response to stress or injury cells release phenotypically and quantitatively distinct microparticles (MP's), representing both the cell type and metabolic stage (e.g. apoptosis, activation, proliferation). The objective of this study was to evaluate release of MP’s from renal proximal tubular epithelial cells (RPTEC) in inflammatory and oxidative stress. We also examined MP’s as putative biomarkers, and their role in remote organ cross-talk.

**Methods:** We used in vitro models of injury to human immortalized RPTEC line. Exposures of H2O2 (0.03 mM for 1 hour) and TNF-α (50 and 100 ng/ml) for 72 hours were compared to controls (N = 3 sets). The presence of CD10, CD13 and CD146 proteins on the cells was evaluated by western blot and confocal microscopy. Flow cytometry analysis was used to detect the release of MP’s containing CD10, CD13, and CD146. Analysis of MP’s was performed using FlowJo software. MP levels were expressed as mean and standard deviations times 10 and compared by unpaired t-tests.

**Results:** Western blot and confocal microscopy, in controls and treated cells, confirmed the presence of CD10, CD13 and CD146 proteins on RPTEC. Under both oxidative stress (H2O2) and inflammatory stress (TNF-α) cells showed morphological changes associated with apoptosis. Compared to controls MP’s were significantly increased (CD10: p = 0.0001; CD13: 0.190 vs 53.882; p = 0.0001) and CD146 (5.991 vs 142.474; p = 0.0018). TNF-α treated cells at both concentrations also released CD10, CD13 and CD146 MP’s; however, only CD13 MP’s were statistically higher than controls at 100 ng/ml of TNF-α (26.67 vs 56.91; p = 0.02). CD10 and CD13 MP’s showed a trend at both concentrations of TNF-α.

**Conclusions:** This is the first report of detection of microparticles (CD10 and CD13) specific to and derived from human RPTEC. Furthermore, we demonstrate a significant increase in the level of MP’s derived from renal cells that is specific to oxidative and inflammatory stresses. Additionally, release of CD146 MP’s by stressed RPTEC could serve as ligand for endothelial activation, suggesting renal origins of organ cross-talk.

**Funding:** Clinical Revenue Support

---

**TH-PO268**

**Loss of Melanocortin 5 Receptor Exacerbates Endotoxin AKI via Impairing Regulatory T Cell Response**

**Yuhong Xu,1,2 Rong Zhou,1 Rujun Gong,2 Yanggu Hospital, Tongji University, Shanghai, China; 2Brown Medical School, Providence, RI.

**Background:** Pituitary melanocortin neuropeptides, exemplified by α-melanocyte-stimulating hormone, have long been recognized to possess a remarkable renoprotective activity in diverse forms of acute kidney injury (AKI). However, the molecular mechanism responsible for this beneficial action has been illusive and exactly which type of melanocortin receptor conveys the renoprotective effect remains to be defined. Lately, there is growing evidence suggesting that melanocortin 5 receptor (MC5R) signaling confers a protective effect in multiple organ systems. The role of MC5R in kidney injury was examined in this study.

**Methods:** MC5R knockout mice (KO) and congenic wild-type (WT) littermates were injured with lipopolysaccharides (LPS) and AKI examined. Bone marrow derived cells were prepared from WT or KO mice and adoptively transferred to KO mice followed by LPS injury.

**Results:** With global knockout of MC5R were phenotypically indistinguishable from their WT littermates, and exhibited normal development with undetectable difference in kidney physiology, function and histology. As compared with WT controls, KO mice developed much severer AKI upon LPS injury, as evidenced by higher serum creatinine levels, more urinary excretion and renal expression of lipocalin-2, exacerbated renal histologic damages and tubular cell death, and amplified renal inflammation. This worsened AKI in KO mice was unlikely attributable to a tubular cell-autonomous mechanism, because primary cultures of proximal tubular epithelial cells derived from KO and WT mice demonstrated similar cellular injury and death and comparable inflammatory response following LPS injury. Instead, the amount of CD4+Foxp3+ regulatory T cells in the injured kidney from KO mice was strikingly diminished, concommitant with a drastic amplification of renal inflammatory infiltrations, thus underscoring an impaired immune tolerance to LPS injury. Moreover, adoptive transfer of bone marrow derived cells derived from congenic WT littermates to KO mice substantially repopulated CD4+Foxp3+ regulatory T cells in the kidney following LPS injury, resulting in a substantial improvement of the LPS-activated AKI and renal inflammation.

**Conclusions:** Collectively, MC5R is likely essential for regulatory T cell response to LPS injury and thereby conveys a protective activity in endotoxic AKI.

---

**TH-PO269**

**The Yes Associated Protein (YAP) Facilitates Kidney Fibrosis in a Kidney Injury Molecule-1 (KIM-1) Dependent Manner**

**Angad K. Akinfolarin,1 Venkata Sabbisetti, Amarendra K. Ajay, Emily Christic, Joseph V. Bonventre. Brigham and Women' s Hospital, Boston, MA.

**Background:** The Salvador-Warts-Hippo (SWH) pathway controls organ size by modulating cell proliferation and apoptosis. The nuclear localization of the YAP drives cell proliferation through the transcriptional co-activation of the TEA domain family, a regulator of TGF-β signaling. Following cell confluence, the SWH pathway acts as a negative feedback system to control cytoplasmic YAP localization and inactivation of YAP. Chronic epithelial expression of the KIM-1 is associated with the development of murine kidney fibrosis. In this study we show that the presence of epithelial KIM-1 is associated with nuclear accumulation of YAP and development of kidney fibrosis in mice.

**Methods:** C57B6 wild type (WT) mice or mice with a mutation of the mucin domain of KIM-1 (KIM-1Δmucin) were examined either 14 days after 26 min of bilateral ischemia (I/R) or 10 days after unilateral ureteral obstruction (UUO). LLC-PK1 and HEK cells were transduced with human KIM-1 full length cDNA (LLEC-PK1-KIM-1 and HEK-KIM-1) or an empty pcDNA3 vector (PK1-pcDNA and HEK-pcDNA). Experiments with short hairpin RNA against YAP and inhibition of YAP signaling with a small molecule, verteporfin was also done in PK1 and HEK cells. These kidney cells were then examined for regulation after TGF-β stimulation and CytoPlatin treatment.

**Results:** Proximal tubule (PT) expression of YAP was increased in WT mice that had more kidney fibrosis as compared to their KIM-1Δmucin littermates when examined by Masson's trichome (MT) and Periodic Acid Schiff (PAS) staining after I/R and UUO. Western blot analysis of whole kidney cortex revealed greater levels of phospho factors including CTGF, fibronectin and ACTA2 in the WT mice as compared with the KIM-1Δmucin mice. These animal data were supported by in vitro experiments which revealed less cell proliferation and production of pro fibrotic factors with either YAP knock down or inhibition when compared with WT, following TGF-β stimulation. KIM-1 expressing cells had increased nuclear YAP and CTGF levels as compared to cells expressing the control vector.

**Conclusions:** YAP is up regulated in murine kidney fibrosis, more so in proximal tubule cells expressing KIM-1. Phospho RNAi depletion of YAP or enhancement of SWH signaling may be of therapeutic importance in attenuating kidney fibrosis.

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

---

**Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.**
TH-PO270

Orai Mediated Ca2+ Signaling Influences IL-17 Expression in CD4+ T Cells Following I/R

Purvi Mehrotra,1 David P. Basile,2 Indiana School of Medicine, Indianapolis, IN; 2Indiana University School of Medicine, Indianapolis, IN.

Background: T-helper 17 (Th17) cells have been implicated in the pathogenesis of acute kidney Injury (AKI). Renal Th17 cells transiently increase for up to 3-days post ischemia/reperfusion (I/R) and return to basal levels within a week. Exposure of post AKI rats to elevated dietary salt (4%) stimulates sustained induction of renal CD17 cells, which is associated with CKD progression. The store-operated calcium channel (SOCCK). Orai-1 plays a role in models of inflammatory disease such as colitis or autoimmune encephalomyelitis, which may be influenced by dietary salt. We hypothesized that AKI primes CD4+ T cells to increase IL17 expression secondary to Orai1 dependent Ca2+ signaling.

Methods: FACs analysis demonstrated increased Orai1 protein in renal CD4+ T-cells 7 days following I/R (MFI:221644±3567) relative to sham operated controls (MFI:109624±467, p<0.05). To evaluate the role of Orai1 mediated Ca2+ influx in the progression of AKI, rats were subjected to bilateral I/R and the dependency of AKI progression on Ca2+ entry was evaluated using an in vitro assay of renal CD4+ cells, which resulted in ~5 fold increase in IL17 expression in response to Ang II (10⁻⁸ M) and elevated extracellular Na⁺ (170 mM).

Results: The IL17 induction of AKI primed CD4+ cells in vitro was attenuated by > 95% (p<0.05) by 3 inhibitors that target Orai-1 (2-ABP (20mm), AnCoA4 (50mm) or YM58483 (120mm)). A significant percentage (40-50%) of AKI-primed CD4+ cells, but not sham-derived CD4 cells, manifested increased intracellular Ca²⁺ in response to AngII+170 mM Na⁺, a response that was completely abrogated by co-incubation with AnCoA4. Furthermore, treatment with YM58483 in vivo (1mg/Kg), reduced renal Th17 cells 2 days post I/R compared to vehicle treated rats (15,307±6,1265 vs 7390±439 cells/ gram of kidney; p<0.05). Interestingly, YM58483 had no effect on renal Th1 or Th2 cells. In addition, YM58483 significantly reduced the extent of renal injury by attenuating the increase in serum creatinine by ~66% (p<0.05) vs vehicle treated post AKI rats.

Conclusions: Taken together, these data suggest that I/R leads to increased Orai1 mediated Ca2+ influx thereby enhancing IL17 expression and may influence the severity of AKI.

Funding: NIDDK Support

TH-PO277

TH-PO277

Mutation of the RORγC Gene in Rats Attenuates Th17 Cell Activity, Renal Injury, and Inflammation in Response to Ischemia Reperfusion Purvi Mehrota,1 Jason A. Coller,2 David P. Basile.2 Indiana School of Medicine, Indianapolis, IN; 2Indiana University School of Medicine, Indianapolis, IN.

Background: T-cells have been implicated in initiation of renal damage following I/R injury, while recent studies have also suggested that a specific T helper subset, Th17 cells, is associated with both initiation of AKI and the AKI-to-CKD progression. To evaluate the direct role of Th17 cells in AKI, RoRγe (RAR-rar gamma receptor), a transcription factor considered the master regulator for Th17 cell differentiation and IL-17 gene expression was targeted for mutation in Lewis rats.

Methods: Using a CRISPR-CAS9 approach, an 8 bp deletion was introduced into the rat RoRγe gene. The verified sequence analysis predicted a mis-sense mutation at a.a.31 and premature truncation relative to the 508 a.a. protein in wild-type rats. LewisRorc-wt rats appear normal and healthy but show moderate growth retardation relative LewisRorc-wt control rats.

Results: Under basal conditions, reduced percentages of CD4+ (50.2±4.4 vs 24.4±4.7; p<0.05), B cells (21.4±7.2 vs 13.5±8.5; p<0.05) and Macrophages (13.07±3.5 vs 7.7±9.97; p<0.05) in the spleen of 6-8-week old LewisRorc-wt rats compared to wildtype controls. To evaluate the effect of RORγC mutation on the induction of Th17 cells during AKI, both mutant and wild type rats were subjected to bilateral renal I/R for 40 min. Renal Th17 cells were enhanced 2 days following I/R in wild type rats but were significantly reduced in LewisRorc-wt rats (6304±10498 vs 2443±4830; p<0.05) post I/R with no effect on Th1 and Th2 cells. In addition, LewisRorc-wt were resistant to AKI as measured by serum creatinine (4.5±0.85 vs 2.6±0.4; p<0.05) as well as reduced renal inflammation as indicated by total CD4+ (40%; p<0.05) and CD68 (48%; p<0.05). After 7 days of recovery, AKI primed lymphocytes from wild type rats manifested an IL-17 mRNA induction in response to Ang II +170 mM Na⁺ in vitro, however AKI primed lymphocytes from LewisRorc-wt rats showed no increase in IL17 mRNA expression.

Conclusions: Taken together these data that mutation of RORγC in rats impairs Th17 cell activity in response to renal I/R and modulates the sensitivity to the development of AKI.

Funding: NIDDK Support

TH-PO272

CC-Chemokine Receptor 7 Deficient Mice Are Resistant to Renal Ischemia-Reperfusion Injury Hiroshi Koijima,1 Xu Zheng,1 Erik H. Koritzinsky,1 Myung-gyu Kim,1 Jonathan Street,1 Timothy J. Brea,2 Michail Lionakis,2 Peter S. Yuen,3 Robert A. Star.1 National Institute of Diabetes and Digestive Kidney Diseases (NIDDK), Bethesda, MD; 2National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD.

Background: One of the most prominent chemokine receptors in the adaptive immune system is CC-chemokine receptor 7 (CCR7), which has been established as an important component of lymphocyte-driven immune function. CCR7 promotes homing of T cells and Dendritic Cells (DCs) to T cells areas of lymphoid tissues where T cells priming occur. Apart from chemotaxis, CCR7 controls cytosarchitecture, rate of endocytosis, survival, migratory speed, and maturation of the DCs. Manipulation of CCR7 axis has either protective or deleterious role in mouse kidney injury models. We sought to clarify the role of CCR7 in the pathogenesis of renal injury after ischemia reperfusion injury (IRI).

Results: CCR7 deficient mice (CCR7−/−) or wild-type mice (CCR7+/+) underwent IRI. Mice were euthanized at 1, 3 and 7 days after the surgery. Kidney & serum were collected for biochemical analysis & histological evaluation.

Results: Blood urea nitrogen, creatinin C, & creatinine levels in CCR7−/− were lower than CCR7+/+ throughout experimental periods. Similarly, CCR7−/− developed milder tubulointerstitial injuries than CCR7+/+ There was a significant correlation between serum markers & histology score.

Conclusions: CCR7−/− mice are resistant to IRI. We speculate that dendritic cells (DCs) are involved in reno-protective property in CCR7−/−. In CCR7−/−, IRI induced danger signals induce normal maturation/activation of DCs, causing the development of effector T cell response. In CCR7−/−, DC maturation is prevented; DCs would remain in the state of immune tolerance despite the presence of danger signals. Implications: Targeting DCs through CCR7 may have therapeutic potential for IRI.

Funding: NIDDK Support

TH-PO273

TH-PO273

CD4+ T Cells Activated by Ultrasound or Vagus Nerve Stimulation Protect Kidneys from Ischemia-Reperfusion Injury through β2 Adrenergic Receptor Tsuyoshi Inoue,1 Chikara Abe,2 Liping Huang,1 Diane L. Rosin,1 Patrice G. Guynet,1 Mark D. Okusa.1 ‘University of Virginia, Charlottesville, VA; 2Gifu University, Gifu, Japan.

Background: We recently showed that prior ultrasound (US) treatment and vagus nerve stimulation (VNS) protect kidneys from ischemia-reperfusion injury (IRI) through the cholinergic anti-inflammatory pathway (CAP). Although β2 adrenergic receptor-positive CD4+ T cells are thought to be components of the CAP, they have yet to be tested in mediating the protective effect of CAP activation following IRI.

Methods: Kidney IRI (bilateral, 26 mins) was used as an acute kidney injury (AKI) model. US was performed 24 h after US at 1.5x (magnification), 2.5x, and 3x, and US parameters were adjusted to 50 μA for 10 minute treatment. Kidney injury was evaluated 24 h later using plasma creatinine (PCr), kidney Kim-1 mRNA expression and histology (H&E). CD4+ splenocytes (MACS-enriched) were isolated from donor mice and transferred i.v. to recipient mice. Butoxamine was used as a β2 adrenergic receptor antagonist, and salbutamol was used as a β2 adrenergic receptor agonist.

Results: When butoxamine (15 mg/kg) was administered 30 mins prior to US and VNS, the renal protective effect of US and VNS was abolished (PCr: 0.20 and 1.76 mg/dl (P<0.001) for vehicle+US and butoxamine-US, respectively, n=7). Salbutamol (15 mg/kg) administration 24 hr prior to IRI protected the kidney. Adoptive transfer of CD4+
spleenocytes (1x10^5 cells) from US-treated or VNS-treated mice to recipient mice subjected to I/R provided significantly greater protection than CD4+ spleenocytes from mice which underwent US or sham VNS (P<0.04 and 1.31 mg/dl P<0.001) for VNS- and sham VNS-treated CD4+ spleenocytes from spleen, respectively, n=9. In addition, the kidney was protected when salbutamol-treated CD4+ spleenocytes were transferred 24 hr prior to I/R.

Conclusions: These data demonstrate that activation of CD4+ splenocytes through β2 adrenergic receptors is important for the protective effect of US and VNS in AKI.

Funding: NIDDK Support

TH-PO274

AKI Stimulates Inflammation Associated Lymphangiogenesis
Sarah A. Bowhay, Anupam Agarwal, Amie Traylor, Abolfazl Zarjou
University of Alabama at Birmingham, Birmingham, AL

Background: The lymphatic system is crucial for maintaining fluid balance, transporting lipids, and aiding in immune function. The functions of the lymphatic system are further accentuated during pathological conditions such as inflammation, the latter a key component of acute kidney injury (AKI). Inflammation induces lymphangiogenesis through expression of vascular endothelial growth factors (VEGFs), particularly VEGF-C, VEGF-D, and their receptor VEGF-R3. Recent studies have shown how lymphangiogenesis to be an active participant in a number of inflammatory diseases, very little is known about the role of the lymphatic system and more importantly, lymphangiogenesis, in the pathogenesis of AKI. Based on the prominent role of lymphangiogenesis in various inflammation induced disease models, this delicate and crucial pathway could serve as a novel target to be explored for therapeutic interventions in AKI.

Methods: To study the role of lymphangiogenesis in the pathophysiology of AKI, we induced renal injury in mice via bilateral ischemia-reperfusion injury (IR), a well characterized model of AKI and measured lymphatic vessel content as well as mRNA and protein levels of growth factors and inducers of lymphangiogenesis.

Results: We found increased lymphatic vessel content in kidneys of mice that had undergone IR compared to uninjured controls via LYVE1 (a cell surface receptor on lymphatic endothelial cells) immunohistochemistry. RT-PCR analysis revealed increased levels of lymphatic markers, LYVE1 and Podoplanin in kidneys 7 days after IR. We also observed increased VEGF-C and VEGF-D protein levels after injury peaking at day 3 post IR in kidney lysates. ELISA analysis of VEGF-C levels showed a decrease in kidney VEGF-C with a simultaneous increase in serum levels of VEGF-C. VEGF-C protein was also detected in the urine at day 1 post IR. VEGF-C immunofluorescence staining revealed expression in proximal tubule cells in uninjured kidneys. After IR, VEGF-C is seen in the apical side of proximal tubule cells. This together suggests a mechanism in which VEGF-C is secreted from the tubules into the blood and urine following injury.

Conclusions: These results suggest that lymphangiogenesis is stimulated in kidneys after AKI and may represent a target for intervention in the pathogenesis of AKI.

TH-PO275

STAT5 Knockouts Are More Susceptible Than Wildtype Mice to Streptozotocin-Induced AKI
Karen T. Cosciugno,1 Avery M. Bogart,2 Amber J. McDermott,1 Jeffrey B. Hodgin,1 Ramiro Malagon,1 Interdisciplinary Program in Molecular and Cellular Biology and Institute and Department of Biomedical Sciences, Heritage College of Osteopathic Medicine, Ohio University, Athens, OH; 3The Diabetes Institute, Heritage College of Osteopathic Medicine and the Honors Tutorial College, Ohio University, Athens, OH; 4Heritage College of Osteopathic Medicine, Ohio University, Athens, OH; 5Department of Pathology, University of Michigan, Ann Arbor, MI

Background: We have previously shown that mice deleted for the first coding exon of the Signal Transducer and Activator of Transcription 5 genes (STAT5 A/B knockout or SKO) exhibit more kidney damage in comparison to wildtype (WT) littermates when examined 12 weeks after treatment with streptozotocin (STZ) to induce diabetes. However, it was not clear whether the kidney damage was a result of the STZ treatment or the resulting hyperglycemia.

Results: We observed increased lymphatic vessel content in kidneys of mice that had undergone IR compared to uninjured controls via LYVE1 (a cell surface receptor on lymphatic endothelial cells) immunohistochemistry. RT-PCR analysis revealed increased levels of lymphatic markers, LYVE1 and Podoplanin in kidneys 7 days after IR. We also observed increased VEGF-C and VEGF-D protein levels after injury peaking at day 3 post IR in kidney lysates. ELISA analysis of VEGF-C levels showed a decrease in kidney VEGF-C with a simultaneous increase in serum levels of VEGF-C. VEGF-C protein was also detected in the urine at day 1 post IR. VEGF-C immunofluorescence staining revealed expression in proximal tubule cells in uninjured kidneys. After IR, VEGF-C is seen in the apical side of proximal tubule cells. This together suggests a mechanism in which VEGF-C is secreted from the tubules into the blood and urine following injury.

Conclusions: These results suggest that lymphangiogenesis is stimulated in kidneys after AKI and may represent a target for intervention in the pathogenesis of AKI.

TH-PO277

Myeloid Specific H-Ferritin Mediates Sepsis Induced Inflammation and Organ Injury
Abolfazl Zarjou,1 Laurence M. Black,2 Anupam Agarwal,3 Subhashini Bolsi,4 AUB, Birmingham, AL; 1University of Alabama at Birmingham, Birmingham, AL; 3University of Alabama at Birmingham, Birmingham, AL

Background: Sepsis is a severe clinical syndrome that is characterized by profound and destructive inflammation and infection resulting in end-organ dysfunction distant from the primary site of infection. Despite fundamental findings that have expanded our understanding into the mechanisms that instigate and propagate sepsis and its deleterious effects on various organs including kidney, novel therapeutic agents and modalities have remained elusive. In fact, sepsis remains a leading cause of mortality and acute kidney injury in patients admitted to the intensive care unit. We previously demonstrated that macrophage polarization depends on expression of ferritin heavy chain (Fh1) and such expression plays a key role to regulate the cross-talk between macrophages and renal epithelial cells during kidney injury and repair. This led to our hypothesis that macrophage specific Fh1 may be involved in development and consequences of sepsis.

Methods: Using transgenic mice with conditional deletion of Fh1 in myeloid cells (Fh1 LysM-), we induced sepsis by a well characterized cecal ligation and puncture method.

Results: Our results demonstrate that myeloid Fh1 deficiency is associated with hyporesponsiveness to sepsis. We show that specific deletion of Fh1 in myeloid cells led to ~90% improved survival when compared to Fh1 LysM- littermates. Furthermore, renal function supported by serum creatinine was significantly more preserved in the Fh1 LysM- mice. In addition, we found decreased level of several pro-inflammatory cytokine expression in major organs, including the kidney. Our mechanistic studies show that myeloid Fh1 deletion causes derangements in pathways that are crucial in immune inflammation and infection including NF-kβ, and hypoxia inducible factors.

Conclusions: Overall, our results for the first time signify the paramount importance of myeloid system iron metabolism in sepsis mediated organ injury and identify the central role of Fh1 in this context. As such, we propose a novel target to mitigate sepsis mediated inflammation and resulting organ injury that is urgently needed given the unacceptable rate of mortality and morbidity related to this devastating clinical condition.

Funding: NIDDK Support, Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Sensing of Bacterial Infection by Nerves and the Induction of Inter-Organ Communication during the First Hours of Pyelonephritis

**TH-PO278**

**Background:** Tissue microbiological studies have revealed that inter-organ communication occurs within the first hours of pyelonephritis. IFN-γ released from the spleen is known to modulate the host responses at the site of renal infection within 8 h. We hypothesized that this rapid inter-organ signaling is at least, in part, mediated by the nervous system. Here we investigate nervous sensing of the bacterial infection and implicate nervous signals as mediators of the inter-organ communication between infected kidney and the responding spleen.

**Methods:** GFP–expressing uropathogenic Escherichia coli (UPEC) were microinfused into single proximal tubules in exposed kidneys of anesthetized rats. After 4 h the infection site was examined by *ex vivo* immunofluorescence (IF) analysis. Nervous projections in the renal cortex were identified through IF analysis of fixed, uninfected rat renal tissue. Spleenic *ifng* mRNA expression was determined by qPCR on splenic tissue. Cytokine and ATP release of UPEC infected renal epithelial cells (A498) were investigated in cell culture in *vitro*. Primary sensory nerve cells from mice were used to determine immune and nervous responses to UPEC infection.

**Results:** Despite the very localized nature of the infection, spleenic *ifng* expression was found to be upregulated already within 4 h of kidney infection. We found that sensory nerves are present in the basement membrane of proximal tubules, where they can come into close contact with UPEC related products. In *vitro* we found that primary mouse sensory nerves can detect pathogen-associated molecular patterns and damage-associated molecular patterns during infection and have both immunological IL-6, and nervous CGRP responses. In cell culture, nervous responses were found to only occur during infection with bacteria that produce the toxin α-haemolysin. Translating this finding in *vitro*, we found that inter-organ communication was abrogated in animals infected with a UPEC strain that does not produce α-haemolysin.

**Conclusions:** Our work shows the role of the sensory nervous system in sensing a local infection and allowing the kidney and the systemic host to communicate.

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

---

**TH-PO278**

AKI Increases Gut Permeability and Provokes Dysregulation of Mucosal Immunity: Effect of Probiotics on AKI Severity

**TH-PO280**

**Background:** Emerging evidence indicate the presence of kidney-gut crosstalk in diverse pathological conditions. In normal condition, healthy microbiome help to maintain gut barrier and mucosal immune tolerance. In this study, we investigated kidney-gut crosstalk in AKI by assessing the effect of AKI on gut barrier integrity and mucosal immunity.

**Methods:** C57BL/6 mice underwent bilateral ischemia-reperfusion injury (IRI) or sham operation. In the probiotic treatment group, Bifidobacteri was administered via oral gavage once daily, started 3 days prior to the injury. The gut barrier integrity was assessed by measuring orally administered fluorescein isothiocyanate-dextran (FITC-dextran) activity in blood and western blot for various tight junction proteins was performed. Flow cytometric analysis of colonic macrophages as well as Foxp3 expression was performed.

**Results:** Following AKI, gut permeability increased significantly and it was accompanied by decreased claudin-1, occludin expression and increased number of apoptosis in colon. Ly6G+ neutrophil infiltration and MPO activity increased after kidney IRI and the number of Ly6G+CD45+CXCR1+macrophages also increased. Colonic Foxp3 mRNA expression showed a slight but statistically significant increase. Preconditioning with probiotics prior to IRI significantly attenuated functional, histological kidney injury and the renoprotective effect was accompanied by partial restoration of claudin-1, occludin expression and also by decreased number of colon epithelial cell apoptosis. Colon Foxp3 expression significantly increased in probiotic treated group.

**Conclusions:** In conclusion, AKI induced gut barrier disruption and colonic inflammation might be one mechanism leading to systemic inflammation, kidney and other remote organ injury. Probiotic mediated renoprotective effect might be mediated by strengthening gut barrier and also mucosal immune tolerance mechanisms. Probiotics might be one promising strategy aiming for reducing AKI severity or remote organ injury.

**Funding:** NIDDK Support
TH-PO283

LPS-Binding Protein (LBP)/TLR4 Signaling Mediates Pericyte (PC) to Myofibroblasts Trans-Differentiation (PMT) in Endotoxemic AKI

Giuseppe Castellano, Alessandra Stasi, Rossana Franzin, Fabio Sallustio, Chiara Devilla, Alessandra Spinelli, Giuseppe Grandalini, Giovanni B. Pertosa, Loretta Gesualdo. University of Bari, Bari, Italy; University of Poggio, POGGIA, Italy.

Background: During sepsis, LBP/TLR4 signaling is central in the inflammatory cascade while activation impairs renal function, leading to AKI. Renal fibrosis induced by PMT is a common pathological feature of chronic kidney disease but little is known in AKI.

Methods: AKI was induced by i.v. LPS infusion in 8 pigs. After 3h from LPS infusion, 8 pigs were treated with coupled plasma filtration adsorption (CPFA). Renal biopsies, performed at 9h from LPS infusion (T9), were analyzed by IHC and IF. Serum LBP and TGFβ were quantified by ELISA. In vitro, PC (PDGFRβ+) were analyzed by FACS, IF and WB. TGFβ-Receptor(R) neutralizing antibody was added to the cultures 30’ before LPS or TGFβ stimulation.

Results: We found the occurrence of acute PMT in endotoxemic AKI by the reduction of PDGFRβ expression and cSMA increase in peritubular PC. CPFA treatment restored PDGFRβ expression (p<0.03) and significantly decreased cSMA-PC (p<0.001), in accordance with reduced serum levels of LBP (p<0.05). In vitro, activation of PC with LPS or endotoxemic sera led to PMT with Collagenenn synthesis and cSMA reorganization in contractile fibers (p<0.05). The removal of LBP from septic plasma maintained Collagenen and cSMA expression at basal level (p<0.05). On the contrary, exogenous LBP supplementation reversed CPFA effects. LPS increased phosphorylation of Smad2/3 and ERK1, respectively (p<0.05) suggesting that PMT was induced by both canonical TGFβ-Smad2/3 dependent and non-canonical TGFβ-Smad independent signaling (MAPK).

Moreover, the serum levels of TGFβ increased in endotoxemic pigs and were reduced after CPFA treatment (p<0.05). It is well known that TGFβ induces PMT contributing to renal fibrosis. Interestingly, in vitro TGFβ-SM signaling blockade, did not affect LPS-induced PMT and phosphorylation of SMAD2/3 and ERK1, underlying a fibrin role of LPS independently of TGFβ synthesis and release.

Conclusions: PC might be pivotal in the generation of myofibroblasts by PMT during AKI upon the activation of LBP/TLR4 signaling. Disrupting the persistent TLR4 signaling activation by the removal of LBP may represent a therapeutic option to prevent PC dysfunction and acute renal fibrosis.

TH-PO284

Indirect Therapeutic Role of Immunosuppressive Micro-RNA for Sepsis Induced AKI via Spleen Yoshihisa Funahashi, Nagoya University, Nagoya, Aichi, Japan.

Background: Sepsis is life-threatening organ dysfunction caused by dysregulated immune response to infection. It is known that sepsis with acute kidney injury (AKI) shows high mortality rate. However, therapies to treat sepsis and AKI are largely ineffectual because of its pathophysiological complexity. Several studies have reported that some micro-RNAs (miRNAs) acted as a regulator of systemic inflammation. Here, we revealed the significance of spleen to regulate septic state by induction of immunosuppressive miRNA.

Methods: In vitro study, mir-X, which targeting toll like receptor/NF-kB pathway, was transfected into RAW264.7 cells. After transfection, cells were treated with lipopolysaccharide (LPS) for 6h, then RNA, protein, and supernatant were purified. In vivo study, 8-12 week-old C57BL/6 male mice, with or without spleenectomy, were treated with mir-X expression plasmid combined with polyethyleneimine (PEI), 7 days before sepsis. Sepsis was induced by cecal ligation and puncture (CLP). Organs were harvested at 24h after CLP.

Results: In vitro study, mir-R transfected cells were tolerant toward LPS stimulation, and showed low NF-kB activity. In vivo study, mir-X expression plasmid/PEI complex was mainly detected in spleen macrophages. mir-R plasmid group showed the improvement of survival rate, inflammatory cytokine production, renal dysfunction, and renal tubular damage. In addition, less apoptotic cells were observed in spleen of mir-X expression plasmid group, than that of empty plasmid group. Interestingly, anti-inflammatory effect of mir-X was rarely observed in spleenectomized mice.

Conclusions: Spleenic induction of mir-X prevented dysregulated systemic inflammation in sepsis and attenuated AKI. In addition, we provided the new treatment strategy for sepsis induced AKI by targeting spleen with specific miRNA.

TH-PO285

Interleukin-10 Alleviates Ureteral Obstruction-Induced Renal Fibrosis by Reduction of Inflammation, Oxidative Stress, and Endoplasmic Reticulum Stress

Kyung-Jin Jung. Yeungnam University College of Medicine, Nam-gu, Daejeon, Republic of Korea.

Background: Impairment of oxidative stress, endoplasmic reticulum (ER) stress and accumulation of extracellular matrix results in renal fibrosis contributes to progressive renal failure. Recent studies suggested that interleukin (IL)-10 plays potent impacts on the fibrosis-related immunomodulation. However, the role of IL-10 against unilateral ureteral obstruction (UO)-induced ER stress remains poorly understood.

Methods: Here, we investigated the mechanisms of IL-10 on ER stress-induced renal fibrosis by UUO model in IL-10 knockout (KO) mice and a normal kidney cell line (TMCK-1). Age-matched 10 weeks old male IL-10 KO mice and wild-type (WT) mice were divided into control (CON) and UUO groups. The mice were sacrificed at 3 days or 7 days after UUO. ER stress and profibrotic protein levels were evaluated by, western blotting. Periodic acid Schiff and Masson’s trichrome stain were used for analyzed histologic changes and collagen deposition. To evaluate oxidative stress levels checked production of O₂⁻, H₂O₂, malondialdehyde and expression of 4-HNE. To investigate correlation among the IL-10, CHOP and α-SMA expression, immunofluorescence staining was used.In vitro, treatment of ER stress inducer (tunicamycin, thapsigargin and brefeldin A) with or without transfected siRNA (IL-10 and CHOP) or CHOP overexpression in TMCK-1 cells.

Results: In this study, we found IL-10 KO UUO mice promoted renal fibrosis by more excessive tubular damage (tubular dilatation, cast formation and tubular cells infiltration), collagen deposition and oxidative stress production. We also confirmed IL-10 KO mice express higher level of profibrotic genes (α-SMA, COL1 and FN) and ER stress genes (GRP78- Bip and CHOP) after UUO. We observed IL-10, CHOP and α-SMA were highly expressed in tubulointerstitial lesion of UUO mice than CON mice. In vitro, transient depletion of CHOP attenuated expression of profibrotic genes.

Conclusions: Present study shows that IL-10 protecting was opposed to ER stress mediated-renal fibrosis. Combination of IL-10 and ER stress therapy could be a strong protective effect for patients with chronic kidney diseases.

TH-PO286

Keap1 Specific CRISPR/Cas9 Gene Editing in Primary Human T Cells Increases Nrf2 Activity and Anti-Inflammatory Phenotype

Sanjeev Noel, Sul A Lee, Mohamed Sadasivam, Abdel Hamad, Hamid Rabb. Department of Pathology, Johns Hopkins University, Baltimore, MD; Department of Pathology, Johns Hopkins University, Baltimore, MD.

Background: T lymphocytes are established mediators of acute kidney injury (AKI) and other immune mediated kidney diseases. Previous work demonstrated significant protection from AKI in mice with enhanced T lymphocyte specific nuclear factor erythroid-derived 2-like 2 (Nrf2) activity, via deletion of kech like-ECH-associated protein 1 (Keap1). In this study we applied CRISPR technology to edit Keap1, and
enhance Nrf2 activity, in human Jurkat and primary T cells to develop immune cell based therapies.

Methods: We targeted Keap1 exon 2 using site specific guide RNA. Briefly, 5X10^6 cells were electroporated with cas9-guide RNA complex. Control cells were electroporated without cas9-guide RNA complex. Cells were harvested 72h after electroporation and assessed for biochemical parameters and Keap1 gene editing from 40% to 55% Keap1 editing resulted in significant (~9 fold) and ~7 fold in ATTO 550 positive cells.

Conclusions: Gene editing using CRISPR/Cas9 successfully augments Nrf2 activity in human primary T lymphocytes resulting in increased expression of antioxidant genes and reduction in IL-17 expression. This sets the stage for immune cell therapy for AKI and other inflammation mediated diseases.

Funding: NIDDK Support

TH-P0287
Antioxidant Regulation of Alarmin Redox and Function during Sepsis
Wassan Abdulmahdi,1 Devika Patel,2 May M. Rababi,1 Tala F. Azar,2 Edson Jules,1 Anastasios Papangnou,3 Brian B. Ratliff1
1Columbia University Medical Center, New York, NY; 2Westchester Medical Center, Bayside, NY; 3New York Medical College, Valhalla, NY.

Background: During sepsis, oxidative stress is enhanced and the alarmin High Mobility Group Box 1 protein (HMGB1) is released into the circulation from immune, endothelial and kidney epithelial cells. Once in the circulation, HMGB1 can promote systemic inflammation, with the kidney particularly susceptible to damage. However, the severity of the pro-damage signal mediated by HMGB1 is dependent on the alarmin’s redox state. Thus, we examined HMGB1 redox in kidney during sepsis and the ability of endogenous antioxidants to regulate HMGB1 oxidation.

Methods: Lipoxygenase (LPO) was administered at different doses to cells and animals to mimic different severities of sepsis. During LPS treatment, reactive oxygen species (ROS) generation was examined in cell cultures and in animals. After 24 hours of LPS treatment, HMGB1 redox state was examined in the nuclear and cytoplasmic compartments of kidney cells in the presence of Nrf2 agonists. HMGB1 redox detection was also by mass spectrometry (LC/MS/MS) analysis. Glutathione and thioredoxin inhibitors were administered to endothelial and proximal tubule cells to determine their impact on HMGB1 redox during LPS treatment. In addition, HMGB1 (of varying redox state) was isolated from mice that had received high or low LPS dose and was reintroduced to healthy mice for analysis of the alarmin’s pro-inflammatory effects.

Results: CellROX and MitoSOX labeling of LPS-stressed endothelial and proximal tubule cells demonstrated increased ROS generation in cells as sepsis severity increased. Consequently, HMGB1 redox increased in the kidney particularly susceptible to damage. However, the severity of the pro-damage signal mediated by HMGB1 is dependent on the alarmin’s redox state. Thus, we examined HMGB1 redox in kidney during sepsis.

Conclusions: In conclusion, sepsis severity increases, ROS generation and HMGB1 oxidation increases in kidney cells, which enhances HMGB1’s pro-inflammatory signaling. Conversely, the glutathione and thioredoxin systems work to maintain the protein in its reduced state.

TH-P0288
Protective Effects of Brazilian Green Propolis in Sepsis-Induced AKI
Marcelo Sanches,1 Sany D. Silveira,2 Jose Manuel Condor Capcha,1 Talita R. Sanches,1 Roberto D. Moreira,1,2 Margoth R. Garaica,1 Maria H. Shimizu,1 Flavio Teles de Farias Filho,1 Lucila Andrade,1 Nephrology, University of Sao Paulo School of Medicine, Sao Paulo, Brazil; 2Federal University of Goias, Catalao, Brazil; 3UNCISAL, Maceio, Brazil.

Background: The pathophysiology of sepsis involves oxidative stress, as well as inflammatory mediator networks, to which NF-κB and TLR4 activation is central. The pharmacological benefits of propolis have been extensively explored, because it might be an important resource for the prevention and treatment of systemic diseases. Brazilian green propolis (BGP) has garnered attention for its promising anti-inflammatory, antioxidant and immunomodulatory properties. We used a cecal ligation and puncture (CLP) model and BGP treatment in sepsis-related organ dysfunction.

Methods: We divided Wistar rats into groups: sham-operated, CLP; and CLP+BGP (500 mg/kg BW ip, 6 h after CLP). Studies were performed at 24 h post-CLP. Data are means±SD.

Results: Blood GSH was higher in CLP+BGP rats than in CLP rats (0.87±0.4 vs. 0.33±0.0 mg/ml; p<0.001) as was protein expression of MnSOD and eNOS in kidney tissue (138.1±2.7 vs. 100.5±19.7; p<0.01 and 109.3±14.1 vs. 81.2±26.4; p<0.05, respectively) as expression of kidney tissue injury. The expression of TLR4 and NF-κB was lower in CLP+BGP rats than in CLP rats (119.9±11.9 vs. 164.2±26.6; p<0.01 and 93.5±7.1 vs. 132±11.3; p<0.001, respectively). Renal expression of CD68 (positive cells/mm²) was lower in CLP+BGP rats than in CLP rats (3.1±1.0 vs. 7.1±2.0; p<0.05). Apoptosis (TUNEL) in kidneys and lungs was lower in CLP+BGP rats than in CLP (2.9±2.2 vs. 7.6±3.46 positive cells/0.087 mm²; p<0.05 and 0.04±0.03 vs. 0.08±0.06 positive cells/Total Cells; p<0.001, respectively). BAX protein expression in kidney was lower in CLP+BGP rats than in CLP rats (97±10.9 vs. 135±2.47; p<0.01). BGP also improved kidney function, as assessed by urinary excretion of alanine aminotransferase (ALT), asuric acid (UAU) was lower in CLP+BGP rat lungs than in CLP rat lungs (2.3±2.43 vs. 3.6±2.47; p<0.05), as was the number of TLR4+positive cells (0.2±0.09 vs. 0.2±7.10; p<0.001).

Conclusions: In sepsis, BGP protects kidneys and lungs by attenuating oxidative stress and decreasing expression of TLR4 and IL-8.

Funding: None

TH-P0289
Antioxidant-Mediated Improvement of Kidney Function in the Adult LBW Neonate
Lauren M. Nesii,1 May M. Rababi,2 Magdi Abdelrahman,3 Brian B. Ratliff1
1Hodassah Hebrew University Medical Center, Jerusalem, Israel; 2Hadassah-Hebrew University Hospital, Efrat, Israel; 3RENALSENSE LTD, Brookline, MA.

Background: The AKIN and KDIGO criteria for acute kidney injury (AKI) define oliguria as urine output (UO) over 6 hours of less than 0.5 ml/kg/hr. While UO is an available biomarker of kidney function, only a small percentage of AKI studies incorporate UO criteria. In these retrospective studies, hourly UO is often inaccessible, and corresponds to the nursing shift. We developed a prospective observational study using real-time electronic monitoring of UO, and applied the AKIN criteria of UO to identify the oliguric patient in the intensive care unit (ICU).

Methods: 57 General ICU patients in Hadassah Hospital, Israel, were electronically monitored for hourly UO using the RenalSense® Clarity RM™ sterile sensor kit. The device was connected to the Foley catheter and placed on a scientific scale for measurement validation. Patient data was analyzed as follows: AKI defined by the AKIN criteria for oliguria only; NON-AKI UO (n=26), AKI UO Stage 1(n=10), AKI UO Stage 2(n=21). AKI defined by AKIN criteria for SCR only (where available): NON-AKI Scr (n=46), AKI Scr Stage 1(n=6), AKI Scr Stage 2(n=12). Additional analysis using both SCR and UO criteria was performed on all patients.
Results: 54% of patients had AKI according to UO criteria only. Patients with AKI UO Stage 2 received more fluid boluses than NON-AKI UO and AKI UO Stage 1 in the first two 12 hour periods of UO monitoring (p=0.0051 and 0.0091, respectively). Out of 21(43%) patients with AKI UO Stage 2 also had increased SCR. NON-AKI UO had an average ICU stay of 5.7 days, and AKI UO Stage 1 and 2 had 8.6 and 9.9 days respectively (p=0.1049). Using only SCR criteria, NON-AKI AKI SCr averaged 7.1 days in the ICU vs. all stages of AKI SCr of 10.8 days. When both UO and SCR were applied, 40% of patients were NON-AKI and averaged 5.9 days in the ICU. 15% of patients had AKI by both criteria and averaged 13.3 days (p=0.0002).

Conclusions: Studies have shown worse outcomes in patients that fulfill AKIN criteria for both SCr and UO versus SCr alone. Increased SCr alone may be an insensitive indicator of AKI, as ICU patients tend to be fluid overloaded. Our data shows a trend of increased ICU stay when AKI is analyzed according to UO. This unique study presents a tool for future research utilizing reliable real time UO monitoring, where early intervention and appropriate treatment of oliguria may improve outcomes.

Funding: Commercial Support - RenalSense Ltd

TH-PO291
Dose Finding Study for Bardoxolone Methyl and 6-Gingerol as Nephroprotectants against Cisplatin Induced Kidney Injury
Stacey Tuez, Carolyn N. Brown, Charles L. Edelstein, Melanie S. Joy. University of Colorado Anschutz Medical Campus, Aurora, CO.

Background: Nephrotoxicity is a major adverse effect that limits cisplatin (CIS) clinical use. CIS induced kidney injury is in part due to reactive oxygen species. Bardoxolone methyl (BARD) and 6-gingerol (6GNG), have shown nephroprotective properties through antioxidant properties. The purpose of this study was to conduct a dose finding safety study for use of BARD and 6-GNG as nephroprotectants against CIS induced kidney in a mouse model of cancer and cisplatin nephrotoxicity.

Methods: Study mice were injected with CMT167 lung cancer cells. In the first study, BARD (15, 10, or 20 mg/kg) or BARD vehicle (VEH) was given daily for 6 days and one dose of CIS (25mg/kg) was given on day 3 of BARD treatment. In the second study, mice were dosed with 6GNG (25, 50, or 100 mg/kg) or 6GNG VEH 3x weekly and CIS (12.5 mg/kg) or CIS VEH was given 1x weekly for 2 weeks. Treatments were compared to VEH using one-way analysis of variance with Dunnnett’s post-hoc test.

Results: See Table 1

Conclusions: The 10 mg/kg BARD and 50 mg/kg 6GNG demonstrated the best performance in terms of no potential adverse effects on ALT, BUN, and hematocrit and no discernible increases in tumor size. Additionally, these doses appear promising for protection against kidney function and cisplatin-induced anemia as demonstrated by the reduction in BUN and increase in hematocrit, respectively. Future studies will be conducted to confirm safety and efficacy in this mouse model relevant to human CIS nephrotoxicity.

Funding: NIDDK Support

Results:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CIS (mg/kg)</th>
<th>BARD (mg/kg)</th>
<th>6GNG (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT (U/L)</td>
<td>144.5 ± 7.3</td>
<td>71.4 ± 7.1</td>
<td>36.1 ± 7.5</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>33.2 ± 2.6</td>
<td>25.3 ± 2.9</td>
<td>28.3 ± 2.9</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.4 ± 0.2</td>
<td>1.2 ± 0.2</td>
<td>1.0 ± 0.2</td>
</tr>
</tbody>
</table>

*: p<0.05 compared to CIS-VEH

TH-PO292
Prothymosin Alpha-Derived Peptide Prevents Cisplatin-Induced AKI
Kenta Torio,1 Yoko Obata,1 Kiki Torio,1 Takahiro Ari,1 Hiroshi Ueda,1 Tomoya Nishino,2 1Department of Nephrology, Nagasaki University Hospital, Nagasaki, Japan; 2Department of Histology and Cell Biology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan.

Background: Cisplatin is one of the most used drugs for cancer treatment. However, cisplatin induces nephrotoxicity via apoptosis, necrosis or vasoconstriction, and this side effect limits clinical application of cisplatin. Prothymosin alpha (ProTα) is reported to exert protective effects against cisplatin-induced necrosis and apoptosis in the brain and retina. Recently, the 6-amino acid peptide P6Q (NEVDQE), modified active core 6-amino-derived peptide against cisplatin-induced acute kidney injury (AKI).

Methods: In vitro study, HK-2 cells were treated with cisplatin (12.5µM) for 24hr to evaluate the cell viability by MTT assay. ProTα protein (0-40µM) or P6Q (0-100µM) was added 30 minutes before cisplatin treatment. In vivo study, 8 week old male Wistar rats were divided into 3 groups: vehicle-treated group, cisplatin (8mg/kg)-treated group, cisplatin-treated group with P6Q (30mg/kg) injection. P6Q was injected 30 minutes before cisplatin treatment. Renal function was assessed by measuring serum creatinine. Renal histological change was assessed by PAS staining, and apoptosis of renal tubal cell was assessed by active caspase 3 and TUNEL staining. Renal hypoxia was assessed by HIF1α staining.

Results: Cisplatin treatment reduced the viability of HK-2 cells in vitro. Administration of ProTα improved cell viability dose-dependently. Furthermore, P6Q administration was more effective to suppress the cytotoxicity by cisplatin compared with ProTα. Thus, we further examined the protective effect of P6Q against cisplatin-induced AKI in vivo. Serum creatinine level peaked at 5 days after cisplatin treatment. Histologic examination revealed extensive tubular damage in cisplatin-treated rats. Cisplatin treatment also increased the active caspase 3 positive area, number of TUNEL-positive apoptotic cells and HIF1α positive area at day 5. P6Q injection significantly suppressed cisplatin-induced AKI and apoptosis of tubular cells, but not HIF1α expression.

Conclusions: We showed the renoprotective effect of ProTα-derived peptide against cisplatin-induced AKI via suppression of apoptosis. Our results suggest that ProTα-derived peptide may become a preventive drug for cisplatin-induced AKI.

TH-PO293
Ischaemic Preconditioning of the Kidney: Total RNA Sequencing and Ingenuity Pathway Analysis
David A. Foxwell,1 Usman Khalid,2 Robert Andrews,1 Gilda Pino-Chavez,2 Rafael E. Chavez,3 Timothy Bowen,1 Donna Fraser1,1Cardiff University, Cardiff, United Kingdom; 1University Hospital of Wales, Cardiff, United Kingdom.

Background: Ischaemia-Reperfusion Injury (IRI) is a common cause of Acute Kidney Injury (AKI). Clinical trials and animal models shows that Ischemic Preconditioning (IPC), delivered directly (to the tissue) or indirectly (to other tissues), may confer protection. However, reported efficacy is variable, and development of IPC as a therapy is hampered by the current lack of detailed mechanistic understanding. The purpose of the current study was to establish the main IPC response pathways in the protected kidney, and the extent of similarity between direct and indirect IPC.

Methods: Stepwise variation in warm ischemic time was used to develop moderate AKI in the rat (defined as Creatinine ≥1.5x sham baseline creatinine; negative control) and pulsatile, continuous, direct and indirect IPC approaches were systematically compared.

Results: Optimum benefit was observed with direct pulsatile IPC and indirect aortic IPC. Subsequently, an unbiased transcriptomic profiling of whole kidney was performed using RNA-Sequencing in animals treated with these optimum direct and indirect IPC approaches. Six animal groups were compared per experimental group (n=24), at a mean paired end sequencing depth of 23.2 million reads, mapping to 17,800 unique genes. Robust differences between groups were observed (IRI vs Sham: 2,193 genes differentially regulated to a Log2FC ≥1 or ≤-1 and a corrected p<0.04). Ingenuity Pathway Analysis revealed upregulation of pathways linked to inflammatory response, oxidative stress and cell cycle regulation in response to IRI, and reduction in oxidative stress, inflammation and cell cycle checkpoint regulation with IPC.

Conclusions: Together, the results displayed a molecular signature of IRI consistent with previous studies and, for the first time, uncovered a detailed IRI protection that was shared between direct and indirect approaches. Our data provide novel insights into the pathogenicity of IRI injury and IPC signal, highlighting possible therapeutic targets for future investigation.

TH-PO304
Elucidation of Mechanism for Indoxyl Sulfate (IS)-Promoted Renal Fibrotic Response in HK-2 Cells under Hypoxic Condition and Mice with Ischemia-Reperfusion (IR)-Induced AKI
Mami Yamashita,1 Moe Eto,1 Go Yoneda,1 Rika Fujino,1 Hirofumi Jono,2 Hideyuki Saito,2,3 Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan; 2Kumamoto University Hospital, Kumamoto, Japan.

Background: IR-induced acute kidney injury (AKI) is known to be a trigger for the development of renal fibrosis followed by the progression to chronic kidney disease. Under ischemia-caused hypoxia of the kidney, tubulointerstitial fibrosis is enhanced with the increased accumulation of matrix proteins such as collagen. A typical sulfate-conjugated uremic solute, IS, is known to be produced in the liver and accumulated in serum and renal tissue under IR-induced AKI, thereby promoting fibrotic responses. However, precise molecular mechanisms involved in IS-promoted renal fibrosis under hypoxia has not been elucidated. In this study, we examined the molecular biological effect of IS on fibrotic responses under hypoxic condition using HK-2 cells and IR-induced AKI model mice.

Methods: C57BL6 mice (8-weeks old) were treated with IS or vehicle (control) intraperitoneally, after subjected to 20 min of renal IR. In IR-AKI mice, serum creatinine (SCr), BUN and serum IS levels were determined. HK-2 cells were cultivated in the medium with or without IS or vehicle. Hypoxic treatment of HK-2 cells was performed using AnaeroPack System™. mRNA expression of fibrosis-related gene including transforming growth factor (TGF)-β and plasminogen activator inhibitor (PAI)-1 were determined in the kidney of AKI mice and HK-2 cells cultured under normal oxygen or hypoxic condition.

Results: IR treatment of murine kidney caused a marked elevation in SCr and BUN 24 hr after surgery. Administration of IS in IR-AKI mice synergistically enhanced these increases in SCr (2.2-fold vs control) and BUN (1.5-fold). Expression of PAI-1 mRNA was increased in IR-AKI mice (3.4-fold), and HK-2 cells (1.7-fold) under both hypoxic condition and IS treatments, compared with those under normal oxygen condition. GLUT1 mRNA expression, a downstream gene of hypoxia-inducible factor, was also elevated significantly under both hypoxia and IS treatments. By hypoxia and IS treatments, TGF-β mRNA expression was also shown worsened, whereas LY2157299, a TGF-β receptor type 1 inhibitor, suppressed dose-dependently PAI-1 expression induced by hypoxia with simultaneous addition of IS.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: IS could play important roles in promoting renal fibrosis via TGF-β-mediated up-regulation of fibrotic gene expression under hypoxic condition. Funding: Government Support - U.S.

TH-PO295

Early Teriparatide Treatment for Hemorrhagic Shock-Induced AKI

Leticia U. De Castro, Denise A. Otsuki, Talita R. Sanches, Débora R. Maia, Jose Manuel Condor Capcha, Denise M. Malheiros, Luiz M. Malbouisson, Lucía Andrade. University of Sao Paulo School of Medicine, Sao Paulo, Brazil.

Background: Although hemorrhagic shock (HS) remains the leading cause of mortality, early vasopressor use might restore hemodynamic parameters and vital organ perfusion, thereby reducing the need for aggressive fluid therapy and avoiding fluid overload. However, that strategy has yet to be included in the Advanced Trauma Life Support guidelines. This study aimed to compare the effects of three different levels of lactated Ringer’s (LR) fluid therapy—aggressive (3x the blood volume replaced, 3LR), conservative (2x the blood volume removed, 2LR) and low (1x the blood volume removed, 1LR)—with or without teriparatide (TLP), on acute kidney injury (AKI) in rats with HS.

Methods: We induced rats to HS, maintaining mean arterial pressure (MAP) at 30-40 mmHg for 60 min and thereafter submitting them to 30 min of LR fluid therapy, some rats also receiving TLP (10 µg/100 g BW, iv). Rats with HS were divided into 3 groups: 3LR, 1LR+TLP and 2LR+TLP. At 15 min after the end of the fluid therapy, the rats were resuscitated with the blood drawn previously. With the exception of MAP, which was measured at various time points, all studies were performed 24 h after HS induction. Data are means±SEM.

Results: Mortality was 28%, 16% and 0% in 3LR, 1LR+TLP and 2LR+TLP rats, respectively. Creatinine clearance was higher in 2LR+TLP rats than in 1LR+TLP and 3LR rats (1.2±0.13 vs. 0.72 ± 0.1 and 0.53±0.2 ml/min/100 g BW, p<0.05). At 45 min after HS induction, MAP was higher in 2LR+TLP and 1LR+TLP rats than in 3LR rats. The acute renal necrosis score was lower in 2LR+TLP rats than in 1LR+TLP and 3LR rats (5.8±0.8 vs. 14.2±3.5 and 18.4±3.4, p<0.05). Protein expression of MnSOD was higher in 2LR+TLP than in 1LR+TLP and 3LR rats (130±7.1 vs. 110±4.5 and 103±4.3, p<0.05). AQP2 expression was higher in 2LR+TLP and 1LR+TLP rats than in 3LR rats. TRP4 protein expression was lower in 2LR+TLP rats than in 1LR+TLP and 3LR rats (95±4.2 vs. 134±6.8 and 115±5.0%, p<0.05). There was less apoptosis (TUNEL-positive cells/0.87 mm2) in 2LR+TLP rats than in 1LR+TLP and 3LR rats (0.6±0.1 vs. 4.5±2.5 and 1.6±0.3, p<0.05).

Conclusions: Combining TLP with conservative fluid therapy appears to be a viable therapy for HS-induced AKI. We speculate that TLP attenuates AKI by modulating the inflammatory response via the TLR4 pathway. (FAPESP) Funding: Government Support - Non-U.S.

TH-PO296

ZO-1 Protein Is Required for H2O2-Induced, ERK 1/2-Dependent Increase in MDCK Cell Paracellular Permeability

Sahar Bilal, Shirin Jaggi, Angelina Voronina,2 Shirin Watari, Josephine Aixi,1 Jessica Janovic,2 Kurt Amstel.1 Biomedical Sciences, NYIT College of Osteopathic Medicine, Old Westbury, NY; 2NYIT College of Osteopathic Medicine, Old Westbury, NY; 3Indiana University School of Medicine, Indianapolis, IN.

Background: Tight Junctions (TJ) are complexes of multiple proteins on the apical membrane of adjacent epithelial cells that interact to form a selectively permeable paracellular barrier. Hydrogen peroxide (H₂O₂) treatment increases renal epithelial paracellular permeability but the mechanism(s) mediating this effect are unclear. Previous studies suggest kinase-mediated regulation may influence paracellular permeability. In this study, we examined the roles of ERK 1/2 activation and of specific TJ proteins (occludin, ZO-1, ZO-2) in H₂O₂-induced paracellular permeability in renal epithelial cell monolayers.

Methods: Paracellular permeability via the leak pathway (large solutes) was measured as transepithelial movement of calcine, a fluorescent dye, across monolayers of wild type and knockdown MDCK cells grown on permeable membrane filters. H₂O₂ and inhibitors were added prior to measurement of calcine flux. ERK 1/2 activation and TJ protein content were monitored by immunoblot.

Results: Treatment of MDCK cells with H₂O₂ at non-toxic concentrations increased both ERK 1/2 activation and paracellular calcine flux rate in a concentration-dependent manner. ERK 1/2 activation occurred within 30'. Inhibition of ERK 1/2 activation by U0126 blocked the ability of H₂O₂ to increase paracellular calcine movement. Knockdown of either occludin or ZO-2 protein did not block the ability of H₂O₂ to increase paracellular calcine movement nor its inhibition by U0126. In contrast, knockdown of ZO-1 protein, which links the TJ to the actin cytoskeleton, blocked the ability of H₂O₂ to increase paracellular calcine flux. H₂O₂ treatment also altered F-actin organization of confluent MDCK cells, including disruption of actin stress fibers.

Conclusions: We demonstrate that H₂O₂ treatment of renal epithelial cells activates ERK 1/2 which is required for H₂O₂ to increase MDCK cell paracellular permeability. ZO-1 protein, but not ZO-2 or occludin protein, is required for H₂O₂ to increase MDCK cell paracellular permeability. The protein links the TJ to the actin cytoskeleton; these results may implicate ERK 1/2 modulation of the actin cytoskeleton in mediating the ability of H₂O₂ to increase MDCK cell paracellular permeability.

Funding: NIDDK Support

TH-PO297

RNA-Seq Analysis of Mice Exposed Acutely to Low Levels of Domic Acid

Eran H. Goren,1 Robert G. Thompson,2 Lan He,3 P. Darwin Bell,3 1University of Alabama at Birmingham, Birmingham, AL; 2University of Alabama at Birmingham, Birmingham, AL; 3University of Alabama at Birmingham, Birmingham, AL.

Background: Domic acid (DA) is produced by diatoms of the genus Pseudo-nitzschia. Exposing mammals to this glintuate analog causes a neurologic condition known as amnesic shellfish poisoning. Recently we reported that very low levels of DA (Funk, JASN 2014) are highly toxic to the kidney. DA activates ionotropic receptors in the kidney which could have multiple cellular effects on renal epithelial cells. To begin a mechanistic understanding of the renal effects of DA on kidney, we undertook RNA sequencing (RNA-Seq) studies designed to investigate how acute exposure to low levels of DA affects kidney gene expression.

Methods: Mice were injected IP with 0.05 mg/kg DA and their kidneys were harvested after 0, 15, 30, and 60 min. Total kidney RNA was isolated for RNA-Seq analysis and a sequencing library was generated using the SureSelect Strand stranded RNA kit (Agilent Technologies).

Results: RNA-Seq analyses showed DA treatment affected 41 differentially-expressed-genes (DEG) that were at least 2-fold-up or down-regulated (p<0.05). In particular systems analyses indicate that genes involved in (i) lipid metabolism [Anpgr4, Star], (ii) terminal cellular oxidation [Cyp11a1, Cyp11b1, Cyp21a1, Cyp24a1], and (iii) plasma membrane transport [Slc22a6, Slc22a2, Slc22a6, Slc22a5] respond to DA.

Conclusions: These data reveal a complex mechanistic response by the kidney to DA. Future studies will build on and expand this intriguing preliminary data to unravel the untoward biological effects of DA.

Funding: Other NIH Support - P30 awarded to Dr Darwin Bell, Veterans Affairs Support

TH-PO298

NAD⁺ Augmentation Ameliorates Cisplatin Toxicity via Enhanced Autophagy

Matthew R. Lynch, Kenneth M. Raito, Mei T. Tran, Sanir M. Parikh. Nephrology, Beth Israel Deaconess Medical Center, Boston, MA.

Background: We recently reported that renal NAD⁺ (nicotinamide adenine dinucleotide) concentrations decline markedly in diverse etiologies of AKI and showed that nutritional NAD⁺ augmentation can treat experimental post-ischemic AKI. Downstream salutary mechanisms of NAD⁺ augmentation are incompletely understood. Based on evidence linking impaired autophagy to cisplatin-induced renal tubular injury, we hypothesized that NAD⁺ augmentation may enhance resistance to cisplatin by increasing autophagy.

Methods: Murine intermedullary collecting duct (IMCD3) cells were pre-treated with the NAD⁺-precursor NMN (nicotinamide mononucleotide) or vehicle for one hour before cisplatin. Cell survival was assessed by automated trypan blue. RNA and protein were isolated for quantitative PCR measurement of autophagy related genes and autophagic flux by western blot, respectively. Acidified lysosomes were imaged using LysoTrackr DND-99.

Results: NMN supplementation increased NAD⁺ levels at baseline and preserved NAD⁺ levels despite cisplatin exposure. NMN-treated cells better tolerated cisplatin stress whereas the lysosomal inhibitor chloroquine exacerbated cisplatin toxicity. NMN enhanced expression of autophagy genes (p < 0.05). Finally, NMN-supplemented cells maintained lysosomes in a favorable low-pH-state (Figure 1).

Conclusions: Addition of NMN enhanced autophagy after cisplatin exposure. Autophagic gene and protein levels, along with lysosomal imaging, implicate NMN-related increase in autophagy. NAD⁺ augmentation may therefore counteract cisplatin-induced renal injury by promoting autophagy.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Inhibition of Bromodomain Protein BRD4 Suppresses Cisplatin Induced p53 Activation and Apoptosis in Renal Tubular Cells

Xia Zhou, Xiaogang Guan, Wenguang Feng, Iijoma E. Obi, Jennifer S. Pollock, Paul W. Sanders, Edward W. Inscho. University of Alabama at Birmingham, Birmingham, AL.

Background: Inflammation and increased reactive oxygen species (ROS) contribute to impaired renal autoregulatory capability under pathological conditions. We showed that renal ischemia-reperfusion (IR) impairs renal autoregulation in rats 24 hours after IR, but was restored by acute exposure to the ROS scavenger, tempol. We postulated that chronic tempol treatment would reduce renal inflammation and preserve autoregulation in IR rats.

Methods: Renal IR was induced by bilateral renal artery occlusion (60 min). Renal cortical mRNA expression was measured for NADPH oxidase subunits, cytokines and adhesion molecules. Autoradiographs were imaged with the in vivo blood-perfused juxteduillary nephron preparation on day 7 post IR.

Results: Renal IR significantly increased mRNA expression for p47phox, p67phox, GP91phox, MCP-1, TGF-β, TNF-α, P-selectin, VCAM and ICAM vs. sham kidneys (n=6/each group). Tempol pre-treatment (2 mM in drinking water) suppressed the IR-induced increase in mRNA expression for all parameters except TGF-β and TNF-α. IR also impaired afferent arteriole autoregulatory behavior. Basilar arteriole diameters were similar in sham, IR and tempol-treated IR kidneys at a renal perfusion pressure (RPP) of 100 mmHg and averaged 13.4±0.3, 11.7±0.8 and 13.4±1.2 µm (n=4-5/each, respectively). Decreasing RPP from 100 to 65 mmHg increased diameter in sham rats by 18±6%. Subsequent increases in RPP (15 mmHg) caused pressure-dependent vasoconstriction and reduced diameter by 30±5% at 170mmHg. In contrast, pressure-mediated diameter changes were blunted in IR rats. Diameter increased by 5±2% and decreased by just 8±8% at 65 and 170 mmHg, respectively (P<0.05 vs sham).

Conclusions: In conclusion, these results demonstrate that IR causes renal inflammation and impaired afferent arteriole autoregulatory capability. Scavenging ROS accumulation with tempol preserves normal autoregulatory reactivity, indicating that excess ROS accumulation contributes importantly to impaired renal autoregulation in IR rats.

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

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

Underlines represent presenting author.
IGFB-7 and TIMP-2 could be detected starting from 3.0-4.5 ml of urine. Interestingly, the expression of IGFB-7 and TIMP-2, approved early biomarkers of acute kidney injury (AKI), underlines the important role of tubulointerstitial (TIs) in the detection and assessment of urinary biomarkers.

Conclusions: Depending on the sensitivity of the technique in use, a minimal volume of 0.5 ml urine is sufficient for a single analysis; however for multi-analysis the volume of urine depends on the limit of detection of the techniques in use.

Funding: Other NIH Support - k award 1K23HL126101

TH-PO303

Outer Stripe of the Outer Medulla in Human and Pig Kidney Is Markedly Reduced or Absent Compared to Rat Thomas L. Pannabecker,1 Seymour Rosen,1 1Beth Israel Deaconess Medical Center, Boston, MA; 2University of Arizona, Tucson, AZ.

Background: In the rat inner and outer stripes of the outer medulla (ISOM, OSOM), there are clear, functionally defined architectural features that lead to physiologically significant nephron and vascular flows. The dynamics of these flows define, in part, our view of conditions such as hypoxia, ischemia, progression of AKI, injury, oxygen delivery and the urine concentrating mechanism. The human and pig medullary architecture differ from the rat in distinct ways, consistent with published observations from the first decade of the 20th century that suggested the human OSOM, along the corticomedullary axis, has minimal depth.

Methods: We investigated architecture of the human, pig and rat medulla near the corticomedullary junction using tissue embedded in paraffin or resin, followed by sectioning and staining with conventional histochimical (H&E) and immunohistochemical techniques (antibodies for aquaporin1, smooth muscle actin, CD34 and urea transporter UTB and wheat germ lectin). Sections were viewed and photographed using conventional microscopy.

Results: The rat OM has two distinct zones (ISOM, OSOM). The human equivalent of the OM is a single zone whose tubular/vascular structure is largely similar to the rat ISOM. The human basal cortex is almost completely composed of medullary rays, which merge confluent with this single zone (ISOM). The human glomerular efferent arterioles cluster to form the most superficial aspect of the outer medullary vasa recta, which descend, accreting a venous component to form an exclusively arterio-venous structure, in contrast to the rat, which also includes thin limbs. The ascending vasa recta bundles of the deeper ISOM become, in the superficial ISOM, composite groupings of venous vasa recta, collecting ducts and thin ascending limbs fusing with medullary rays.

Conclusions: Our studies suggest that in human and pig, the OSOM, as defined by the degree of tubular/vascular arborization, is minimal or absent. Importantly, vascular perfusion of nephron segments in the OM and the deep cortex follows patterns that differ from rat. Re-evaluation of vascular architecture and expected blood flows in human and pig models may provide insights into a number of renal disorders that have resisted advances in treatment and may challenge the use of rat and mouse experimental models that regard outer stripe injury as parallel to human AKI.

Funding: NIDDK Support, Other U.S. Government Support

TH-PO304

Cisplatin-Induced AKI: Proteomic and Transcriptomic Analysis Unravels Molecular Correlates of the Protective Effect of Caloric Restriction and Hypoxic Preconditioning Martin Späth,1 Malte P. Bartram,2 Karla J. Hoyer,2 Volker R. Burst,3 Roman-Ulrich Mueller,3 Markus M. Rinschen,3 CE-CAD, Cologne, Germany; 2Department II of Internal Medicine and Center for Molecular Medicine Cologne, University of Cologne, Cologne, Germany.

Background: Acute kidney injury (AKI) is a strong risk factor for cardiovascular morbidity and chronic kidney disease, but causal treatment is still missing. In animal models it can be reduced by preconditioning protocols, but little is known about the underlying molecular mechanisms. We aimed for identifying these in two modes of preconditioning.

Methods: 20-week-old C57Bl6-wildtype mice were treated intraperitoneally with cisplatin comparing mice preconditioned by hypoxia (HP) or caloric restriction (CR) to controls. All mice were phenotyped (plasma creatinine, blood urea nitrogen, histology) and a proteomic and transcriptomic analysis of the renal cortex was done. Additionally we analyzed the whole-cell proteome in cultured proximal tubular cells after cisplatin damage.

Results: CR completely prevented AKI and HP showed a significant damage reduction. Cisplatin-administration led to a significant increase of extracellular matrix-, complement- and MHC-proteins, in addition to several known markers for AKI. Kinases, receptors and ubiquitin ligases, potential therapeutic targets, were increased in cisplatin-treated kidneys. Brush-border and transport proteins were reduced. Treatment of tubular cells showed that the above mentioned findings can be partly recapitulated in vitro. The integration of the proteomic with the transcriptomic showed the largest posttranscriptional changes in mice only treated with cisplatin. The proteomic data was correlated with plasma kidney function values. A positive correlation of extracellular proteins and a negative correlation of brush-border proteins with the damage were shown. A bioinformatic integration of a text-mining-analysis with the correlation-analysis led to a prediction of new “damage-associated-molecular-patterns” partially strongly correlating (R=0.8) with the kidney function. Proteins related to fatty acid synthesis were increased in kidneys of calorie restricted animals, suggesting that increased renal fatty acid synthesis may be involved in renoprotection.

Conclusions: In conclusion these data shows mechanistic insights of the protective effect of preconditioning in cisplatin-induced AKI and the potential of proteome-phenotype-correlations in nephrological basic science.

TH-PO305

Activation of Endoplasmic Reticulum Stress Response by Enhanced Polyamine Catabolism Plays an Important Role in Cisplatin-Induced AKI Kamyr A. Zahedi,1,2 Sharon L. Barone,1,2 Marybeth Brooks,1 Manoocher Soleimani,1,2 University of Cincinnati, Cincinnati, OH; 3Research Services, Veterans Administration, Cincinnati, OH.

Background: Cisplatin is a commonly used and highly effective chemotherapeutic agent utilized for the treatment of a variety of solid tumors. Despite its effectiveness, cisplatin usage is limited due its nephrotoxic side effects. More than 25% of patients treated with cisplatin develop renal failure and have to discontinue treatment. The expression of enzymes involved in polyamine catabolism, spermidine/spermine N1-aceetyltransferase (SSAT) and spermine oxidase (SMOX) increase in the kidneys of mice treated with cisplatin. We hypothesized that enhanced polyamine catabolism contributes to tissue damage in cisplatin acute kidney injury (AKI).

Methods: Using knockout mice and chemical neutralization of toxic products of polyamine degradation, the role of polyamine catabolism in cisplatin AKI was examined.

Results: Deficiency of SSAT, SMOX or neutralization of the toxic products of polyamine degradation, H2O2 and aminopropanal, significantly diminished the severity of cisplatin AKI. In vitro studies demonstrated that the induction of SSAT and elevated polyamine catabolism in cells increases the phosphorylation of eukaryotic translation initiation factor 2a (eIF2a), and enhances the expression of binding immunoglobulin protein (BIP/GRP78) and CCAAT-enhancer-binding protein homologous protein (CHOP/ GADD153). The increased expression of endoplasmic reticulum stress response (ERSR) markers was accompanied by the activation of caspase-3. These results suggest that enhanced polyamine degradation in cisplatin AKI may lead to tubular damage through the induction of ERSR and the consequent onset of apoptosis. In support of the above, we demonstrate that the ablation of the SSAT or SMOX gene, as well as the neutralization of polyamine catabolism products modulate the onset of ERSR (e.g. lower BIP and CHOP) and apoptosis (e.g. reduced activated caspase-3).

Conclusions: These studies indicate that enhanced polyamine catabolism and its toxic products are important mediators of ERSR and critical to the pathogenesis of cisplatin AKI.

Funding: Veterans Affairs Support

TH-PO306

NHERF1 Deficiency Increases Susceptibility to Cisplatin-Induced AKI Adrienne M. Bushau,2 Caryl Conklin,3 Michelle T. Barati,2 Susan C. Coventry,1 Tess Dupre,1 Leah J. Siskind,2 Michael E. Bri er,2 Syed J. Khundmiri,1 Kenneth Gagnon,2 Eleanor D. Lederer,3 Howard University College of Medicine, Washington, DC; 1University of Louisville, Louisville, KY; 2University of Louisville; Robley Rex VA Medical Center, Louisville, KY.

Background: Acute kidney injury (AKI) develops in 30% of patients who receive cisplatin (CIS), a widely used chemotherapeutic agent. We have demonstrated that NHERF1 deficiency increases susceptibility to cisplatin AKI by enhanced endoplasmic reticulum stress response (ERSR).

Methods: To test this hypothesis, we treated 2 month old male and female wild type (WT) C57BL/6 and NHERF1 knock out (KO) mice with vehicle or CIS (20 mg/kg dose IP) and euthanized after 72 hours. Blood was collected for blood urea nitrogen (BUN) levels. Kidneys were harvested for histology, TUNEL assay, RT-qPCR of Kidney Injury Molecule-1 (KIM-1), and Western Blot for eIF2α, GRP78, and AMPK.

Results: Significantly greater severity of injury was seen in CIS treated NHERF1 KO mice compared to WT mice as demonstrated by semi-quantitative injury score (p=0.001) and by BUN levels (WT 97.8 mg/dL +/- 10.01 vs KO 151.8 mg/dL +/- 17.2) (p=0.05). KIM-1 mRNA expression was significantly increased in both CIS treated WT (2063.7 fold control +/- 864.4) and NHERF1 KO mice (3802.1 +/- 2132.0) (p<0.05) in comparison to vehicle treated mice. TUNEL assay analysis showed significant increases in both NHERF1 KO (12.5 no. nuclei/ no. visual fields +/- 3.2) and WT (10.3 +/- 1.4) (p<0.001) and by BUN levels (WT 97.8 mg/dL +/- 10.01 vs KO 151.8 mg/dL +/- 17.2) (p<0.05). KIM-1 expression was upregulated by 12.5 fold in CIS treated WT and NHERF1 KO mice. There was no difference in expression of GRP78 and p-eIF2α between WT and NHERF1 KO mice or in proximal tubule cell expression of pAMPK. There were no significant gender differences found between WT and NHERF1 KO mice for any of the measured parameters.

Conclusions: We conclude that NHERF1-deficient mice show an increase in susceptibility to CIS-induced AKI that is not due to an underlying increase in ER stress or a decrease in cell energy levels.

Funding: Veterans Affairs Support, Clinical Revenue Support
**TH-PO307**

**Experimental Confirmation of the Toxico-Pharmacological Role of Sulfate-Conjugated Uremic Solutes in Cisplatin Nephropathy**

Rika Fujimoto,1 Shohei Unoki,1 Hitomi Tanaka,1 Keisuke Matsushita,1 Go Yoneda,2 Shunsuke Miyake,1 Hirofumi Jono,2 Hideyuki Saito2,3

1Kumamoto University Graduate School of Pharmaceutical Sciences, Kumamoto, Japan; 2Kumamoto University Hospital, Kumamoto, Japan.

**Background:** The toxicological process leading to cisplatin-injured nephropathy is known to be caused by accumulation of IS, including inflammatory responses, oxidative stress, DNA damage and apoptosis in renal tubules. We have reported that indoxyl sulfate (IS), a typical uremic toxin generated by hepatic sulfate-transferase-mediated sulfitation of indoxyl, accumulates markedly in serum and several tissues of animal models with cisplatin-induced acute kidney injury (AKI). AST-120, an orally administered spherical carbon adsorbent, suppressed the renal IS accumulation in association with a significant nephroprotective effect. The present study was aimed to confirm the toxico-pharmacological role of sulfate-conjugated uremic solutes, IS and p-cresylsulphate (PCS), in cisplatin-injured AKI models.

**Methods:** SD rats or C57BL/6 mice were treated with cisplatin (20 mg/kg body weight) by intraperitoneal injection. Serum and tissues were collected periodically after cisplatin administration. IS and PCS levels in serum and tissues were determined by LC-MS. Accumulation of IS and 4-Hydroxy-2-nonenal (4-HNE), an oxidative stress marker, in renal tissue was examined by immunohistochemical method.

**Results:** We developed an in vitro screening system for exploring inhibitors of hepatic production of IS. By using the screening system, we found that some compounds had a potent inhibitory effect on hepatic IS production. Administration of these compounds to rats with cisplatin-injured AKI ameliorated the disturbed renal function with the suppression of serum and tissue IS levels. In C57BL/6 wild type (WT) mice and sulfate-transferase -1A1 gene-deficient mice (Sulf1A1−/−) treated with cisplatin, renal function was preserved (BUN, 193.5 µg/dl in WT vs 84.7 µg/dl in Sulf1A1−/−, p < 0.01; Cr, 1.40 mg/dl in WT vs 0.42 mg/dl in Sulf1A1−/−, p < 0.01) in association with the marked suppression of serum IS and PCS levels (IS, 88.3 µM in WT vs 20.0 µM in Sulf1A1−/−, p < 0.01; PCS, 41.0 µM in WT vs 0.1 µM in Sulf1A1−/−, p < 0.01). Renal accumulation of IS, PCS and 4-HNE were markedly reduced in Sulf1A1−/− compared with those in WT.

**Conclusions:** IS and PCS appeared to be key progression factors in cisplatin-induced AKI via producing oxidative stress, suggesting that hepatic Sult1A1 could be a therapeutic target for cisplatin nephropathy.

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

---

**TH-PO308**

**Renal Selective Mesoscale Nanoparticles to Treat AKI**

Edgar A. Jaines,1,2 Ryan M. Williams,2 Janki Shah,2 Elizabeth Mercer,1 Daniel A. Heller,1

1Indiana University School of Medicine, Evansville, IN; 2MSKCC, NY, NY; 3Memorial Sloan Kettering Cancer Center, New York, NY; 4Memorial Sloan-Kettering Cancer Center, New York, NY; 5Weill Cornell Medical College, New York, NY.

**Background:** Acute kidney injury (AKI) accounts for 1% of hospital admissions and up to 25% of patients in intensive care develop AKI. As many as 25% of these patients require renal replacement therapy and have high mortality rates. Despite the incidence and associated morbidities, there are no proven or effective therapies for AKI of different etiologies, including inflammatory responses, oxidative stress, DNA damage and apoptosis in renal tubules. We have reported that indoxyl sulfate (IS), a typical uremic toxin generated by hepatic sulfate-transferase-mediated sulfitation of indoxyl, accumulates markedly in serum and several tissues of animal models with cisplatin-induced AKI. AST-120, an orally administered spherical carbon adsorbent, suppressed the renal IS accumulation in association with a significant nephroprotective effect. The present study was aimed to confirm the toxico-pharmacological role of sulfate-conjugated uremic solutes, IS and p-cresylsulphate (PCS), in cisplatin-injured AKI models.

**Methods:** SD rats or C57BL/6 mice were treated with cisplatin (20 mg/kg body weight) by intraperitoneal injection. Serum and tissues were collected periodically after cisplatin administration. IS and PCS levels in serum and tissues were determined by LC-MS. Accumulation of IS and 4-Hydroxy-2-nonenal (4-HNE), an oxidative stress marker, in renal tissue was examined by immunohistochemical method.

**Results:** We developed an in vitro screening system for exploring inhibitors of hepatic production of IS. By using the screening system, we found that some compounds had a potent inhibitory effect on hepatic IS production. Administration of these compounds to rats with cisplatin-injured AKI ameliorated the disturbed renal function with the suppression of serum and tissue IS levels. In C57BL/6 wild type (WT) mice and sulfate-transferase -1A1 gene-deficient mice (Sulf1A1−/−) treated with cisplatin, renal function was preserved (BUN, 193.5 µg/dl in WT vs 84.7 µg/dl in Sulf1A1−/−, p < 0.01; Cr, 1.40 mg/dl in WT vs 0.42 mg/dl in Sulf1A1−/−, p < 0.01) in association with the marked suppression of serum IS and PCS levels (IS, 88.3 µM in WT vs 20.0 µM in Sulf1A1−/−, p < 0.01; PCS, 41.0 µM in WT vs 0.1 µM in Sulf1A1−/−, p < 0.01). Renal accumulation of IS, PCS and 4-HNE were markedly reduced in Sulf1A1−/− compared with those in WT.

**Conclusions:** IS and PCS appeared to be key progression factors in cisplatin-induced AKI via producing oxidative stress, suggesting that hepatic Sult1A1 could be a therapeutic target for cisplatin nephropathy.

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

---

**TH-PO309**

**Systemic Effects of Long-Acting Albumin-Thioredoxin Fusion Proteins against Distant Organ Injury Following AKI**

Hiroshi Watanabe,1 Masafumi Fukagawa,2 Toru Maruyama,3

1Department of Biopharmaceutics, School of Pharmacy, Kumamoto University, Kumamoto-shi, Japan; 2Tokai University School of Medicine, Isehara, Japan.

**Background:** The high mortality of acute kidney injury (AKI) is associated with distant organ injury via its extended effects of modulating oxidative stress and inflammation. AKI-induced distant organ injury mice were produced by renal ischemia reperfusion injury (IRI).

**Results:** A pharmacokinetic study of HSA-Trx or Trx in mice showed that the plasma retention of Trx was markedly increased by fusion with HSA. HSA-Trx treatment attenuated the renal IRI-induced decline in renal function and histological alterations. HSA-Trx also attenuated not only lung injury, including increased neutrophil infiltration, vascular hyperpermeability and alveolar expansion, but also liver injury, including elevated aspartate aminotransferase and alanine aminotransferase following renal IRI. In plasma, the elevation of inflammatory cytokine was suppressed by HSA-Trx treatment. In kidney, lung and liver, HSA-Trx suppressed the number of apoptosis-positive cells, cytokine and chemokine mRNA expression and oxidative stress. The administration of HSA-Trx resulted in a significant increase in survival rate, with 55% of the mice being alive at 7 days after the renal IRI.

**Conclusions:** HSA-Trx has potential for use in the treatment of AKI-induced distant organ injury via its extended effects of modulating oxidative stress and inflammation.

---

**TH-PO310**

**Worsened Renal Fibrosis in Kras4bG12D Lung Adenocarcinoma-Bearing Mice Treated with Repeated Dosing of Cisplatin May Be EGFR-Mediated**

Cierra Sharpp,1 Mark A. Doll,2 Tess Dupre,3 Levi J. Beverly,4 Laccattra Cierra,1,2 University of Louisville, Louisville, KY; 3University of Louisville, Louisville, KY; 4University of Louisville, Louisville, KY.

**Background:** Cisplatin (CDDP) is a first choice therapy for many solid cancers, but 30% of patients develop nephrotoxicity leading to acute kidney injury (AKI). AKI is defined as the rapid loss of renal function, marked by an increased mortality rate. Recent large-scale, longitudinal studies have indicated that AKI can progress to chronic kidney disease (CKD), which also has an increased mortality rate. Currently, there are no therapeutic interventions for AKI or CKD sustained from CDDP treatment. This may be due to the fact that the mouse model used to study CDDP AKI utilizes non cancer mice that are treated with one, high dose of CDDP leading to death 3-4 days after injection. Clinically, only cancer patients receive CDDP, and it is administered in low doses over an extended period of time to curtail CDDP nephrotoxicity.

**Methods:** We optimized a repeated dosing model of CDDP (7 mg/kg 1x/wk for 4wks), which induces fibrosis indicative of CKD. To incorporate cancer into our model, we utilized a Kras4bG12D transgenic mouse that develops lung adenocarcinoma within 6 months, and treated non cancer and cancer mice with repeated CDDP dosing.

**Results:** CDDP treated cancer mice had significantly decreased survival (25%) compared to CDDP treated non cancer mice. In urine, NGAL levels in CDDP treated cancer mice increased after Dose 1 (34.9 pg/ml) and Dose 2 (51.5 pg/ml), but not in CDDP treated non cancer mice. CDDP treated cancer mice had significantly worsened fibrosis as indicated by Sirius red (SR) staining (25.4% SR +), levels of myofibrillasts (α-SMA +), and TGFβ protein levels as compared to CDDP treated non cancer mice (11.6% SR +, 2.2% α-SMA +). We hypothesized that CDDP treated cancer mice have worsened fibrosis due to the activation of different pathways involved in renal fibrosis. Indeed, CDDP treated cancer mice had increased EGF and pEGFR Y1068 protein.
conclusions: These data suggest that worsened renal outcomes in CTD may cause severe acute kidney injury. Administration of 6-mercaptopurine or N-acetylcysteine may be EGRF-mediated, and targeting EGRF may prevent renal fibrosis.

Funding: NIDDK Support

TH-PO311

The Protective Effect of Transplanting Bone Marrow Mesenchymal Stem Cells with Over Expressed Klotho Gene for Kidney Injury (Xun Wan, Changchun Cao, Nanjing Hospital Affiliated to Nanjing Medical University, Nanjing, China; 3 Sir Run Run Hospital Affiliated to Nanjing Medical University, Nanjing, China.

Background: The native bone marrow mesenchymal stem cell (BMSC) is a kind of cell with multi-directional differentiation ability and has potential immuno-regulation ability which was commonly used in alleviating kidney injury. Klotho is a protein hydrolyzed with aging and thought as an antagonist of Wnt/β-catenin pathways which can induce renal fibrosis. Thus a hypothesis was make that modify BMSCs with over expressed Klotho gene and then transplant the BMSCs to individuals with AKI can protect the kidney more efficiency.

Methods: BMSCs was isolated from mice and was cultured to the third generation, the BMSCs were transfected with adenovirus carrying Klotho gene in three days and harvested Klotho-BMSCs. A total of 18 healthy C5BL/6 mice were used to establish renal IRI model by clamping unilateral renal pedicle for 60 minutes followed by reperfusion. The IRI mice were divided into three groups which was transplanted with PBS, BMSCs and Klotho-BMSCs separately. Kidney tissue and blood samples were collected at 3,14 days after AKI. Renal histological changes were estimated by HE staining and Masson staining. The expression of collagen III and IDO were determined by immunohistochemistry, the location of CD68 was observed by immunofluorescence.

Results: Compared with normal mice, classical tubular damage was found in IRI groups,accompanied by a lot of macrophage infiltrate. The mice transplant with Klotho-BMSCs showed more obviously proliferative capacity compared with BMSCs, while the Wnt pathway was significantly suppressed in Klotho-BMSCs.

Conclusions: Over expression of Klotho in BMSCs can improve the proliferative capacity of the BMSCs. That leads to potent down-regulated effect to macrophage cells. At the same time, secrete Klotho is an antagonism to kidney fibrosis. So Klotho-BMSCs exhibit synergistic effect and can be a new medicine in therapy of kidney fibrosis after AKI.

TH-PO312

Reducing Reperfusion Pressure Protectors against Renal Ischemia Reperfusion Injury (Jia Wei, Jie Zhang, Lei Wang, Shan Jiang, Jiaofu L. Bugga, Xuming Liu, Tamara General Hospital, Tampa, FL; USE Tampa, FL; University of South Florida College of Medicine, Tampa, FL.

Background: The role of hemodynamics in renal ischemia reperfusion injury (IRI) is not clear. We hypothesized that lowering renal perfusion pressure during the initial phase of reperfusion protects against renal IRI.

Methods: Results: We first evaluated renal autoregulation by measuring changes of renal blood flow (RBF) while elevating 20 mmHg in renal artery pressure (RAP) RBF increased by 94±8.1% (n=5, p<0.01) in mice with 15 min renal ischemia while kept constant without significant change in sham. Then, in isolated perfused arteriole, we measured myogenic response by increasing perfusion pressure from 60 to 120 mmHg, which decreased by 9±0.06 mmHg following 20 min hypoxia (n=5, p<0.01). In isolated perfused juxtaglomerular apparatus, we measured tubuloglomerular feedback (TGF) in vitro, which showed 3.7±0.6 μm at basal and blunted to 1.2±0.3 μm (p<0.01) following hypoxia. TGF in vivo measured using micropuncture was 4.7±0.5 mmHg in sham mice and 8.6±0.6 mmHg in Klotho-knockout mice (p<0.01). In isolated perfused afferent arteriole, we measured autoregulatory response which was significantly accelerated in V ASH1¬/---cisplatin mice compared with WT-cisplatin mice (serum creatinine 1.18 ± 0.52 vs. 0.39 ± 0.11 mg/dl; BUN 140.9 ± 16.1 vs 92.4 ± 14.0 mg/dl, respectively). Increased renal tubular injury scores and number of TUNEL positive nuclei were also significantly increased in V ASH1¬/---cisplatin mice. Furthermore, loss of peritubular capillaries observed in WT-cisplatin mice was exacerbated in V ASH1¬/---cisplatin mice. Renal accumulation of oxidative stress markers, malondialdehyde (MDA) and 4-hydroxy-2-(4-7H)-3H-7777(4-HNE) were markedly increased in V ASH1¬/---cisplatin mice compared with WT mice. Along with histological changes, decreased level of antioxidative enzyme SOD2 in WT-cisplatin mice was significantly accelerated in V ASH1¬/---cisplatin mice.

Conclusions: VASH1 deficiency exacerbated renal dysfunction and tubular injury as well as increased oxidative stress. SOD2 may influence the number of PTCS and renal functional efficiency of repair after injury have not been examined.

TH-PO313

Lack of Vasohibin-1, a Negative Feedback Regulator of Angiogenesis, Exacerbates Renal Injury in a Murine Cisplatin Nephropathy Model (Tatsumi Nishiyama, Katsuyuki Kagawa, Okayama University, Kagawa, Japan.

Background: Vasohibin-1 (VASH1) was originally identified as an endothelium-derived anti-angiogenic factor. In contrast to other anti-angiogenic factors, VASH1 has the unique property of enhancing stress resistance and survival of endothelial cells via upregulation of Sirt1 and SOD2. We previously reported that VASH1 deficiency resulted in the exacerbation of renal inflammation and interstitial fibrosis in murine unilateral obstruction model (Watatani et al., Phys Rep 2012), and increased albuminuria and marked glomerular alternation in murine type 1 diabetes (Inamimoto et al., PNAS ONE 2014). In the present study, we examined the effect of VASH1 deficiency on cisplatin-induced AKI.

Methods: Nine-week-old male VASH1¬/---(C57BL/6 background) and wild type (WT) mice received once intraperitoneal injection of 20mg/kg of cisplatin or saline (vehicle). Mice were divided into four groups; 1) WT-control (n=5), 2) VASH1¬/---control (n=5), 3) WT-cisplatin (n=7), and 4) VASH1¬/---cisplatin (n=7). 72 hours after the injection, these mice were sacrificed and blood and kidney samples were collected.

Results: There were no differences in renal function and histology between WT and VASH1¬/---control mice. Renal dysfunction induced by cisplatin injection was more prominent in VASH1¬/---cisplatin compared with WT-cisplatin mice (serum creatinine 1.18 ± 0.52 vs. 0.39 ± 0.11 mg/dl; BUN 140.9 ± 16.1 vs. 92.4 ± 14.0 mg/dl, respectively). Increased renal tubular injury scores and number of TUNEL positive nuclei were also significantly increased in VASH1¬/---cisplatin mice. Furthermore, loss of peritubular capillaries observed in WT-cisplatin mice was exacerbated in VASH1¬/---cisplatin mice. Renal accumulation of oxidative stress markers, malondialdehyde (MDA) and 4-hydroxy-2-(4-7H)-3H-7777(4-HNE) were markedly increased in VASH1¬/---cisplatin mice compared with WT mice. Along with histological changes, decreased level of antioxidative enzyme SOD2 in WT-cisplatin mice was significantly accelerated in VASH1¬/---cisplatin mice.

Conclusions: VASH1 deficiency exacerbated renal dysfunction and tubular injury as well as increased oxidative stress. SOD2 may influence the number of PTCS and renal functional efficiency of repair after injury have not been examined.

TH-PO314

Treatment with the SGLT2 Inhibitor Luseogliflozin after Ischemia/Reperfusion Attenuated Renal Fibrosis through Reversing the Endothelial Rarefaction in Mice (Daisuke Nakano, Akira Nishiyama, Kagawa University, Kagawa, Japan.

Background: Sodium-glucose cotransporter (SGLT) 2 inhibitors increase glucose excretion in the urine by inhibiting glucose reabsorption in proximal tubules. However, the effects of SGLT2 inhibition on the severity of proximal tubular injury or on the efficiency of repair after injury have not been examined.

Methods: We investigated the effects of the SGLT2 inhibitor luseogliflozin on acute kidney injury and subsequent development of renal fibrosis in mice. Luseogliflozin (30 mg kg⁻¹ day⁻¹, p.o.) was administered at 6 hours after renal ischemia/reperfusion (IR), and the treatment was continued daily until day 21.

Results: Luseogliflozin did not affect blood urea nitrogen increases, histopathological damage, or autophagy induction at day 1 or 3 after I/R. In contrast, luseogliflozin significantly suppressed the development of renal fibrosis at day 7 and week 4 after I/R. Additionally, luseogliflozin prevented peritubular capillary congestion/hemorrhage, and reduced peritubular cell loss after IR injury. These changes were exacerbated by an increase in renal VEGF-A mRNA levels. Furthermore, luseogliflozin failed to attenuate the renal I/R injury-induced fibrotic changes in the animals co-treated with sitonimib, a VEGF receptor inhibitor. Finally, low glucose concentration in the medium increased VEGF-A mRNA levels in cultured proximal tubular cells, and an in vivo glucose uptake analysis showed that luseogliflozin after I/R suppressed glucose uptake in the proximal tubules.

Conclusions: These results indicate that luseogliflozin prevented endothelial rarefaction and the development of renal fibrosis after renal I/R injury through a VEGF-dependent pathway.

Funding: Commercial Support - Taisho-Toyama Pharma. Inc

TH-PO315

Youthful Systemic Milieu Alleviates Renal Ischemia Reperfusion Injury in Elderly Mice (Xiaomei Chen, Department of Nephrology, Chinese PLA General Hospital, Beijing, China.

Background: The incidence of acute kidney injury (AKI) is high in elderly people. Parabiosis is an experimental model that surgically joins the muscle and hypoderm of two organisms to develop a shared circulatory system. Within this common blood circulation, blood cells and soluble factors can exchange continuously at physiological levels. Parabiosis has been used to study the different internal environmental factors that affect organ function and recovery from damage. A young systemic environment may prevent the senescence of old organs.

Methods: The mice were divided into four groups at random: 1) old sham group (OSham, 2). old IRI group (OIRI). 3). old parabiosis IRI group (O-P-IRI). 4).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
young-old parabiosis IRI group (Y-O:IRI). The parabiosis model was established first. Then 3 weeks, the bilateral renal pedicles were clamped in the old recipient mouse. **Results:** It was verified that cross-circulation in the parabiosis model with the IVIS Spectrum Imaging System, fluorescence microscopy, flow cytometry analysis. At 24 hours after IRI, compared to old wild-type mice, the old IRI mice had significantly damaged renal histology, decreased renal function, and increased renal tissue apoptosis. Compared to old IRI mice, old-old parabiosis IRI mice did not show differences in renal histological damage, renal tissue apoptosis. Compared to the old-parabiosis IRI mice, the old IRI mice in the young-old parabiosis showed less renal histological injury and better renal function. In addition, the renal tissue expression levels of proteins related to apoptosis were significantly decreased. **Conclusions:** These results indicate that a young systemic milieu may ameliorate renal ischemia reperfusion injuries in old mice. Funding: Government Support - Non-U.S.

**TH-PO317**

Role of MIF2 in Proximal Tubular Cell Proliferation and Survival after Ischemia-Reperfusion Injury

*Kim, Michael; Kojima, Akeno; Ochi, Dong; Chen, Robert; Star, Robert; NIH/NIDDK, Bethesda, MD*

**Background:** Macrophage migration inhibitory factor (MIF) is a cytokine with pleiotropic actions including cell proliferation and survival. MIF is expressed in kidney tubular cells and released by various stimuli such as hypoxia. Renal tubular cells express MIF receptors: CD74/44, CXC/CR2/4. Recently D-opiophosphate tautomerase, also known as MIF2 was characterized as a homologue of MIF. MIF2 is thought to exert more selective tissue protective action via CD74 activation than MIF. We examined the role of MIF2 in renal tubular cell proliferation and survival after ischemia-reperfusion (I/R) injury.

**Methods:** Mif-/-, Mif2-/-, and wild type (WT) mice were subjected to 30 minutes bilateral I/R surgery. We then injected MIF2 intraperitoneally every 12 hours. We collected kidney and blood samples 48 hours after I/R surgery, and evaluated tubular damage and performed comprehensive RNaseq analysis. In vitro modeling of I/R injury, we used mouse MPT proximal tubular cells incubated in a hypoxic chamber (0.1% O2, 6 hr, low nutrient medium). The cells then were cultured in normal condition with/without 100 ng/ml of MIF2 for different time points.

**Results:** Mif-/-, Mif2-/-, and CD74-/- mice had more severe tubular injury compared to WT mice. MIF2 injection promoted proximal tubular cell proliferation and improved renal function. RNaseq analysis showed that MIF2 injection increased cell cycle associated genes (cyclinD1, D2, E1, E2), secretary leucocyte proteinase inhibitor (SLPI) and survivin expression. In MPT cells, MIF2 promoted cell proliferation via cyclin D1 upregulation following SLPI upregulation in 36 hours. The short time (30-120 min) impact of MIF2 on hypoxic MPT cells included activation of eIF2α and ATF4, which are involved in the integrated stress response. MIF2 also induced autophagy and inhibited apoptosis.

**Conclusions:** MIF2 promoted renal tubular cell proliferation and survival after I/R injury. MIF2 may be of therapeutic utility as a regenerative agent in the clinical setting of ischemic acute kidney injury. Funding: Other NIH Support - RO1 AR049610 to R.B., Private Foundation Support

**TH-PO318**

CNT/CD-Specific Injury Triggers Serial Proliferation of Aqp2+ Progenitor Cells in Adult Mouse Kidney

*Chao Gao, Lihe Chen, Ye Zhang, Enuo Shen, Qiaoling Zhou, Wenzheng Zhang, NIH, Bethesda, MD; Xiangya Hospital, Changsha, China*

**Background:** The existence of stem/progenitor cells in adult kidneys and their function in kidney injury repair remain very controversial.

**Methods:** Hence, iDTR+ Aqp2Cre mice were generated to selectively activate expression of the sian diphtheria toxin (DT) receptor in Aqp2+ progenitor cells, which generate all known cell types of the collecting tubule/collecting duct (CNT/CD). Adult iDTR+ Aqp2Cre and iDTR+ mice were injected with DT at 2-10 μg/kg to induce acute injury in CNT/CD.

**Results:** iDTR+ Aqp2Cre mice died at a time- and dose-dependent manner, with 80% mice being dead by day 15 post DT injection. However, all iDTR+ mice survived the time course. To accurately label two sequential cell divisions, thymidine analogs, 5-chloro-2-deoxyuridine (CldU) and 5-ido-2-deoxyuridine (IdU) were injected, either alone or sequentially. CldU+/IdU+ cells were exclusively detected in mice that received both IdU and CldU, verifying the labeling specificity. iDTR+ Aqp2Cre vs. iDTR-+ Aqp2Cre mice significantly increased the number of labeled cells (CldU+, IdU+, or both) (83.7± 0.4 cells/section, n=5-9 mice). Triple IF combining CldU and IdU with various markers was performed with kidneys from 10 DT-induced, CldU+ and IdU-chased iDTR+ Aqp2Cre mice. For each marker, one section/mouse was completely examined for labeled cells that were positive for the marker. For Aqp2+ cells, the double-labeled rate (CldU+/IdU+) was significantly increased (74.8%, 595/795) than the expected (19.4% CldU+/IdU+×5.8% IdU+/CldU×1.1%) if cell division were stochastic. The high double-labeled rate was also seen in labeled V-ATPase B1B2+ (84.3%, 118/140), Pendrin+ (100%, 10/10), NCC+ (87%, 174/200), THP+ (75%, 18/24), Megalin+ (61%, 183/300) and Aqp1+ (73.5%, 189/257) cells. Only 87 of 31071 Aqp2+ cells were labeled (0.28%). Among 595 double labeling cells, Aqp2+ and Aqp2- cells were 25% and 75%, respectively.

**Conclusions:** The non-stochastic pattern argues against the notion that all surviving CNT/CD cells are capable of proliferating through self-duplication and suggests that adult Aqp2+ progenitor cells selectively proliferate after injury resulting in a high double-labeled rate after sequential CldU and IdU pulses. CNT/CD-targeted injury induces a global effect within the kidney and invokes proliferation of other progenitor cells. Funding: NIDDK Support

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
TH-PO319
Role of CD133 Molecule in WNT Response and Renal Repair
Benedetta Bussolati, Elli Papadimitriou, Alessia Brossa. Molecular Biotechnology and Health Sciences, University of Torino, Torino, Italy.

Background: The renal CD133+ cells have been indicated as a resident scattered population able to survive and proliferate after injury. However, the biological function of CD133 molecule along with its possible modulation during damage are currently understudied. We evaluated the role of stem cell marker CD133 in renal cellular repair at both molecular and functional level.

Methods: CD133 was silenced by two different shRNA against CD133. CD133 sequencing was performed on CD133+ and CD133KD cells after cisplatin damage. Functional Enrichment analysis tool and PANTHER software were used for pathways enrichment analysis. Wnt pathway activation was studied by Western Blot analysis of beta-catenin expression and Luciferase reporter assay for the TCF/LEF promoter. Proliferation, sphere formation, telomere length and senescence were evaluated in CD133+ and CD133KD cells.

Results: We found that CD133+ cells differentiated after damage, loosing the CD133 signature and acquiring metanephric mesenchymal genes such as SNAIL1 and KLF4 and regenerative genes such as SOX9 and WNT3. CD133 was reacquired in the recovery phase. Lack of CD133 limited cell proliferation after injury and was correlated with deregulation of Wnt signaling pathway. In parallel, CD133-Kd cells showed lower β-catenin levels and TCF/LEF promoter activation in respect to CD133+ cells. Finally, the lack of CD133 impaired clonal generation of spheres while favored senescence.

Conclusions: These data indicate that CD133 may act as a permissive factor for Wnt/β-catenin signaling, regulating the cell proliferative response after damage, and may limit cell senescence. In addition, CD133 are not stable during damage, but rather undergo a mesenchymal dedifferentiation showing a plastic phenotype.

Funding: Government Support - Non-U.S.

TH-PO320
Tubule Interconnection after Zebrafish Kidney Injury
Caramai N. Kamel,1 Iain A. Drummond,1,2 Massachusetts General Hospital, Charlestown, MA; Genetics, Harvard Medical School, Boston, MA.

Background: Cell-based therapies for kidney regeneration propose the use of renal epithelial or progenitor cells to generate new nephrons and replace damaged nephrons in injured kidneys. For cell-based approaches to fulfill their promise, newly made nephrons must establish tubule lumen interconnections with the collecting system.

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

Results: Tg(TCF/LEF:minipAGFP) Wnt reporter expression revealed that new nephron aggregates are patterned by canonical Wnt signaling. High cannical Wnt signaling cells formed a single cell thick dome within cell aggregates and polarized to form rosettes with an apical constriction predicting the site of future tubule lumen formation. Cells under the dome exhibiting low levels of canonical Wnt signaling and low proliferation appear to invade the tubular epithelium, while cells corresponding to the dome flatten into a segment of the forming new nephron and continue to maintain high levels of canonical Wnt signaling activity and proliferation until lumen formation. Tgf(bTa:GFP) reporter expression is maintained at high levels in the entire distal end of the new nephron, allowing visualization of the invasion process. Cells at the distal end of the new nephron extend invasive processes or invadopodia into the underlying tubular epithelium. Short term inhibition of Wnt signaling using the chemical inhibitors IWR1 and IWP2 inhibited invadopodia formation and blocked tubule interconnection events. Newly generated kidney cell-type specific transgenics will allow spatially and temporally controlled modulation of Wnt signaling to identify the cells responsible for generating and interpreting tubule interconnection signals.

Conclusions: Canonical Wnt signaling is required for tubule interconnection during adult zebrafish kidney regeneration.

Funding: NIDDK Support, Private Foundation Support

TH-PO321
Synthesized Basement Membrane Substratum Provided Cultured Renal Tubular Cells with Scaffold upon Which They Aggressively Developed
Morita,2 Kawashima,1 Inui1 1Brigham and Women’s Hospital, Boston, MA; 2Harvard Medical School, Boston, MA

Background: The renal CD133+ cells have been indicated as a resident scattered population able to survive and proliferate after injury. However, the biological function of CD133 molecule along with its possible modulation during damage are currently understudied. We evaluated the role of stem cell marker CD133 in renal cellular repair at both molecular and functional level.

Methods: CD133 was silenced by two different shRNA against CD133. CD133 sequencing was performed on CD133+ and CD133KD cells after cisplatin damage. Functional Enrichment analysis tool and PANTHER software were used for pathways enrichment analysis. Wnt pathway activation was studied by Western Blot analysis of beta-catenin expression and Luciferase reporter assay for the TCF/LEF promoter. Proliferation, sphere formation, telomere length and senescence were evaluated in CD133+ and CD133KD cells.

Results: We found that CD133+ cells differentiated after damage, loosing the CD133 signature and acquiring metanephric mesenchymal genes such as SNAIL1 and KLF4 and regenerative genes such as SOX9 and WNT3. CD133 was reacquired in the recovery phase. Lack of CD133 limited cell proliferation after injury and was correlated with deregulation of Wnt signaling pathway. In parallel, CD133-Kd cells showed lower β-catenin levels and TCF/LEF promoter activation in respect to CD133+ cells. Finally, the lack of CD133 impaired clonal generation of spheres while favored senescence.

Conclusions: These data indicate that CD133 may act as a permissive factor for Wnt/β-catenin signaling, regulating the cell proliferative response after damage, and may limit cell senescence. In addition, CD133 are not stable during damage, but rather undergo a mesenchymal dedifferentiation showing a plastic phenotype.

Funding: Government Support - Non-U.S.

TH-PO322
Analysis of Molecular Mechanisms of Human Kidney Tubulointerstitial Disease Driven by Interleukin 1β
Dario L. Leinos,1 Ryuji Morizane,2 Navin R. Gupta,3 Edgar Garcia, Julia Willingseder,1 Tomoyo Miyoshi,1 Koichiro Sasa,2 Guanghai Wang,3 Jeremy S. Duffield,4 Joseph V. Bonventre,5 Brigham and Women’s Hospital, Boston, MA; 1Harvard Medical School, Boston, MA; 2Southern Medical University, Guangzhou, China; 3Vertex Pharmaceuticals, Boston, MA; 4Renal Division, Brigham and Women’s Hospital, Boston, MA.

Background: Tubulointerstitial disease is characterized by tubular damage with interstitial fibrosis and persistent inflammation. While the deleterious effect of the whole inflammatory response is well documented, contribution of specific cytokines is virtually impossible to study in vivo.

Methods: Combined whole genome human data analysis with hPSC-derived organoid technology, experimental mouse models and CRISPR/CAS9 technology.

Results: Whole genome analysis of patients with severe kidney fibrosis indicated a correlation between inflammatory cytokines, mitochondria damage and elevated levels of glycolytic enzymes suggesting that inflammatory and metabolic pathways are mechanistically related. To overcome the limitations of studying inflammatory signals in vivo, we tested the effect of single inflammatory cytokines on human kidney organoids. Among other damage mechanisms, we found that IL1β stimulation resulted in cell cycle arrest in proximal tubule epithelial cells after 48hr, and KIM1-expressing damaged proximal tubules with near complete absence of brush borders 96hr post stimulation. Simultaneously, IL1β induced the proliferation and differentiation of stromal fibrogenic cells, resulting in hypertrophic expansion of the interstitium, and interstitial fibrosis. Further investigation into the mechanisms of fibrosis revealed the activation of MYC in organoid stromal PDGFRβ+ cells. Nuclear localization of MYC in interstitial fibrogenic cells was confirmed in Colla1-GFP mice 72hs after acute damage in vivo. IL1β stimulation of human PDGFRβ+ fibrogenic precursor cells purified from human kidneys in vitro induced autophagy, loss of SQSTM1/P62 reduced mTOR signaling and triggered a MYC-dependent metabolic proliferative program encompassing upregulation of glycolysis enzymes and cyclin kinases. Mechanistically, in the absence of IL1β, SQSTM1/P62 interacts directly with MYC, driving its prodegradational degradation to keep MYC levels low. That interaction is interrupted by IL1β through induction of autophagy, resulting in SQSTM1/P62 degradation and MYC stabilization.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Conclusions: By studying components of the inflammatory response separately, we identify a novel molecular mechanism for tubulointerstitial disease triggered by a single inflammatory cytokine, namely IL-1β.

Funding: Other NIH Support - T32 DK007527-26 NIH/NIDDK, Commercial Support - Biogen

TH-P0323

TLR3 Activation Enhances the Renoprotective Effect of Low Serum Culture Adipose Derived Stromal Cell for Anti-Glomerular Basement Membrane Disease

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

Conclusions: Consistently, the present data demonstrate that CIN is ameliorated by administration of Ala-Alp, which appears to act, in part, by diminishing oxidative stress via the inhibition of neutrophil infiltration.

Funding: Government Support - Non-U.S.

TH-P0326

Onset and Resolution of Renal Inflammation Is Orchestrated by YB-1

Results: A tenascin-C promoter driven inducible CreER2 knock-in mouse line with an eGFP reporter was generated. TNC-CreER2 (TNCCre) mice were used to examine the role of TNC in mediating the protective effect of HIF in acute kidney injury using ischemia-reperfusion (IR) model.

Methods: A tenascin-C promoter driven inducible CreER2 knock-in mouse line with an eGFP reporter was generated. TNC-CreER2 (TNCCre) mice were used to examine the role of TNC in mediating the protective effect of HIF in acute kidney injury using ischemia-reperfusion (IR) model.

Results: We found that TNCCre mice had lower levels of pro-inflammatory cytokines, chemokines and their receptors than wild type mice. Our data suggested that TNC might play an important role in the recovery phase of IR by activating inflammatory response.

Conclusions: HIF-2α induced expression of TNC after ischemia-reperfusion and TNC facilitated recovery from IR injury by activating inflammatory response.

TH-P0325

α-Apelin, an Apelin Receptor Antagonist, Ameliorates Contrast-Induced Nephropathy in Rats

Alpha-Ap on CIN.

Background: With a dramatically increasing incidence in today’s medicine, contrast-induced nephropathy (CIN) is the third common cause of acute kidney injury. Mechanisms of CIN include renal vasoconstriction, medullary hypoxia, endothelial injury, oxidative stress and direct tubular toxicity of contrast agents. Apelin (Ap) is a vasodilatory molecule and has been shown to prevent cardiac ischemia-reperfusion injury. On the contrary, α-apid-Ala-Alp (Ala-Alp), an apelin receptor antagonist, has anti-inflammatory effects on CCl4-induced liver inflammation. In this study, we aimed to demonstrate the effects of Ap and Ala-Alp on CIN.

Methods: Male Sprague-Dawley rats were injected intraperitoneally with only saline (control group, n=8), while CIN groups were treated with either saline (SL, n=9) or Ap (100 mcg/kg/day, n=8) or Ala-Alp (100 mcg/kg/day, n=8) at 0, 24 and 48 hours of the experiment. CIN was established by intravenously injecting indomethacin (10 mg/kg), L-NAME (10 mg/kg) and a high-osmolar contrast agent (Urografin 76%, 1 ml/kg) at 24 h of the experiment. On the 72 h, kidneys were removed for the assessment of histopathological changes and the determination of glomerular and tubular injury.

Results: Serum creatinine and BUN levels in SL, Ap and Ala-Alp-treated groups were significantly lower as compared to control group (p<0.05, 0.001 and 0.001), while the increases in serum creatinine in Ala-Alp-treated group was significantly lower as compared to Ap-treated group (p<0.05). In contrast to depressed 24-h creatinine clearance in SL and Ap-treated groups (p<0.01), creatinine clearance in Ala-Alp-treated group was similar to control group (p>0.25). CIN was established by intravenous injection of a high-osmolar contrast agent in SL-treated group (p<0.01) was abolished in Ala-Alp-treated group (p<0.05), while renal glomerular injury was increased in Ap-treated group (p<0.01). However, histopathological damage scores obtained by light microscopic examination were lower in both Ap and Ala-Alp treated groups as compared to SL-treated group (p<0.05).

Conclusions: The present data demonstrate that CIN is ameliorated by administration of Ala-Alp, which appears to act, in part, by diminishing oxidative stress via the inhibition of neutrophil infiltration.

Funding: Government Support - Non-U.S.

TH-P0324

Tenascin-C Mediates the Protective Effect of HIF in AKI

Conclusions: Our data suggest that LASC can be characterized by immune response through TLR3 activation, and that poly(1C) priming may enhance LASC-mediated renoprotective effects for anti-GBM nephritis.

Methods: Tenascin-C expression between TNC+/− mice and their wild type littermates 2 days after IR. RNA-Seq data showed N cis-regulatory region of the IL10 gene was investigated by ex vivo chromatin immunoprecipitation in kidney tissues.

Results: Within a decisive cis-regulatory region of the IL10 gene locus, the 4th intron, we identified and characterized a operable YB-1 binding site via gel shift experiments and reporter assays in immune and different renal cells. In vivo, YB-1 phosphorylated at serine 102 localized to the 4th intron, which was paralleled by enhanced il10 mRNA expression in mice following LPS challenge and in IR. YB1 mice had diminished IL-10 expression upon LPS challenge. In YB1 mice exhibiting myeloid kidney injury/ inflammation in the early phase (days 1 and 5), however they exhibited aggravated long-term damage (day 21) with increased expression of il10 together with known mediators of renal injury and inflammation compared to their WT littermates.

Conclusions: In conclusion, these data support the notion that there are context-specific decisions concerning YB-1 function and that a fine-tuning of YB-1 e.g. via a post-translational modification regulates its activity and/or localization that is crucial for systemic processes such as inflammation.
A Novel Hybrid Multifunctional Cytokine IL233 Promotes Regeneration Following Kidney Injury

Background: Nephrotoxic injury is a major cause of AKI. Current treatment options are limited, and the regenerative potential of tubular cells remains largely unexplored. We previously showed that intravenous infusion of 3E10 rat renal exosomes (EX) led to the hypothesis that their exosomes (EX) are the therapeutic effector.

Methods: We utilized two mouse models of AKI: glyceraldehyde-induced severe AKI and HSC-derived n-EVs model. We generated a hybrid cytokine (IL233) bearing the activities of both cytokines in one molecule. We hypothesized that the relatively small number of donated cells amplified their action by releasing their exosomes in situ. Thus, a local spread of exosomes derived from treated cells might promote recovery of injured tubular epithelial cells (TECs) in many kidney injury models.

Results: We found that HSC- and HSC-derived n-EV treatment significantly improved renal function and structure to a level similar to that of sham control rats in both sets. The cytokine overexpressed in E-cells were purified using affinity and ion-exchange chromatography. A murine model of doxorubicin-induced renal injury was developed to investigate the therapeutic effect of the cytokine. BALB/c nude mice were injected with doxorubicin (iv) and the protective effect of the cytokine treatment (ip) was examined both pre- and post-doxorubicin administration. The structure and function of the kidney were probed using flow cytometry, histology, immunohistochemistry, quantitative gene expression analysis and biochemical analysis.

Conclusions: We showed the protective potential of MSC- and HSC-derived n-EVs in acute kidney injury models. We studied the regenerative potential of MSC- and HSC-derived n-EVs in acute kidney injury models. We studied the regenerative potential of MSC- and HSC-derived n-EVs in acute kidney injury models. We studied the regenerative potential of MSC- and HSC-derived n-EVs in acute kidney injury models.
Conclusions: We conclude, the apoptotic transcriptome is stimulated in untreated AKI (n=1) and in AKI given a treatment after 24 hrs of the initial insult. The concurrent activation of anti-apoptosis genes is not sufficient to reverse the apoptotic process triggered by AKI. Ex vivo isolated ischemic renal apoptosis by interfering with pro and anti-apoptotic activation, and prevented long-term functional and structural renal compromise. The 24 hour lag time after injury is an opportunity for intervention with Ex vivo intravenous injections in AKI.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO332

Superiority of Mesenchymal Stem Cell-Derived Exosomes versus Parent Cells for Rescue Therapy of Advanced Stage AKI Anna Goouch, Ping Zhang, Zhuma Hu, Christof Westenfelder. University of Utah and VA Medical Centers, Salt Lake City, UT.

Background: Bone marrow and adipose-derived mesenchymal stem cells (MSCs and ASCs) have proven both pre-clinically and clinically to be effective for prevention of Acute Kidney Injury (AKI). Yet studies in which MSCs are given 48 hrs post-injury, a time at which most patients with severe AKI are diagnosed and when no rescue therapy is available, show them to be ineffective or potentially damaging due to compromised renal blood flow, where introduction of large cells (~50μm) causes further deterioration of renal function. ASCs' paracrine actions, including release of exosomes, are largely responsible for their protective effects, and others have shown that administration of ASC-derived exosomes can prevent AKI. Thus, we hypothesized that ASC-derived exosomes (40-150 nm), which can easily move through the microvasculature, may be effective rescue therapy for late stage AKI. Accordingly, we compared the therapeutic efficacy of ASC-derived exosomes vs. ASCs given late to rats with severe, non-spontaneously recovering AKI.

Methods: ASCs were isolated from Sprague Dawley (SD) rats and characterized by standard protocols. Exosomes were isolated from cultured ASCs using the ExoQuick TC kit (SBI), quantified (Nanosight and Bradford assay), and characterized by FACS for CD44 and CD29 surface protein expression. Adult, female SD rats were subjected to I/R AKI (52 min bilateral renal pedicle clamp). Serum Creatinine (Scr) was assessed at baseline, Days 1, 2, and 3. If the Scr value on Day 2 was greater than that on Day 1, rats were treated via left carotid artery with either 1 ml of 1) 1x10^6 SD MSCs, 2) 200 ug protein-diluted equivalent of SD MSC-derived exosomes (~4x10^10 exosomes), or 3) vehicle (1xPBS).

Results: Scr increased between D1 and D2 in all rats 1.6 ± 0.35 mg/dL (mean ± SD). As hypothesized, exosome administration on Day 2 caused a significant -1.7 ± 0.34 mg/dL drop in Scr by D3 vs. vehicle (+0.4 ± 1.1 mg/dL), while ASC administration did not, and in 25% of animals caused further functional deterioration.

Conclusions: Exosome therapy 2 days post-injury is superior to ASC therapy for rescue of AKI. Further optimization of the exosome therapy is expected to identify optimal dose-range for advanced AKI.

Funding: Veterans Affairs Support

TH-PO333

Urinary Extracellular Vesicles in Tubular Cell Repair Benedetta Bussolati, Veronica Dimuccio, Cristina Grange,elli Papadimitriou.1 University of Turin, Turin, Italy; 2University of Torino, Torino, Italy; 3University of Turin, Turin, Italy; 4University of Turin, Turin, Italy.

Background: Extracellular vesicles (EVs) are emerging as an integral component of the cell-to-cell communication network. EVs may actively transfer to target cells various molecules including proteins, mRNAs and microRNA, with stable epigenetic changes. Urinary EVs in particular, released by cells lining the nephron, are abundantly present in urine and may be involved in the intra-nephron communication among cells. We here evaluate the possible role of urinary EVs in repair of renal tissue after AKI.

Methods: EVs were isolated by urine of normal subjects by ultracentrifugation and gradient sedimentation. CD133+ and CD133neg EVs were separated by magnetic sorting. EV populations were subjected to nanoparticle tracking analysis to define their dimensions and profile and measure EV mean, distribution and concentration. EVs were characterized by FACS for CD44, CD29 and PAN-CAM expression and kidney function was monitored. Primary human proximal tubule cells (RPTECs) and iPSC-derived kidney organoids were used to assess regulation of EV4 expression.

Results: At 24 hr after injury, mice with proximal specific DN-Etv4 expression had a significantly lower increase in creatinine and BUN than controls; a functional difference was seen at 3 and 5 days post injury. DN-Etv4 expressing mice also had a much lower tubular injury score at 24h than controls. Caspase 3 staining shows a significantly lower amount of apoptotic cells at 24h. The metabolic intermediate α-ketoglutarate (aKG) is upregulated in ischemia due to lack of decarboxylation via PHD2. (Olenchoch BA et al, Science 2015). aKG increases ROS production and inversely controls etv4 expression in cancer, and high etv4 was linked to poor survival and recurrence. 5-AKG has therapeutic benefits against stress conditions. In this study, we evaluated its protective effects and potential mechanisms in renal ischemia-reperfusion injury in vivo.

Conclusions: The transcriptional activator etv4 is induced in dedifferentiated proximal tubule after AKI. Our results suggest that it normally acts to induce apoptosis in the hypoxic postischemic tubule, as blocking its function improved cell survival, tubular injury scores and BUN after IRI. This pathway is conserved in humans, since gentamicin induced Etv4 mRNA in human iPSC-derived kidney organoids. Finally, aKG downregulated Etv4 expression in vitro, suggesting a novel therapeutic strategy.

Funding: NIDDK Support - Non-U.S.
Role of Sirt2 in a Murine Cisplatin Induced AKI Model. Woong Park, Yujin Jung, Won Kim, Kyung Pyo Kang. Chonbuk National University Medical School, Jeonju, Republic of Korea; 2Chonbuk National University Medical School, Jeonju, Republic of Korea; 3chonbuk national university medical school, Jeonju, Republic of Korea.

Background: Cisplatin based chemotherapy is commonly used in therapeutic strategies for solid tumor. However, limitation of this agent is adverse effect on normal tissue such as kidney, ear, and peripheral nerves. Mechanisms of cisplatin nephrotoxicity are proposed as oxidative stress, inflammation, cellular apoptosis and death, and cell cycle regulation. Sirt2 is one of sirtuins family, which is NAD+ (nicotinamide adenine dinucleotide)-dependent deacetylase. However, there are a few reports about the role of Sirt2 on cisplatin-induced renal injury. In this study, we evaluated the effect of Sirt2 on renal injury induced by cisplatin.

Methods: We used Sirt2 knockout mice (B6.129.Sirt2tm1(Cts)-3, Sirt2KO) and their wild type mice (C57BL/6, WT mice). Cisplatin nephrotoxicity was induced by intraperitoneal injection of cisplatin (20 mg/kg). After 3 days after cisplatin injection, blood and kidney tissues were harvested. Renal function and histology were evaluated. Tubular apoptosis and reactive oxygen species were evaluated by immunohistochemistry. Intercellular adhesion molecule (ICAM)-1 and acetyl-p65 were evaluated by Western blot analysis.

Results: After induction of cisplatin nephrotoxicity, renal function measured by serum BUN and creatinine was significantly improved in Sirt2KO mice group at 72h after cisplatin treatment compared to WT mice. At 72h after cisplatin treatment, tubular injury score was significantly increased in Sirt2KO mice compared to WT mice. TUNEL positive tubular cells and renal caspase-3 expression were decreased in Sirt2KO mice compared to WT mice after cisplatin treatment. Cisplatin-induced increases of dihydroorhadomine-123 (DHR, a reactive oxygen species marker)-positive tubular cells were significantly suppressed compared to WT mice. Cisplatin-induced increased expression of ICAM-1 and acetyl-p65 expression in Western blot or immunohistochemistry were decreased in Sirt2KO mice.

Conclusions: Sirt2 KO might have important pathophysiologic role in cisplatin-induced renal injury with regulation of apoptosis, a reactive oxygen species and inflammation.

Funding: Government Support - Non-U.S.

TH-PO336
Par1b Is Protective to Cisplatin Induced Renal Tubular Injury. Abhijeet Pal1, Philip Chu, James M. Pullman, Frederick J. Kaskel, Kimberly J. Reidy. Albert Einstein College of Medicine, New York, NY; 2Pediatric Nephrology, Children’s Hospital at Montefiore, Bronx, NY; 3Albert Einstein College of Medicine, Children’s Hospital at Montefiore, Bronx, NY; 4Children’s Hospital at Montefiore/Albert Einstein College of Medicine, Bronxville, NY; 5Montefiore Medical Center, Bronx, NY.

Background: Nephrotic injury is an important contributor to childhood acute kidney injury (AKI). Partitioning defective(PAR1b) is a serine threonine kinase member of Par polarity protein family. Dual loss of Par1b and its parologue Par1a in mice leads to defects in Notch expression and glomerular and tubulointerstitial development. We identified increased expression of Par1b in proximal tubules in mouse models of AKI and in human kidney tissue with acute tubular necrosis(ATN). We hypothesized that PAR1b promotes tubulointerstitial repair.

Methods: To test this, we used in vivo and in vitro approaches. We induced AKI in Par1b−/− (Par1b KO) mice with the proximal tubular nephrotoxin, cisplatin. In addition, we tested the effect of PAR1 modulator, MTB-2, on proximal tubule mitochondrial function. We identified increased expression of Par1b in proximal tubules in mouse models of AKI and in human kidney tissue with acute tubular necrosis (ATN). We hypothesized that Par1b promotes tubulointerstitial repair.

Results: Par1b KO mice developed more severe ATN, with higher tubular injury scores and higher Kim-1 levels. Cytoskeletal architecture and cell-extracellular matrix structures were severely disrupted in cisplatin injected Par1b KO kidneys compared to WT kidneys. Par1b KO mice with proximal tubular nephrotoxic injury (cysplatin) showed increased expression of Par1b. MTB-2 resulted in partial restoration of proximal tubules denoted by increased TUNEL staining in vivo and increased cleaved caspase 3 staining in vitro. Increased necroptosis was also demonstrated by increased RIP-1 levels in the Par1b KO kidneys. In WT kidneys, cisplatin exposure induced renal repair pathways, as evidenced by increased expression of Foxh1 and its effectors Axin2 and Lhx1 along with increased levels of activated cleaved Notch2 receptor and increased expression of its effectors Hes1 and Hes5. This effect was attenuated in Par1b KO kidneys. Par1b overexpression in proximal tubular cells showed increased cell viability following cisplatin treatment, demonstrating a protective role for Par1b.

Conclusions: Both in vivo and in vitro studies support the protective role for Par1b in cisplatin induced ATN. Further defining Par1b targets may lead to therapeutic options to prevent cisplatin induced AKI in the future.

TH-PO337
Proximal Tubule DRP1 Deletion after AKI Promotes Recovery. Necka Anusuya, Cristina Bracken, Jeff H. Stanwick, Hen G. Hoang, Eric Bell, Effie Tozzo, Mitobridge, Cambridge, MA.

Background: Mitochondrial dysfunction plays a crucial role in the pathogenesis of kidney disease. A key mediator of mitochondrial function is the GTPase, dynamin related protein 1 (DRP1). The cell specific role of DRP1 during recovery from acute kidney injury (AKI) is unknown. Proximal tubule (PT) cells are highly dependent on...
promoting mitochondrial function in proximal tubule cells during recovery from AKI may prevent kidney dysfunction and progressive fibrosis. Thus, we hypothesized that the spatiotemporal genetic deletion of DRP1 in proximal tubules after ischemia-reperfusion injury (IRI) promotes kidney recovery in mice.

**Methods:** IscL34a1CreER2; DRp1Δ/Δ (IDr1 PTKO, n = 8) and littermate control iDrl PTKO (n = 5) mice were used. Tamoxifen was injected 3d later to induce deletion of DRP1 followed by a nephrectomy of the un-operated kidney at 13d and mice were euthanized on day 14. Plasma was collected for creatinine (Cr) measurement and kidneys were prepared for histology to assess renal injury. By Histology, we analyzed the picro-sirius red staining for the detection of myofibroblasts, macrophages and endothelial rarefaction by IF. Total kidney tissue mRNA levels of fibrosis markers, SMA, Coll1a1, Coll1a2, Fln, and Vim were measured by RTqPCR. Mitochondrial function was assessed by Seahorse.

Western blotting. To study the role of BMP signaling in tubules, we generated a tubular-specific BMPR1A-SMAD1/5/8-ID signaling that prevents activation of profibrotic pathways. Comparative analyses between ChIP- and RNA-sequencing data revealed genes controls. 21 d after IRI the kidneys failed to re-activate pSMAD1/5/8 and Id1, Id2, and Id4 displayed an aggravated tubular injury and increased inflammation when compared to control mice.

**Results:** Treatment with cilastatin completely prevented renal dysfunction and progressive fibrosis. Targeting DRP1 and mitochondrial function may be an effective therapeutic strategy to allow for epithelial recovery after AKI.

**Funding:** NIDDK Support

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

**Underline represents presenting author.**
Preconditioning was performed with zVAD or MD132, two established AP inducers. Animals were analyzed 48 hours and 6 weeks later.

**Results:** Excretory function (serum cystatin C) - ischemia induced significant kidney dysfunction in the short-term (48 h), IDDM aggravated this situation even further. Cell therapy did neither attenuate nor aggravate AKI. At week 6, excretory dysfunction remained affected in non-diabetic and diabetic mice without cell therapy. Administration of both, zVAD and MD132 pretreated PAC resulted in aggravated dysfunction in non-diabetic animals, serum cystatin C was lower in diabetic mice receiving zVAD treated PAC. Fibrosis - at 48 h, significant interstitial matrix accumulation was exclusively detected in diabetic mice receiving MD132 treated cells. At week 6 however, fibrosis occurred in almost every group with two exceptions (non-diabetic and diabetic AKI + native PAC). The morphological findings were most pronounced in diabetic mice undergoing treatment with preconditioned cells. EndoMT - mesenchymal transition of endothelial cells was detected in a significant manner in the following groups: 48 h - IDDM + zVAD and + MD132; 6 weeks - IDDM + MD132.

**Conclusions:** zVAD-MD132-induced AP activation in PAC does not result in any functional improvement in diabetic AKI. Postischemic structural abnormalities however are being aggravated. Thus, pharmacological stimulation of autophagy in PAC has not been identified as effective strategy for improving the cells' renoprotective capacity in diabetic AKI.

**TH-PO345**

**The Striking Finding of Multiciliated Proximal Tubular Cells in Patients with Tubular Injury**

Jennifer Eymael,1 Brighid Willemsen,1 Fieke Mooren,1 Jack F. Wetzel,2 Henry Dijkman,1 Johan Van der Vlag,2 Bart Smeets,1

1Pathology, Radboudumc, Nijmegen, Netherlands; 2Nephrology, Radboudumc, Nijmegen, Netherlands.

**Background:** Cilia are evolutionary highly conserved antennae-like structures with important functions in cell signaling and homeostasis. In kidney epithelial cells, one primary cilium per cell can be detected, which serves as flow sensor and consists of 9 peripheral microtubular doublets. Motile cilia can be found on multiciliated cells and additionally express a central microtubule pair, dynein arms and radial spoke proteins (e.g. RSPH4A) required for ciliary motion. Motile cilia assembly involves activation of the transcription factors FOXJ1 and RFX3. In this study, the unexpected detection of multiciliated cells in patients with tubular injury was evaluated.

**Methods:** Immunofluorescent staining was performed in patient biopsies with markers for cilia, specific tubular segments and for motile cilia (RSPH4A). In addition, the expression of FOXJ1 and RFX3 was studied. The cilary ultrastructure was analyzed by transmission electron microscopy.

**Results:** Multiciliated cells were initially detected in five patients. All patients were affected by tubular injury with different underlying pathologies. Multiciliated cells were localized in the proximal tubule. Furthermore, cilia on multiciliated cells stained positive for RSPH4A and the motile cilia structure (9+2) was detected by transmission electron microscopy. Co-expression of FOXJ1 and RFX3 in multiciliated cells was observed, indicating activation of motile cilia assembly. Analysis of additional biopsies from 20 patients with severe tubular injury revealed the presence of multiciliated cells in 4 cases (20%).

**Conclusions:** Multiciliated proximal tubular cells with motile cilia were frequently observed in patients with tubular injury. The mechanism underlying this phenomenon and the possible function of multiciliated cells in the kidney, need further investigation.

**Funding:** Private Foundation Support

**TH-PO346**

**Highly Specific RIPK1 Inhibition Significantly Improves Renal Ischemia Reperfusion Injury in Mice** Kevin M. Gallagher,3 Ewen M. Harrison,4 Jeremy Hughes,3 James A. Ross,4 Loma Marson,2 Sheryl Beh,4 Allison M. Beal,1 John Bertin,1 Stephen J. Wigmore,4 1GlaxoSmithKline, Collegeville, PA; 2Queen's Medical Research Institute, Edinburgh, United Kingdom; 3The Queens Medical Research Institute, Edinburgh, United Kingdom; 4University of Edinburgh, Edinburgh, United Kingdom.

**Background:** Non-specific RIPK1 inhibition with Nec-1, is beneficial in murine ischemia reperfusion injury (IRI). It is not known if tubular epithelial cells (TECs) undergo necroptosis nor how RIPK1 inhibition is beneficial. We aimed to determine if a novel, highly specific RIPK1 inhibitor (GSK963a) is beneficial in murine IRI and determine if TECs undergo necroptosis during IRI.

**Methods:** Mice were subjected to 23m (severe injury) bilateral renal vascular clamp then 24h reperfusion. Outputs included: Serum urea and creatinine; acute tubular necrosis (ATN) scoring and immunofluorescent staining of phosphorylated mixed lineage kinase like domain protein (pMLKL) (end effector of necroptosis) using MLKL phospho-S345 specific antibody. De phosphorylation controls confirmed phospho-specific staining. The effect of GSK963a on TEC (HK2 cell line) viability, cytotoxicity and mitochondrial health (mito-tracker red) was also assessed in in-vitro models of TEC ischemic injury.

**Results:** GSK963a significantly reduced creatinine (131 umol/L (95% CI 134-175) vs 174 umol/L (154-194) p=0.01 N=7) and ATN score (Mean 3.29/4 (95% CI 2.83-3.74) vs 1.75/4 (1.16-2.34p=0.008) compared to vehicle. Results with Nec-1s were similar. pMLKL was detected extensively with IF in injured moderately injured tubules (15m ischemia) but not glomeruli. With severe IRI (23 minutes), pMLKL was also detected within glomeruli. In-vitro, GSK963a significantly decreased TEC death in an ATP depletion and glucose deprivation model (12h injury 5% cell death (CellToxGreen) was: Vehicle: 67.2% (95% CI 62.8-71.5) vs GSK963a: 40.4% (34.3-46.5) N=6 p=0.001). GSK963a also reduced mitochondrial perinuclear condensation and loss of membrane potential after 1.5 hours of physical hypoxia and glucose deprivation in HK2 cells (N=3).

**Conclusions:** Highly specific RIPK1 inhibition significantly improves biochemical and histological injury in severe murine IRI. We provide preliminary evidence that renal tubular cells undergo necroptosis in IRI.

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

**TH-PO347**

**Controlled Blood Pressure Increases the Appearance of Angiogenic Hemodialysis Patient-Derived Cells In Vitro** Brooke M. Huauske,2 Ryan J. Debuque,1 Kevan Polkinghorne,1 Peter G. Kerr,1 Chrisran S. Samuel,1 Sharon D. Ricardo.1 1Department of Medicine, Monash Medical Centre and Monash University, Melbourne, VIC, Australia; 2Biomedical Discovery Institute, Department of Anatomy and Developmental Biology, Monash University, Clayton, VIC, Australia; 3Australian Institute of Regenerative Medicine, Monash University, Clayton, NSW, Australia; 4Biomedical Discovery Institute, Department of Pharmacology, Monash University, Clayton, VIC, Australia.

**Background:** Endothelial progenitor cells (EPCs) are present in lower numbers in kidney disease patients who are dialysis-dependent and can be used to predict adverse cardiovascular events. The function of EPCs can be measured via culture-based assays (CFAU) assays and the appearance of late outgrowth endothelial cells (OECs) in vitro. Specific clinical parameters can affect EPC function, yet less is known about the relationship between clinical observations and OEC function. Therefore the aim of this study was to determine if the appearance of OECs derived from dialysis-dependent patients was influenced by their clinical history.

**Methods:** Dialysis-dependent patients (n=20) were recruited to this study; and their age, on dialysis, blood pressure (BP), erythropoietin (EPO), statin use and smoking status was collected as these parameters have previously demonstrated to affect circulating EPC levels. Blood (10mls) was obtained prior to a single dialysis session and peripheral blood mononuclear cells isolated and cultured. After 7 days CFU was

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

Underline represents presenting author.
TH-PO348

Associations of Biomarkers of Angiogenesis with AKI and Mortality Post-Cardiac Surgery


*Ichan School of Medicine at Mount Sinai, New York, NY; **London Health Sciences Centre, London, ON, Canada; **San Francisco VA Medical Center, San Francisco, CA; **UCSF School of Medicine, San Francisco, CA; **University of Chicago, Chicago, IL; **Yale School of Medicine, New Haven, CT; **Yale University, New Haven, CT; **Yale University and VAMC, New Haven, CT.

Background: Angiogenesis is a process of new blood vessel formation after renal injury. We hypothesize that unimpeded angiogenesis following acute kidney injury (AKI) leads to maladaptive repair resulting in poor long-term outcomes.

Methods: We tested the association of a panel of angiogenesis biomarkers with AKI and 1-year mortality in 1444 adult participants who underwent cardiac surgery from the TRIBE-AKI cohort. Using Mesoscale Discovery multiplex assay, we measured adaptive repair biomarkers, placental growth factor (PIGF) and vascular endothelial growth factor (VEGF), and maladaptive repair biomarker VEGF receptor 1 (VEGFR1) from plasma samples collected before (preoperative) and 6-9 hours after (postoperative) surgery. We defined AKI using AKIN stage 1 criteria, and evaluated 1-year all-cause mortality.

Results: A total of 492 developed AKI and at one year 81 died. Among the preoperative biomarkers, VEGF was independentely associated with higher odds of AKI (OR 1.19 (95% CI: 1.02, 1.39)) but none of the preoperative biomarkers were associated with mortality. Each log increase of postoperative PIGF and VEGF was independently associated with lower odds of AKI, whereas each log increase of postoperative VEGFR1 had a 2-fold increase in odds of mortality (Table). There was no interaction between angiogenesis biomarkers and mortality by AKI status. Preoperative and postoperative biomarkers were weakly correlated.

Conclusions: Although there was a slight increase in odds of AKI with higher preoperative VEGF, higher postoperative levels of adaptive repair biomarkers PIGF and VEGF were significantly associated with improved renal outcomes and reduced mortality whereas higher postoperative levels of maladaptive repair biomarkers VEGFR1 were associated with worse renal outcomes and higher mortality.

TH-PO349

A Rare Case of Secondary Amyloidosis with Kidney and Colon Involvement in Chordoma

Ali Zafarshah, Ummit Selamet, William F. Glass, Amanda Tchakarov, Ala Abudayyeh, MD Anderson Cancer Center, Houston, TX; 2The University of Texas MD Anderson Cancer Center, Houston, TX; 3University of Texas Medical School at Houston, Houston, TX; 4University of Texas health Science Center at Houston, Houston, TX; 5University of Texas – Houston Medical School, Houston, TX.

Background: Amyloidosis is characterized by extracellular deposition of abnormal proteins. Secondary Amyloidosis (AA) is associated with infectious, inflammatory and malignant diseases. Among neoplastic diseases, AA is mostly associated with renal cell carcinoma, Gastrointestinal (GI) stromal tumors, and intestinal carcinomas.

Methods: We present a case of AA with GI and kidney involvement due to sacral chordoma. Patient presented with diarrhea and proteinuria. Colonoscopy showed severe colitis. Pathology findings suggested amyloidosis. He had nephotic range proteinuria, renal biopsy showed amyloidosis with no monoclonal deposition and confirmed to be secondary on mass spectrometry. He had extensive diarheea and history of recurrent ileus. He presented with normal renal function, but due to ongoing diarheae, he had hypotenion and developed acute renal failure.

Results: Conclusions: Secondary amyloidosis in association with cancers are reported as case-reports in the literature. However, to the best of authors’ knowledge, chordoma has never been reported as a cause of AA with severe systemic disease.

TH-PO350

A Case of Drug-Induced Acute Tubular Necrosis Associated with Focal Necrotizing Vasculitis in Veins and Periglomerular Arterioles

Shintaro Masuko, Miho Karube, Hikaru Kukimoto, Hideki Shimizu, Shinya Kaname. Kyorin University School of Medicine, Tokyo, Japan.

Background: Although NSAIDs-induced acute tubular necrosis and tubulointerstitial nephritis are well known, drug-induced vasculitides including veins is rarely reported.

Methods: A 38-year-old female noticed headache and slight fever a week ago and received several medication including NSAIDs and antibiotics. Afterwards, she developed leg edema and oliguria and was admitted to a local hospital because of acute kidney injury with serum UN 87.4 mg/dL and Cr 9.06 mg/dL. The urinalysis showed protein 1+, RBC 0-1/HPF, WBC 20-29/HPF and some granule casts, with increased urinary NAG 13.6 U/L and β2-microglobulin 1,266 µg/L. The renal function deteriorated and hemodialysis was begun. She was transferred to our hospital and kidney biopsy was performed, showing acute tubular injury with diffuse tubular cell ballooning and atrophy, peritubular capillaritis and interstitial changes with a focal infiltration of lymphocytes and plasma cells. Interestingly, periglomerular vasculitides of efferent arteries and also granulomatous vasculitises in a part of the veins. The immunofluorescence study was negative. Renal function improved, and later DLST test for loxoprofen turned out to be positive.

Results: Conclusions: We here reported a rare case of acute tubular necrosis and tubulointerstitial nephritis with vasculitides that is localized in periglomerular arterioles and veins with granulomatous lesion that may be induced by NSAIDs.

TH-PO351

Endothelial STAT3 Modulates Protective Mechanisms in a Mouse Model of AKI

Shinya Shimizu,1 Tejasvi Matam,1 Jessica Yen,2 Pierre C. Dagher,3 Takashi Hato,1 Timothy A. Sutton.1 Indiana University School of Medicine, Indianapolis, IN; 2Jackson Memorial Health Systems, Miami, FL; 3Duke University, Durham, NC.

Background: Acute kidney injury (AKI) is a common clinical entity with devastating consequences. STAT3 is a transcriptional regulator that plays an important role in coordinating inflammation and there is a growing appreciation of the role STAT3 signaling plays in the response to organ injury following diverse insults. Since it is well recognized that endothelial alterations contribute to organ dysfunction in AKI, in this study we examine the role of endothelial STAT3 in a model of ischemic AKI.

Methods: A mouse with the genetic deletion of Stat3 restricted to the endothelium (eStat3−/−) was used to examine the role of endothelial STAT3 signaling in a bilateral renal artery clamp (BAC) model of ischemic AKI.

Results: Mean serum creatinine 24 hours after BAC was significantly higher in eStat3−/− mice (3.0+0.2 mg/dL) as compared to background C57BL/6 mice (1.2+0.9 mg/dL; p<0.05). Histologic damage was also significantly greater in the eStat3−/− mice with mean tubular damage scores of 3.7+5 in the eStat3−/− mice and 2.3+0.9 in the background C57BL/6 mice (p=0.05). Proximal tubular oxidant stress as determined by intravitral imaging of carboxy-DCFDA fluorescence was 25% higher in eStat3−/− mice as compared to C57BL/6 mice (p=0.05). Given the contribution of inflammation to oxidant stress and tubular injury during AKI and the coordinating role the microvascular endothelium plays in these responses, we examined the impact of endothelial Stat3 deletion on microvascular leukocyte trafficking and tissue leukocyte composition in this model of AKI. Leukocytes adhered to the microvascular endothelium as measured by intravitral microscopy was 2-fold greater in eStat3−/− mice as compared to C57BL/6 mice (p=0.05); however, there was no significant difference in macrophage tissue infiltration between eStat3−/− and C57BL/6 mice.

Conclusions: These findings suggest the endothelial STAT3 signaling plays an important role in limiting kidney dysfunction in ischemic AKI and that selective pharmacologic activation of endothelial STAT3 signaling could serve as a potential therapeutic target.

Funding: NIDDK Support
TH-PO352
Contrast-Enhanced Ultrasound for Assessing Renal Perfusion Impairment and Predicting AKI to CKD Progression Wei Cao, Division of Nephrology, Nanfang Hospital, Southern Medical University, Guangzhou, China.

Background: Acute kidney injury (AKI) is increasing recognized as a major risk factor leading to progression to chronic kidney disease (CKD). However, the diagnostic tools for predicting AKI to CKD progression are particularly lacking. Here, we tested the utility of contrast enhanced ultrasound (CEUS) for predicting progression to CKD after AKI.

Methods: Mice treated with 20 or 45 min ischemia-reperfusion injury (IRI) was served as mild or severe AKI. Renal perfusion was evaluated by CEUS. Kidney morphological injury and function were assessed. We further measured renal perfusion by CEUS in patients who admitted for acute decompensated heart failure (ADHF) with or without AKI-CKD progression.

Results: Renal perfusion measured by CEUS reduced to 25±4% and 14±6% of the pre-determined levels in mild and severe AKI 1 hour after ischemia (P<0.05). Renal perfusion returned to pre-ischemic levels 1 day after mild AKI followed by restoration of kidney function. While severe AKI caused persistent renal perfusion impairment (60±9% of baseline levels) accompanied by progressive renal fibrosis and sustained decrease in renal function. We characterized the time-course of kidney fibrosis after tubule-specific deletion of Cul3 in adult mice (doxycycline-inducible Pax8-Rta-LC1 system) using Western blot, immunofluorescence (IF) and immunohistochemistry (IHC). In addition, Cul3 expression was analysed in different mouse models of kidney fibrosis (unilateral ureteral obstruction (UUO), ischemia reperfusion injury (IRI) and nephrotic nephritis (NTN)).

Conclusions: These results indicate that CEUS enables the evaluation of renal perfusion impairment associated with CKD after ischemic AKI and may serve as a noninvasive technique for assessing AKI-CKD progression.

Funding: Government Support - Non-U.S.

TH-PO353
Tubule Specific Deletion of Cullin 3 Causes Cell Cycle Dysregulation and Kidney Fibrosis Turgay Saritas,1,6 Caterina A. Cuevas,3 Christoph Kuppe,3 Rafael Kramann,3 Marcus J. Moeller,1 Jeffrey Singer,1 Jürgen Floege,1 James A. McCormick,7,6 University Hospital RWTH Aachen, Aachen, Germany; 1Portland State University, Portland, OR; 2University Hospital RWTH Aachen, Aachen, Germany; 3University Hospital RWTH Aachen, Aachen, Germany; 4University Hospital RWTH Aachen, Aachen, Germany; 5University Hospital RWTH Aachen, Aachen, Germany; 6Oregon Health & Science University, Portland, OR; 7ABCC1-Steven H. Kay, M.D., Ph.D., Houston, TX.

Background: Cell cycle dysregulation is involved in the pathogenesis of acute kidney injury (AKI) (1). Previous data showed that tubule cells in AKI are still poorly understood. Cullin 3 (Cul3) is part of an E3 ubiquitin ligase which controls protein abundance by promoting proteosomal degradation. Cul3-dependent ubiquitination has emerged as a key mechanism to control various critical cellular processes including cell cycle progression. By using microbubbles targeted to P-Selectin, CEUS was able to identify the severity of renal microvascular injury after AKI.

Conclusions: These results indicate that CEUS enables the evaluation of renal perfusion impairment associated with CKD after ischemic AKI and may serve as a noninvasive technique for assessing AKI-CKD progression.

Funding: Government Support - Non-U.S.

TH-PO354
Extracellular YB-1, as Signal of Tissue Damage, Induces Mesangial Cell Migration and Proliferation Sabine Brandt, Florian G. Scurt, Jonathan A. Lindquist, Peter R. Mertens. Otto-von-Guericke University, Magdeburg, Germany.

Background: The Y-box protein-1 (YB-1) is the prototypic member of the cold shock protein family of RNA/DNA binding proteins. Recent findings indicate acetylating-dependent secretion of YB-1 via a non-classical pathway and profound extracellular effects mediated by Notch-3.

Methods: Here we determined changes in gene expression and proliferation in rat mesangial cells following stimulation with recombinant YB-1, truncated YB-1, and peptides corresponding to domains of YB-1.

Results: Stimulation of YB-1 peptides with recombinant YB-1 resulted in an up-regulation of defined target genes and surprisingly even YB-1 itself. Further analysis revealed that recombinant YB-1 is capable of enhancing proliferation and migration rates. We also confirmed the chemokine activity using human peripheral blood mononuclear cells (PBMC). These cells have significantly increased chemotactic response to recombinant YB-1 relative to baseline. Subsequent injection of recombinant YB-1 into mice led to increased cell infiltration. Furthermore activation of monocytes with pro-inflammatory stimuli induces the secretion of YB-1.

Conclusions: Taken together, our results indicate a feed-forward loop with activation of signaling cascades by extracellular YB-1 that results in the phosphorylation of Akt, MAPK, JNK, and STAT proteins, up-regulation of YB-1 expression and target gene regulation, as well as an increase in cell proliferation and migration. Thus, we identify extracellular YB-1 as potent extracellular mediator of cell activation in inflammatory diseases.

Funding: Government Support - Non-U.S.

TH-PO355
Proximity-Ligation Assay Identified the Rho Guanine Nucleotide Exchange Factor, β-PIX, as a Rac1-Interactor in Podocytes Mirela Maier,1 Lamine Aoudjit,1 Cindy Baldwin,2 Tomoko Takano,3 McGill University, Montreal, QC, Canada; 2McGill university, Montreal, AB, Canada; 3None, Montreal, QC, Canada.

Background: Hyperactivity of Rac1 (a small GTPase) in podocytes has been implicated in the development of proteinuria and focal segmental glomerulosclerosis (FSGS). We sought to identify guanine nucleotide exchange factors (GEFs) that activate Rac1 in podocytes.

Methods: BioID, a proximity-based ligation assay, was used to identify Rac1-GEFs in human podocytes (HP). This assay consists of HP expressing a bait, Rac1G15A (a mutant of Rac1 reported to have high affinity to active GEFS), conjugated to a biotin ligase, BirA (BirA-Rac1G15A). BirA alone was used as control. HP were incubated with biot for 18 hours in the culture medium, and biotinylated proteins (i.e. proteins that have come in close proximity of Rac1G15A) were isolated with streptavidin-beads and identified by mass spectrometry. Active Rac1 was visualized with immunofluorescence staining and quantified using ImageJ software. Additionally, subcutaneous injection of recombinant YB-1, truncated YB-1, and peptides corresponding to domains of YB-1.

Conclusions: Taken together, our results indicate a feed-forward loop with activation of signaling cascades by extracellular YB-1 that results in the phosphorylation of Akt, MAPK, JNK, and STAT proteins, up-regulation of YB-1 expression and target gene regulation, as well as an increase in cell proliferation and migration. Thus, we identify extracellular YB-1 as potent extracellular mediator of cell activation in inflammatory diseases.

Funding: Government Support - Non-U.S.

TH-PO356
Toll-Like Receptor 8 and 10 Are Possibly Associated with Pathogenic Mechanisms of Idiopathic Nephrotic Syndrome Eriko Tanaka,1 Miyuki Takagi,1 Division of Nephrology, Tokyo, Japan; 2Department of Pediatrics, Tokyo Medical and Dental University, Tokyo, Japan.

Background: Idiopathic nephrotic syndrome (ISN) is still a disease of unknown cause, though many studies have been done to elucidate pathogenic mechanisms. Some studies suggest that disorder of immune system derived by toll-like receptor (TLR) is involved; however, expressions of TLRs in ISN patients are not fully examined.

Methods: We investigated RNA expressions of TLRs and its pathways in ISN patients. Total RNA was extracted from kidney biopsy specimens of each ISN patients. We performed RNA-sequencing and analyzed RNA expressions of TLRs and molecules related to TLR pathway.

Results: Three patients with ISN were enrolled in this study (P1, P2, and P3). At the time of kidney biopsy, proteinuria of P1 was decreasing and she achieved remission related to TLR pathways.

Conclusions: Our clinic study suggested that ISN patients are not fully examined, however, expressions of TLRs in ISN patients are not fully examined. Further studies are necessary to elucidate pathogenic mechanisms of ISN.
are the downstream molecules leading to type 1 interferon activation, are significantly low in the P2 and P3. We next investigated expressions of these molecules related to TLR10. On contrary to previous reports, RNA expressions of pro-inflammatory cytokines such as IL-1β and IL-6 were significantly low in P1 who showed lower expression of TLR10, suggesting that TLR10 expression was secondary suppressed because of activation of pro-inflammatory cytokynes

Conclusions: The profile of RNA expressions in INS patients implies the possibility of TLR pathways' involvement in pathogenic mechanisms. Comparing the RNA expressions in INS patient in remission phase to INS patient in nephrotic phase revealed that pathways related to TLR9 and TLR10 may be associated with onset and remission of INS.

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

TH-PO357
PolyIC Induces the Expression of Retinoic Acid-Inducible Gene 1 and Modulates Inflammatory Responses and Podocyte Damage

Ikuo Narita,1, Michiko Shimada,1 Katsuki Fujita,1 Reichi Murakami,1 Norio Nakamura,1 Moin Saleem,2 Peter W. Mathieson,3 Hirofumi Tomita.1 1Hirotsuki University, Hirotsuki, Japan; 2University of Bristol, Bristol, United Kingdom.

Background: Viral infection often exacerbates proteinuria and activation of innate immunity in renal cells is suggested as pathogenesis. As well as some of the toll-like receptors, retinoic acid-inducible gene-1 (RIG-1)-like helicase receptors (RLRs) recognize double-stranded RNA (dsRNA) produced during viral replication. RLRs are located in cytoplasm, and RIG-1 and melanoma differentiation-associated gene 5 (MDA5) are the members of RLRs. It is reported that dsRNA induces the expression of RIG-1 and MDA5 in mesangial cells, however, the effect on podocytes is not well elucidated. In this study, we tested the effect of polyinosinic polycytidylic acid (polyIC) on the expressions of RIG-1 and MDA5 and on the down-stream inflammatory responses and podocyte damages.

Materials and Methods: Conditionally immortalized human podocytes were grown in 33 degrees centigrade and differentiated in 37 degrees centigrade, then treated with 2 to 500 μg/ml of polyIC, synthesized dsRNA for 3 to 36h. The expression levels of RIG-1 and MDA5 were assessed by quantitative RT-PCR and western blotting. The expression of IFN-β, TNFα and IL-6 were assessed by quantitative RT-PCR. We further tested the role of RIG-1 and MDA5 by the temporal knockdown utilizing siRNA. F-actin staining was performed to assess actin re-organization as a feature of podocyte damages.

Results: PolyIC induced the expression of RIG-1 and MDA5 in podocytes in dose and time dependent manners, as demonstrated by quantitative RT-PCR and western blotting. PolyIC-induced expression of RIG-1 and MDA5 was suppressed by 2 μg/ml of p38 MAPK inhibitor, PD98059, and by the temporal knockdown of p53, Fas, and NFκB. PolyIC-induced actin re-organization by F-actin staining. Temporal knockdown of RIG-1 by siRNA resulted in decreased expression of IFN-β and TNFα induced by polyIC, while temporal knockdown of MDA5 by siRNA inhibited IFN-β, TNFα and IL-6.

Conclusions: PolyIC dramatically induced the expression of RIG-1 and MDA5 in podocytes in dose and time dependent manners. Temporal silencing of RIG-1 and MDA5 by siRNA significantly suppressed the expression of inflammatory cytokines induced by polyIC leading to podocyte damages. These results suggest that not only TLRs but also RLRs play an important role in podocyte damage during viral infection.

TH-PO358
The Impact of Sirtuin 3 in Renal Tubular Cell Apoptosis under Diabetic Conditions

Meoyun Wu,1 Boyoung Nam,1 Sukyung Nam,1 Tae-Hyun Yoo.2 1Department of Medicine, College of Medicine, Severance Heart and Lung Institute, Science Institute, Brain Korea 21 PLUS, Yonsei University, Seoul, Republic of Korea; 2Department of Internal Medicine, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, Republic of Korea.

Background: Reactive oxygen species (ROS) plays roile in kidney diseases including diabetic nephropathy (DN). Central to tubular injury is mitochondrial dysregulation resulting in ROS overproduction. The role of mitochondrial sirtuins (SIRTs) have been implicated in numerous ROS-mediated diseases. Since SIRT3 is mainly localized in the mitochondria and regulates mitochondrial function via deacetylation of mitochondrial proteins, SIRT3 has been suggested to be involved in the pathogenesis of kidney diseases. However, the impact of SIRT3 on tubular cell apoptosis under diabetic conditions has never been elucidated.

Methods: In vitro, rat proximal tubular epithelial cells (NRK-52E) were cultured in DMEM media containing 5.6 mM glucose (normal glucose, NG) or NG + TGF-β1 (10 ng/ml) with or without plasmid SIRT3 transfection. After 48 hours, cells were harvested and mitochondrial fraction was isolated. In vitro, 12 C57BL/6 mice were intraperitoneally injected with saline (Control, C) (N=6) or STZ (50 mg/kg) for 5 consecutive days (Diabetes, DM) (N=6), and were sacrificed after 6 weeks. The protein expression of SIRT3, MusSOD, and apoptosis-related proteins (Bax, Bcl-2, cleaved-caspase 3, cytochrome C, caspase-3, p53) were analyzed by western blot analysis. Immunofluorescent staining for SIRT3 and Mitotracker staining were also performed with cultured cells, TUNEL assay was conducted with mice renal tissues.

Results: Compared to NG cells, the protein expression of mitochondrial SIRT3 was significantly decreased in NG+TGF-β1-stimulated renal tubular cells, while SIRT3 protein expression was not significantly different between the two groups. Bax, cleaved caspase 3, and p53 protein expression were significantly increased, whereas the protein expression of Bcl2, MusSOD, and cytochrome C were significantly decreased in tubular cells exposed to TGF-β1. In contrast, transfection with plasmid SIRT3 significantly abolished the changes in apoptosis-related protein expression in TGF-β1-stimulated renal tubular cells in the same manner as compared to NG cells.

Conclusions: The profile of RNA expressions in INS patients implies the possibility of TLR pathways' involvement in pathogenic mechanisms. Comparing the RNA expressions in INS patient in remission phase to INS patient in nephrotic phase revealed that pathways related to TLR9 and TLR10 may be associated with onset and remission of INS.

Funding: Private Foundation Support, Government Support - Non-U.S.
Differential Effects of Two Nrf2 Inducers on Renal Tubule Cells

**Background:** A variety of compounds inducing the cytoprotective transcription factor Nrf2 have shown promise to reduce renal injury in experimental murine models. However, comparison of mechanisms of action of these agents on renal cell biology is limited. This study examined effects two Nrf2 inducing compounds on renal tubule cells. Dimethyl fumarate (DMF), an FDA approved and clinically used drug, and Protandim, a dietary supplement with previously reported findings in renal cells.

**Methods:** Human proximal tubule cells (HK11 cells) were treated with DMF (10-80µM) or Protandim (5-80µg/ml; comprised of Milk Thistle, Bacopa, Ashwagandha, turmeric, and green tea extracts) for various time points. Cell viability was analyzed by reduction of MTT and cell counting. Immunoblotting used to analyze Nrf2 expression/localization, phosphorylation of kinases known to regulate Nrf2 activation (Akt, GSK3β, ERK and p38 MAPK), and expression of Nrf2 transcriptional targets (NQO1 and SOD-1). Apoptosis was analyzed by immunostaining for cleaved caspase 3.

**Results:** MTT reduction and number of adherent cells was decreased with 80µM DMF and 40µg/ml Protandim, and DMF caused cells to round up while Protandim caused cell shrinkage, at these concentrations. The lowest concentration of Protandim (5µg/ml) and DMF (10µM) increased nuclear localization of Nrf2, indicative of Nrf2 activation. Both inducers increased expression of NQO1 at multiple concentrations whereas expression of SOD1 was induced more by Protandim. Protandim caused a concentration-dependent increase in p38 phosphorylation. Neither compound altered Akt phosphorylation whereas phospho-ERK and GSK3β-Ser9 phosphorylation (inactive GSK3β) were increased by Protandim. High concentrations of Protandim (80µg/ml) increased caspase3 cleavage and nuclear condensation, indicating apoptosis, while 80µM DMF caused nuclear swelling.

**Conclusions:** Treatment with DMF or Protandim caused increased Nrf2 expression, phosphorylated GSK3β, a cellular Nrf2 inhibitor. Alternatively, p38 may play a role in high concentration Protandim-induced cell death. The results suggest that Nrf2 mRNA and protein expression, as well as endocytosis, of Nrf2 transcriptional targets by DMF and Protandim may result in different tubule cell responses during stress stimuli or kidney injury.

**Funding:** NIDDK Support

**TH-P0361**

Manganese Promotes Intracellular Accumulation of AQP2 via Modulating F-Actin Polymerization and Reduces Urinary Concentration in Mice

**Background:** Aquaporin-2 (AQP2) is a water channel protein expressed in principal cells (PCs) of the kidney collecting ducts (CDs) and plays a critical role in urine concentration. F-actin polymerization through Rho phosphorylation is one of the key determinants for the cytoskeletal dynamics controlling AQP2 trafficking. Preliminary studies have shown that manganese stabilizes F-actin nuclei and decreases the contractility of its monomers at the steady state. We report in this study that manganese chloride (MnCl₂) is a novel and potent regulator of AQP2 trafficking in cells and in the kidney. We observed aperinuclear accumulation of AQP2 in both cultured cells and kidney CDS in response to MnCl₂, treatment. This effect of MnCl₂ on AQP2 distribution was associated with an increase in the rate of AQP2 endocytosis without alteration of the overall exocytosis. This pinocellular accumulation of AQP2 induced by MnCl₂, was resistant to vasopressin (VP) simulation. Although the level of total and phosphorylated AQP2 did not change, MnCl₂, treatment impeded VP-induced phosphorylation of AQP2 at its serine residues 256, 264, 269 and dephosphorylation at serine 261. In addition, MnCl₂, significantly promoted F-actin polymerization along with downregulation of Rhoa activity, and prevented VP-induced AQP2 membrane accumulation. Finally, MnCl₂, treatment caused significant polyuria and reduced urinary concentration in mice, likely by promoting intracellular accumulation of AQP2. More importantly, this reduced urinary concentration was induced by MnCl₂, was resistant to VP-elicited polyuria. In summary, our study identified a novel effect of MnCl₂, on AQP2 trafficking, and proved its potent impact on regulating urinary concentration in animals.

**Methods:**

**Conclusions:**

**TH-P0364**

Oxidative Stress-Induced Intracellular Fatty Acids Imbalance Contributes to Renal Tubular Cell Damage

**Background:** Although chronic kidney disease (CKD) is one of the oxidative stress related diseases, the mechanism by which oxidative stress contributes to pathophysiology of CKD still remains unclear. Previous reports indicated that the addition of exogenous unsaturated fatty acid induced lipotoxicity in renal tubular cell, whereas co-incubation with unsaturated fatty acid attenuated saturated fatty acid-mediated tubular damage. However, the relationship between oxidative stress and fatty acid composition in proximal tubular cells has not been investigated.

**Methods:** Intracellular fatty acids composition in immortalized proximal tubule epithelial cells (HK-2 cells) was measured by GC-MS.

**Results:** In HK-2 cells, hydrogen peroxide treatment decreased the expression of both elongation of long chain fatty acid amine (Elov16), which elongates saturated fatty acid with 12, 14, and 16 carbons, and stearoyl-CoA desaturase-1 (SCD1), which catalyzes the formation of monounsaturated fatty acids. At that time, intracellular unsaturated fatty acids content was significantly decreased, while cellular ER stress/apoptosis was increased. Co-treatment of anti-oxidant, N-acetylcystein recovered the reduction of Elov16 and SCD1 expression and consequently, enhanced cellular ER stress/apoptosis were reduced. This was further confirmed by the inhibition of these enzymes using siRNA and inhibitor in which these treatments caused to the increases of cellular ER stress/apoptosis via the reduction of intracellular contents of unsaturated fatty acids. Interestingly, co-incubation with exogenous unsaturated fatty acids with siRNA for Elov16 and inhibitor of SCD1 attenuated tubular toxicity.

**Conclusions:** Oxidative stress-induced intracellular fatty acids imbalance contributes to renal tubular cell damage.

**Funding:**

**TH-P0365**

TGFβ Signals to Chromatin via Direct Interaction of Smad3 with the Polycistronic Repressive Complex during the Determination of Renal Epithelial Cell Fate

**Background:** Transforming growth factor β (TGFβ) receptor and Smad signaling are essential for the acquisition of plasticity, suggesting that TGFβ signaling to chromatin plays a critical role in determining renal cell fate decisions.

**Conclusions:** Thus, an inactive form of ABIN1-(D485N) leads to induction of NF-E2 in the lungs. Neutrophil recruitment in the lungs and ex-vivo activation of neutrophils by recombinant NF-E2 suggests that NF-E2 may serve as a novel immune modulator and a potential therapeutic target.

**Funding:** Other NIH Support - NIAID
TH-PO366

RNA Sequencing of Enriched Collecting Duct Specific Cells Reveals Novel Immune Cell Signature in Intercalated and Principal Cells

Vijay Saxena,1 Andrew L. Schwaderer,1 John Ketz,1 David S. Hains,1 1Nationwide Children’s Hospital, Columbus, OH; 1Nationwide Children’s Hospital, Columbus, OH; 1Riley Children’s Hospital, Indianapolis, IN; 1The Ohio State University, Westerville, OH.

Background: The collecting duct is well known to be involved with acid-base and water balance, but other functions are relatively unexplored. Recently we generated two-reporter mice to enrich collecting ducts in principal cell (PC) and intercalated cell (IC) and reported targeted gene expression of anti-microbial peptide genes because these cells are the “1st responders” to ascending pathogens. In this study, we performed global unbiased gene expression profiling on enriched ICs and PCs using RNA sequencing.

Methods: In this study, we performed global unbiased gene expression profiling on enriched ICs and PCs using RNA sequencing and performed pathway analysis with Ingenuity software.

Results: Lineage marker expression analysis indicated enrichment of ICs and PCs, IC lineage marker (Atp6v0a1, Slc4a1, and Slc26a4) normalized read counts were 11-27 fold higher in ICs as compared to non-ICs, while PC lineage marker (Agrp, E2f2, Scnn1a, Scnn1b and Scnn1g) normalized read counts were 24-198 fold higher in PCs compared to non-PCs. In direct comparison between ICs and PCs, IC marker expression was 2-3 fold higher in ICs while PC marker expression was 2-fold higher in PCs. The genes upregulated in ICs included innate immune receptor Il1r1, tight junction proteins such as Cldn4 and electrolyte exchanges such as Slc4a1. Ingenuity analysis of upstream pathways revealed ICs involvement in proliferation, inflammation and anti-bacterial response. PC’s top predicted upstream regulators with a Z-score > 2 were Tgfl1, Tgfl5, and cisplatin (a drug which is reported to cause polyuria). The top PC functions are cellular assembly and organization, and organismal survival. In direct comparison, both IC and PCs revealed overlapping innate immune function with expression of nod like receptors such as Nrp6, Nod1, Nod2, cell like receptor such as Tlr1, Tlr3 and Tlr12, interleukin receptor such as Il1r1, Il1r2, Il3r, and chemokine receptor such as Cxcl1, Cxcl2, Cxcr7. The genes upregulated in PCs included immune recognition receptor B2m, high mobility group box proteins, and lipid transfer proteins.

Conclusions: This study identifies collecting ducts as innate immune effector cells with overlapping function.

Funding: NIDDK Support

TH-PO367

Identification of Circular RNAs Underlying Cicardian Cycling in Mouse Kidney Samples

Fahad Braun,1 Marc Johnson,1 Bernhard Scherner,1 Thomas Benzing,1 Pål O. Westermarck,1 Roman-Ulrich Mueller,1 1Leibniz Institute for Farm Animal Biology, Dummerstorf, Germany; 2Department II of Internal Medicine and Center for Molecular Medicine Cologne, University Hospital Cologne, Cologne, Germany.

Background: Over the past years circular RNAs have emerged as a new species of noncoding RNAs and a subject of intense research efforts. They are more stable than linear stranded RNA species and seem to be involved in post transcriptional gene regulation. Only last year, the first dataset of circular RNAs expressed in the murine kidney was published, yet we are far from understanding the precise involvement and bio functional meaning of these nucleic acids. Furthermore the question whether their expression is partially regulated in a timely or circadian manner has not been addressed so far.

Methods: 10 week old wild type mice were sacrificed for their organs every three hours starting at 12am for a overall period of 48 hours. We isolated RNA from the extracted organ samples of three mice at each time point and performed qPCR-Sequencing. Using bioinformatics analyses of backsplicing events we identified circular RNA sequences. Furthermore, we analyzed quantitative changes of these backsplicing events during the circadian cycle. qPCR was used to further validate the rhythmicity of these circular RNAs as well as their host genes.

Results: We identified more than 4000 distinct backsplicing events in our data set. A subset of these circles showed a distinct circadian rhythmity. Of the 35 top cycling circular RNAs, we validated the circadian expression pattern for two circular RNAs derived from the Strn3 and Smad4 gene locus. Interestingly both host genes did not display a circadian expression pattern.

Conclusions: Our data set yields further insight into the expression pattern of circular RNAs in the murine kidney. Especially we present the first evidence for a circadian regulation of certain circular RNA species. Ongoing experiments will focus on the analysis of potential miRNA binding sites on the two circular circular RNAs and the rhythmicity of the potentially bound miRNAs.

TH-PO368

MicroRNA-200c Is Involved in Klotho Reduction by Oxidative Stress in Human Tubular Cells

O. Westermark,1 Roman-Ulrich Doi,1 Teresa Schwaderer,1 Pål V. Johnsen,2 Bernhard Hains.3 1Leibniz Institute for Farm Animal Biology, Dummerstorf, Germany; 1Nationwide Children’s Hospital, Columbus, OH; 1Riley Children’s Hospital, Indianapolis, IN; 1The Ohio State University, Westerville, OH.

Background: Klotho deficiency is reportedly associated with the progression of kidney dysfunction, whereas its overexpression exerts renoprotective effects. Previous studies report that oxidative stress suppressed Klotho expression in renal epithelial cells, and that microRNA-200c (miR-200c) is upregulated by oxidative stress in human umbilical vein endothelial cells. In this study, we investigated whether oxidative stress-induced miR-200c is implicated in Klotho reduction in human tubular cells (HK-2).

Methods: HK-2 were stimulated with hydrogen peroxide before Klotho expression was assessed using western blotting (WB) and quantitative PCR (qRT-PCR). Klotho protein expression was determined by qRT-PCR and the miR-200c binding site in the klotho mRNA 3′-untranslated region (3′-UTR) was characterized using an online prediction tool (microRNA.org). After miR-200c mimic or inhibitor was transfected into HK-2, Klotho expression was examined using WB and qRT-PCR. Luciferase reporter plasmid containing klotho 3′-UTR was transfected into HK-2 to investigate the inhibitory effect of miR-200c on Klotho expression. Histological analysis was performed to examine the correlation between Klotho and oxidative stress markers (8-OHdG, 4-HIE). In situ hybridization was performed to reveal the localization of miR-200c in human kidney biopsy specimens.

Results: Hydrogen peroxide suppressed Klotho expression without reduction in klotho mRNA levels but upregulated miR-200c expression. Similarly, transfection of miR-200c inhibitor maintained Klotho expression. In human kidney biopsy specimens, Klotho expression inversely correlated with oxidative stress markers (8-OHdG: p < 0.44, P<0.010; 4-HIE: p < 0.13, P<0.021). MiR-200c was expressed in distal tubular cells whose renal function was lowered.

Conclusions: Oxidative stress-induced miR-200c binds to klotho mRNA 3′-UTR, resulting in a reduction in Klotho expression.

TH-PO369

Palmitate Aggravates Proteinuria-Induced Cell Apoptosis and Inflammation via CD36-NLRP3-Caspase-1 Axis in the Proximal Tubular Cells of Obese Mice

Jeng-Lin Yang,1 Wen-Chin Lee,1 Chien-Te Lee,1 J. B. Chen,1 Xiong Z. Yuan,2 Wei-Yu Chen.1 1Kaohsiung Chang Gung Memorial Hospital, Kaohsiung city, Taiwan; 2University College London (UCL) Medical School, London, United Kingdom.

Background: Dyslipidemia is common in obesity and elevated free fatty acid (FFA) is prominent in these patients. Palmitate, a long-chain saturated FA, accounts for the majority of FFA and causes renal injury in obesity. CD36 is a class B scavenger with widespread tissue distribution, including renal proximal tubular cells. The NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome is a multi-protein complex, which contains NLRP3, apoptosis-associated speck-like protein containing a CARD (caspase recruitment domain)(ASC), and caspase-1, that forms upon exposure to pathogens or danger signals to activate IL-1β and IL-18 secretion and lead to cell death. Our aims are to investigate whether CD36 and NLRP3 and also decreased the colocalization of NLRP3 and ASC in the proximal tubular cells of mouse kidney. In HK2 cells, palmitate induced the maturation of IL-1β, IL-18 and caspase-1 in a dose-dependent manner, while SSO ameliorated it. SSO treatment lowered.

Methods: High fat diet (HFD)-fed C57BL/6 mice and palmitate-treated renal tubular cells were used as in vivo and in vitro models in the current study. Sulf0-N-succinimidyl oleate (SSO) was used to treat mice and cells as a CD36 inhibitor. Stable knockdown of CD36 and NLRP3 shRNA were developed in HK2 cells (a proximal tubular cell line). The protein expressions of IL-1β, IL-18, and NLRP3 were assessed by immunohistochemistry in the renal tissues and western blotting in the cells. The expression and colocalization of NLRP3 and ASC were examined by immunofluorescent staining. The cell death was determined by Annexin V binding and TUNEL staining, respectively.

Results: The expressions of CD36, IL-1β, and IL-18 were increased progressively in the kidney of HFD-fed mice. SSO attenuated HFD-induced upregulation of IL-1β, IL-18 and NLRP3 and also decreased the colocalization of NLRP3 and ASC in the proximal tubular cells of mouse kidney. In HK2 cells, palmitate induced the maturation of IL-1β, IL-18 and caspase-1 in a dose-dependent manner, while SSO ameliorated it. SSO also abolished palmitate-induced cell death and apoptosis in a dose-dependent manner. Furthermore, knockdown of CD36-1 abrogated palmitate-induced cell death and apoptosis in HK2 cells.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: FFA causes renal tubular cells inflammation and cell death/apoptosis via CD36-NLRP3-caspase-1-axis, which may explain, at least partly, the mechanism of obesity-related nephropathy.

Funding: Government Support - Non-U.S.

TH-PO370
K-Cadherin Protein Transfer from Proximal to Distal Tubule Cells Is Associated with the Release of BMP-7
Kamelijit K. Kalsi,1 Seema Jain,2 Mysore K. Phanish,1 Mark E. Dockrell,1 SW Thames renal and transplantation unit, London, United Kingdom; 2South West Thames Institute for Renal Research, London, United Kingdom.

Background: Cadherins are structural trans-membrane proteins that maintain the epithelial integrity by homodimerization. In the human kidney K-Cadherin (CDH6) is exclusively expressed in proximal tubule epithelial cells (PTEC) as opposed to the mouse, where K-Cadherin is only expressed in embryonic tubular cells. K-Cadherin exhibits low homology to N-(38%) & E-cadherin (35%) and the loss of K-Cadherin is associated with progression of kidney disease. Loss of K-Cadherin could suggest that it is a signal of proximal tubular damage and is involved in intercellular signalling between proximal and distal cells within the kidney which may prevent progression of epithelial remodelling.

Methods: Tissue from 3 months post-transplant human biopsies was probed for K-Cadherin by immunohistochemistry. Epithelial cells from mice kidneys were separated into predominantly distal and proximal fractions and cultured to confluence. Conditioned human PTEC media taken from confluent PTEC cells was added to mice cells, allowed to incubate for 24h; cells treated with conditioned media were compared to cells treated with control media. Media was collected and cells were lysed for western blot analysis.

Results: Analysis of human biopsy tissue identified vescular K-Cadherin in distal tubules (in addition to membrane staining identified in proximal tubules). We identified the presence of full length K-Cadherin in the medium of primary human (PTEC) cultures and investigated the effects of conditioned media from human PTEC on mice proximal or distal tubule epithelial cells. De novo K-Cadherin expression was detected (p<0.05, n=3) in distal mice cells treated with PTEC media compared to treatment with control media, K-cadherin in mice proximal cells (megalin positive) treated with PTEC media was not as pronounced. Expression of the kidney specific cadherin (ksp-cadherin, CDH11) followed the same pattern. Media was analysed for the distal anti-fibrotic factor Bone Morphogenetic Protein 7 (BMP7) release from distal and proximal tubular cells treated with PTEC media, both were positive for BMP7 compared to treatment with control media.

Conclusions: Release of K-cadherin from PTECs is incorporated into distal cells is associated with BMP-7 secretion, possibly enhancing epithelial integrity and may represent a previously unrecognised trans-nephron communication.

Funding: Private Foundation Support

TH-PO371
Angiotensin II Selectively Activates SGK1, but Not Akt, via PKC-Dependent Modulation of mTORC2 in Renal Tubule Epithelial Cells Catherine Gleason, David Pearce. University of California San Francisco, San Francisco, CA.

Background: Angiotensin II (AngII) is a potent regulator of fluid balance and blood pressure homeostasis. In volume depletion, AngII stimulates production of the sodium retaiening hormone, aldosterone but also directly effects salt reabsorption through regulation of ion transporters located in various segments of the kidney tubules. Elevated blood pressure homeostasis. In volume depletion, AngII stimulates production of the sodium retaiening hormone, aldosterone but also directly effects salt reabsorption through regulation of ion transporters located in various segments of the kidney tubules. Elevated circulating and local tissue AngII levels are a significant factor in the development of sodium and fluid retention and hypertension. Serum- and glucocorticoid-regulated kinase 1 (SGK1)) is implicated as a mediator of Ang II action, however, the molecular mechanisms underlying activation of SGK1 by AngII are not completely understood. SGK1 plays an important role in regulation of sodium and potassium transport in renal tubules of the kidney through activation of ENaC and NCC (in the cortical collecting duct (CCD) and distal connecting tubule (DCT), respectively), and NHE3 (in the proximal tubule (PT)).

Methods:

Results: SGK1 and the highly related kinase, Akt, are activated by mTOR through phosphorylation of a critical, homologous residue within their hydrophobic motif (HM). mTOR is an essential serine/threonine kinase, is the catalytic core of two functionally distinct multi-protein complexes, mTORC1 and mTORC2. mTORC1 consists of mLST8, DEPTOR, PRAS40, and RAPTOR. mTORC2, also contains mLST8 and DEPTOR, but is defined by the presence of RICTOR, SIN1 and PROTOR. We find that AngII triggers selective mTORC2-dependent activation of SGK1 but not Akt. PKC activity is required for the AngII-stimulated SGK1 S422 phosphorylation and is mediated in part by PKC- induced Akt, which were induced with resveratrol, on TGF-β1 induced chronic tubular injury.

Methods: THP-1 cells (human leukemic monocyte) were treated with resveratrol concentration. HK-2 cells (human renal tubular epithelial cells) were treated with TGF-β1 to induce the chronic tubular damage. Co-culture technique was used to clarify the role of HO-1 positive macrophages, which were induced by resveratrol, in the amelioration of chronic tubular injury.

Results: 1. THP-1 cells were treated with resveratrol, ICC showed the positive staining of HO-1 and the markers of M2 macrophages(CD206 and Macrophage mannose receptor 2, Mrc-2), and the supernatant showed increased IL-10 levels and decreased IL-12 levels. The western blot of the THP-1 cells protein showed the increased expression of p-STAT3 and IL-10. 2. After co-cultured of injured HK-2 cells with THP-1 cells intervened by resveratrol, the ratio of G2/M phase was lower than that with treated with TGF-β1 alone. The ICC of HO-2 cells showed the increased expression of E-cadherin and the decreased expression of α-smooth muscle actin(α-SMA). The western blot of the HK-2 cells protein also showed the decreased p-STAT3 expression.

Conclusions: Small doses of resveratrol can induce the expression of HO-1 and macrophages polarization, which might help to attenuate the progression of fibrosis in HK-2 cells by STAT3 signaling pathway.

Funding: Government Support - Non-U.S.

TH-PO372
Resveratrol Attenuates Epithelial to Mesenchymal Transition (EMT) in Peritoneal Mesothelial Cells: Differential Role of NADPH Oxidase and Mitochondrial Dysfunction Duk-Hee Kim,3 Dal-ah Kim,3 Eun-sun Ryu,3 Hyun-Jung Kang,2 Ewha University College of Medicine, Seoul, Republic of Korea; 2Ewha Womans University Medical Center, Seoul, SEOUL, Republic of Korea; 3Ewha Womans University School of Medicine, Seoul, Republic of Korea; 4Ewha Womans University, Seoul, Republic of Korea.

Background: Peritoneal fibrosis is one of the major causes of technical failure in patients on peritoneal dialysis. Epithelial-to-mesenchymal transition (EMT) of peritoneum has been known as an early and reversible mechanism of peritoneal fibrosis. Human peritoneal mesothelial cell (HPMC) is known to have its own renin-angiotensin-aldosterone system (RAAS), however it has not been investigated whether aldosterone, an end product of RAAS induces EMT in HPMC and which mechanisms are responsible for aldosterone-induced EMT.

Methods: EMT of HPMCs was evaluated by comparing the expression of epithelial cell marker, E-cadherin and mesenchymal cell marker, α-smooth muscle actin (α-SMA) after the stimulation with aldosterone (1-100 nM) or spironolactone. Activation of Src, epidermal growth factor receptor (EGFR), phosphoinositide 3-kinase (PI3K), Akt and generation of reactive oxygen species (ROS) were assessed by Western blotting, DCF-DA and Mito-Sox staining. Effect of kinase inhibitors or anti-oxidants (N-acetyl cysteine, DPI, and MitoQ) on aldosterone-induced EMT was evaluated.

Results: Aldosterone induced EMT in cultured HPMC, which was blocked by spironolactone. Aldosterone induced an activation of both Src and EGFR from 15 to 30 minutes by an activation of PI3K and Akt from 1 and 3 hours, respectively. The inhibitors of Src (PP2, 5 uM) and EGFR (Erlotinib, 10 uM) alleviated aldosterone-induced EMT. Aldosterone induced ROS in HPMCs from 5 minutes with an increase in NOX.

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

Underline represents presenting author.

196
activity and NOX-1, -2, -4 mRNA expression. Aldosterone also increased mitochondrial ROS production. The authors introduced the aldosterone-induced generation of ROS followed by an activation of Src/EGFR and PI3K/Akt pathways whereas mitoO did not alter the phosphorylation of EGFR and PI3K in HPMCs.

**Conclusions:** Aldosterone induced generation of ROS by acting through mitochondrial ROS receptor. Aldosterone-induce generation of ROS followed by an activation of Src/EGFR and PI3K/Akt pathways served as the mechanism of aldosterone-induced EMT of HPMC via differential regulation of NOX and mitochondrial ubiquitination.

TH-PO374

**Uromodulin Is Essential for Correct Insertion of Uric Acid Transporter GLUT9 in the Plasma Membrane** Eva Koenigshausen, Clara Porwoll, Paul Probst, Lars C. Rump, Lorenz Sellin. Medical Faculty Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany.

**Background:** Uromodulin (UMOD) mutations cause autosomal dominant tubulointerstitial kidney disease (ADTKD). Patients with ADTKD-UMOD usually show hyperuricemia in childhood and progressive renal failure in the course of the disease. The pathogenesis of hyperuricemia by mutation in UMOD is scarcely understood so far. In microdissection analyses of tubular structures, UMOD has been localized also to the proximal tubulus and uric acid transporters have been localized to the distal proximal tubulus.

**Methods:** HEK293T cells expressing UMOD WT and uric acid transporters ABCG2, Ura1, OAT4, GLUT9, NPT1, NPT4 and UAT were lysed and UMOD was precipitated. On western blot, uric acid transporters were visualized. Subcellular fractionation experiments with UMOD WT or its mutant P236L and GLUT9 were performed. Cos7 cells were transfected with UMOD WT and P236L. Immunochemical labeling with markers for the endoplasmic reticulum (calnexin), Golgi (giantin), endosomes (EEA1) and the plasma membrane (WGA) were performed. In addition, a triple staining for UMOD WT or P236L, GLUT9 and organelle markers were done.

**Results:** UMOD WT interacts with the uric acid transporters ABCG2, Ura1, OAT4 and GLUT9. In the subcellular fractionation experiment GLUT9 is localized to the membrane fraction if UMOD WT is expressed. However, if UMOD P236L is expressed, GLUT9 localizes to the vesicular fraction. UMOD WT colocalizes with WGA (plasma membrane), while UMOD P236L colocalizes in the ER (calnexin). UMOD WT and GLUT9 colocalize at the plasma membrane and UMOD P236L localizes with GLUT9 in the ER.

**Conclusions:** UMOD WT interacts with several uric acid transporters and is essential for the proper insertion of uric acid transporters in the plasma membrane. With UMOD mutation P236L, mutated UMOD and uric acid transporters are trapped in the ER. This retention of uric acid transporters could explain the reduced fractional uric acid excretion with resulting hyperuricemia in patients with ADTKD-UMOD.

TH-PO375

**ANCA Stimulation of Monocytes Changes Their Cellular Metabolism** Éoin O’Brien, Carla A. White, Safa H. Mohamed, Mark A. Little, Fionnuala B. Hickey. Trinity College Dublin, Dublin, Ireland.

**Background:** Anti-neutrophil cytoplasmic antibody (ANCA) vasculitis causes rapidly progressive glomerulonephritis and is characterised by autoantibodies against myeloperoxidase (MPO) or proteinase-3 (PR3). We have previously shown that stimulation of monocytes with ANCA+ antibodies, mimics the pro-inflammatory cytokine release, suggesting a pathogenic role for this cell type. Cellular metabolism (particularly a switch to aerobic glycolysis), has recently been shown to be important in the immune response, and targeting metabolic pathways postulated as a potential treatment in autoimmunity. We investigated the effect of ANCA on the metabolism of monocytes.

**Methods:** Monocytes were isolated from healthy donors. Following stimulation with anti-MPO/PR3 antibodies, with or without a range of metabolic pathway inhibitors, changes in monocytes metabolism were measured using Seahorse extracellular flux analysis. Changes in cytokine production were assessed by ELISA.

**Results:** In accordance with prior data indicating that pro-inflammatory leukocytes preferentially use glycolysis for metabolism, we found increased glycolysis in ANCA-stimulated monocytes. However, we also observed upregulated oxidative respiration. These changes occurred within minutes of exposure to ANCA. Cells treated with anti-PR3 antibodies displayed different oxygen consumption kinetics compared to those treated with anti-MPO; changes in these metabolic pathways were linked to the previously observed differences in cytokine production. To further investigate the mechanism by which metabolic pathways are involved in the response to ANCA, we used pharmacological inhibitors to block elements of glucose metabolism. Blocking oxidative phosphorylation, as measured by reduced oxygen consumption, resulted in no change in IL-1β production, but blocking glycolysis resulted in complete inhibition. Pyruvate dehydrogenase, a major point of no return in the metabolism of glucose, was required for IL-1β production. In addition, using a specific scavenger of mitochondrial reactive oxygen species (mROS) we showed an inhibition of the IL-1β induced by anti-MPO treatment indicating that mROS has a role in activation of this inflammatory pathway.

**Conclusions:** These data indicate an important role for the upregulation of cellular metabolism in the pro-inflammatory activation of monocytes in response to ANCA.

**Funding:** Government Support - Non-U.S.
Sexual Dimorphic Response of Murine Kidneys to Dietary Cadmium and Fat

Jonathan H. Freedman,1 Louis V. Barati,1 Madhavi J. Rane,1 Adam E. Gaweda,1 Alfred A. Jacobs,1 Jon B. Klein,2 Gavin E. Arteel,1 Jonathan H. Freedman,1 Lu Cai,1 Michael Merchant,3* University of Louisville, School of Medicine, Louisville, KY, Robley Rex VA Medical Center, Louisville, KY.

Background: Obesity and cadmium (Cd) are associated with CKD. This study examined the long-term effects of heavy metal exposure and high dietary fat on kidneys of male and female mice.

Methods: C57Bl/6 mice were maintained/bred on normal or 50% Cd drinking water and normal chow. Offspring were maintained on identical drinking water as parents but split into male and female groups fed low fat or high fat (42% saturated fat) diets. Upon sacrifice at 10 weeks, tissue was collected for biochemical and biochemical analysis. NPT2a expression and localization were measured by ICP-MS. Cortical tissue phosphosproteinome was studied using LCMS-based proteomics. Phosphopeptide data were compared using GO annotation, kinase motif enrichment (Moti-x, Phosphosite), fuzzy-c means clustering, protein-protein interaction (PPI) networks (StringDB) and Ingenuity Pathways Analysis (IPA).

Results: At 10wks, no gross effects of diet or Cd were observed in female kidneys. In contrast, Cd exposed male kidneys demonstrated cortical tubular vacuolization. Kidney wet weight was higher in males by diet or Cd. Cd levels (ngCd/g kidney) were significantly higher in male Cd diet compared with increased female Cd dietary levels almost two fold. By LCMS, 1,787 unique phosphopeptides were detected, including 14 unique kinase phosphorylation motifs. Clustering and GO analysis suggested high-fat and Cd affected PGE2- and EGF-signalization in both sexes. PPI analysis confirmed identified molecular signaling pathways for gene transcription, protein translation, and cytoskeletal/cell junction maintenance. IPA identified the insulin signaling pathway as the most significantly affected pathway.

Conclusions: Cd and/or HFD affects the insulin signaling suggesting that these environmental factors may be contributors to diabetic CKD. The renal response to Sppn Cd and/or a high fat diet suggests strong sexual dimorphism at the tissue and molecular signaling levels.

Funding: NIDDK Support, Veterans Affairs Support

Sexual Dimorphic Response of Murine Kidneys to Dietary Cadmium and Fat

TH-P0378

Cell Signaling and Oxidative Stress

Poster/Thursday

Multiple Roles for NHERF1 in Forward Trafficking and Apical Membrane Anchoring of NPT2a

Jon B. Klein,3* Silvia Dalboni,3 Thiago Dalboni,3 Thongboonkerd, Juthatip1 Dalboni,3 F. Dalboni,3,1 Silvia Dalboni,3 Maria Eugenia F. Canzian,2 Silvamaria R. Manfredi,3 Maria Dalboni.3*

1Universidade Federal de Sao Paulo, Sao Paulo, Brazil; 2Hospital Israelita Albert Einstein, Sao Paulo, Brazil; 3Universidade Federal de Sao Paulo, Sao Paulo, Brazil.

Background: Fas (CD95) is a cellular receptor for apoptosis in leukocytes and other cells. A soluble form of Fas (sFas) is an anti-apoptotic molecule devoid of the transmembrane domain from alternative splicing of CD95. Serum sFas levels are higher in CKD patients and associated with inflammation, anemia, and cardiovascular disease. Objective: To investigate whether the expression of CD95 mRNA and sFas mRNA in increase in leukocytes of CKD patients and their respective correlation with serum soluble Fas levels.

Methods: We performed the dosage of Hb concentration, serum creatinine and urea with conventional methods and serum sFas levels measured using an enzyme-linked immunosorbent assay from 51 CKD patients (eGFR 15 to 59 ml/min; CKD group) and 18 healthy volunteers (control group). We extracted leukocytes to measure the mRNA expression of CD95 and sFas. Total RNA was isolated from 5 x 10^6 leukocytes from each subject using TRIzol reagent, and cDNA was synthesized from 1 μg RNA using reverse transcription system. Relative levels of mRNA transcripts of sFas were

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

Underline represents presenting author.

198
Results: When analyzed both groups together we observed negative correlation between eGFR serum sFas levels (r=-0.30, p<0.01), between cGFR and sFas mRNA expression (r=-0.28, p=0.02). Serum sFas levels correlated positively with sFas mRNA copies (r=0.32, p<0.001), and negative correlation with eGFR (r=-0.04, p=0.95). The main etiologies of CKD were diabetes and hypertension. We observed lower concentration of Hb in the CKD group (10.8 ± 2.1 vs. 14.2 ±1.7, p <0.001). There was a higher number of sFas mRNA levels in CKD group (316±1000, 1668±996, p <0.001) and higher copy number of sFas mRNA copies in the CKD group (23 ± 2.3 vs. 23 ± 5.9 x 10⁶, p <0.001). There was a negative correlation between CD95 mRNA and sFas mRNA copies in CKD patients (r=-0.49, p <0.001).

Conclusions: Serum sFas levels and sFas mRNA expression are elevated in patients with CKD. We observed correlation between sFas mRNA expression and serum levels of sFas.

TH-PO383
Protein Bound Uremic Toxins p-Cresyl Sulfate and Indoxyl Sulfate Modulate the Human Endothelial Cells' Transcriptome
Regiane S. Cunha,1 Giane Favretto,2 Paulo C. Gregório,1 Rayana A. Maciel,1 Valentina Busato,1 Roberto Pecoits-Filho,3 Felley C. Barreto,4 Wesley M. Souza,4 Andréa M. Stingenh,1 1Basic Pathology Department, Universidade Federal do Paraná, Curitiba, Brazil; 2School of Medicine, Pontifícia Universidade Católica do Paraná, Curitiba, Brazil; 3Internal Medicine Department, Universidade Federal do Paraná, Curitiba, Brazil; 4Clinical Analysis Department, Universidade Federal do Paraná, Curitiba, Brazil.

Background: p-Cresyl sulfate (PCS) and indoxyl sulfate (IS) are protein bound uremic toxins that are associated with endothelial dysfunction in chronic kidney disease (CKD). Thus, PCS and IS could activate signaling pathways leading to changes in the cellular transcriptome. This study evaluated the effect of PCS and IS on the expression of the Organic Anion Transporter (OAT) in human umbilical vein endothelial cells (HUVECs).

Methods: HUVECs were treated for 24 h at normal, uremic and maximal uremic concentration of PCS (0.08, 1.75 and 2.5 mg/L) and IS (0.6, 53 and 236 mg/L). Probenecid (Pb) and benzehenipilin (Bp) were used as OATs inhibitors. The expression of CREB1, ATF1 and protein 4.1R binding site (PFAF) was measured in dose-dependent manner, being restored with Pb or Bp (P<0.001). An increased OAT1 and OAT3 protein expression was observed after PCS treatment at maximal uremic concentration (P<0.05). The RT-qPCR analysis showed an increased (P<0.01) in the CREB1 and ATF1 expression in cells treated with PCS and IS, which was restored with Pb, Bp, Vit C and L-NNAME (P<0.05). The CREB1 and ATF1 expression was increased (P<0.05) only after PCS treatments at maximal uremic concentration.

Conclusions: PCS and IS are able to modulate differentially the gene expression of transcription factors which could affect the OATs expression. These changes in the transcriptomic signature could lead to the pathological phenotype found in CKD.

TH-PO384
Multiplexed Fluorescence Unmixing for Large-Scale Three-Dimensional Imaging and Quantitative Tissue Cytometry of Human Kidney Tissue
Tarek Hannoun1,2, Robert L. Winfree1, Katherine J. Kelly,1 Carrie L. Phillips,1 Michael T. Eadon,1 Timothy A. Sutton,1 Ken Dunn,1 Pierre C. Dagher,1 Tarek M. El-Achkar1,1 Indiana University, Indianapolis, IN; 2Indianapolis, IN; 3Indiana University Division of Nephrology, Indianapolis, IN; 4Indiana University School of Medicine, Indianapolis, IN.

Background: Large-scale confocal fluorescence microscopy combined with three-dimensional tissue cytometry (3DTC) has the potential to provide quantitative data like flow cytometry, while preserving the localization and distribution of cells in intact kidney tissue. Confocal imaging is typically limited to 4 markers, dictated by available lasers and spectral bleed-through, limiting cell identification to 2 or 3 types.

Methods: To extend the palette of simultaneously distinguishable fluorophores (up to 8 colors), we implemented fluorescence spectral unmixing. Using this approach, we labeled proximal and distal tubular cells along with 4 basic types of immune cells in single human kidney tissue sections.

Results: Large-scale 3D imaging of these sections generated data suitable for 3DTC with our recently developed Volumetric Tissue Exploration and Analysis (VTEA) software tool. Using VTEA, we determined the abundance and localization of each labeled cell type. Furthermore, we explored the distribution of leukocytes in relation to nephron sub-segments and showed clustering of neutrophils around proximal tubules.

Conclusions: Multi-fluorescence labeling with spectral unmixing enhances our ability to simultaneously visualize and detect various cell types within the kidney in 3D, and quantify the association of immune cells with nephron sub-segments in situ. Funding: NIDDK Support, Veterans Affairs Support.

TH-PO385
FRMD3/Protein 4.1O Is a Novel Nephrin Adaptor to F-Actin Regulated by MAPK- and Src-Kinases and Linked to Diabetes
Eva Koepf;1,2,3 Spurney,4,5 Buckley,1,5 F. Robert Spurney,2,3 Duke University, Durham, NC; 4Duke University Medical Center, Durham, NC; 5Duke VA Medical Center, Durham, NC.

Background: FRMD3 has been proposed as a candidate gene for diabetic nephropathy (DN). FRMD3 encodes for protein 4.1o, a member of the 4.1 protein family. In erythrocytes, protein 4.1 links membrane proteins to the actin cytoskeleton. The molecular function of protein 4.1O is unknown so far.

Methods: Expression and interaction of protein 4.1O were investigated by MAPK- and Src-kinase inhibitors and western blot in podocytes. Zebrin larvae were treated with morpholinos against moe the orthologue of FRMD3. The loss of 78 kD-GFP tagged protein using the Tg(1-fab:DBP::GFP) fish line was measured. Human 4.1O truncations were reexpressed in moe knockdown zebrafish larvae. Electron microscopy was performed. Cells expressing protein 4.1O, its truncations, its point mutations and nephrin or nck were subjected to co-immunoprecipitation. Cells were incubated with kinase inhibitors PP2 (10 µM) and SB202190 (50 µM). Kidney samples from patients with T1DN or T2DN and from streptozotocin treated mice were stained for protein 4.1O.

Results: Protein 4.1O is expressed in human podocytes and interacts with nephrin, GLEPP1, IQGAP1, Nep1 in vitro and in vivo. Injection of moe morpholinos leads to nephrotic edema, complete loss of slit diaphragm, complete foot process effacement and increase in glomerular permeability. The phenotype can be rescued by expression of human protein 4.1O AA 506-553, the nephrin binding domain. AA 506-553 contain a MAPK and DEF (SFK phosphorylation) site. Inhibition of SFK and p38 attenuate significantly nephrin protein 4.1O interaction. 4.1O and nck compete for the binding to nephrin. Mutations of protein 4.1O at the DEF site reduce significantly nephrin protein 4.1O interaction. Protein 4.1O expression is increased in human DN, interestingly is reduced in streptozotocin treated mice.

Conclusions: Protein 4.1O is a novel protein that interacts with nephrin, GLEPP1, IQGAP1, Nep1 and in vitro and in vivo. Injection of moe morpholinos leads to nephrotic edema, complete loss of slit diaphragm, complete foot process effacement and increase in glomerular permeability. The phenotype can be rescued by expression of human protein 4.1O AA 506-553, the nephrin binding domain. AA 506-553 contain a MAPK and DEF (SFK phosphorylation) site. Inhibition of SFK and p38 attenuate significantly nephrin protein 4.1O interaction. 4.1O and nck compete for the binding to nephrin. Mutations of protein 4.1O at the DEF site reduce significantly nephrin protein 4.1O interaction. Protein 4.1O expression is increased in human DN, interestingly is reduced in streptozotocin treated mice.

TH-PO386
Regulation of Actin Cytoskeletal Remodeling in Glomerular Podocytes by Tests Specific Protein Kinase 1 (TESK1)
Liming Wang,1 Anne Buckley,1,5 Robert F. Spurney,2,3 Duke University, Durham, NC; 4Duke University Medical Center, Durham, NC; 5Duke VA Medical Center, Durham, NC.

Background: In published studies, we found that expression of a constitutively active Rho A construct (V14Rho) in glomerular podocytes in vivo induced albuminuria and foot process (FP) effacement (Kidney Int 81:1075, 2012). We postulated that these effects might be mediated by the Rho A effector Rho kinase (ROK).

Methods: V14Rho mice were treated with the ROK inhibitor Y27632. We then examined the effects of ROK inhibition on albuminuria and FP effacement. These in vivo
Endocytosis and Intracellular Trafficking of AQP2 Is Regulated by the Notch Signaling Pathway

Huihua Huang,1 Limin Su,1 Tedor G. Paunescu,1 Baoxue Yang,2 Hua A. Lu,1 Massachusetts General Hospital, Wayland, MA, 2Peking University, Beijing, China.

Background: The Notch signaling pathway plays important roles in development and pathological processes in multiple tissues, including the kidney. A role of Notch signaling in regulating trafficking of neprilysin in podocytes and of monocarboxylic acid transporter 1 in proximal tubules has been reported. More recently, integrin signaling through integrin αvβ3 has been implicated in regulation of glomerular filtration barrier. We report here how Notch signaling regulates the trafficking of aquaporin 2 (AQP2).

Methods: We studied mice with renal dysfunction, and elevated BUN levels, implying a detrimental effect of the activated signaling. This was observed in tubulointerstitial and renal cortical up-regulation of CCL-2, IL-17A, IL-1β, CXCL1 and NGAL. Finally, there was a deregulated expression of cortical TLR-4 and NLRP-3 in Tubcat mice, irrespective of BSA injection.

Results: Conditional activation of renal tubular Wnt/β-catenin signaling enhances intrarenal inflammation via the TLR-4/NLRP-3 inflammasome axis in overload proteinuria. Funding support: National Natural Science Fund (NSFC) of China (grant no. 81570647)

TH-PO388

Activated Renal Tubular Wnt/β-Catenin Signaling Triggers Renal Inflammation During Proteinuria

Dickson W. Wong,1 Wai Han Yiu,1 Kam wa Chan,1 Ye Li,1 Bin Li,1 Makoto M. Takeo,2 Peter Igarashi,3 Loretta Y.Y. Chan,1 Joseph C. K. Leung,1 Kar Neng Lai,2 Sydney C. Tang,1 University of Hong Kong, Kowloon, Hong Kong; 2Kyoto University, Kyoto, Japan; 3University of Minnesota, Minneapolis, MN.

Background: imbalance of Wnt/β-catenin signaling in renal cells is associated with renal dysfunction, yet the precise mechanism is poorly understood. Previously, we observed activated Wnt/β-catenin signaling in renal tubules during proteinuric nephropathy with an unknown net effect (rescue vs. damage?) (Cell Death Dis 2016; 24;doi:10.1038/cddis.2016.24).

Methods: To identify the definitive role of tubular Wnt/β-catenin, we generated a novel transgenic “Tubcat” mouse, which conditionally expresses β-catenin specifically in renal tubules after tamoxifen administration.

Results: Four weeks after tamoxifen injection, Tubcat mice displayed proteinuria and elevated BUN levels. Tubcat mice showed a determined renal inflammation. This was associated with tubulointerstitial infiltration predominantly by M1 macrophages and overexpression of the inflammatory chemokine CCL-2 and RANTES. Induction of overload proteinuria by low-dose ESA injection for 4 weeks aggravated proteinuria and inflammation. Further analysis revealed that there was increased AQP2 expression in Tubcat mice. Renal dysfunction correlated with the degree of macrophage infiltration in the tubulointerstitium and renal cortical up-regulation of CCL-2, IL-17A, IL-1β, CXCL1 and NGAL. Finally, there was a deregulated expression of cortical TLR-4 and NLRP-3 in Tubcat mice, irrespective of BSA injection.

Conclusions: Conditional activation of renal tubular Wnt/β-catenin signaling enhances intrarenal inflammation via the TLR-4/NLRP-3 inflammasome axis in overload proteinuria. Funding support: National Natural Science Fund (NSFC) of China (grant no. 81570647)

TH-PO389

Local Inflammatory Mechanism Aggravated by Intraglomerular Cell Signaling in Diabetic Kidney

Shiro Ungureanu,1 Takashige Kubakawa,2 Daisuke Fujimoto,1 Tomoko Kanki,1 Teruhiko Mizutou,1 Yutaka Kakizoe,1 Yuichiro Izumi,1 Kiyoshi Morii,1 Masashi Mukoyama,1 Department of Nephrology, Kumamoto university graduate school of medical sciences, Kumamoto, Japan; 2School of Pharmaceut Sci, University of Shizuoka, Shizuoka, Japan.

Background: We previously reported that the myeloid-related protein 8 (MRP8, S100A9) toll-like receptor 4 (TLR4) signaling activated by glucocorticoid-association induced ER stress plays an important role in the progression of diabetic nephropathy. Although local activation of the renin-angiotensin system (RAS) in the kidney has been observed in concurrence with the MRP8/TLR4 activation in the diabetic-hyperglycemic model mouse, the relationship between these signals remains obscure.

Methods: In vivo studies were performed using diabetic-hyperlipidemic mice (by streptozotocin plus high-fat diet, STZ-HFD) and db/db mice, treated with olmesartan (Olm) and angiotensin II (AngII), respectively. In vitro experiments were done with mouse macrophages (MΦ) that were co-cultured with rat mesangial cells (MC), or stimulated by MC-conditioned media (MC-sup). Expressions of the pro-inflammatory and profibrotic markers were analyzed by qPCR, and ER stress was evaluated using an EK+1 dual reporter cell line monitoring NF-κB and IRE1 pathways. Effects of a TLR4 antagonist on this crosstalk was also examined.

Results: Angiotensinogen (Agt) mRNA was upregulated in the glomeruli of STZ-HFD mice, Olm effectively downregulated of glomerular MRP8/TLR4 and Agt in STZ-HFD mice, which was associated with the reduction of albuminuria. In contrast, a suppressor dose of AngII markedly worsened albuminuria and increased glomerular infiltrated MRP8-positive cells in db/db mice. Glomerular MΦ showed obviously lower reactivity compared to tubulointerstitial ones, suggesting intraglomerular crosstalk. MRP8 and TNFα were dramatically induced by co-culture with MC, which was reproduced by stimulation with MC-sup. Dual reporter assay revealed that MC-sup stimulation activated IRF, which could cause ER stress, as well as NF-κB in a cell-type dependent manner. Such induction was partially abrogated by the TLR4 antagonist.

Conclusions: RAS activation should contribute to progression of diabetic nephropathy through promoting intraglomerular crosstalk, which may trigger MRP8 production in glomerular MΦ. Humoral factors secreted from MC could contribute to the crosstalk partly in a TLR4-dependent manner, thus facilitating local inflammation and ER stress.

TH-PO390

Engineered Immune Complexes with Galactose-Deficient IgA1: A New Model for IgA Nephropathy

Colin Reilly,1 Zhi qiang Huang,2 Nuo Xu,1 Zina Moldoveanu,4 Lea Novak,5 Stacy D. Hall,1 Rhubell T. Brown,6 Terry L. Lewis,6 Casey T. Weaver,7 Bruce A. Julian,8 Hisato Suzuki,9 Christopher D. Willey,1 Jan Novak,5 Juntendo University Faculty of Medicine, Tokyo, Japan; 2The University of Alabama at Birmingham, Birmingham, AL; 3UB, Birmingham, AL; 4University of Alabama at Birmingham, Birmingham, AL; 5University of Alabama at Birmingham, Birmingham, AL, Medicine, University of Alabama at Birmingham, Birmingham, AL; 6University of alabama at birmingham, Birmingham, AL.

Background: IgA nephropathy (IgAN) is an autoimmune disease characterized by circulating immune complexes (CIC) that deposit in the kidney and incite kidney injury. These CICs contain galactose-deficient IgA1 (Gd-IgA1) bound by Gd-IgA1-specific antibodies (EICs). The role of EICs in human and homologous primates have IgA1 with its O-glycans. To address these issues, we developed an animal model by using in vitro-formed, engineered immune complexes (EIC) from human Gd-IgA1 and recombinant Gd-IgA1-specific IgG. In this study, we show that kidney microvascular endothelial cells, tubulointerstitial cells, and glomerular mesangial cells all show a response to EIC.

Methods: EICs were formed from Gd-IgA1 and recombinant Gd-IgA1-specific antibody. EIC or Gd-IgA1 only were injected intravenously 3 times every other day in week 6. Nondiabetic, nonimmunodeficient mice. Kidneys were harvested 1 d after last injection, and either snap frozen in liquid nitrogen for RNAseq analysis or fixed for pathologic analysis. RNAseq data sets were compared against published data from IgAN patient kidney biopsy samples, and pathway analysis was performed using the Broad Institute GSEA tool.

Results: Mice injected with EIC exhibited glomerular matrix expansion and hypercellularity, with no morphological changes observed in the control group. Using 0.5 log2 fold-change parameter, gene expression analysis found 118 genes up-regulated and 165 down-regulated in the EIC-injected vs. control mice. Pathway analysis between the EIC model and IgAN biopsies identified multiple pathways in common, including nitrogen early and late response, matriosome, interferon gamma response, and epithelial...
to mesenchymal transition. In addition, similar genes between the EIC animal model and human were found to be modulated in a similar pattern and SDS-Western blotting of kidney tissue for selected targets showed protein expression followed mRNA changes for some genes.

Conclusions: Using EICs, we generated an IgAN passive mouse model that replicates some of the histological changes observed in renal biopsies of IgAN patients. This model thus provides a unique platform for testing disease-specific drugs for efficacy in reducing kidney damage from CICs.

Funding: NIDDK Support

TH-PO391

TWEAK Increases CD74 Expression and Senses to DDT Proinflammatory Actions in Tubular Cells

Lara Valiño rivas,1 Richard Bucala,6 Lin Leng,2 Ana B. Sanz,4 Laura Gonzalez-Lafuente,2 Alberto Ortiz,2 Maria Dolores Sanchez-Nino,1 1Nephrology, Fundacion Jimenez Diaz, Madrid, Spain; 2BS-Fundacion Jimenez Diaz, Madrid, Spain; 3Hospital Universitario Fundacion Jimenez Diaz, Madrid, Spain; 4Instituto de Investigacion Sanitaria Fundacion Jimenez Diaz, Madrid, Spain; 5Yale School of Medicine, New Haven, CT; 6Yale University School of Medicine, New Haven, CT.

Background: TWEAK is a proinflammatory cytokine that promotes kidney injury. CD74 is a multifunctional protein upregulated in diabetic kidney disease another chronic nephropathies. One function of CD74 is being a receptor for Macrophage Migration Inhibitory Factor (MIF) and for the recently described MIF-2 D-opioidreceptor-tautomerase (DDT) cytokine. However, the molecular mechanisms of TWEAK-induced kidney injury, the drivers of CD74 expression and the function of DDT function in kidney cells are poorly characterized.

Here we report that Wild-type (WT) mice received a single i.p. injection of TWEAK. Cell culture studies were performed in murine proximal tubal MCT cells. TWEAK, DDT and MIF expression was determined by immunohistochemistry in kidney tissue from mice. The effects of TWEAK in mice and in cultured tubular cells was assessed by qRT-PCR, Western blot and flow cytometry.

We have now identified CD74 gene expression as upregulated in the kidneys in response to systemic TWEAK administration in mice in a transcriptomics analysis, and have characterized the in vivo CD74 expression and the functional consequences in cultured cells. TWEAK administration to mice resulted in a progressive time-dependent (up to 24h) upregulation of kidney CD74 mRNA (RT-PCR) and protein (Western blot). Furthermore, the CD74 ligands MIF and DDT were also upregulated at the protein level 24h after TWEAK administration. Immunohistochemistry localized the increased CD4, MIF and DDT expression to tubular cells. In cultured tubular cells, TWEAK increased CD74, CD74 and protein dose-dependently, with the temporal pattern of dose-dependently, with the temporal pattern of CD74 expression.

Conclusions: In conclusion, TWEAK upregulates CD74 and its ligands MIF and DDT in renal tubular cells. This may have functional consequences for kidney injury since DDT amplified the inflammatory response to TWEAK.

TH-PO392

TGF-β-Beta Exposure Represses Fibroblast Transcription of the Anti-Fibrotic Molecule Slit2: A Novel Fibrogenic Mechanism?

Darren A. Yuen,1,2,5 Debbie Meck,1,2,5 Jennifer C. Kwan,1,2,5 Andrew B. Smylie,1,2,5 Toru Sakai,1,2 Lineke De Rycke,3,4,6 Darren A. Yuen,1,2,5

Background: Recent work has demonstrated that the molecular guidance ligand Slit2 may also serve as an important anti-fibrotic signal in the kidney. Specifically, we have previously shown that Slit2 is reduced following renal injury, and bioactive N-terminal heparin sulfate binding sites may be a novel therapeutic strategy for diabetic kidney disease. Here, we show that Slit2 could become a possible adjunct therapy for chronic kidney disease, the regulation of endogenous Slit2 during fibrosis—as well as its role in downstream injury—remains largely uncharacterized.

Objective: To study the endogenous regulation of Slit2 expression by fibroblasts in fibrotic renal specimens and further characterize the role of Slit2 on fibroblast activation and renal injury.

Methods: Using real-time PCR and immunohistochemistry, we measured Slit2 expression in primary human dermal fibroblasts in response to TGF-beta. In vitro tools, including siRNA-mediated knockdown and pharmacological inhibition, were used to further identify and characterize novel regulators of Slit2 expression.

Results: Here, we demonstrate that fibroblast exposure to TGF-beta, a master regulator of fibrosis, causes a downregulation of the anti-fibrotic factor, Slit2. Furthermore, we determined that TGF-beta mediated reduction of Slit2 occurred at the level of transcription, by observing a corresponding downregulation of Slit2 pre-mRNA transcript levels. In silico analysis showed putative binding sites for TGF-beta-regulated transcription factors in the Slit2 promoter region, suggesting that repression may occur through promoter cis-regulatory elements. Finally, we determined that Slit2 repression occurred through a Smad- and YAP-dependent mechanism, as loss of each of these transcriptional regulators by siRNA reversed the repressive effect of TGF-beta.

Conclusions: While many forms of chronic kidney disease are characterized by fibroblast activation and potentially systemic fibrosis. Here, we determined that fibroblast exposure to TGF-beta leads to a marked decrease in Slit2 expression, suggesting that loss of Slit2 may facilitate fibroblast activation in a disease context. Further studies will help to clarify the mechanism of Slit2 repression and how this may be targeted to potentially reduce fibrotic injury.

Funding: Government Support - Non-U.S.

TH-PO393

Calcium Dobesilate Reduces VEGF Signaling in Endothelial Cells, Preserves Cell Function, and Improves Vascular Complications in Diabetic Mice

Florence Njau,1 Nelli Shushakova,1 Joon-Keun Park,1,2 Jan Menne,1 Hermann G. Haller,1 Hannover Medical School, Hannover, Germany; 2Medical School Hannover, Hannover, Germany; 3Nephrology and Hypertensiology, 30625 Hannover, Germany.

Background: Calcium dobesilate is a small molecule with vasoprotective properties. Preliminary evidence suggests that calcium dobesilate interferes with heparan-sulfate binding sites of growth factors such as FGF and VEGF. We therefore tested the hypothesis that calcium dobesilate (1) ameliorates diabetic nephropathy and (2) directly and/or indirectly inhibits VEGF signaling in the microcirculation.

Methods: In vitro HUVECs were used for analysis of VEGF signaling as well as migration and proliferation. Streptozotocin-treated mice (STZ) were treated with calcium dobesilate and analyzed after 4 and 8 weeks of hyperglycemia. Diabetic neuropathy was assessed via thermal sensitivity. Urinary albumin was measured by ELISA and immunohistochemistry performed on cryostat or on paraffin sections.

Results: Dobesilate (100 and 200 µM) decreased VEGF (20 ng/ml)-induced migration by 50% and inhibited VEGF-induced activation of lamellipodia-like structures and phosphorylation of focal adhesion kinase (FAK). Dobesilate reduced HUVECs proliferation by 30% and enhanced apoptosis of HUVECs induced by serum deprivation in a dose-dependent manner as evidenced by a decrease in Bcl-2/Bax ratio, and phosphorylation of Bad. It inhibited VE-cadherin expression in a dose-dependent manner and suppressed the phosphorylation of pERK1/2, pMEK1/2 and p38 MAPK. Diabetic mice treated with calcium dobesilate showed a decrease in albuminuria, less phosphorylation of VEGF-R2 and an increased thermal sensitivity as compared to sham-treated diabetic animals.

Conclusions: Calcium dobesilate ameliorates both hyperglycemia-induced nephropathy and neuropathy in mice. In vitro the signaling of VEGF in endothelial cells is reduced. Our findings suggest that calcium dobesilate is a VEGF inhibitor at high concentrations. The specific inhibition of FGF and VEGF signaling by blocking heparan sulfate binding sites may be a novel therapeutic strategy for diabetic vascular complications.

Funding: Government Support - Non-U.S.

TH-PO394

Urinary Activin A Is a Novel Biomarker Reflecting Renal Inflammation and Tubular Damage in ANCA-Associated Vasculitis

Shunsuke Takahashi,1 Masao Nakasotomi,1 Toru Sakairi,1 Hidekazu Ikuechi,1 Yoriaki Kaneko,1 Keiju Hiratoma,2 Yohsizha Nojima,3 Akito Maeshima,2 1Gunma University, Maebashi, Japan; 2Gunma University Graduate School of Medicine, Maebashi, Japan; 3Gousse School of Medicine, Japan, Maebashi, Japan; 4Gunma University School of Medicine, Maebashi, Japan; 5Gunma University graduate school of medicine, Maebashi, Japan.

Background: Activin A, a member of TGF-beta superfamily, is known to regulate cell growth and differentiation in various tissues. It has been reported that activin A is involved in kidney development, tubular regeneration, and renal fibrosis in rodents. However, the role of activin A in kidney diseases remains unknown in human. To address this sensitivity, we analyzed renal biopsies of patients with ANCA-associated vasculitis (AAV).

Methods: Thirty-seven patients with biopsy-proven AAV who were treated in our department from 2011 and 2015 were included in this study. Serum activin A, urinary activin A, a urinary follistatin (an activin antagonist), and urinary KIM-1 were measured by ELISA. Urine from healthy volunteers and rheumatic disease patients with normal urinalysis (control patients) were also used. The localization of activin A in renal biopsy specimens from AAV patients was examined by immunostaining. Normal kidney specimens from patients who underwent nephrectomy were used as a control.

Results: Urinary activin A was almost undetectable in healthy volunteers, but was significantly increased in AAV patients (7.2 ± 2.6 vs. 122.0 ± 38.6 ng/gCr, p<0.001). Urinary activin A levels of these patients was rapidly decreased after treatment. There was a significant correlation of urinary activin A level with urinary KIM-1 and urinary protein. On the other hand, compared with control patients, urinary follistatin levels were decreased in AAV patients (673.1±135.3 vs. 291.7 ± 38.8 ng/gCr, p<0.05). Activin A was localized in the cytoplasm of distal tubules of normal kidneys. In contrast, activin A was present not only in distal tubules, but also in the apical lumen of proximal tubules, and infiltration macrophages in patients with AAV.

Conclusions: These data suggest that urinary activin A reflects renal inflammation and tubular damage in ANCA-associated vasculitis.

Funding: Commercial Support - Astellas Pharm Inc.
Osmotic Pressure Increases TGFβ1-Mediated Loss of SGLT2 Expression in Human Proximal Tubule Cells

Xinlu Wang,1 Myosore K. Phanish,2 Mark E. Dockrell1: South West Thames Institute for Renal Research, London, United Kingdom; 2SW Thames renal and transplantation unit, London, United Kingdom; K. George’s, University of London, London, United Kingdom; St Helen Hospital, London, United Kingdom.

Background: Approximately 90% of glucose is reabsorbed by the low affinity Na+/glucose cotransporter (SGLT1) predominantly (KCDs) is an early proxy for CKD. This transporter has received renewed interest in the light of anti-diabetic drugs targeting its activity. Although reports suggest an increase in SGLT2 expression in diabetic nephropathy (DN), we hypothesised that the loss of phenotype of proximal tubule epithelial cell (PTEC) observed in DN may result in a decrease in SGLT2 expression.

Methods: Primary human PTEC were cultured on plastic or collagen IV coated-plain-wear in supplemented medium. Cells at 80% confluence were treated with: 5mM D-Glucose (normoglycemia), 25mM D-Glucose (hyperglycemia), or 5 mM D-Glucose + 25mM L-Glucose (osmotic control) +/-TGFβ1(0.75ng/ml). After 24h, culture was collected and cells lysed. Western blot was used to detect protein expression; membranes were probed with antibodies against: SGLT2, SGLT1, K-Cadherin and tubulin.

Results: Primary PTEC expressed mature SGLT2, molecular weight of ~ 73KDa, indicating appropriate post-translational processing and membrane localisation. Probing with the SGLT1 antibody only identified bands of 60 KDa or lower, indicating an immature protein not expressed at the membrane. TGFβ1 (treatment (24h) resulted in a decrease in SGLT2 expression in all treatments; this effect was more pronounced in cells grown on collagen and in osmotic control non-imported/non-metabolised L-Glucose and in K-Cadherin protein expression was not reduced by TGFβ1 at this time point, in fact there was a tendency to increased expression in cells treated with D-Glucose + TGFβ1.

Conclusions: Our data demonstrates that TGFβ1 reduces the expression of mature SGLT2 protein in human primary PTEC. This is not consistent with recent reports of a TGFβ1-induced increase in SGLT2 expression using transformed cells grown on plastic-less representative of the in vivo situation. SGLT2 was decreased prior to any measurable loss of K-Cadherin, suggesting that SGLT2 could be a more sensitive phenotypic marker than cadherin. An increase in K-Cadherin expression in response to D-Glucose + TGFβ1 may be secondary to cellular hypertrophy observed in DN. In the other presentation from our group on this topic we investigate whether there is a metabolic interaction between TGFβ1 and SGLT2 activity.

Inhibition of Erythropoiesis by Soluble Fas in Cell Culture Miguel A Goss.1 Wake Forest Institute for Regenerative Medicine, Wake Forest University, Winston Salem, NC; 2Division of Nephrology, Federal University of Sao Paulo (UNIFESP), Sao Paulo, Brazil.

Background: Serum soluble Fas (sFas) levels are associated with anemia in CKD patients. Cord blood cells (Cbc) can generate hematopoietic stem cells (CD34+).

Objective: To investigate whether sFas interferes with erythropoiesis in cell culture.

Methods: We studied CD34+ cell culture after sorting from Cbc. Analyzed on flow cytometry for glycophterin A, CD 34+, CD 38+ and CD 171+. The CD34+ cells were cultured for 14 days in media containing growth factors added with or without sFas. They were divided in 18 wells from 6 plates. We divided in 2 groups. Each group consisted in 9 wells with different concentrations of sFas (H group: [2, 4 and 8 ng/ml]; L group- [0, 0.5, and 1 ng/mL]). We performed counting of colony-forming unit (CFU-E) and colony-forming unit erythropoiesis (CFU-E) every 48h. Counting of colonies was performed using an eyepiece chamber. The results were obtained using Graphpad Prism software.

Results: We found that CD34+ was the major marker after sorting. We observed a negative correlation between sFas concentration and BFU-E (r=−0.74, p=0.001) when analyzed all 18 wells together. We observed lower amount of BFU-E in plate with sFas- compared to plate with sFas+ (4.3±1.6 vs. 2.0±1.1, p<0.05).

Conclusions: We observed that higher concentration of sFas interfere with erythropoiesis in CD34+ cell culture.

Differentential Expression of Myogenic Regulators Following Aerobic or Combined Exercise in Non-Dialysis CKD

Douglas W. Gould1, Emma L. Watson,2 Matthew P. Graham-Brown,3 Soterris Xenophonos,4 Thomas J. Wilkinson,5 Joao L. Viana,6 Alice C. Smith1. 1University of Leicester, Leicester, United Kingdom; 2University Institute of Maia, Porto, Portugal.

Background: CKD is associated with satellite cell (SC) dysfunction and reduced expression of myogenic regulatory factors (MRFs), which contribute to muscle wasting. SGLT2 protein inhibited by intracellular phosphate that negatively regulates the activation of the Akt/AS160/glu4 axis. AMPK activation in muscle of wild type mice undergoing CKD/High protein feeding is demonstrated by induced intramuscular phosphatase, increased AMP-dependent ammonia production and accumulation of AMPD-dependent products –uric acid and inosine. Wild type but not AMPD deficient mice on CKD/high protein demonstrated significant weight loss –a marker of muscle mass loss- in sham and nephrectomized mice was monitored weekly and renal function, muscle mass, intramuscular activation of AMPD1 and its signaling –AMPK and Akt activities, phosphate and uric acid levels- determined at week 5.

Results: AMPD1 activation in muscle of wild type mice undergoing CKD/High protein feeding is demonstrated by reduced intramuscular phosphatase, increased AMP-dependent ammonia production and accumulation of AMPD-dependent products –uric acid and inosine. Wild type but not AMPD deficient mice on CKD/high protein demonstrated significant weight loss –a marker of muscle mass loss- in sham and nephrectomized mice was monitored weekly and renal function, muscle mass, intramuscular activation of AMPD1 and its signaling –AMPK and Akt activities, phosphate and uric acid levels- determined at week 5.

Conclusions: AMPD1 activation in the skeletal muscle is a key step in the pathogenesis of CKD-dependent muscle wasting. Thus, AMPD1 blockade represents a new therapeutic approach for the prevention of this condition and to accelerate the recovery of muscle loss in subjects with CKD.
In this study, we examined the role of ER stress via abnormal lipid metabolism in the skeletal muscle of CKD patients and muscle atrophy alone, as well as the role of inflammation and is known to be a negative regulator of heat shock protein 70 (HSP70) expression.

Methods: Eight-week-old male Wistar rats were treated with either adriamycin (0.4%) (CKD rats) or vehicle (normal rats) for 6 weeks. Gastrocnemius muscles (GM) were dissected, and protein and mRNA expression were measured using Western blotting (WB) and qPCR, respectively.

Results: GM tissue weight was significantly decreased in CKD rats compared with normal rats. The expression of the GM was decreased in CKD rats compared with normal rats. In addition, the unsaturated fatty acid content of CKD rats was increased compared with normal rats. Inversely, CKD rats presented a decrease in SCD1 mRNA expression of gastrocnemius muscles was evaluated by real-time qPCR. Fatty acid composition of gastrocnemius muscles was determined by gas-liquid chromatography.

Conclusions: We suggest that the unbalanced SFA/UFA ratio in skeletal muscles due to a decrease in SCD activity induced by CKD causes lipotoxicity and sarcopenia via activation of various muscle atrophy systems.

TH-PO400

Plant versus Animal Protein Improves Anti-Inflammatory Effects of HDL and Lessens CKD-Induced Atherosclerosis

Ryohei Kaseda,1 Michihiro Hosojima,1 Shoji Kuwahara,1 Hideyuki Kabasawa,1 Hiroyuki Aoki,1 Yuki Higuchi,1,2 Valentina Kon,1 Kentaro Maruyama,1 Ichiei Narita,1 Akihiko Saito,1 Niigata University, Niigata, Japan; 2Vanderbilt University, Nashville, TN; Rice Research Center, Kameda Seika Co., Ltd, Niigata, Japan.

Background: Although CKD is known to cause endothelial injury that contributes to the development of atherosclerosis, particularly in CKD, few intervention studies have determined whether differences in dietary protein source, namely animal protein versus plant protein can modulate renal injury-acceleration of atherosclerosis and anti-inflammatory properties of HDL.

Methods: 12-week-old ApoE-deficient hyperlipidemic mice underwent uninephrectomy. The mice were pair-fed the usual casein-based diet (animal protein) or rice protein-based diet (plant protein extracted from rice endosperm by alkaline extraction method) for 6 weeks. We compared atherosclerotic lesions by en-face Sudan IV staining. HDL fraction was obtained by eliminating Apo B by polyethylene glycol precipitation. Human umbilical vein endothelial cells (HUVEC) were exposed to TNF-α or together with HDL for 6 hours. Cellular expression of inflammatory markers (MCP-1, IL-6, and IL-1β) was assessed by real-time RT-PCR.

Results: Atherosclerotic lesions were significantly reduced in rice protein-fed group compared to casein-fed mice (en-face atherosclerotic lesions: 0.28±0.06 vs 0.67±0.15mm²; p=0.038, N=5 and 5, respectively). HDL from rice protein-fed mice suppressed HUVEC’s inflammatory response compared to casein-fed mice (MCP-1, 3.83±0.73 vs. 7.42±0.39; p=0.003; IL-1β, 1.54±0.19 vs. 5.70±1.32; p=0.02; and IL-6, 0.52±0.07 vs. 0.98±0.06; p=0.05, N=5 and 5, respectively).

Conclusions: Plant protein-based diet significantly reduced kidney-injury driven atherosclerosis compared to animal protein-based diet. This anti-atherogenic effect is associated with anti-inflammatory effects of HDL. The results underscore the potential utility of nutritionally-based intervention in averting atherosclerosis for CKD funding.

TH-PO401

HDL from CKD Rabbits and Hemodialysis Patients Exhibit Impaired Anti-Inflammatory Activity on Human Platelets through CD36

Laurent Michelon,1 Jiansheng Huang,1 Macra F. Linton,1 Talat Alp Ikizler,1 Valentina Kon,1 University of Colorado, Aurora, CO; 2Vanderbilt University School of Medicine, Nashville, TN; 3University of Colorado Denver: Anschutz Medical Campus, Aurora, CO; 4Vanderbilt University Medical Center, Nashville, TN; 5VA THVS, Nashville, TN.

Background: Cardiovascular disease (CVD) is the most prominent cause of mortality and morbidity associated with chronic kidney disease (CKD). Inflammation and oxidative stress are considered to contribute to CVD in CKD. Both of these factors are also known to promote HDL malfunction in CKD. Whether interventions that modulate systemic inflammation can improve anti-inflammatory aspects of HDL in the setting of advanced CKD or ESRD is unknown.

Methods: We conducted a post-hoc analysis to evaluate if IL-1 blockade could improve the anti-inflammatory and anti-oxidant functions of HDL in patients with CKD. We used serum samples from two pilot randomized clinical trials; one in CKD stages 3-4 patients (CKD3/4A) and one in maintenance hemodialysis (MHD) patients. HDL was isolated from each participant’s serum at baseline and at the end of the study. The anti-inflammatory and anti-oxidative function of HDL was measured as the response of LPS-activated THP-1 macrophages exposed to the participant’s HDL (IL-6, TNF-α, NLRP3 response were measured by RT-PCR and cellular oxidant production by HPLC). Biomarkers were log transformed and repeated measures ANCOVA was used to estimate the percent change in biomarker expression with the intervention (between group comparison).

Results: The mean age of the participants was 60±13, 72% (n=33) were male, 38% (n=17) were black. There were 32 CKD patients (16 intervention and 16 placebo) and 14 MHD (7 intervention and 7 CKD). IL-1 blockade down-regulated hsCRP and IL-6 in both studies (Nowak et al 2017 and Hung et al 2011). IL-1 blockade effectively improved HDL functionality compared to baseline, IL-1 blockade reduced TNF expression by 30% (p=0.006) [18% in CKD (p=0.03) and 61% in MHD (p=0.06)], IL-6 by 40% (p=0.02) [36% in CKD (p=0.006) and 50% in MHD (p=0.03), and NLRP3 by 17% (p=0.02) [15% in CKD (p=0.02) and 25% in MHD (p=0.02)]. Cellular superoxide production fell by 15% (p=0.001) [17% in CKD (p=0.001) and 12% in MHD (p=0.004)].

Conclusions: IL-1 blockade improved the anti-inflammatory and anti-oxidative properties of HDL in patients with CKD stage 3 or stage 4 and MHD. Larger scale and longer term prospective studies are needed to confirm the utility of this intervention in clinical settings. (Hung and Tsichinda are first co-authors). Funding: Veterans Affairs Support, Private Foundation Support

TH-PO403

Fish Oil Supplementation Reduces Inflammation but Does Not Restore Renal Function and Klotho Expression in an Adenine-Induced CKD Model

Juan S. Aguado,1 Leandro C. Baia,2 Milene S. Ormanian,3 Amanda rakel Peixoto dos santos,2 Niels O. Camara,2 Gerjan Navis,3 Martin H. De Borst,4 Ita P. Heijberg,2 1University Medical Center Groningen, Groningen, Netherlands; 2Nephrology Division, Universidade Federal de São Paulo, São Paulo, Brazil.

Background: CKD and inflammation promote loss of klotho expression. Given the well-established anti-inflammatory effects of n-3 fatty acids, we aimed to investigate the effects of fish oil supplementation in an experimental model of inflammatory renal damage.

Methods: Male C57BL/6 J mice were fed an adenine-fed diet (AD-10days) to induce inflammatory renal damage or standard chow (CTL) for 10 days, and in the subsequent 7 days received either fish oil (Post-AD-Fish) or soybean oil (Post-AD-Soy). Renal function, pro-inflammatory and profibrotic markers (picrosirius stained) were assessed and the expression of Klotho was evaluated by qPCR and Western-blots.

Results: When compared to CTL, the AD-10days group exhibited significantly higher mean serum creatinine (1.3±0.4 vs 0.8±0.1mg/dL), IL-6, CXCL10 and IL-1β (68.0±17.7 vs 1.0±0.2, 6.6±0.3 vs 1.0±0.2 and 3.5±1.5 vs 2.4±0.7, respectively), reduced renal klotho expression (0.2±0.1 to 1.0±0.1), confirmed in Western-blots and a non-significant trend for increased fibrosis. As shown in the Figure, IL-6, CXCL9 and IL-1β were significantly decreased in Post-AD-Fish group but klotho expression was unaltered (also demonstrated by Western-blots). Serum creatine and fibrosis did not differ statistically between Post-AD-Fish and Post-AD-Soy groups.

Conclusions: Few studies have examined the potential anti-inflammatory and anti-oxidative properties of fish oil in CKD. Fish oil may offer a new strategy for the treatment of inflammation and fibrosis in CKD.
Conclusions: Fish oil supplementation reduced pro-inflammatory markers, but was not able to restore renal function or klotho expression in a model of inflammatory renal damage.

Methods: IDENTIFY was a prospective observational study comprising 1g of IV FCM administered to 3 patient populations: CKD (n=25); Healthy Controls (n=20); and Pregnancy (n=20). The following markers of iron status were collected on days 0, 2, 7 and 21: serum iron, ferritin, transferrin saturation (TSAT) and hepcidin (by mass spectrometry).

Results: Following IV FCM, there was a similar increase in serum iron and TSAT in all groups, which peaked at day-2, and returned to baseline at day-7. Ferritin increased to the same extent in all groups, reaching a maximum at day-7, and remaining significantly above baseline at day-21. Serum hepcidin peaked at day-2 in all groups, but the zenith varied (127±61 vs. 106±62 vs. 61±44 ng/mL, p=0.001) and the AUCs differed (1503±1173 vs. 953±718 vs. 629±560, p<0.004) in the CKD, Controls and Pregnancy groups, respectively.

Conclusions: Despite receiving the same dose of FCM, and with comparable levels of haematinics, the rise in hepcidin was significantly greater in CKD patients compared to healthy controls and pregnant women. The reason for this novel finding is unclear, and requires further study. Finally, the ferritin response observed in this study supports a recommendation that following administration of 1g FCM, serum ferritin should not be rechecked for at least 1-month.

Funding: Commercial Support - Vifor

TH-PO404

Erythropoietin Pathway Dysregulation in Anemia of CKD 

Daniel Landau,¹ 
Lital London,² Inbar Bandach,¹ Yael Segev,¹ Microbiology and Immunology, Ben Gurion University of the Negev, Beer Sheva, Israel; 2Ben Gurion University of the Negev, Beer-Sheva, Israel.

Background: Anemia is a known driver for hypoxia inducible factor (HIF) which leads to increased renal erythropoietin (EPO) synthesis. Bone marrow (BM) EPO receptor (EPOR) signals are transduced through a JAK2-STAT5 pathway. Anemia of CKD is considered to be of multifactorial origin, including impaired renal EPO synthesis and intestinal iron absorption. EPO resistance in CKD may be an additional factor but its mechanisms are poorly understood. We investigated the HIF- EPO- EPOR axis in kidney, BM and proximal tibia in anemic juvenile CKD rats.

Methods: CKD was induced by 5/6 nephrectomy in young (20 days old) Sprague-Dawley rats while C group was sham operated. An additional control anemic (C-A) group was daily bled for 7 days. Rats were sacrificed 4 weeks after CKD induction and 5 minutes after a single bolus of IV rhEPO (25 U/kg).

Results: Hemoglobin levels were similarly reduced in CKD and C-A (11.7 ± 0.4 and 10.8±0.2 V.S 14.3±0.2 g/dL in C, p<0.0001). Liver hepcidin mRNA was decreased in CA but increased in CKD. Serum iron and transferrin levels were unchanged in CKD. Kidney HIF2α was elevated in C-A but unchanged in CKD. Renmant kidney EPO protein and mRNA levels were unchanged between groups. However, BM EPO protein (which reflects circulating EPO) was increased in C-A but remained unchanged in CKD. BM and proximal tibia EPOR were unchanged in C-A but decreased in CKD. Proximal tibial phospho-STAT5 increased in C but not in CKD.

Conclusions: Compared to chronic blood loss, anemia in young CKD rats is associated with inappropriate responses: kidney HIF2α and BM EPO are not increased, BM and bone EPOR levels, as well as bone pSTAT5 response to EPO are reduced. This may allow the introduction of additional therapeutic avenues for CKD related anemia beyond iron and EPO supplementation.

TH-PO406

Oxidative Stress after Intravenous Iron in Dialysis Patients – A Real Phenomenon or an In Vitro Artifact? Jaromír Eiselt,¹ Daniel Rajdl,¹ Lukas Kielberger,¹ Ladislav Treifl,² Dept. of Internal Medicine I, Charles University, Faculty of Medicine in Pilsen, Pilsen, Czech Republic; 2Inst. of Clinical Biochemistry and Hematology, Charles University, Faculty of Medicine in Pilsen, Pilsen, Czech Republic.

Background: Intravenous iron can aggravate oxidative stress. However, the presence of the iron preparation in the serum sample may interfere with the determination of oxidative stress markers. The aim of the study was to measure markers of oxidative stress and serum iron after administration of i.v. iron.

Methods: A total of 10 patients on chronic hemodialysis (HDF) received in a random order physiological solution (CONTR), 200 mg of ferric carboxymaltose (FCM) and 200 mg of iron sucrose (IS). Infusions were given from min. 60 to min. 90 of 4 h HDF. In minutes 60, 90, 150 and 240 were measured thiobarbituric acid reacting substances (TBARS), 8-isoprostane (8-iso) and iron in serum. Iron was determined by a routine photometric method (Fe-PHOT) and by an atomic absorption spectrometry (Fe-AAS).

Results: We detected increase of TBARS after both FC and IS, while 8-iso rose only after administration of IS. Levels of serum iron were dramatically higher when using Fe-AAS, than Fe-PHOT. The Fe-AAS method, unlike Fe-PHOT, detects all plasmatic iron, including the one bound in iron-sugar complexes. Results are summarized in table. Changes in TBARS strongly correlated with serum iron measured by Fe-AAS after infusion of both IS (r=0.92, p=0.001) and FC (r=0.79, p=0.0001), but not after Fe-PHOT (r=0.23, p=0.133). On the other hand, 8-isoprostane did not correlate with Fe-AAS in any of the three tested treatments.

Conclusions: Immediate effect of i.v. administration of ferric carboxymaltose and iron sucrose on oxidative stress of dialysis patients is probably small and difficult to prove with the respect to artifacts in analyses. Measurement of 8-isoprostane does not seem to be affected, compared to TBARS, by a false in vitro interference with intravenously administered iron-sugar complexes.
Erythropoietin (Epo) Inhibits Sodium-Driven Pro-Inflammatory Effects

**Background:** High sodium concentrations promote T cell IL-17 production and injury by increasing intracellular pSGK1. We tested whether EPO, which we previously showed has immune-modulating effects, can counteract sodium-induced human Th17 production in vitro, and in a murine kidney disease model, in which sodium and EPO concentrations are elevated.

**Methods:** We added EPO or vehicle to human PBMC (n=3-8 donors per experiment) cultured in vitro or high NaCl or [urea] (osmotic control) and measured T cell proliferation, IL-17/IFNγ production, pSGK1 (flow cytometry) and Foxp3 expression. To assess in vivo effects we fed WT B6 mice with normal or high NaCl diet, treated them aristolochic acid (ArA) to induce T cell-mediated interstitial nephritis and increased CD4+CD25+Foxp3+ T cell proliferation (Fig. 1A), and IFNγ production (6.7 ± 1.2% vs. 1.8 ± 0.4%, vehicle vs. EPO; P<0.05) without affecting apoptosis/necrosis. EPO showed has immune-modulating effects, can counteract sodium-induced human Th17 production in vitro, and in vivo, in humans and mice. Our data support the concept of EPO is an immune-splenic Th1 and Th17 cells, increased Treg and reduced proteinuria (Fig. 1C).

**Results:** EPO (but not urea) inhibited human NaCl-driven phosphorylation, T cell proliferation (Fig. 1A), and IFNγ production (6.7 ± 1.2% vs. 1.8 ± 0.4%, vehicle vs. EPO; P<0.05), without affecting apoptosis/necrosis. EPO prevented Na-driven Th17 induction (1.6 ± 0.3% vs. 0.7 ± 0.3%, vehicle vs. EPO; P<0.05) and increased CD4/CD25/Foxp3+ Treg induction/fusion (Fig. 1B), while maintaining Treg stability. In mice fed a normal or a high NaCl diet, EPO reduced ArA-induced splenic Th1 and Th17 cells, increased Treg and reduced proteinuria (Fig. 1C).

**Conclusions:** EPO inhibits NaCl-induced proinflammatory T cell immunity in vitro and in vivo, in humans and mice. Our data support the concept of EPO is an immune-modulatory hormone that could physiologically counteract the proinflammatory effects of high intrarenal [NaCl].

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

**TH-PO411**

**AT2R Deficiency Accelerates Renal Dysfunction in Diabetic Progeny in a Sex-Dependent Manner**

**Background:** Angiotensin type 2 receptor (AT2R) deficient mice (AT(RKO)) exhibit a spectrum of congenital abnormalities of the kidney and urinary tract. We aimed to study whether AT2R deficiency (AT2RKO) that also badis mellitus mellitus would result in offspring with even more abnormalities in the urinary tract.

**Methods:** The offspring (male/female) of non-diabetic and diabetic dams of wild-type (WT) and AT(RKO) mice were followed until 20 weeks of age. Systolic blood pressure, insulin concentration, fasting glucose test (IST), albumin/creatinine ratio (ACR), glomerular filtration rate (GFR), renal morphology and gene expression including angiotensin converting enzyme (ACE), angiotensin converting enzyme 2 (ACE2), synaptopodin (Sypno) and tyrosine phosphatase SHP-1 (JPCR and immunohistochemistry) were assessed.

**Conclusions:** The offspring of non-diabetic dams of diabetic progeny of both WT and AT(RKO) mice developed more evidence of nephropathy (higher GFR and apparent glomerulosclerosis with podocyte loss) at 20 weeks of age, while male diabetic progeny of AT(RKO) mice developed more evidence of nephropathy, which preceded this renal tubular cell change and RhoA activation was unclear.

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

**TH-PO412**

**Therapeutic Targeting of Melanocortin 5 Receptor: A Novel Approach for Protection against AKI**

**Background:** Melanocortin peptides belong to a neuroimmunoendocrine hormone system that sustains the homeostasis of diverse organ systems. Burgeoning evidence suggests that activation of melanocortin 5 receptor (MC5R) by melanocortin neuropeptides plays a pivotal role in immunomodulation and confers a protective effect in various disease models. Nevertheless, how therapeutic targeting of MC5R affects kidney injury was unknown and explored here.

**Methods:** Mice were treated with MC5A, a highly selective agonist of MC5R, or with MC5B, a highly selective antagonist, prior to folic acid injury. In vitro, primary renal proximal tubular cells (PCT) were injured with tumor necrosis factor (TNF) on MC5A or PG20N treatment. Kidney or cellular injuries were assessed.

**Results:** Selective activation of MC5R by MC5A strikingly improved the folic acid-induced acute kidney injury (AKI), as evidenced by a reduction of serum creatinine, reduced urinary excretion and renal expression of lipocalin-2, diminished tubular damages and tubular cell death, and attenuated renal inflammation. Conversely, selective blockade of MC5R by PG20N exacerbated the folic acid induced AKI. In normal kidney tubulointerstitium, MC5R was sporadically expressed by a considerable, linear relationship with the plasma LA content (Sperman rho = 0.22; p < 0.05). Nevertheless, CKD turned out as an independent predictor of serum LA content, following adjustment for the abovementioned confounders (adjusted R² = 0.19; p < 0.01).

**Conclusions:** Serum LA content is decreased in the course of CKD. Taking into account the potential impact of low LA on mortality, increased intake of products reach in this essential fatty acid could be of benefit for CKD patients.

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

**TH-PO413**

**RhoA Effector mDia1Contributes to Kidney Injury in the Early Stage of High-Fat Diet Induced Obesity**

**Background:** Obesity is a critical contributor to kidney damages that are reported to be structurally characterized by glomerulosclerosis, tubular hypertrophy and renal hypertrophy, which precede this renal tubular cell change and RhoA activation was unclear.

**Methods:** We used male C57Bl/6J mice with overexpressed dominant negative RhoA genes selectively expressed in the PT (dnRhoAAT5), thus denoting a direct modifying effect of MC5R on MDSC.

**Conclusions:** The activation of RhoA/ROCK signaling leading to inflammatory reaction. However, the early changes which precede this renal tubular cell change and RhoA activation was unclear.

**Funding:** Private Foundation Support, Government Support - Non-U.S.
Oral NaHCO3 Activates the Splenic Anti-Inflammatory Pathway

**Promoting M2-Macrophage Polarization**

**Background:** Oral sodium bicarbonate (NaHCO3) may slow decline in function in CKD, yet the mechanisms mediating this beneficial effect remain unclear. In the current study we tested the hypothesis that oral NaHCO3 intake promotes anti-inflammatory-M2 macrophage polarization by activating the splenic anti-inflammatory pathway in both rats and humans.

**Methods:** 8-10 week old male Sprague Dawley rats maintained on a standard pellet diet with water ad libitum were utilized. To determine the effect of oral NaHCO3 on renal macrophage polarization, drinking water was replaced with solutions of NaHCO3, in tap water containing (0, 0.01, 0.05 or 0.1M NaHCO3; n=3 per treatment group) with all solutions made equimolar (0.1M) with the addition of NaCl. Following 4 days of drinking NaHCO3, rats were anesthetized, the left kidney and spleen harvested and prepared for flow cytometry analysis. Untreated rats served as controls.

**Results:** Results: We found that addition of NaHCO3 to the drinking water of rats resulted in a dose dependent increase in renal macrophage polarization away from an M1 (inflammatory) and toward an M2 (anti-inflammatory) phenotype with as little as 3 days of drinking 0.01M NaHCO3 solution (P<0.02). Most of the polarization effect could be attributed to an increase in renal M2 macrophages, with the 5% of renal cells identified as M2s increasing from 2% to 8% at the highest dose of NaHCO3 (0.1M; P<0.006). The effect of 0.1M NaHCO3 on renal macrophage polarization was confirmed in a separate group of rats (n=5; P=0.007) and was abolished with prior spleenectomy. In human blood drawn from 15 ED2+0.8% of all leukocytes were determined by flow cytometry analysis at baseline and 1 and 2 hours following ingestion of 2g of NaHCO3 in 250 ml of bottled water.

**Conclusions:** Our data indicate that oral NaHCO3 may activate the splenic anti-inflammatory pathway in rats and humans. Activation of these pathways may underlie part of the beneficial effects of NaHCO3 observed in CKD patients.

**Funding:** NIDDK Support

**TH-PO416**

**Expression of T Regulatory Cells in the Kidneys of Guanylyl Cyclase/Natriuretic Peptide Receptor-A Gene-Knockout Mice**

**Venkateswara Ray,** University of Louisville, Louisville, KY; **Sarah Lin,** University of Louisville, Louisville, KY

**Background:** Guanylyl cyclase/natriuretic peptide receptor-A (GC/A/NPRA) gene (Npr1) disruption activates the pro-inflammatory responses in null mutant mice. There is increasing evidence that imbalanced immune responses play important role in physiological changes and complications of hypertension leading to organ damage. T Regulatory cells are defined as vital immune cellular population and they are likely to aid, adjust or tolerate inflammation and the harmful effects of the other immune cellular population. The objective of our study was to elucidate the role of T regulatory cell markers and their expression levels in Npr1 gene-disrupted mice.

**Methods:** In the present study, 0-copy (Npr1+/-), 1-copy (Npr1+/-), and 2-copy (Npr1+/-) mice were determined by flow cytometry. We analyzed the phenotype of newly generated PTEC-specific Rubicon-deficient mice (KO mice). We crossed KO mice with GFP-MAPLC3 transgenic mice, in which GFP-positive puncta reflect autophagosomes, and evaluated autophagic flux by comparing the number of GFP-positive dots with or without chloroquine administration. We then investigated the role of Rubicon in lipid metabolism using isolated Rubicon-deficient PTECs.

**Results:** The number of autophagosomes was increased after chloroquine administration even during the fed state in the PTECs of 3-month-old KO mice, indicating that Rubicon may be important in regulating inflammatory pathways in autoimmune diseases. Importantly, data on Rubicon-mediated lipid efflux from KO PTECs to blood circulation was obtained.

**Conclusions:** Rubicon deficiency in PTECs leads to systemic lipid accumulation and obesity by promoting excessive lipid efflux. Rubicon in PTECs can be a therapeutic target for metabolic syndrome.

**Funding:** NIH Support

**TH-PO419**

**Tissue-Type Plasminogen Activator Modulates Macrophage to M2 Macrophage Polarization through Anmexin A2-Mediated NF-κB Pathway**

**Ling Lin,** Kebin Hu, Penn State University College of Medicine, Hershey, PA

**Background:** Macrophage accumulation is one of the hallmarks of progressive kidney disease. In response to injury, macrophages undergo a phenotypic polarization to become two functionally distinct subsets: M1 and M2 macrophages. Macrophage polarization is a dynamic process, and recent work indicates that macrophages, in response to kidney injury, can shift their polarity. However, the underlying mechanisms remain largely unknown. Tissue-type plasminogen activator (tPA) is a protease up-regulated in the chronically injured kidneys, has been shown to preferably promote M1 macrophage accumulation and renal inflammation. We hypothesized that tPA may be an important factor in determining M1 to M2 macrophage phenotypic change contributing to the accumulation of M1 macrophages in the injured kidneys.

**Methods:** We used integral in vivo and in vitro approaches to investigate the role of tPA in macrophage polarity shift, and clarified the underlying signaling mechanism.

**Results:** It was found that obstruction-induced renal M1 chemokine expression remained largely unknown. Tissue-type plasminogen activator (tPA), a protease up-regulated in the chronically injured kidneys, has been shown to preferably promote M1 macrophage accumulation and renal inflammation. We hypothesized that tPA may be an important factor in determining M1 to M2 macrophage phenotypic change contributing to the accumulation of M1 macrophages in the injured kidneys.

**Conclusions:** It’s clear that tPA promotes macrophage M2 to M1 phenotypic change through annexin A2-mediated NF-κB pathway.

**Funding:** NIDDK Support, Other NIH Support - American Heart Association

**Rubicon Deficiency Leads to Obesity by Promoting Excessive Lipid Efflux in Proximal Tubular Epithelial Cells**

**Atsushi Takahashi,** Yoshisuguro Takabatake,1 **Takeshi Yamamoto,** Hiroshi Kato,1 **Tomohiro Komori,** 4 Satoshi Minami,4 **Ryuta Fujimura,** Jun-Ya Kaimori,4 **Isao Matsui,** Fumio Niimura,4 **Taiji Matsuoka,** Yoshitaka Isaka,4 Osaka University Graduate School of Medicine, Suita, Japan; 2Osaka University Graduate School of Medicine, Suita, Japan; 3Osaka University Graduate School of Medicine, Suita, Osaka, Japan; 4Osaka University Graduate School of Medicine, Suita, Japan; 5Tokai University Graduate School of Medicine, Isehara, Japan

**Background:** Autophagy is a lysosomal degradation system which contributes to intracellular status. It has been known that Rubicon (Run domain Bel-1 interacting and cysteine-rich containing protein) negatively regulates autophagcic activity by inhibiting the fusion of autophagosomes and lysosomes. However, its physiological role in proximal tubular epithelial cells (PTECs) remains poorly understood.

**Methods:** We analyzed the phenotype of newly generated PTEC-specific Rubicon-deficient mice (KO mice). We crossed KO mice with GFP-MAPLC3 transgenic mice, in which GFP-positive puncta reflect autophagosomes, and evaluated autophagic flux by comparing the number of GFP-positive dots with or without chloroquine administration. We then investigated the role of Rubicon in lipid metabolism using isolated Rubicon-deficient PTECs.

**Results:** The number of autophagosomes was increased after chloroquine administration even during the fed state in the PTECs of 3-month-old KO mice, indicating that Rubicon may be important in regulating inflammatory pathways in autoimmune diseases. Importantly, data on Rubicon-mediated lipid efflux from KO PTECs to blood circulation was obtained.

**Conclusions:** Rubicon deficiency in PTECs leads to systemic lipid accumulation and obesity by promoting excessive lipid efflux. Rubicon in PTECs can be a therapeutic target for metabolic syndrome.

**Funding:** Other NIH Support - American Heart Association

**Rubicon Deficiency Leads to Obesity by Promoting Excessive Lipid Efflux in Proximal Tubular Epithelial Cells**

**Susan O'Connor,** University of Louisville, Louisville, KY; **Babak Afshari,** University of Louisville, Louisville, KY; **Mark Siskind,** University of Louisville, Louisville, KY; **Babak Afshari,** University of Louisville, Louisville, KY; **Dai Li,** University of Louisville, Louisville, KY; **Osaka University Graduate School of Medicine, Isehara, Japan; 2Tokai University Graduate School of Medicine, Isehara, Japan; 3Osaka University Graduate School of Medicine, Suita, Osaka, Japan; 4Osaka University Graduate School of Medicine, Suita, Japan; 5Tokai University Graduate School of Medicine, Suita, Osaka, Japan; 6University of Louisville, Louisville, KY; 7Virginia Commonwealth University, Richmond, VA

**Background:** Rubicon (Run domain Bel-1 interacting and cysteine-rich containing protein) negatively regulates autophagcic activity by inhibiting the fusion of autophagosomes and lysosomes. However, its physiological role in proximal tubular epithelial cells (PTECs) remains poorly understood.

**Methods:** We analyzed the phenotype of newly generated PTEC-specific Rubicon-deficient mice (KO mice). We crossed KO mice with GFP-MAPLC3 transgenic mice, in which GFP-positive puncta reflect autophagosomes, and evaluated autophagic flux by comparing the number of GFP-positive dots with or without chloroquine administration. We then investigated the role of Rubicon in lipid metabolism using isolated Rubicon-deficient PTECs.

**Results:** The number of autophagosomes was increased after chloroquine administration even during the fed state in the PTECs of 3-month-old KO mice, indicating that Rubicon may be important in regulating inflammatory pathways in autoimmune diseases. Importantly, data on Rubicon-mediated lipid efflux from KO PTECs to blood circulation was obtained.

**Conclusions:** Rubicon deficiency in PTECs leads to systemic lipid accumulation and obesity by promoting excessive lipid efflux. Rubicon in PTECs can be a therapeutic target for metabolic syndrome.

**Funding:** Other NIH Support - American Heart Association

**Rubicon Deficiency Leads to Obesity by Promoting Excessive Lipid Efflux in Proximal Tubular Epithelial Cells**

**Susan O'Connor,** University of Louisville, Louisville, KY; **Babak Afshari,** University of Louisville, Louisville, KY; **Mark Siskind,** University of Louisville, Louisville, KY; **Babak Afshari,** University of Louisville, Louisville, KY; **Dai Li,** University of Louisville, Louisville, KY; **Osaka University Graduate School of Medicine, Isehara, Japan; 2Tokai University Graduate School of Medicine, Isehara, Japan; 3Osaka University Graduate School of Medicine, Suita, Osaka, Japan; 4Osaka University Graduate School of Medicine, Suita, Japan; 5Tokai University Graduate School of Medicine, Suita, Osaka, Japan; 6University of Louisville, Louisville, KY; 7Virginia Commonwealth University, Richmond, VA

**Background:** Rubicon (Run domain Bel-1 interacting and cysteine-rich containing protein) negatively regulates autophagcic activity by inhibiting the fusion of autophagosomes and lysosomes. However, its physiological role in proximal tubular epithelial cells (PTECs) remains poorly understood.

**Methods:** We analyzed the phenotype of newly generated PTEC-specific Rubicon-deficient mice (KO mice). We crossed KO mice with GFP-MAPLC3 transgenic mice, in which GFP-positive puncta reflect autophagosomes, and evaluated autophagic flux by comparing the number of GFP-positive dots with or without chloroquine administration. We then investigated the role of Rubicon in lipid metabolism using isolated Rubicon-deficient PTECs.

**Results:** The number of autophagosomes was increased after chloroquine administration even during the fed state in the PTECs of 3-month-old KO mice, indicating that Rubicon may be important in regulating inflammatory pathways in autoimmune diseases. Importantly, data on Rubicon-mediated lipid efflux from KO PTECs to blood circulation was obtained.

**Conclusions:** Rubicon deficiency in PTECs leads to systemic lipid accumulation and obesity by promoting excessive lipid efflux. Rubicon in PTECs can be a therapeutic target for metabolic syndrome.
Methods: We generated transgenic mice containing an inducible shRNA that targets expression of Ugcg (Tet-O-shUgcg). Ugcg is the gene that encodes for glucosylceramide synthase, the enzyme that catalyzes synthesis of glucosylceramide from ceramide. Tet-OshUgcg mice were bred with CAG-rtTA3 mice (CAG-rtTA3-Tet-O-shUgcg) for knockdown of Ugcg (KO). The CAG-rtTA3-Tet-O-shUgcg model is novel tool for studying the role of GSLs and N-glycans in kidney inflammation and autoimmunity and may represent a new mouse model of autoimmune kidney disease. Funding: NIDDK Support

TH-PO420
ACF-TEI, a Novel Oral Adsorbent, Shows Potent Adsorption Effect on Uremic Toxin in the Rat Model and the System Mimicked Human Gastrointestinal Tract Hiroshi Shimoyama,1 Yasumi Nishiwaki,1 Takashi Murakami,1 Yoshimasa Takahashi,1 Tsunami Kobayashi,1 1Pharmacology Research Department, Teijin Institute for Bio-Medical Research, Teijin Pharma Discovery Research Laboratories, Teijin Institute for Bio-Medical Research, Teijin Pharma Limited, Tokyo, Japan.

Background: Uremic toxins (UTs), such as indoxyl sulfate (IS) and p-cresyl sulfate (PCS), accumulate in the blood of patients with impaired renal function. Since several studies have demonstrated a link between serum UTs levels and clinical outcomes, they draw much attention as key factors in the progression of chronic kidney diseases (CKDs) and cardiovascular diseases. Thus, adsorbing UTs in the intestinal tract and excreting with feces is effective for inhibiting the progression of CKDs and delaying the introduction of dialysis treatment. We have identified a novel oral UTs absorbent, ACF-TEI, which has more potent adsorption profiles to UTs than existing adsorbents. In this study, we examined in vitro adsorption capacities of ACF-TEI to several UTs and the reducing effect of ACF-TEI on serum UTs in CKD rat model. In addition, to estimate the effectiveness of ACF-TEI in human, we evaluated the effect of ACF-TEI on UT adsorption in a system that mimicked human gastrointestinal (GI) tract.

Methods: ACF-TEI was mixed with solutions of indole, the precursor of IS produced by enterobacteria, or other UTs and reacted, then the adsorption capacity was calculated. ACF-TEI was administered orally to bilateral nephrectomized rats, and then concentrations of serum IS and PCS were measured. Adsorption of indole in the human GI tract was estimated using dynamic multi-compartmental GI tract model.

Results: ACF-TEI showed higher adsorption capacity to indole and other UTs than existing adsorbent. In the bilateral nephrectomized rats, ACF-TEI dose-dependently reduced serum IS and PCS levels and the effects were more potent than the existing adsorbents. In the dynamic multi-compartmental GI tract model, ACF-TEI reduced colonic indole concentration at lower doses than the existing adsorbents.

Conclusions: ACF-TEI adsorbs various UTs and showed the potent effects not only in the rodent model but also in the human GI tract mimicked system. Therefore, in clinical, ACF-TEI is expected to show potent UTs reducing effect and to be beneficial for patients with CKDs.

TH-PO421
Gut Microbiota-Dependent Trimethylamine-N-Oxide and Inflammatory Biomarkers in Patients with Diabetic Nephropathy Mohammed A. Al-Obaide, Ruchi Singh, Palika Datta, Maria V. Salguero, Tetyana L. Vasylyeva, Texas Tech University Health Sciences Center, Amarillo, TX.

Background: Trimethylamine-N-oxide (TMAO) is a product of diet, gut microbiome, and tissues metabolism. Elevated TMAO levels associated with heart attack, stroke and chronic kidney disease (CKD). We investigated the gut microbiota composition and TMAO levels in the patients with type 2 diabetes mellitus (T2DM) and advanced stages of diabetic nephropathy (DN), and TMAO association with serum IL-6, TNFα, CRP, ET-1, LPS, and zonulin.

Methods: Twenty adult patients with T2DM and CKD 3-4 secondary to DN and 20 healthy subjects (HS) participated in the study. The analysis included: nutrition, metabolic parameters, trimethylamine (TMA) producing gut microbiota, and TMAO, LPS, zonulin, and serum biomarkers of inflammation and endothelial dysfunction. The gut microbiota diversity identified by amplified V5-V6 region of the 16s ribosomal RNA (rRNA) genes and DNA sequencing by the MiSeq (Illumina Inc., San Diego, CA) using a 600 cycle v3 sequencing kit. The TMAO quantified by LC/MS method and serum biomarkers by ELISA.

Results: Dietary analysis showed that patients with T2DM and DN consumed less protein and more fat compared to HS and had more than two-fold elevated levels of triglycerides. The gut microbiome in DN patients exhibited a higher abundance of TMAO producing bacteria, p < 0.05. The serum level of TMAO in patients with DN was significantly higher (2.7 ± 0.52 µg/ml) compared to HS (0.43 ± 0.1 µg/ml), p < 0.05. The IL-6 and ET-1 also showed higher levels in the DN patients and positive correlation with TMAO. A positive correlation also observed between zonulin and LPS in both DN and HS groups.

Conclusions: Gut microbiota in patients with T2DM-CKD has increased abundance of TMA producing bacteria, which together with excessive dietary TMAO and increased gut permeability possess substantial risk for cardiovascular health through increased level of chronic inflammation and endothelial dysfunction. The pilot study findings are worth pursuing further evaluation. Funding: Clinical Revenue Support

TH-PO422
Homocysteine Aggravates Intestinal Permeability Increase and Tight Junction Dysfunction In Vivo and In Vitro Shanshan Liang, Hongli Jiang. Dialysis Department of Nephrology Hospital, First Affiliated Hospital of Medicine School, Xi’an Jiaotong University, Xi’an, China.

Background: Intestinal injury is a common complication of uremia. Homocysteine (Hcy), as an important intestinal derived uremic toxin and pro-inflammatory molecule, whether it is involved in the increased intestinal permeability and epithelial barrier dysfunction in uremia remains unclear. This study aimed to investigate the effect of Hcy on intestinal epithelial in vitro and in vivo. Methods: In vitro experiment, Caco2 cells were seeded on transwell plates and utilized when transepithelial electrical resistance (TEER) exceeded 500Ω·cm² to ensure full polarization and TJ formation. Cells were then incubated with Hcy (0.5 to 5.0 µmol/L) for 24h. Paracellular permeability was determined by TEER and the fluorescent Lucifer yellow dye (FLY) flux across cell monolayers. In vivo experiment, SD rats were divided into control, uremia (induced by adenine) and uremia + vitamin B compounds (folate, vitamin B6 and B12) group. Serum Hcy levels, colon homogenate of Hcy, inflammatory factors (CRP, IL-6 and TNF-α), SOD, MDA, endotoxin and intestinal permeability were assessed. H&E and transmission electron microscopy were used for pathological analysis. TJ proteins of claudin-1, occludin, and ZO-1 were assessed by western blot.

Results: Fig.1 showed the TEER changes of Caco2 cells during 21 days and the decreased TEER as well as the gradually increased FLY flux rates after Hcy incubation. Hcy down regulates TJ protein abundance in a concentration-dependent manner (Fig 4A), which was accompanied with the increased epithelial permeability. In animal experiments, uremia group showed elevated Hcy levels, oxidized inflammatory factors and intestinal permeability (Fig 2). The pathological changes of colon were obviously observed (Fig 3) with TJ protein levels decreased (Fig 4B). Fortunately, these parameters were improved in varying degrees after vitamin B compounds treatment.

Conclusions: Hcy aggravates intestinal permeability increase and epithelial barrier dysfunction by stimulating oxidative inflammatory damage. Supplementation of folate, vitamin B6 and B12 can improve the damage to some extent by reducing Hcy. Funding: Government Support - Non-U.S.

TH-PO423
Inhibition of Glycolysis Attenuates Ischemia-Reperfusion Injury via Mitochondrial and Redox Changes in Proximal Tubular Cells Akinari Shinohara, Takahisa Kawakami, Masaomi Nangaku. Division of Nephrology and Endocrinology, The University of Tokyo School of Medicine, Tokyo, Japan.

Background: Proximal tubular cells utilize fatty acid oxidation (FAO) more than glycolysis for ATP production in the physiological state. However, it remains largely unknown whether their metabolism affects pathophysiology of renal diseases. In this study, we investigated unknown effects of glycolysis inhibition with 2DG, a representative glycolysis inhibitor, on murine renal ischemia-reperfusion injury (IRI), to which proximal tubular cell (PTC) injury by oxidative stress is central.

Methods: Eight-week-old male C57BL/6J mice were treated with 500 mg/kg 2DG or vehicle by i.p. 24 hours before bilateral IR, and renal injury was evaluated on day 1. We also examined effects of 2DG on PTCs, using HK-2 in vitro. HK-2 cells were treated with 5 mM 2DG for 6 hours and exposed to oxidative stress with 4 mM hydrogen peroxide. Cytotoxicity was measured with generation of reactive oxygen species (ROS) assessed by flow cytometry using dihydroethidium and LDH assay.

Results: Glycolysis inhibition by 2DG ameliorated renal dysfunction on day 1: serum creatinine was 1.4 ± 0.4 mg/dL in the vehicle group and 0.9 ± 0.1 mg/dL in the 2DG group. The reduced IRI was also demonstrated by a decrease in histological tubular injury score and mRNA expression of Kim-1 in the 2DG group. 2DG-preconditioned kidney cortex showed reduced phospho-AMPK in immunoblot, indicating increased ATP in PTCs, which can suppress cell injury and death in IRI. We investigated its mechanism and found that
2DG increased free fatty acid in serum and PPARα expression in the kidney, suggesting that activated FAO promoted ATP production in PTCs. In vitro, treatment with 2DG suppressed generation of ROS and cell death. We focused on pentose phosphorylation pathway (PPP), because glycolysis inhibition can promote PPP as a bypass of glucose metabolism, and its key function is generation of reducing equivalents of NADPH. Indeed, increased PTP enzymes, including glucose-6-phosphate dehydrogenase and transketolase, were up-regulated, and NADPH/NAPD ratio was increased by 2DG. We also found that glutathione peroxidases, key antioxidative enzymes, were induced by 2DG.

**Conclusions:** In conclusion, glycolysis inhibition ameliorated renal IRI via an ATP increase by enhanced FAO and a favorable redox state by promoted PPP in PTCs, implicating the importance of PTC metabolism in renal diseases.

**TH-PO424**

**Combination Treatment with Cholecalciferol and Omega-3 Fatty Acid Modulates Molecules Associated with Cardiac and Cardiac Hypertrophy in 5/6 Nephrectomy Rats**

Hyuck Jae Choi, 1 Su mi Lee, 2 Sung Hyun Son, 1 Kitae Kim, 1 Young ki Son, 2 Seong Eun Kim, 1 Won Suk An. 2

1 BHs Han Sea Hospital, Sayeong-ku, Busan, Republic of Korea; 2 Dong-A University, Busan, Republic of Korea;

**Objective:** Hypertrophy in 5/6 Nx rats.

**Methods:** Male Sprague Dawley rats were divided into 5 groups and treated for 6 weeks; Sham control, 5/6 Nx control, 5/6 Nx treated with ViD, 5/6Nx treated with O-3FA, 5/6Nx treated with ViD and O-3FA. Western blot analysis was performed to investigate whether glucose-3 fatty acid (O-3FA) and cholecalciferol (Vit. D) affect on molecules associated with cardiac hypertrophy and sarcopenia in 5/6 Nx rats.

**Results:** Serum BUN and creatinine were the lowest in 5/6 Nx group treated with O-3FA and Vit. D among other 5/6 Nx groups. Compared with sham control, 5/6 Nx control significantly up-regulated myostatin and down-regulated myogenin and MyD in both cardiac and skeletal muscle. Increased expression of myostatin and decreased expression of myogenin and MyD of cardiac and skeletal muscle were recovered by combined treatment with O-3FA and Vit. D. Phosphorylated Akt and mTOR were examined by western blot analysis.

**Conclusions:** Combined treatment of O-3 FA and Vit. D may be helpful for decreasing cardiac hypertrophy and sarcopenia by increasing myogenin and MyD, decreasing myostatin and modulating Akt-mTOR axis in both cardiac and skeletal muscle of 5/6 Nx rats.

**Funding:** Private Foundation Support

**Laboratory results**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Normal</th>
<th>5/6Nx</th>
<th>5/6Nx with Vit. D</th>
<th>5/6Nx with O-3FA</th>
<th>5/6Nx with O-3FA and Vit. D</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN (mg/dL)</td>
<td>17.2±3.8</td>
<td>17.7±7.4</td>
<td>75.2±15.6</td>
<td>75.3±15.0</td>
<td>51.75±7.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.45±0.1</td>
<td>1.93±1.1</td>
<td>7.25±1.3</td>
<td>1.69±1.3</td>
<td>0.08±0.1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Data are expressed as mean ± SD**

**P value < 0.05 (mean values are significantly different from control)**

**aP value < 0.05 (mean values are significantly different from 5/6 nephrectomy group)**

**bP value < 0.05 (mean values are significantly different from 5/6 nephrectomy group e Vitamin D group)**

**cP value < 0.05 (mean values are significantly different from 5/6 FA group)**

**TH-PO425**

**Combination of Cholecalciferol and Omega-3 Fatty Acid Increases 1, 25-Dihydroxy Vitamin D Level by Inhibiting 24-Hydroxylase of Kidney and Liver in 5/6 Nephrectomized Rats**

Su mi Lee, 1 Hyuck Jae Choi, 1 Kitae Kim, 1 Sung Hyun Son, 1 Young ki Son, 2 Seong Eun Kim, 1 Won Suk An. 2

1 BHs Han Sea Hospital, Sayeong-ku, Busan, Republic of Korea; 2 Department of Internal Medicine, Dong-A University, Busan, Not Applicable, Republic of Korea.

**Background:** Cardiac hypertrophy and sarcopenia are common in dialysis patients and result in high probability for morbidity and mortality. Akt-mTOR axis is related with cardiac hypertrophy and muscle atrophy. The present study aimed to investigate whether omega-3 fatty acid (O-3FA) and cholecalciferol (Vit. D) affect on molecules associated with cardiac hypertrophy and sarcopenia in 5/6 Nx rats.

**Methods:** Male Sprague Dawley rats were divided into 5 groups and treated for 6 weeks; Sham control, 5/6 Nx control, 5/6 Nx treated with Vit.D, 5/6Nx treated with O-3FA, 5/6Nx treated with Vit. D and O-3FA. Western blot analysis was performed to investigate whether glucose-3 fatty acid (O-3FA) and cholecalciferol (Vit. D) affect on molecules associated with cardiac hypertrophy and sarcopenia in 5/6 Nx rats.

**Results:** Compared with control, all the other groups, except for 5/6 Nx treated with Vit.D, significantly increased Akt and mTOR expression in cardiac muscle and increased p-Akt and mTOR expression in skeletal muscle of 5/6 Nx rats. Combined treatment with O-3FA and Vit. D reduced expression of Akt and mTOR in cardiac muscle, increased expression of p-Akt and mTOR and significantly decreased in liver and kidney of 5/6 Nx control compared to sham control. Combined treatment with O-3FA and Vit. D decreased the expression of myostatin and decreased expression of myogenin and MyD in both cardiac and skeletal muscle. Increased expression of myostatin and decreased expression of myogenin and MyD of cardiac and skeletal muscle were recovered by combined treatment with O-3FA and Vit. D. Phosphorylated Akt and mTOR were examined by western blot analysis.

**Conclusions:** Combined treatment of O-3FA and Vit. D may be helpful for decreasing cardiac hypertrophy and sarcopenia by increasing myogenin and MyD, decreasing myostatin and modulating Akt-mTOR axis in both cardiac and skeletal muscle of 5/6 Nx rats.

**Funding:** Private Foundation Support

**Laboratory results**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Normal</th>
<th>5/6Nx</th>
<th>5/6Nx with Vit. D</th>
<th>5/6Nx with O-3FA</th>
<th>5/6Nx with O-3FA and Vit. D</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN (mg/dL)</td>
<td>17.2±3.8</td>
<td>17.7±7.4</td>
<td>75.2±15.6</td>
<td>75.3±15.0</td>
<td>51.75±7.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.45±0.1</td>
<td>1.93±1.1</td>
<td>7.25±1.3</td>
<td>1.69±1.3</td>
<td>0.08±0.1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Data are expressed as mean ± SD**

**P value < 0.05 (mean values are significantly different from control)**

**aP value < 0.05 (mean values are significantly different from 5/6 nephrectomy group)**

**bP value < 0.05 (mean values are significantly different from 5/6 nephrectomy group e Vitamin D group)**

**cP value < 0.05 (mean values are significantly different from 5/6 FA group)**

**TH-PO427**

**Restriction of Both P and Caloric Intake Decrease Renal Damage Induced by Cafeteria-Style Diet**

Igancio Lopez, 1 Pablo Esquinas, 1 Rafael Rios-Varo, 1 Carmen Pineda, 1 Ana Isabel Raya Bermudez, 1 Mariano Rodriguez, 2 Escolastico Aguilera-tejero, 1 1Animal Medicine and Surgery, University of Cordoba, Cordoba, Spain; 2Hospital Universitario Reina Sofia, Cordoba, Spain; Universidad Nacional de Colombia, Bogota, Colombia.

**Background:** Energy dense diets, which also tend to be rich in P (caferetera-style diets), are associated to metabolic syndrome, diabetes and kidney disease. In this study, renal damage after feeding a diet rich in P and calories was investigated. In addition, the influence of P and caloric intake restriction on renal pathology was assessed.

**Methods:** Wistar rats (n=32) were divided in 4 groups (n=8) and fed either: normocaloric (3518 kcal/kg) with normal P (0.6% diet (NC-HP), hypercaloric (5241 kcal/kg) with high P (1.2%) diet (HC-HP), HC with low P (0.2%) diet (HC-LP), and hypocaloric (1314 kcal/kg) with HP diet (HC-HP). After 210 days, renal tissue was obtained and processed for optical (OM) and electronic microscopy (TEM). Lesions were

**Conclusions:** Vitamin D deficiency was correlated with hematuria in female subjects, particularly after menopause. Further interventional studies are warranted to address whether the correction of vitamin D deficiency lowers the hematuria risk.
Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Glomerular Filtration Rate (ml/min/1.73 m²)</th>
<th>BMD Bone Mineral Density (g/cm²)</th>
<th>Tubular Apoptosis (%)</th>
<th>Tubular Calcium (%)</th>
<th>Fibrosis (%)</th>
<th>Calcification (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC-LP</td>
<td>10.037 ± 0.17a</td>
<td>0.811 ± 0.037</td>
<td>2.42 ± 0.776</td>
<td>1.75 ± 0.46</td>
<td>5.25 ± 0.767</td>
<td>0.1 ± 0.013</td>
</tr>
<tr>
<td>HC-LP</td>
<td>3.85 ± 0.436</td>
<td>-0.075 ± 0.06</td>
<td>2.57 ± 0.76</td>
<td>1.57 ± 0.46</td>
<td>6.25 ± 0.767</td>
<td>0.01 ± 0.013</td>
</tr>
<tr>
<td>HC-LP</td>
<td>16.522 ± 2.76a</td>
<td>1.5503 ± 0.53</td>
<td>1.25 ± 0.46</td>
<td>0.7522 ± 0.36</td>
<td>0.7522 ± 0.36</td>
<td>0.0150 ± 0.003</td>
</tr>
<tr>
<td>HC-LP</td>
<td>12.307 ± 2.8a</td>
<td>1.121 ± 0.35</td>
<td>1.1261 ± 0.35</td>
<td>0.8951 ± 0.35</td>
<td>1.1261 ± 0.35</td>
<td>0.1570 ± 0.054</td>
</tr>
</tbody>
</table>

Values are mean ± SE; a, b, c For each parameter, data with different superscripts are significantly different. Key: TH-PO424

Caleprotein Particle Contributes to the Synthesis and Secretion of Fibroblast Growth Factor 23 Induced by Dietary Phosphatoma Intake Kenichi Akivama,1,2 2Tokyo Women’s Medical University, Tokyo, Japan; 1Center for Molecular Medicine, Jichi Medical University, Shimotsuke, Japan.

Background: It has been reported that the synthesis and secretion of fibroblast growth factor 23 (FGF23) induced by phosphate may also contribute to the synthesis and secretion of fibroblast growth factor 23 (FGF23) induced by phosphate. However, this phenomenon is still unclear. Highly concentrated phosphate and calcium are crystalized and formed calcium-phosphate (CaP) particles with some proteins including fat-membrane in extracellular fluid. CaP is considered the pathogenesis of some complications such as an inflammatory response in chronic kidney disease. The role of CPP on the synthesis and secretion of FGF23 was investigated.

Methods: Rat osteoblastic cell line (UMR-106 cell) was treated with various doses of phosphate or artificial made CPP for 4 and 24 hours. Protein level of FGF23 in the medium and mRNA expression level of FGF23 were analyzed. Serum phosphate, FGF23 and CPP levels and FGF23 mRNA expression level in cranial bone were also evaluated in C57BL/6J mice 2 and 6 hours after phosphate administration using a feeding tube and 10 days after switching to the high phosphate diet.

Results: Both phosphate and artificial CPP treatments for 4 and 24 hours significantly increased FGF23 protein level in the medium of UMR-106 cell at dose-dependent manner. The upregulation of FGF23 mRNA expression level was observed only 24 hours after both treatments. The supplementation of citrate as an inhibitor of CPP formation canceled all of these findings. The significant increases of serum CPP and serum FGF23 levels compared with control treatment were observed 2 and 6 hours, respectively after the treatment. Both phosphate and FGF23 mRNA expression level in cranial bone did not change in these mice. Significant increases of serum phosphate, CPP and FGF23 levels and upregulation of FGF23 mRNA expression level in cranial bone were confirmed in mice fed high phosphate diet for 10 days.

Conclusions: These findings confirm that CPP but not phosphate itself might be contributing to the dietary phosphate-induced both postprandial secretion and sustained high level of serum FGF23 level.

TH-PO429

In Vivo Responses of Phosphorus-Based Food Additives with Different Forms Toru Fujii, Kiyoharu Kawai, Hiroko Segawa, Ai Hanazaki, Kayo Ikuta, Aoi Kushi, Ichiro Kaneko, Sawako Tateumi, Ken-ichi Miyamoto. Tokushima University, Tokushima, Japan.

Background: Hyperphosphatemia causes hyperparathyroidism and ectopic calcification in patients with chronic kidney disease, and dietary management for blood phosphate levels in patients with kidney disease is considered to be important. Both organic and inorganic phosphate (Pi) are present in regularly consumed foods, such as eggs, and daily products. Pi is included in foods as an additive. Phosphorus-containing food additives have different effects in the body. In the present study, to consider the mechanism, we investigated several responses of diet containing mono or polyphosphate on whole body.

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

Underline represents presenting author.

TH-PO430

Narrowing the Phosphate Divide: A Comparison between UK and Chinese Haemodialysis Patients Yan Song,1 Patrick J. Highton,2 Barbara P. Vogt,3 Annabel Brirute,4 Ken Wilund,4 Alice C. Smith,1 James Burton,1 1University of Leicester, Leicester, United Kingdom; 2Loughborough University, Loughborough, United Kingdom; 3Universidade Estadual Paulista UNESP, Botucatu, Brazil; 4University of Illinois, Urbana, IL.

Background: Management of hyperphosphatemia requires a multi directional approach. Dietary restriction of phosphate (Pi) is often inadequate by itself; other strategies, such as extended dialysis and Pi binders are often necessary. Designing an effective intervention to manage hyperphosphataemia, whilst balancing Pi restriction and maintaining adequate protein intake, requires a thorough understanding of dietary Pi. In addition, perception and habits related to dietary behaviour may be influenced by ethnicity and culture. The aim of the study was to contrast data about Pi intake on dialysis and non-dialysis days with haemodialysis (HD) patients from UK and China.

Methods: In this cross-sectional study, 24-hour diet recall interviews were undertaken with patients in UK and China during four normal dialysis sessions distributed evenly in two consecutive weeks. Patients were asked to recall food intake for the previous 24 hours on dialysis and non-dialysis days. Demographic and clinical data were collected from patients’ medical records. Nutrients and China Food Composition were used as nutrition database for UK and Chinese dietary data respectively.

Results: A total of 83 patients were recruited (UK, n=40; China, n=43). The UK patients were older (56.8 ± 11.7 years vs. 42.1 ± 9.7 years, P=0.001) with a higher body mass index (BMI) than the Chinese cohort (26.6 ± 5.9 vs. 21.3 ± 2.7 kg/m², P<0.001). Although energy intake was comparable between populations (UK, 25.3 ± 3.1 kcal/kg/d; China, 23.0 ± 1.3 kcal/kg/d, P=0.12), UK patients reported higher Pi intake on both dialysis (0.91g/d vs 0.72g/d, P=0.039) and non-dialysis days (0.90g/d vs. 0.73g/d, P=0.004) than their Chinese counterparts. Despite higher dietary intake, serum Pi levels in UK patients were lower compared to those in China (1.59g/d ± 0.44 mmol/L vs 2.11g/d ± 0.53 mmol/L, P<0.001). There was no difference in the number of patients prescribed Pi binders between two groups (UK, n=8; China, n=9, P=0.567).

Conclusions: Despite higher BMI and dietary intake, and with no difference in prescribed Pi binding medications, UK patients had lower serum Pi concentrations than their Chinese counterparts. Strategies to improve compliance with medications and increasing dialysis Pi removal would have a greater impact on hyperphosphataemia than increased nutritional support in Chinese HD patients.

TH-PO431

Use of Urinary Metabolomics to Identify Potential Pathways Associated with Hyperuricemia in Hispanic Children: The Viva La Familia Study Sario Voruganti,1 Izel Vazquez-Vidal,4 Baba B. Mass,1 Robert P. Mohney,2 Nitesh R. Mehta,1 Anthony G. Cornuzzze,3 Shelley A. Cole,4 Nancy F. Butte,4 1Baylor Coll Medicine, Houston, TX; 2Baylor College of Medicine, Houston, TX; 3Metabolon, Inc., Durham, NC; 4Nutrition Research Institute, University of North Carolina at Chapel Hill, Kannapolis, NC; 5Texas Biomedical Research Institute, San Antonio, TX; UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL, CHARLOTTE, NC; 6University of North Carolina at Chapel Hill, Kannapolis, NC.

Background: Hyperuricemia (elevated serum uric acid) is associated with increased risk for gout, cardiovascular and kidney disease. Studies have shown hyperuricemia in children to be predictive of hypertension in adulthood. Our aim in this study was to identify urinary metabolites and pathways associated with hyperuricemia in a cross-sectional study of 260 Hispanic children from the Viva La Familia Study.

Methods: Urinary metabolomics profiling was conducted in 130 hyperuricemic and 130 normouricemic children using ultra-high performance liquid chromatography mass spectrometry. Hyperuricemia was characterized using upper most quartile of serum uric acid. All children were excluded with gout, arthritis, or other events that can cause hyperuricemia. Urinary samples were collected as a single void of urine in a 24-hour period. One ml of urine was acidified with 20 µl of 10N HCl and centrifuged at 15,000 g for 10 minutes. The supernatant was used for analysis. The urinary samples were extracted using a modified solid phase extraction (SPE) method and derivatives were prepared for mass spectrometry analysis. Metabolites were identified using the Human Metabolome Database (HMDB) and searched against the public domain human low-mass metabolite spectral database (LHMD) using XCMS software. Statistical differences in mean urinary metabolite levels and ratios between hyperuricemic and normouricemic groups were determined using the Mann-Whitney U test.

Results: A total of 703 urinary metabolites were identified, of which 377 metabolites were significantly different between the two groups. Key differences were found in amino acids, steroids and xenobiotics metabolic pathways, with 262 metabolites being higher in hyperuricemic than normouricemic patients. Metabolites that were significantly higher in the hyperuricemia group belonged to histidine (formiminoglutamate and methylhistidine), methionine (S-adenosylhomocysteine (SAH)), nicotinate and nicotinamide (nicotinamide

Methods: C57B6 male mice were fed a test diet (low Pi diet, control Pi diet, high Pi diet) for 12 weeks. During the study, mice were weighed weekly. KJ2P204 (CP and HP1), and K53P010 (HP2) were used for phosphate additives.

Results: There were remarkable differences on blood, fecal, and urine biochemical analysis data between HP1 and HP2 diet groups. Though HP1 and HP2 diet significantly increased FGF23 mRNA levels in several tissues, only HP2 diet increased fibrosis marker mRNA level in the kidney, urinary volume, and renal calcification. To identify the different response between HP1 and HP2 diet, renal and intestinal Pi regulating factors expression and activity were examined. There were no significantly different renal Pi regulating molecules between HP1 and HP2. However, we found differences on several intestinal molecules expression and activity levels between HP1 and HP2.

Conclusions: Intestine might detect different luminal monophosphate and polyphosphate form. It is necessary to consider about not only the phosphate content but also the form of the phosphorus-containing food additives.

Funding: Government Support - Non-U.S.

Funding: Government Support - Non-U.S.
N-oxide and 1-methylisocitraminonitrile), steroid (epiandrosterone glucuronide and cortisol glucuronide) and purine (dimethylurate) metabolite under study. The metabolites that were significantly lower in hyperuricemia group were derivatives of glycine, serine, threonine, N-acetylcysteine, N-acetylseryine, glutamate and gamma-aminobutyrate, and xenobiotics (teratole, caffeine acid sulfate, valine, saccharin, etc.).

Intromediate: A key enzyme that catalyzes the conversion of xanthine to uric acid and nicotinamide N-oxide to nicotinamide, is also a major enzyme in xenobiotics metabolism. Elevated levels of formimimoglutamate indicate folate deficiency whereas thought is to inhibit xanthine oxidase.

Conclusions: Our targeted primary metabolomics profiling not only revealed different pathways in hyperuricemic and normouricemic children, but also demonstrated a link between xanthine oxidase, xenobiotics and folate in hyperuricemia.

Funding: NIDDK Support

TH-PO432

Targeted Metabolomics of Adolescent CKD

Ellen Brooks,1,2 Shannon Hammond,3 Craig B. Langman,2,4 Bradley A. Warady,1 Susan L. Furth,1 Feinberg School of Medicine, Northwestern University, Chicago, IL; 2Northwestern University, Chicago, IL; 3The Children’s Hospital of Philadelphia, PA; 4The Children’s Mercy Hospital, Kansas City, MO; 5Kidney Disease, Ann & Robert H. Lurie Children’s Hospital of Chicago, Chicago, IL.

Background: Dysregulation of amino acids, biogenic amines, and phosphatidylcholines (PCs) have been described in advanced chronic kidney disease (CKD) in adults. Metabolic alterations related to oxidative stress and inflammation in children with mild to moderate CKD may have greater significance for risk of secondary morbidities since growth and development are not complete.

Methods: In this cross-sectional study, 24 CKD groups were matched for age and gender but had differing measured (gGFR by iohexol clearance and CKD stage [n=20 per CKD group with 10 glomerular (G) and 10 non-glomerular (NG) disorder per group]. Targeted plasma metabolomics were completed at the Proteomics and Metabolomics Shared Resource, Duke University, Durham, NC using Biocrates Life Sciences AG, Austria.

Results: The median (Md) and interquartile range (IQR) gGFR of the groups differed as planned: 74.3 (67.4, 82.9) CKD 2 vs. 32.8 (24.3, 35.5) mL/min/1.73m² CKD 3.

Conclusion: Higher (p=6.79E-7 to 4.4E-4), Kyn was greater in NG vs. G (p=0.009) and alanine was higher (p=0.001) in G vs. NG (p=0.045).

Correlations of different variables with the ratio of change in FFA levels during HEGC

TH-PO433

Systemic Oxalosis with Retinopathy Secondary to Vitamin C in a Patient on Peritoneal Dialysis

Matthew R. D’Costa,1,2 Nelson S. Winkler,1 Dawn S. Milliner,1 Suzanne M. Norby,1 LaTonya J. Hickson,1 John C. Lieszke, Mayo Clinic, Rochester, MN.

Background: We report a case of systemic oxalosis involving the eyes and joints due to long-term use of high-dose vitamin C in a peritoneal dialysis (PD) patient.

Methods: A 76-year-old female presented to the hospital with a 1-month history of decreasing vision and polyarthralgias. She had received ESRD secondary to autosomal dominant polycystic kidney disease and underwent a related kidney transplant 10 years earlier. Due to declining allograft function, biopsy was performed 1 year before admission revealing severe arteriosclerosis, focal segmental glomerulosclerosis, and early transplant glomerulopathy but no calcium oxalate (CaOx) crystals. She initiated hemodialysis (HD) 6 months later and transitioned to PD 2 months prior to admission. At presentation, ophthalmologic exam revealed crystalline retinopathy consistent with CaOx deposition. Fluorescein angiography demonstrated significant retinal non-perfusion, and optical coherence tomography showed hypereflective deposits throughout the inner and outer segments. Plasma oxalate (µmol/L) was markedly elevated at 187 ± 60 µmol/L (normal < 1.7 µmol/L). Urine oxalate/creatinine ratio was high (0.18 mg/mg) while urine glycolate, glycine and 4-hydroxy-2-oxoglutarate were normal. Genetic testing confirmed absence of pathogenic changes in AGAT, GRHPR and HOGA1. Stool analysis did not suggest significant dietary malabsorption and she had no previous gastrointestinal, diueresis, or other gastrointestinal symptoms. While excessive intake of high oxalate foods was not identified, she reported chronic use of high-dose vitamin C of up to 4 grams per day for many years. With discontinuation of vitamin C and nearly daily HD for 2 weeks, predialysis POx fell markedly to 30-50 µmol/L. Serial funduscopy examinations remained stable in the setting of mild improvement in visual acuity and marked improvement in joint pain.

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

TH-PO434

Lipotropic Actions of Insulin in Patients with CKD

Axel Aselehe,1 Serpel mugre Degger,1 Feng Sha,1 Aihua Bian,1 Thomas G. Stewart,2 Charles D. Ellis,2 Adriana Hung,3 Talat Alp Ikizler,3 Vanderbilt University Medical Center, Nashville, TN; 4Vanderbilt University Medical Center, Nashville, TN; 5Vanderbilt University Medical Center, Nashville, TN; 6Vanderbilt University Medical Center, Nashville, TN.

Background: Resistance to the metabolic actions of insulin is common in patients with CKD. We examined the acute effects of hyperinsulinemia on free fatty acid (FFA) levels during hyperinsulinemic euglycemic clamp (HEGC) study in patients with CKD and controls without kidney disease.

Methods: All participants underwent HEGC, where a fixed insulin infusion was started to achieve hyperinsulinemia with subsequent IV dextrose administration to maintain euglycemia (steady state). Peripheral resistance to insulin actions on glucose were assessed by Glucose Disposal Rate (GDR). Free fatty acid levels were measured at baseline and during steady state.

Results: We studied 165 individuals; 73 controls (59% females, 51% AA, median age 50 [IQR 38.61] and 92 patients with CKD (31.5% females, 51% AA, median age 60, [IQR 46.57]). FFA levels decreased similarly in response to insulin in all four groups: 88% in the control group, 89% in CKD Stages 3-4, 90% in HD and 86% in PD patients (p < 0.05 only for PD vs controls). Higher body mass index, fat mass, lean mass and Leptin Adiponectin Ratio were associated with lower rates of decrease in FFA levels. Increased age, higher baseline POx levels, higher baseline adiponectin, higher GDR were significantly associated with higher rate of decrease in FFA levels. Leptin, C- reactive protein and interleukin-6 were not significantly associated with the change in FFA.

Correlations of different variables with the ratio of change in FFA levels during HEGC

TH-PO435

An Epigenetic Mechanism Controls Muscle Protein Synthesis in Mice with CKD

Liping Zhang,1 William E. Mitch.1 Baylor College of Medicine, Houston, TX; 2Nephrology, Baylor College of Medicine, Houston, TX.

Background: For patients with chronic kidney disease (CKD), loss of muscle mass is frequent leading to morbidity. Unfortunately, there are no approved, regularly effective treatments that overcome muscle wasting in part because mechanisms causing muscle protein losses are still being uncovered. Previously, we showed that CKD induces muscle wasting via increased protein degradation with decreased protein synthesis. The former is due to activation of caspase-3 and the ubiquitin-proteasome system (UPS) but mechanisms impairing muscle protein synthesis are unknown. Now, we show that CKD stimulates a chromatin modifying protein, NO66, in muscle resulting in reduced protein synthesis.

Methods: Mice with whole body deletion of NO66 (NO66-/-) were created by crossing transgenic, Sox2-cre mice with NO66floxed mice. Mice with muscle-specific NO66 knockout (NO66-/-mus) were created by crossing tamoxifen-inducible, Pax7-cre mice with NO66floxed mice. CKD (subtotal nephrectomy) was created in mice and those with BUN >80 mg/dL were studied.

Results: Our hypothesis that expression of NO66 in muscles suppresses protein synthesis. During testing of this hypothesis, we found that NO66 mice exhibited a 30-35% increase in muscle mass vs. responses in NO66floxed controls. Secondly, in NO66-/- mice the muscle wasting from CKD was blocked. To test the role of NO66 in muscle, we studied mice with muscle-specific NO66-/-KO (NO66-/-mus) and found there was an increase in muscle mass. To determine the mechanism underlying NO66-induced regulation of muscle mass in mice with CKD, we performed mass-spectrometry assays and found that NO66 forms a repressive complex with two histone-modifying proteins, retinoblastoma binding protein 4 (RBBP4) and histone deacetylase 2 (HDAC2). This
complex represses expression of muscle genes and the transcription of ribosomal DNA via CEBPdelta mechanism. Lastly, we performed a RNA-seq analysis using soleus muscles and identified that absence of NOG6 stimulates a ribosomal biogenesis signaling pathway

Conclusions: We have uncovered a new CKD-initiated pathway that proceeds via a novel genetic mechanism that regulates muscle protein synthesis

Funding: NIDDK Support, Other U.S. Government Support, Commercial Support - Atara Biotherapeutics, Private Foundation Support

TH-PO436

Eliminating SIRPα Replicates Exercise Induced Remodeling and Prevents Cardiac Dysfunction in CKD Jiao Wu,1 Giovanni Davogusto,2 Zhaoyong Hu,1 Yanlin Wang,1 Heinrich Taegeitmeyer,2 William E. Mitch,1 Sandhya S. Thomas.1,1 Baylor College of Medicine, Houston, TX; 2The University of Texas Health Science Center at Houston, Houston, TX; 1Michael E. DeBakey Veteran Affairs Medical Center, Houston, TX.

Background: A major consequence of chronic kidney disease (CKD) is uremic cardiomyopathy characterized by left ventricular hypertrophy (LVH), systolic and diastolic dysfunction. Even at early stages of CKD with near normal GFR, and normal blood pressure, LVH is present, which suggests an unidentified trigger unrelated to pressure overload. We now find that elevations of a novel protein, signal regulatory protein alpha (SIRPα) in CKD cardiac muscle not only adversely influences insulin signaling cardiac fibrosis, but also cardiac dysfunction classically associated with CKD. Suppression of SIRPα reverses CKD-induced cardiac dysfunction and promotes exercise-induced cardiac remodeling.

Methods: SIRPα whole body mutant (Mt) mice and wild type mice (WT) were compared after 8 weeks of subtotal nephrectomy. Cardiac function was analyzed in vivo with M-mode and doppler echocardiography. N=8-9 mice/group, results are presented as mean±SD.

Results: Hearts of SIRPα Mt sham mice exhibit eccentric LVH compared with WT sham (LV mass/height 1.53±0.167 vs 1.32±0.216, p=0.04; Relative wall thickness 0.519±0.052 vs 0.608±0.098, p=0.03), preserved systolic function (EF 70.69±4.826 vs 65.90±5.304) as well as diastolic function (E/A 1.812±0.521 vs 1.499±0.254). However, in WT Sham vs. WT CKD mice there is evidence of cardiac dysfunction characterized by reduced diastolic function (EDF %) (65.90±5.304 vs 53.11±21.302, p = 0.016) and reduced cardiac output (CO) ml/min (19.4±3.342 vs 15.493±2.474, p=0.03). Doppler analysis revealed diastolic dysfunction in WT CKD as well (E/A 1: 1.499±0.254 vs 1.146±0.102, p=0.008). In WT CKD mice systolic blood pressure was not different than WT Sham suggesting changes observed are not due to pressure overload. On the contrary, in SIRPα Mt mice, induction of CKD did not significantly affect cardiac function (EF 70.64±9.826 vs 65.81±6.588, CO: 24.702±70.649 vs. 24.0.0±20.7 kg/m2 , p>0.05 for all).

Conclusions: In conclusion, suppression of SIRPα replicates exercise induced cardiac remodeling, similar to marathon-runners, as evidenced by eccentric LVH, preserved EF and diastolic function. Furthermore, hearts of SIRPα Mt mice were protected against CKD-induced cardiac dysfunction. Therefore, SIRPα may prove to be a key mediator for prevention of CKD-associated cardiomyopathy.

Funding: Other NIH Support - Dr. and Mrs. Harold Selzman, Veterans Affairs Support

TH-PO437

Biased Mortality Risk Associated with Change in Normalized Protein Catabolic Rate Due to Residual Kidney Function among Hemodialysis Patients Yoshitsuugu Obi,1 Elani Streja,1 Ricke Erigiuchi,2 Melissa Soohoo,1 Connie Rhee,1 Csaba P. Kovessy,1 Kamyar Kalantar-Zadeh.1 1UC Irvine, Orange, CA; 2Katzuka Hospital, Fukuoka, Japan; 1University of Tennessee Health Science Center, Memphis, TN.

Background: Dietary protein intake among hemodialysis (HD) patients is estimated by dialysis urea clearance-based normalized protein catabolic rate (nPCRdial) and created 15 groups of combined nPCRdial and nPCRtotal and ΔnPCRdial, adjusted mortality risk was incrementally higher across lower nPCRdial and nPCRtotal, ΔnPCRdial does not adequately capture true changes in protein intake, leading to a biased evaluation of associated mortality risk among HD patients with nPCRdial.

Method: We identified 10,066 HD patients with data on rCLurea at both the 1st and 2nd years. rCLurea was used to calculate nPCRdial and ΔnPCRdial, and created 15 groups of combined ΔnPCRdial and ΔnPCRtotal. All-cause mortality risk was estimated using Cox models with adjustment for 25 clinically relevant factors.

Results: Median (IQR) age was 66 (55-76) years, 57% were male, 46% white and median vintage was 4.6 months. Between year follow-up, there were 264(42.9%) deaths(614 in inflamed;1777 in non-inflamed). The protective effect of high BMI was observed in inflamed patients(HR (95% CI) Q1:2.48 (2.10-2.94); Q2:1.73 (1.44-2.09); Q3:1.77 (1.44-2.17); Q4:1.44 (1.16-1.80); and Q5:1.46 (1.18-1.81)); however this effect was mitigated in non-inflamed HD patients(HR (95% CI) for Q1:1.27 (1.08-1.49); Q2:1.06 (0.91-1.24); Q3:0.99 (0.85-1.10); Q4:0.93 (0.80-1.09); and Q5:1.00 (ref)). Further analysis showed that these findings were restricted to Europeans but not in Asians and United states subjects (Fig1).

Conclusions: Our results showed that inflammation may impact the relationship between BMI and survival. Further studies are needed to better understand the interaction between inflammation and the BMI in HD patients.

Funding: NIDDK Support

Figure 1. All-cause mortality by BMI and inflammation stratified by Region; adjusted Cox regression analysis
Eculizumab and ECMO Rescue-Therapy of Most Severe ARDS in a Young Boy with Goodpasture’s Syndrome

Keywords: Goodpasture’s Syndrome, Neutrophils, ECMO, ARDS, CMV

Methods:
1. Eculizumab was administered as a single dose of 15 mg/kg on the day of ECMO initiation.
2. ECMO therapy was continued for a total of 24 days, after which it was stopped.

Results:
- Eculizumab significantly reduced neutrophil infiltration and lung damage.
- ECMO therapy helped maintain pulmonary function and prevented further harm.

Conclusions:
Eculizumab and ECMO rescue-therapy were effective in treating severe ARDS due to Goodpasture’s Syndrome.

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

213
intake was below the WHO-recommended intake (90-120 mmol/d, 3.5-4.7 g/d) in 87.4% of patients with Moderate to Severe CKD, 49.878, OR = 4.90, 95% CI 3.12-7.48, P < 0.0001. In addition, we found that dietary caloric restriction improves adiponectin and resistin levels in Stage 3-4 CKD patients with limited effect on leptin levels. LAR (Leptin-Adiponectin Ratio) decreased statistically significantly in response to both diet and exercise whereas leptin levels did not change by either treatment (Figure-1).

Conclusions: Our data suggest that dietary caloric restriction improves adiponectin and resistin levels in Stage 3-4 CKD patients with limited effect on leptin levels. LAR improved in response to both interventions indicating a potential beneficial effect of exercise intervention to the overall metabolic milieu.

Funding: Veterans Affairs Support

Effect of diet and exercise on Adiponectin and LAR levels in study groups compared to usual care.

TH-PO445
Cardiovascular Outcomes in CKD Patients with Sickle Cell Disorders
Kabir O. Olamiran, Nwamaka D. Eneanya, Andrew S. Allegretti, Dihua Xu, Ravi I. Thadhani, Massachusetts General Hospital, Boston, MA.

Background: Sickle cell disease (SCD) patients are known to be at risk for ischemic stroke (CVAs), heart failure (HF) and chronic kidney disease (CKD). However, cardiovascular (CV) outcomes in SCD CKD patients have not been described. Additionally, sickle cell trait (SCT) is independently associated with CKD. However, the effect of SCT on concurrent CKD on CV outcomes has not been explored.

Methods: We performed a multi-hospital retrospective cohort study in Boston using adult KDGDC electronic CKD patient database from 2005-2017. Chart review was used to ascertain the following exposures: SCT with CKD, SCD with CKD and the reference group (RG; black race with CKD with normal hemoglobin electrophoresis). Outcomes were identified using diagnosis codes and defined as incident coronary heart disease (CHD), heart failure (HF) and CVAs. Exposures and outcomes confirmed by diagnosis code only were then added for sensitivity analysis.

Results: 960 CKD subjects were initially included (241 SCT CKD, 45 SCD CKD, 674 RG). The mean baseline GFR in SCD CKD patients was higher vs the RG despite similar clinical and laboratory variables (pcut-off = 0.001). In analysis according to eGFR, the statistical significance regarding coronary artery calcification was weakened in lower eGFR group. Circulating cTnT levels is a fair screening test according to eGFR, the statistical significance regarding coronary artery calcification was weakened in lower eGFR group. In receiver operating curve analysis, area under the curve was above 0.8, regardless of the eGFR subgroup.

Conclusions: Elevated concentration of cTnT was independently associated with the degree of severity of CAP in the CKD population of Korea. In subgroup analysis according to eGFR, the statistical significance regarding coronary artery calcification was weakened in lower eGFR group. Circulating cTnT levels is a fair screening test for the detection of coronary artery calcification in a subgroup with eGFR over 60 mL/ min/1.73m².

Funding: Government Support - Non-U.S.

TH-PO447
Hypertension (HTN) Modifies the Association of Coronary Artery Calcification (CAC) with CV Events in CKD and Non-CKD Individuals
Lucille Parker Gregg, Beverley Adams-Huet, Xilong Li, James Delemos, Susan Hedaya. UT Southwestern, Dallas, TX.

Background: Few studies examine whether HTN and CKD modify the association of CAC with CV events. We evaluated these associations at various CAC cutoffs with fatal or nonfatal CV events.

Methods: We studied 2,288 asymptomatic participants of the Dallas Heart Study followed for a median of 13 years. Cox proportional hazards determined associations of CAC with CV events (CV death, myocardial infarction, stroke, CV revascularization, or hospitalization for heart failure or atrial fibrillation), adjusted for age, sex, race, smoking, HTN, diabetes, hyperlipidemia, HDL cholesterol, and CKD. Interactions for CAC (defined as cTnT>0.06 ng/mL/mi; 75th percentile) and HTN (blood pressure >140 mmHg or on medication therapy for HTN) with CAC were tested at various CAC cutoffs, with a p-value of <0.1 considered significant.

Results: We performed a multi-hospital retrospective cohort study in Boston using adult KDGDC electronic CKD patient database from 2005-2017. Chart review was used to ascertain the following exposures: SCT with CKD, SCD with CKD and the reference group (RG; black race with CKD with normal hemoglobin electrophoresis). Outcomes were identified using diagnosis codes and defined as incident coronary heart disease (CHD), heart failure (HF) and CVAs. Exposures and outcomes confirmed by diagnosis code only were then added for sensitivity analysis.

Results: 960 CKD subjects were initially included (241 SCT CKD, 45 SCD CKD, 674 RG). The mean baseline GFR in SCD CKD patients was higher vs the RG despite similar clinical and laboratory variables (pcut-off = 0.001). In analysis according to eGFR, the statistical significance regarding coronary artery calcification was weakened in lower eGFR group. Circulating cTnT levels is a fair screening test according to eGFR, the statistical significance regarding coronary artery calcification was weakened in lower eGFR group. In receiver operating curve analysis, area under the curve was above 0.8, regardless of the eGFR subgroup.

Conclusions: Elevated concentration of cTnT was independently associated with the degree of severity of CAP in the CKD population of Korea. In subgroup analysis according to eGFR, the statistical significance regarding coronary artery calcification was weakened in lower eGFR group. Circulating cTnT levels is a fair screening test for the detection of coronary artery calcification in a subgroup with eGFR over 60 mL/ min/1.73m².

Funding: Government Support - Non-U.S.
Results: There were 170 (7.4%) participants with CKD and 811 (35.4%) with HTN. There were 232 CV events: 161 (19.9%) in those with HTN vs. 71 (4.8%) without HTN, and 60 (35.3%) in those with CKD vs. 172 (8.1%) without CKD. P=0.01 for each. CAC was associated with CV events in all non-CKD and non-HTN groups for each CAC cutoff point, but was not associated with CV events at any cutoff in individuals with both CKD and HTN. There was a CACxHTN interaction for a CAC cutoff of 10 Agatston units, aHR 3.12 (2.20, 4.42) in non-CKD and 1.17 (0.68, 1.99) in CKD, P=0.001, but no CACxHTN interaction for other CAC cutoffs. There was a significant HTNxCAC interaction at all tested cutoffs of CAC, such that CAC was less predictive of CV events in individuals with HTN (Figure).

Conclusions: CAC was more strongly predictive of CV events in individuals without HTN, but did not add to traditional risk factors for predicting CV events in hypertensive CKD participants.

Funding: NIDDK Support, Other NIH Support - National Center for Advancing Translational Sciences, award number UL1TR001105 to the University of Texas Southwestern Medical Center, Private Foundation Support

Figure. Adjusted hazard ratios for CV outcomes at multiple CAC cutoffs in CKD and non-CKD individuals, stratified by HTN status

TH-PO448

Differential Effects of Arterial Stiffness versus Fluid Overload on High Blood Pressure According to Renal Function in Patients at Risk of Cardiovascular Disease Jaeewo Kwon,1 Seung Hyeok Han,2 Meiyan Wu,3 Boyoung Nam.2 1Department of Internal Medicine, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, Republic of Korea; 2Department of Internal Medicine, College of Medicine, Severance Biomedical Science Institute, Brain Korea 21 PLUS, Yonsei University, Seoul, Republic of Korea.

Background: Pathogenesis of hypertension is multifactorial in patients with chronic kidney disease (CKD). In this study, we explored the relative contribution of arterial stiffness and fluid overload to blood pressure (BP) in these patients. We evaluated 1531 patients of Cardiovascular and Metabolic Disease Etiology Research Center-High Risk (NCT02003781), a prospective observational cohort study of high risk patients with cardiovascular disease.

Methods: BP, arterial stiffness, and volume status expressed as an extracellular water/total body water ratio (ECW/TBW) were measured by 24-h BP monitoring, pulse wave velocity (PWV) and bioelectrical impedance analysis measurement, respectively.

Results: In patients with CKD, multiple linear regression analysis showed that both PWV and ECW/TBW were significantly associated with 24-h systolic BP (SBP) the area under the receiver operating characteristic curves (AUCs) for predicting 24-h SBP ≥130 mmHg significantly increased after PWV was added to conventional factors regardless of CKD status. However, the AUCs did not increase in ECW/TBW-based models. When a cut-off level of 24-h SBP was defined as 140 mmHg, predictability of ECW/TBW for elevated BP significantly improved in patients with CKD, but not in those without CKD. This association was further confirmed by the net reclassification and integrated discriminant improvements, RMSE with adjusted R², and interaction effects. In summary, as kidney function declines, fluid overload significantly contributes to high BP. The impact of fluid overload on BP is only observed in late stage of hypertension in patients with CKD.

Conclusions: Our findings suggest that a stepwise approach is required in the management of hypertension, depending on CKD stages.

TH-PO450

Elevated Pulse Amplification in Advanced Kidney Diseases Tsuneo Takenaka. International University of Health and Welfare, Sanno Hospital, Tokyo, Japan.

Background: The progression of chronic kidney disease (CKD) inverts arterial stiffness gradient. However, central haemodynamic pressure profiles in CKD have not been fully examined. A cross-sectional study was performed to assess the relationship between CKD stage and central haemodynamic processes.

Methods: The subjects were 202 hypertensive patients who had undergone echoangiography and had their serum creatinine levels. Radial tonometry was applied in all patients to measure central blood pressure, and they were classified according to six CKD stages based on their estimated glomerular filtration rate (eGFR).

Results: Central (PP2) and brachial pulse pressure (PP) were elevated at stages 3a and 3b, respectively. Diastolic blood pressure (DBP) at stage 1 was higher than at the other stages. The left ventricular mass index (LVMI) was greater at CKD stages 3b-5 than that at stage 1. Either PP or PP2 is sensitive in detecting the presence of left ventricular hypertrophy (LVH), raising the possibility that central hemodynamic changes in CKD progression contribute to lowering the power of PP2 in predicting LVH in treated hypertensive patients. Age, weight, pulse rate, brachial blood pressures, and antihypertensive medication differed among the six stages. As shown in figure, pulse amplification adjusted with these confounders was the lowest in CKD stages 3a and 3b.

Conclusions: The present observations that LVMI was increased at CKD stages 3b-5 support that cardiovascular risk is higher in CKD stages 3b and later. Our findings indicate that pulse amplification is inverted in CKD stages 4 and 5, and suggest that aortic stiffening inadequately reduces PP in advanced CKD, which accounts for a high prevalence of micro- as well as macrovascular diseases of the brain and kidney. Taken together, these results implicate that CKD3b comes of age as an index for timely cardiovascular screening.

Funding: Government Support - Non-U.S.
Nondialysis-Dependent CKD

Body Composition Is Associated with Clinical Outcomes in Patients with Nondialysis-Dependent CKD Szu-Chun Hung, Ting-yun Lin,2 Taipei Tzu Chi Hospital, Taipei County, Taiwan; 3Taipei Tzu Chi Hospital, Taipei City, Taiwan.

Background: An inverse relationship between body mass index (BMI) and mortality has been demonstrated in patients with nondialysis-dependent chronic kidney disease (CKD). However, it is unclear whether increased muscle mass or body fat confers the survival advantage. We investigated the impact of body composition on the composite outcome of death or cardiovascular events in a prospective cohort of 326 patients with stage 3-5 CKD who were not yet on dialysis.

Methods: Lean mass and body fat were determined using the Body Composition Monitor (BCM), a multifrequency bioimpedance spectroscopy device, and were expressed as the lean tissue index (LTI) and fat tissue index (FTI), respectively. Patients were stratified as High (above median) or Low (below median) BMI, as High or Low LTI, or as High or Low FTI.

Results: During a median follow-up of 4.6 years, there were 40 deaths and 68 cardiovascular events. In Cox proportional hazards models, High BMI, but not High LTI or High FTI, predicted a lower risk of both the composite and its components (reference: Low BMI,Low FTI group).

Conclusions: LTI can provide better risk prediction than can BMI alone in nondialysis-dependent CKD patients. High LTI/High FTI appears to be associated with best outcomes. The optimal body composition for improving the prognosis of CKD needs to be determined.

Cox proportional hazards model for time to primary composite outcome

<table>
<thead>
<tr>
<th>Body composition</th>
<th>Unadjusted HR (95% CI) P-value</th>
<th>HR (95% CI) P-value</th>
<th>HR (95% CI) P-value</th>
<th>HR (95% CI) P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (High vs. Low)</td>
<td>0.72 (0.47–1.11) 0.336 0.87 (0.57–1.33) 0.517 0.61 (0.38–1.01) 0.057</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FTI (High vs. Low)</td>
<td>1.11 (0.52–2.37) 0.316 1.36 (0.67–2.78) 0.303 1.06 (0.59–1.85) 0.860</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LTI (High vs. Low)</td>
<td>0.31 (0.18–0.49) 0.000 0.45 (0.26–0.76) 0.025 0.52 (0.33–0.85) 0.012</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TH-PO452

Serum Bicarbonate and Pulse Wave Velocity in CKD – A Report from the CRIC Study

Purpose: Serum bicarbonate (<22 mEq/L) and pulse wave velocity (PWV) were measured in the Chronic Renal Insufficiency Cohort (CRIC) during study year 2. We aimed to test the association between serum bicarbonate and PWV.

Methods: Serum bicarbonate and PWV were simultaneously measured in 3206 participants enrolled in the CRIC study. Serum bicarbonate was analyzed as a continuous variable using the following groups: <22 mEq/L, 22–26 mEq/L (reference group) and >26 mEq/L, and as a continuous variable using restricted cubic splines to accommodate potential nonlinear associations. The models were adjusted for age, sex, race, diabetes, smoking, CVD, hypertension, FGF 23, Calcium, eGFR and proteinuria.

Results: The mean eGFR was 43.3±17ml/min per 1.73m2 and mean serum bicarbonate was 23.9 mEq/L. Participants with serum bicarbonate <22 and >26 mEq/L had significantly higher PWV (10.44 and 9.84 m/s respectively) compared to the reference group (9.47 m/s, p<0.004) (Figure- Panel A). In non-linear models, we found a U-shaped association between serum bicarbonate and PWV (p<0.05), (Figure- Panel B).

Conclusions: In a large cohort of patients with CKD, serum bicarbonate below 22 or above 26 mEq/L was associated with higher PWV. Further studies are needed to determine if there is a direct causal link between acid base abnormalities and vascular stiffness and to define the optimal range of serum bicarbonate in CKD to prevent adverse clinical outcomes.

Funding: Private Foundation Support

TH-PO453

Renal Hyperfiltration and Central Blood Pressures: A Populational Cohort Study

Purpose: Renal hyperfiltration (RFH) in non-diabetic individuals is linked to mortality and cardiovascular events. Whether increased central blood pressure (BP) plays a role in this association is unknown.

Methods: Of the 20,004 CARTAIGENE participants, 14,580 non-diabetics with eGFR ≥50 ml/min/1.73m2 were included. Serum bicarbonate was measured in the baseline visit. Central systolic BP was calculated as the average of central systolic BP (CSBP) obtained from a total of 9 measurements, each taken from the left and right sides. A total of 9,643 participants were included in the analysis.

Results: Baseline characteristics between RFH and non-RFH were similar. Increased central BP was associated with higher PWV in multivariate regression and propensity score matching analyses.

Conclusions: In this populational cohort of non-diabetic individuals, RFH was associated with increased central BP parameters, independently of peripheral BP and other confounders. Whether this explain, at least in part, the increased cardiovascular morbidity and mortality associated with RFH remains to be determined.
**TH-PO454**

Obstructive Sleep Apnea and Cardiovascular Outcomes in CKD Patients Claudio P. Loivos, Julia F. Fernandes, Vagner S. Meira, Carla C. Lemos, Sergio E. Kaiser, Márcia R. Klein, Maria Ines Barretto-Silva, Rachel Bregman. State University of Rio de Janeiro, Rio de Janeiro, Brazil.

**Background:** Chronic kidney disease (CKD) is a non-traditional risk factor for cardiovascular disease (CVD). The frequence of obstructive sleep apnea (OSA) in this population is not well established. CVD and hypertension are related to OSA. The aim was to investigate the presence of OSA in CKD patients, its relation with blood pressure (BP) and cardiovascular outcomes.

**Methods:** Longitudinal study including 74 CKD patients stages 3b-4 (eGFR: CKD-EPI) under regular treatment, for 21 months. Sleep study was performed with the equipoment Watch-PAT200®. OSA diagnosis: apnea-hypopnea index (AHI) ≥ 5 event/h, mild: AHI ≤ 15, moderate: AHI > 15 ≥ 30, severe: AHI > 30 event/h. Blood pressure (BP) was evaluated in office and by 24-hour ambulatory BP monitoring (ABPM). Statistics: SPSS 20.

**Results:** Mean age 63.2 ± 9.3 years, 55% men. Mean eGFR: 28.7 ± 8.3 ml/min/1.73m², 64% CKD stage 4. All patients were under regular treatment for at least 6 months. OSA was present in 70.3% (OSA group, n=52), of which mild form: 50%, moderate: 33%, severe: 17%. Office BP in OSA group, showed higher systolic (SBP) and diastolic BP in all periods (p<0.05) when comparing patients from stages 3b and 4, no differences were observed in office BP and ABPM. AHI showed a correlation with: 24-hour mean PP (R=0.274, p<0.05). When comparing patients from stages 3b and 4, no differences were observed in office BP and ABPM. AHI showed a correlation with: 24-hour mean PP (R=0.274, p<0.05), daytime PP (R=0.281, p=0.028), SBP and diastolic BP in all periods (p<0.05) regardless eGFR values. Among nondippers 77.8% presented OSA. All cardiovascular events (n=7, acute myocardial infarction and/or cerebrovascular accident) occurred in patients with OSA.

**Conclusions:** CKD patients 3b-4 presented high OSA frequency. OSA was associated with higher SBP and PP; both in office measurements and in ABPM, despite a higher usage of antihypertensive drugs in this group. We suggest that the presence of OSA as well as systolic hypertension might be modifiable risk factors for CVD in CKD (3b-4) patients.

**TH-PO455**

The Association of Body Mass Index (BMI) with Mortality and Institution of Renal Replacement Therapy (RRT) in CKD Patients in the CKD-QLD Registry: Queensland, Australia Samuel S. Chan, 1,2 Anne Cameron (Salisbury), 1,2 Zaimin Lemos, 1,2 Helen G. Healy, 1,2 Wendy E. Hoy, 1,2 Kidney Health Service, Royal Brisbane and Women’s Hospital, Metro North Hospital and Health Service, Herston, Queensland, NSW, Australia; 1 CKD.QLD and the NHMRC CKD.CRE, The University of Queensland, Brisbane, QLD, Australia; 1Faculty of Medicine, The University of Queensland, Brisbane, QLD, Australia.

**Background:** Dialysis patients who are overweight and obese are reported to have better survival compared with those with lower BMI. We do not know if this is so in CKD patients.

**Methods:** A retrospective analysis of preterminal CKD patients from two major sites enrolled in the CKD. QLD registry was undertaken between May 2011 and July 2015. Associations of WHO BMI categories with subsequent death without RRT and with RRT were examined using Cox regression modelling, adjusting for hospital site, demographic variables, higher SBP stage, primary renal disease and co-morbidities.

**Results:** Of the 2,059 patients (median age 68, IQR 56-77 yr), median (IQR) BMI was 29.7 (25.9-35.0)kg/m². 216 died without RRT (10%) and 151 started RRT (7%). Median (IQR) ages at death and start of RRT were 78 (IQR 71-84) and 61 (IQR 49-69) yr, respectively. The incidence rates for death and start of RRT was 41.8 and 34.4 per 1000 person-years, respectively. With normal BMI (<25) persons as the referent group, the adjusted hazard ratios (HR) (95% CI) for death were 0.57 (0.40-0.81) p=0.002, for overweight subjects, 0.59 (0.41-0.85) p=0.004, for obese subjects, and 0.94 (0.56-1.60) p=0.83, for morbidly obese subjects. The adjusted HR for RRT were 1.08 (0.69-1.70) p=0.73, for overweight subjects, 1.09 (0.69-1.73) p=0.71, for obese subjects, and 1.04 (0.56-1.92) p=0.90, for morbidly obese subjects.

**Conclusions:** Demographic and clinical characteristics of CKD patients who die without RRT are different to patients who commence RRT. Overweight and obese, but not morbidly obese, subjects appear to be protective against death, compatible with the phenomenon observed in dialysis patients. In some patients, lower BMI may mark ill health and advanced age. However, with adjustments, there is no significant association of BMI with the likelihood of starting RRT.

**Funding:** Government Support - Non-U.S.
Methods: Incident statin users were identified from a cohort of persons with sustained low eGFR (<60 for ≥90 days) receiving care through the Veterans Administration from 2005-08. The cohort was limited to those with filled prescriptions covering ≥67% of days in the first year of use. Exposure was categorized by preponderant dose intensity (high, moderate, low by AHA/ACC guideline) during the first year. The outcome was all-cause mortality following the exposure period. Patients were censored at last VA follow-up or 5 years. We used Cox proportional hazards regression adjusted for relevant covariates.

Results: Of 40,241 persons included, 33.9% received low, 59.9% received moderate, and 6.2% received high-intensity statin therapy. Median age [IQR] was 76 [66-82] years, 32.2% had diabetes, and 91.4% were CKD stage 3. High-intensity users were younger (median age 74) and more likely to have diabetes (34.6%). During 167,850 person-years of follow up, 10,753 persons (26.7%) died. Unadjusted mortality was lower in the high-dose group. After multivariable regression adjustment, mortality risk did not differ across the high-, medium-, and low-intensity groups.

Conclusions: In an older, non-dialysis CKD population of US Veterans, statin therapy intensity over one year was not independently associated with all-cause mortality. This real-world analysis supports the KDIGO lipid guideline, which recommends doses of moderate intensity, although the question of whether lower intensity therapy might be equally effective is raised.

**TH-PO458**

Pre-ESRD Systolic Blood Pressure Trajectory and Post-ESRD Mortality

Keishi Sumida,1 Miklos Z. Molnar,2 Praveen Kumar Potukuchi,3 Fridjof Thomas,3 Elvira Gosmanova,4 John J. Sim,1 Kumihiro Yamagata,5 Kamyray Kalantar-Zadeh,6 Csaba P. Kovessy,7 Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA; 2Nephrology Center, Toranomon Hospital Kajigaya, Kawasaki, Japan; 3Stratton VA Medical Center, Albany, NY; 4University of California Irvine, School of Medicine, Orange, CA; 5University of Tennessee Health Science Center, Memphis, TN; 6University of Tsukuba, Tsukuba, Japan.

Background: Pre-ESRD systolic blood pressure (SBP) shows a reverse J-shaped association with post-ESRD mortality. However, the pre-ESRD association of SBP trajectories (decrease vs. increase vs. stable over time) with post-ESRD mortality is unknown.

Methods: We assessed SBP measurements in the last 3 years prior to dialysis in 39,383 US veterans with incident ESRD. SBP slopes and baseline levels were categorized (<5, ≥5, and <15 mmHg/year for slopes; and <130, ≥130, and ≥150 mmHg for baseline) and combined into 9 mutually exclusive groups with slope of ≥5 mmHg/year and baseline of 130-<150 mmHg as referent. Associations with all-cause post-ESRD trajectories (decrease vs. increase vs. stable over time) with post-ESRD mortality is association with post-ESRD mortality. However, the pre-ESRD association of SBP trajectories (decrease vs. increase vs. stable over time) with post-ESRD mortality is unknown.

Results: The median (interquartile interval) SBP slope and baseline SBP were -0.1 (-0.2 to -0.1) mmHg/year and 140 (133-149) mmHg. Decrease in SBP was associated with higher mortality, with the highest risk seen with SBP slope of ≥5 mmHg/year and baseline of 130-150 mmHg as referent. Associations with all-cause post-ESRD mortality were examined in multivariable-adjusted Cox models.

Conclusions: The median interquartile interval SBP slope and baseline SBP were -0.1 (2.4, -1.9) mmHg/year and 140 (133-149) mmHg. Decrease in SBP was associated with higher mortality, with the highest risk seen with SBP slope of ≥5 mmHg/year and baseline of <130 mmHg (adjusted hazard ratio [95% CI]: 2.02 [1.70-2.40], vs. referent; Figure). Increase in SBP was associated with lower mortality independent of baseline SBP, as was stable SBP in patients with baseline SBP ≥130 mmHg.

**TH-PO460**

Apixaban versus Warfarin in Patients with Atrial Fibrillation (AF) and Stage 4 CKD

John J. Stainer,1 Glenn M. Chertow,2 Stefan H. Hohnloser,2 Daniel Weidig,3 Samira Gareznik,1 Wonkyung Byon,1 Renske D. Lopes,2 John H. Alexander,2 Lars Wallentin,1 Christopher B. Granger,2 BMS, Princeton, NJ; 2Duke Clinical Research Institute, Durham, NC; 3Duke University, Durham, NC; 4J. W. Goethe University, Division of Clinical Electrophysiology, Frankfurt, Germany; 5Pfizer, Groton, CT; 6Stanford University School of Medicine, Palo Alto, CA; 7Upssala Clinical Research Center, Uppsala, Sweden.

Background: Limited safety data exist for direct-acting oral anticoagulants in patients with advanced CKD. In Apixaban for Reduction of Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, we evaluated the effects of apixaban vs. warfarin in stage 4 CKD.

Methods: ARISTOTLE included patients with AF with a serum creatinine ≥2.5 mg/dL and estimated CrCl ≤25 mL/min. Apixaban dose was 5 mg bid or 2.5 mg bid if ≥3 criteria were met: age ≥70, weight ≥60 kg or serum creatinine ≥2.5 mg/dL. We used Cox proportional hazard models to analyze treatment effect stratified by CrCl category (<30 vs ≥30 mL/min). We also evaluated drug exposure by apixaban dose for patients with CrCl <30 mL/min.

Results: Overall 269 patients (median age 81; 61% women) had a CrCl <30 mL/min. The effect of apixaban vs warfarin on stroke or systemic embolism was similar across CrCl categories (p-interaction = 0.50). For those with CrCl <30 mL/min, major bleeding occurred in 7 patients with apixaban and 19 with warfarin (HR 0.34; 95% CI 0.14-0.79), and the median apixaban drug exposure was 5512 ng/mL hr (n=12) for 5mg and 2792 ng/mL hr (n=218).

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

Underline represents presenting author.
ng/ml/hr (n=19) for 2.5mg. The relative safety of apixaban was similar across CrCl categories (Table).

Conclusions: Among patients with Stage 4 CKD in ARISTOTLE, those randomized to apixaban experienced lower bleeding rates compared with warfarin, consistent with the overall population. Studies evaluating the safety and efficacy of apixaban in patients with advanced CKD, including end-stage kidney disease, are needed.

Funding: Commercial Support - Bristol-Myers Squibb/Pfizer

| Bleeding rates per 100 patient-years and hazard ratios for apixaban vs. warfarin |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                               | Apixaban 2.5 mg/100 mg | Apixaban 5.0 mg/100 mg | Warfarin 3 mg/100 mg |
| Major Bleeding                | 4.3% (1.69)         | 5.0% (1.54)     | 7.0% (1.97)     |
| Major non-cardiovascular      | 7.7% (2.13)         | 9.7% (2.74)     | 14.7% (3.87)    |
| Major cardiovascular bleeding| 14.5% (4.91)        | 16.6% (5.37)    | 24.7% (6.65)    |
| Major bleeding                | 26.0% (8.13)        | 30.3% (9.12)    | 39.4% (10.65)   |
| Moderate bleeding             | 5.1% (1.69)         | 6.4% (1.97)     | 7.5% (2.38)     |
| Minor bleeding                | 0.0% (0.00)         | 0.0% (0.00)     | 0.0% (0.00)     |

*For those who had ≥ 2 ischaemic events.

TH-PO461 Cause-Specific Mortality among Patients with CKD and Atrial Fibrillation Sankar D. Naveenathan, Jese D. Schold, Stacey Jolly, Susanna Arrigain, Medina Nalla, Nadja Basals, Wolfgang C. Winkelmayer, Joseph V. Nally, Baylor College of Medicine, Houston, TX; Cleveland Clinic, Cleveland, OH; Kidney Research Institute, Seattle, WA.

Background: Atrial fibrillation (AF) is associated with death in patients with chronic kidney disease (CKD). However, whether the increased mortality in patients with CKD is due to cardiovascular or other causes is unclear. We examined the associations between AF and cause-specific mortality in a large CKD population.

Methods: We included 62,459 patients with eGFR 15-59 ml/min/1.73 m² with AF (based on the presence of ≥ 2 ICD-9 codes for AF). Using the State mortality registry data, we classified deaths as follows: a) cardiovascular; b) malignancy-related; and c) non-cardiovascular/non-malignancy causes. We fitted Cox regression models for overall mortality and separate competing risk models for each cause of death category to evaluate their respective associations with AF. We conducted a separate analysis after excluding patients with pre-existing malignancy.

Results: During a median follow-up of 4.1 years, 19,094 patients died; cause of death was available for 18,854 participants. After adjusting for covarates, AF was associated with 23% increased risk of all-cause mortality, 45% increased risk of cardiovascular mortality and 13% lower risk of malignancy-related mortality in this CKD cohort (Table 1). Proportion of deaths due to ischemic heart disease (23.1% vs 16.5%) and heart failure (13.5% vs 27.5%) were higher in those with AF than among those without AF. Deaths due to cerebrovascular diseases were similar in those with and without AF. Exclusion of those with malignancy at baseline yielded similar results except that no association between AF and malignancy-related deaths was noted. Results were consistent across various stages of CKD.

Conclusions: In a non-dialysis dependent CKD population, presence of AF was associated with higher all-cause and cardiovascular mortality.

Funding: Commercial Support - Development of CCF CKD registry was supported by an unrestricted educational fund to the Department of Nephrology and Hypertension from Amgen, Inc

Table 1. Associations of Atrial fibrillation with all-cause and cause-specific mortality

<table>
<thead>
<tr>
<th></th>
<th>Apixaban 2.5 mg/100 mg</th>
<th>Apixaban 5.0 mg/100 mg</th>
<th>Warfarin 3 mg/100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding</td>
<td>4.3% (1.69)</td>
<td>5.0% (1.54)</td>
<td>7.0% (1.97)</td>
</tr>
<tr>
<td>Major non-cardiovascular Bleeding</td>
<td>7.7% (2.13)</td>
<td>9.7% (2.74)</td>
<td>14.7% (3.87)</td>
</tr>
<tr>
<td>Major cardiovascular Bleeding</td>
<td>14.5% (4.91)</td>
<td>16.6% (5.37)</td>
<td>24.7% (6.65)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>26.0% (8.13)</td>
<td>30.3% (9.12)</td>
<td>39.4% (10.65)</td>
</tr>
<tr>
<td>Moderate bleeding</td>
<td>5.1% (1.69)</td>
<td>6.4% (1.97)</td>
<td>7.5% (2.38)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>0.0% (0.00)</td>
<td>0.0% (0.00)</td>
<td>0.0% (0.00)</td>
</tr>
</tbody>
</table>
| *For those who had ≥ 2 ischaemic events.


Background: Intensive BP lowering may help prevent stroke recurrence, but it can also cause rapid kidney function decline (RFKD). White matter hyperintensities (WMHs) on brain MRI are a marker of cerebral small vessel disease and may suggest small vessel disease in kidneys. We hypothesized that high WMH burden could identify stroke survivors susceptible to RFKD with intensive blood pressure (BP) lowering.

Methods: SPS3 randomized 3,620 participants with lacunar stroke to target systolic BPs 130-150 mmHg vs. < 130 mmHg. We included 2,454 participants with baseline WMHs from brain MRI. We defined RFKD as ≥ 30% decline in eGFR from baseline to year 1. We tested for interaction between BP intervention and WMH severity on the incidence of RFKD in one year.

Results: At randomization, mean age was 63 years and eGFR 81 ml/min/1.73m². Two hundred thirty-four (9.5%) had RFKD at one year—100 (8.1%) in the usual BP and 134 (11.0%) in the intensive BP arm (p = 0.01). The proportion with RFKD increased with higher WMH tertile (8%, 10%, and 11% from lowest to highest tertile). The association of BP target with RFKD was qualitatively higher with increasing WMH tertile (Table), but the interaction was not significant (p = 0.65).

Conclusions: Higher WMH burden was not adequate to distinguish persons most susceptible to rapid kidney function decline in the setting of intensive BP lowering after stroke.

Funding: Other NIH Support - NIH-NIMHD grant R25MD066832 and NIH-NIA grant R01AG046206

TH-PO463 Association of SNPs on FGFR4 and Klotho Genes with LVH and Cardiovascular Outcome in CKD Patients Alexander Sellier, Sarah Seiler, Insa E. Emrich, Danilo Fliesser, Adam M. Zawada, Guinmar Heine, None, Hasbach, Germany; Saarland University Faculty of Medicine, Homburg, Germany; Saarland University Hospital, Homburg, Germany; Saarland University Medical Center, Homburg (Saar), Germany; Saarland University Medical Centre, Homburg/Saar, Germany.

Background: High circulating levels of fibroblast growth factor 23 (FGF23) predict future cardiovascular events in CKD patients even after adjustment for baseline GFR. Recent rodent studies suggest that FGF23 may directly induce left ventricular hypertrophy by activating FGF-receptor 4 (FGFR4) independently from its co-receptor klotho. Ongoing studies however reported a deficiency of soluble klotho, rather than high serum FGF23, to aggravate LVH. To compare the clinical relevance of these pathophysiological pathways, we examined whether SNPs within the FGFR4 and klotho genes affect the risk of prevalent LVH and incident cardiac events in our prospective CARE FOR HOMe study.

Methods: The ongoing CARE FOR HOMe study recruits chronic kidney disease G2-G4 patients, of whom 519 patients consented to DNA isolation and genotyping using qualitative real-time PCR (Gly388Arg for FGFR4 and Phe352Val for klotho). Echocardiography was conducted at baseline by one single physician following American Society of Echocardiography guidelines. All patients were followed for the occurrence of the primary endpoint cardiac decompensation for 4.2 ± 2.1 years.

Results: Carriers of the different alleles of Gly388Arg and Phe352Val did not differ significantly in their left ventricular mass index (Gly388Arg: Gly/Gly: 91.7 ± 28.5 g/m², Gly/Arg: 91.4 ± 24.4 g/m², Arg/Arg: 93.9 ± 28.7 g/m², p = 0.861; Phe352Val: Phe/Phe: 91.1 ± 25.4 g/m², Phe/Val: 92.8 ± 28.2 g/m², Val/Val: 100.9 ± 48.0 g/m², p = 0.379). During follow up, cardiovascular events occurred in 104 patients. Neither Gly388Arg nor Phe352Val was significantly associated with risk of cardiac decompensation in univariate analysis (log rank test: Gly388Arg: p = 0.241; Phe352Val: p = 0.817).

Conclusions: In CKD patients, SNPs of FGFR4 and Klotho are neither associated with LV mass, nor with the risk of future cardiac decompensation. We suggest to analyze the association between SNPs, LV hypertrophy and incident cardiac events in independent large CKD collectives before findings from rodent studies should be transferred to clinical nephrology.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Renal Resistive Index in Cortical but Not in Segmental Arteries Reflects Renal Perfusion in Hypertensive CKD Patients

Arkadiusz Lubas, Stanislaw Niemczyk. Military Institute of Medicine, Warsaw, Poland.

Background: Renal Resistive Index in segmental arteries (RI-S) is a well known marker of cardiovascular and renal organ damage. In many studies it is used as a marker of Renal Perfusion (RP). However this relation was not proved. Renal Resistive Index in cortical arteries (RI-C) is erroneously used as RI-S, because the difference between these indexes is unclear. The aim of the study was to investigate relations between segmental and cortical renal Resistive Indexes and Renal Perfusion.

Methods: Fifty patients (3F, 47M; age 56.6±13.3) with stable CKD (CKD-EPI 57.4 ±28.4 ml/min/1.73m²) and a history of hypertension were enrolled in the study. Ultrasonic color and duplex Doppler examinations of intrarenal arteries in the right kidneys were performed. RI-S was calculated as a mean of 3 measurements. RI-C and RP (arteriovenous mean perfusion [ml/s]) were evaluated with the use of Dynamic Tissue Perfusion Method (PixelFlux software). Echocardiographic Cardiac Index (CI), I; MT, 24-h Pulse Pressure (PP) and renal function expressed as Creatinine and Cystatin based CKD-EPI formula were estimated.

Results: Renal Resistive Indexes were significantly correlated (r=0.63; R=0.40; p<0.001), but RI-S was lower than RI-C (0.684 ±0.075 vs 0.728 ±0.151; p=0.004). In the univariable analysis RI-S and RI-C both were significantly correlated with age, BMI, CI, CKD-EPI, and RI-P. The multivariable regression analysis adjusted to age and BMI showed that CKD-EPI (r=0.001), CI (p=0.005) and PP (p=0.014) independently influenced RI-S. Equation of regression revealed an independent relation (R²=0.41, p=0.001) with PR (p=0.001) and CI (p=0.024). When RI-S was added to the regression equation PR (p=0.001) and RI-S (p=0.001) independently modified RI-C (R²=0.51, p=0.001).

Conclusions: Renal Resistive Index in segmental arteries is independently modified by cardiovascular and renal organ damage parameters with the exclusion of the Renal Perfusion. Although RI-S and RI-C correlate with each other, their values differ significantly. Cortical renal Resistive Index reflects both Renal Perfusion and segmental Resistive Index. Segmental and cortical renal Resistive Indexes cannot be used interchangeably.

Funding: Government Support - Non-U.S.

Methylarginines in CKD

Insa E. Emrich, 1 Adam M. Zawada, 1 Jens Martens-lohrenhoff, 2 Stefan Wagenpeil, 2 Danilo Fiser, 1 Gunnar H. Heine, 3 Stefanie M. Bode-Böger. 1 Institute of Clinical Pharmacology, Medical Faculty, Otto-von Guericke University, Magdeburg, Germany; 2 Saarland University, Homburg, Germany; 3 Saarland University Faculty of Medicine, Homburg, Germany; 4 Saarland University Medical Centre, Homburg/Saar, Germany; 5 University Magdeburg, Magdeburg, Germany; 6 Medical Center, Saarland University, Homburg, Germany.

Background: Patients suffering from chronic kidney disease (CKD) have a substantial burden of cardiovascular disease, whose underlying pathophysiological mechanism cannot fully be explained by traditional risk factors. Therefore, non-traditional cardiovascular risk factors have to be taken into account. As such potential non-traditional risk factors, asymmetric dimethylarginine (ADMA) & symmetric dimethylarginine (SDMA) have been a focus of cardiological research for several years. It has recently been revealed that ADMA & SDMA become acetylated during their degradation. In murine models the acetylated ADMA (Ac-ADMA) & the acetylated SDMA (Ac-SDMA) were significantly associated with kidney function. We now hypothesize that a similar accumulation of Ac-ADMA & Ac-SDMA occurs in humans & (b) Ac-ADMA & Ac-SDMA are more prominent predictors of incident cardiovascular events than ADMA & SDMA.

Methods: Blood samples of 528 CKD patients KDIGO stage G2 to G4 who participated in our CARE FOR HOME study were analyzed. ADMA, SDMA & acetylated metabolites were measured by liquid chromatography – tandem mass spectrometry. All patients were followed annually with standardized interviews during a follow up period of 4.6 ± 2.0 years.

Results: Mean plasma ADMA concentration was 0.49 [0.44; 0.55] µmol/l, mean plasma SDMA concentration was 0.72 [0.59; 0.98] µmol/l, mean plasma Ac-ADMA concentration was 1.24 [0.74; 2.16] µmol/l & mean plasma Ac-SDMA concentration was 1.92 [1.27; 3.04] µmol/l. All four metabolites accumulated in patients with more advanced CKD. While Ac-ADMA was more strongly correlated with eGFR than ADMA, Ac-SDMA was less strongly correlated with eGFR than SDMA. During follow up, 144 patients suffered from a cardiovascular event. In univariate Cox-regression analyses, high plasma levels of all four high plasma levels of all four metabolites were significantly associated with incident cardiovascular events. However, after adjustment for confounders including eGFR & traditional cardiovascular risk factors, only high plasma SDMA remained significantly associated with incident cardiovascular events.

Conclusions: In the future, we need further investigations to analyze the underlying acetylation’s mechanism & we have to clarify the role of SDMA in cardiological pathophysiology.

Analysis of Genome-Wide Arterial Media-Specific DNA Methylation Demonstrates No Epigenetic Evidence of Aging but Reveals New Targets in CKD Associated Cardiovascular Pathology

Anika Dritsoulou, Amin Oomata, 1 Maria Kislikova, 2 Amy P. Webster, 2 John P.➽ Becker, 2 Jih T. Norman, 3 David C. Wheeler, 1 Thomas Oates, 1 Ben Caplin. 1 Centre for Nephrology, University College London, London, United Kingdom; 2 Cancer Institute, University College London, London, United Kingdom.

Background: Cardiovascular disease (CVD) is the primary cause of morbidity and mortality among patients with chronic kidney disease (CKD). In CKD-related CVD, structural and morphological changes occur in the vascular bed leading to arterial stiffness, matrix deposition and calcification that have been described as accelerated arterial aging. These changes are mediated by the activation of vascular smooth muscle cells. Altered DNA methylation has been proposed to mediate the aging process and is also a manifestation of CKD. We aim to investigate tissue specific changes in DNA methylation that occur in CKD-related CVD.

Methods: DNA methylation analysis was performed (Illumina EPIC array) in bisulfite converted genomic DNA, isolated from the arterial media of 25 recipients (CKD patients; end-stage renal disease, donor cardiac and non-donor) and 7 donors (controls; renal artery, during kidney transplantation procedures, after the adventitia was removed and the endothelium was brushed away. Bioinformatics analysis was performed using Bioconductor packages in R (SNP and XY chromosome-related CpG were excluded). BMIQ and Combat analysis were used for normalization and to correct technical variation respectively. DNA methylation age (DMAge) was estimated using the algorithm by Horvath et al. Methylation-specific PCR was used to validate the array data. P-values were adjusted for multiple comparisons.

Results: 3x10⁶ differentially methylated CpGs encompassing 703 differentially methylated regions (DMR) were identified (adj p<0.05) spread across all autosomal chromosomes. Significant enrichment was found in promoters, exons, introns and 5’ UTRs. DMRs were found in or in proximity to interfering RNAs (miR-196b) along with genes associated with vascular remodelling and ECM production (COL17A1, ADAMTS9, MMP2, LOXL1), and signalling mechanisms involved in fibrosis and vascular pathologies (TGFβ1, FGF1/6, SNAI2, GATA3/4/5). DMAge and chronological age were highly correlated but there was no evidence of higher DMAge in CKD cases.

Conclusions: Overall, these data implicate altered arterial media-specific DNA methylation in CKD-related CVD, but this methylation profile does not reflect a process of accelerated aging.

The Role of Neprilysin in CKD

Insa E. Emrich, 2 Nicolas Vodover, 1 Kathrin Untersteller, 2 Hélène Nougué, 2 Sarah Seiler, 4 Danilo Fiser, 2 Alexandre Mebazaa, 3 Jean-Marie Launay, 3 Gunnar H. Heine, 5 Inserm UMR S 942, Paris, France; 2 None, Haschbach, Germany; 3 Saarland University Faculty of Medicine, Homburg, Germany; 4 Saarland University Hospital, Homburg, Germany; 5 Saarland University Medical Centre, Homburg/Saar, Germany.

Background: Since the introduction of sacubitril in clinical cardiology, neprilysin has become a major treatment target for patients suffering from heart failure. Inhibition with sacubitril prolongs survival of patients with systolic heart failure, and elevated plasma neprilysin concentrations predict adverse cardiac outcome in non-nephropathic cohorts. However, natriuretic peptides were recently shown to inhibit plasma neprilysin. As natriuretic peptides accumulate in chronic kidney disease (CKD), we hypothesized that high plasma neprilysin loses its predictive role in patients with impaired renal function.

Methods: We measured plasma levels of neprilysin concentration, neprilysin activity and brain natriuretic peptide (BNP) in 542 CKD G2 - G4 patients within the CARE FOR HOME study. Patients were followed annually for predefined endpoints (a) hospitalization for acute decompensated heart failure, and (b) atherosclerotic cardiovascular events.

Results: During 5.1 ± 2.1 years, 63 hospitalizations for acute decompensated heart failure and 125 incident atherosclerotic cardiovascular events occurred. Plasma BNP was inversely correlated with neprilysin activity (before adjustment for glomerular filtration rate: r = -0.118; p = 0.006; after adjustment: r = -0.193; p < 0.001), but not with neprilysin concentration (r = -0.022; p = 0.603 and r = 0.065; p = 0.132, respectively). Both in univariate Cox-Meier and in multivariate Cox regression analyses, high plasma BNP and low, rather than elevated, neprilysin activity predicted future hospitalization for acute decompensated heart failure, whereas neprilysin concentration was not predictive. Further, BNP was an independent predictor of incident atherosclerotic cardiovascular events, while neprilysin concentration and activity were not.

Conclusions: In line with experimental studies, high natriuretic peptides may inhibit neprilysin activity in CKD. In accordance, high neprilysin activity and concentrations are no predictors of adverse cardiovascular outcome in CKD patients. Thus, neprilysin inhibitors should be implemented with caution in patients with advanced CKD, and further studies are needed to better understand the benefits and risks of neprilysin inhibitors in these patients.

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

Underline represents presenting author.
TH-PO468
Plasma Phospholipid Remodeling Associates with Stroke in CKD
Adil Jadoon,1 Thekselnaycke Rajendiran,1 Jaeman Byun,2 Tanu Soni,2 Subramaniam Pennathur,2 Farsad Afshinmnia.2 1University of Michigan, Ann Arbor, MI; 2University of Michigan, Ann Arbor, MI.

Background: Stroke is a prevalent co-morbidity in chronic kidney disease (CKD). Systematic identification and quantification of complex lipids in stroke are lacking. This study is aimed at comparison of 17 different lipid classes in patient with and without a history of stroke.

Methods: This is a cross-sectional study of CKD patients from Clinical Phenotyping Resource and Biobank Core. Inclusion criteria were age greater than 18 years from all stages of CKD, frequency matched by gender and race among the CKD stages. Baseline demographic and clinical characteristics at the time of enrolment were background variables. Predictors were plasma lipid features identified by an untargeted liquid chromatography/mass spectrometry-based lipidomics platform from plasma samples obtained at the time of enrolment. Outcome was history of stroke. Lipids were internal standard normalized, log2 transformed, underwent calculation of percentage contribution to the corresponding lipid class, logit transformed, and z-score standardized for the downstream analyses.

Results: Overall 214 patients were included consisting of 184 patients without and 30 patients with stroke. Mean age was 60 years (SD=16). There were 104 females (48.6%); 64 patients (29.9%) were African-American and 150 (70.1%) were Caucasians. Distribution of body mass index, blood pressure, serum albumin, total cholesterol, lipoprotein, total triglycerides, and urine albumin-creatinine ratio was not different in patients with and without stroke. Overall we identified 330 lipid features of which 106 (32.1%) consisted of phospholipids including Phosphatidylincholines (PC, n=50), Phosphatidylethanolamine (PE, n=28), Phosphatidylcholine (PCs, n=23), Phosphatidylserine (PS, n=12), Phosphatidylcholine (PCs, n=6), and Phosphatidyl胆methionine (pPCs, n=5). Using a t-test, 36 lipids passed the nominal threshold of p<0.05 comparing patients with and without stroke, of which 23 lipids belonged to one of the phospholipid classes (over representation enrichment p=0.00004). Accordingly, PC-38:4 was the top ranking lipid with 0.73 SD higher level (95% confidence interval: 0.35 to 1.10) in stroke as compared to no stroke.

Conclusions: These findings reveal sustained significant alterations and remodeling in major plasma phospholipid subclasses in stroke in CKD patients. Further research is required to elucidate causality or long term prognostication.

TH-PO469
CALIBRA: A Cardiovascular, Literature-Based Risk Algorithm for CKD Patients
Luca Neri, Francesco Belloccchio, Carlo Barbara, Flavio Mari, Ulrich Tschulena, Stefano Stuard. Fresenius Medical Care, Bad Homburg, Germany.

Background: Current cardiovascular (CV) risk scores may have limited generalizability; do not implement patient-specific prognostic reasoning; require large datasets for derivation and cannot be easily updated as new evidence emerges. CALIBRA is a Knowledge-Driven Bayesian Network risk algorithm overcoming such limitations. We compared CALIBRA predictions against established risk scores and a data-driven model.

Methods: CALIBRA is a Bayesian Network (BN) based on several meta-analyses of original cohort studies on CV risk among CKD patients. For each potential risk factor, all effect sizes were pooled with a fixed effect method and then converted to BN weights using epidemiologic data (incidence of CV events in the population; prevalence of risk factors). CALIBRA implements personalized prognostic reasoning by yielding a summary risk score, by ranking the most impacting risk factors for each patient, by suggesting further diagnostic testing maximizing prognostic accuracy. We evaluated CALIBRA accuracy (AUC) in the EuCid CKD stage 3-5 cohort (2011-2015) and compared it to a data-driven model (logistic regression derived in the same data). We included 32 variables from high quality studies in the final model (e.g.: socio-demographic, life-style, antropometry, comorbidities, biochemistry tests). We used the knowledge-driven model to predict CV occurrence in the validation cohort (n=6239). There were 153 CV hospitalizations in 12 months (0.025 events/100 person*year) in the validation sample. Due to incomplete clinical records, predictions were based on 16.9±2.0 variables per patient. CALIBRA accuracy was similar to the data-driven model (AUC=0.77 for both) (fig.1)

Conclusions: CALIBRA provides unique features of prognostic reasoning along with accurate risk prediction. It represents a valid tool for risk stratification and clinical evaluation. The tool is easily and promptly updatable with the most recent scientific knowledge.

TH-PO470
Design of a Clinical Risk Calculator for Atherosclerotic Renovascular Disease
Diana Vassallo,1 Robert N. Foley,2 Philip A. Kalra.1 1Salford Royal Hospital NHS Foundation Trust, Salford, United Kingdom; 2University of Minnesota, Minneapolis, MN.

Background: Risk stratification in atherosclerotic renovascular disease (ARVD) can influence treatment decisions and facilitate patient selection for revascularization. In this study, we aim to use variables with the best predictive value to design a risk calculator that can assist clinicians with risk stratification and outcome prediction.

Methods: Patients with a radiological diagnosis of ARVD were recruited into a single-center prospective cohort study between 1986 and 2014. Primary clinical end-points included: death, end-stage kidney disease (ESKD) and cardiovascular events (CVE). A stepwise regression model was used to select variables with the most significant hazard ratio for each end-point. The risk calculator was designed using HyperText Markup language (HTML). Survival and CVE-free survival were estimated at 1, 5 and 10 years.

Results: In total 872 patients were recruited into this study with a median follow-up of 54.9 months (20.2-96.0). Only models predicting death and CVE showed good performance (c-index >0.80). The risk calculator (figure 1) showed that while all patients with ARVD had poor longterm survival, revascularization may improve outcomes in patients with better preserved eGFR and lower baseline proteinuria (table 1).

Conclusions: Although this risk calculator requires further independent validation in other ARVD cohorts, this study shows that a small number of easily obtained variables can help predict clinical outcomes and encourage a patient-specific therapeutic approach.

Table 1 Predicted survival probabilities for patients with different clinical phenotypes.
and adverse outcomes of ischemic stroke. However, the impact of impaired renal function on the associations of insulin resistance with stroke outcomes is unknown. Therefore, we sought to investigate the associations of both fasting and post-glucose load insulin resistance indices with ischemic stroke prognosis in non-diabetic patients with impaired renal function.

Among 1968 patients with ischemic stroke without a history of diabetes mellitus in the Abnormal Glucose Regulation in Patients with Acute Stroke across China (ACROSS) study, chronic kidney disease (CKD) stages 3-5 were associated with an increased 1-year mortality (adjusted hazard ratio [95% confidence interval], 1.75 [1.03-3.00]) and poor outcome (adjusted odds ratio 2.23 [1.3-3.46]) only in participants with eGFR<90ml/min/1.73m². In comparison, ISI Q1 vs. Q4 was associated with higher risks of mortality (adjusted hazard ratios: 3.69 [0.95-14.40]; 2.21 [1.02-4.78]; and 1.81 [1.05-3.11]) and of HOMA-IR (Q4) or the lowest quartile of ISI (Q1) in the overall population was defined as insulin resistance. The associations between insulin resistance and stroke outcomes were investigated according to estimated glomerular filtration rate (eGFR).

Secondary outcomes were history of CAD, CHF and peripheral artery disease (PAD).

Conclusions: This prospective study found associations for alterations in gut-microbiome derived SCFAs with advancing CKD and links SCFAs to CVD, suggesting possible contribution of gut microbiome to CKD and its complications.

**TH-PO472**

Left Ventricular Geometry in Type 2 Diabetic Patients with Kidney Disease: Predictive Factors Klotho and FGF23

Filipa B. Mendes,1 Pedro L. Neves,1,2 (1)Centro Hospitalar do Algarve, Faro, Portugal; 2Department of Biomedical Sciences and Medicine, University of Algarve, Faro, Portugal; 3Nephrology, CHA, Faro, Portugal; 4Department of Biomedical Sciences and Medicine, University of Algarve, Faro, Portugal.

Background: Chronic Kidney Disease (CKD) is known to induce a cardiac over-response, which includes left ventricular hypertrophy and fibrosis. Those alterations begin in the early stages of the disease and aggravate as renal functions decline. The this work we evaluated a population of CKD patients to ascertain the potential use of plasmatic Klotho, FGF23 or both as markers for cardiomyopathy in CKD patients

Methods: This prospective cohort study was conducted in our outpatient diabetic nephropy (DN) clinic from 2012 to 2016. For this study we included one hundred and seven (107) patients with stage 2-3 CKD. The mean age was 57±2.7 years and the mean LVM level was 99.3±24.5 g/m². LVH and RWT were used to calculate LV geometry: normal (no LVH and normal RWT), eccentric hypertrophy (LVH and normal RWT), and concentric hypertrophy (LVH and increased RWT). Patients were classified as having LVH if they had LVMI 100 g/m² in women and 131 g/m² in men, and RWT was considered to be increased if ≥0.45.

Results: Multivariate regression analysis demonstrated that diminished eGFR (OR<0.959; 95% CI 0.921 – 0.999; p=0.034) and elevated P (OR=2.859;95%CI; 2.238 – 5.693; p=0.003) levels were associated with a greater risk of Eccentric Hypertrophy but not with Concentric Hypertrophy. On contrary, low Klotho (OR=0.737; 95% CI: 0.603 – 0.910; p=0.033) and high FGF23 (OR=1.051; 95% CI: 1.008 – 1.053; p=0.006) levels were associated with a greater risk of Concentric Hypertrophy. Using the Kaplan-Meier analysis, it was observed that patients’ survival at 60 months was 90.2 % in patients without Hypertrophy, 76.3 % in patients with Eccentric Hypertrophy and 53.6 % in patients with Concentric Hypertrophy (log rank=4.22; p=0.039).

Conclusions: In conclusion, both Klotho and FGF23 serum levels represent good biomarkers of CVD in CKD patients they might be used along with imaging techniques, as diagnostic parameters biomarkers of the CVD.

**TH-PO473**

Gut Microbiome Derived Short Chain Fatty Acids Alter with Advancing CKD and Improve Prediction of Associated Cardiovascular Disease

Adil Jakoon, Anna V. Mathew, Jaeman Byun, Farsad Afrinshima, Subramanian Pennathur. University of Michigan, Ann Arbor, MI.

Background: Short chain free fatty acids (SCFA) are products of dietary complex carbohydrate fermentation by the intestinal microbiota and exert multiple effects on mammalian health and metabolism. However, reports of alterations in SCFAs by CKD and association with CVD are lacking. In this study, utilizing targeted metabolomics by liquid-chromatography mass-spectrometry (LC/MS), we quantified SCFAs at different stages of CKD and analyzed their association with CVD.

Methods: This was a cross sectional observational study of the population in Clinical Phenotyping and Resource Biobank Core. Inclusion criteria are patients with CKD, aged older than 18. Clinical and demographic data at the time of enrollment were gathered. Secondary outcomes were history of CAD, CHF and peripheral artery disease (PAD). SCFAs were measured by LCMS using the plasma at enrolment. We used analysis of variance to compare means by CKD stages, and applied Receiver Operating Characteristics Curve to compare c-statistic of different models.

Results: Overall we enrolled 214 patients, including 36, 99, 61, and 18 patients from stages 2, 3, 4, and 5 respectively. We found caproate increased from 1.4 ug/L from CKD stage 2 to 12.2 ±0.9 ug/L in stage 5 (p=0.001), but a significant increase in mean level of butyrate, valerate, and caproate from stage 2 to stage 5 (p=0.018). Specifically, level of valerate increased from 1.8±0.1 ug/L in CKD stage 2 to 1.9±0.3 ug/L in stage 5 (p=0.006), and caproate increased from 1.6±0.1 ug/L to 2.0±0.4 ug/L from CKD stage 2 to 5. Means±SD of valerate in patients with and without CAD was 1.7±0.08 ug/L and 1.6±0.09 ug/L, respectively (p=0.000). Similarly, this value was 1.8±0.08 ug/L and 1.5±0.03 ug/L in patients with and without CHF, respectively (p=0.037). Compared to a model consisting of age, diabetes, and stages of CKD to predict CAD, addition of valerate significantly improved c-statistic of 0.74 to 0.78 (p<0.029). Future studies: This study can provide a foundation for alterations in gut-microbiome derived SCFAs with advancing CKD and links SCFAs to CVD, suggesting possible contribution of gut microbiome to CKD and its complications.
Conclusions: In adults with CKD, higher GDF-15, gal-3, and sST-2 are associated with increased risk of mortality. Elevated GDF-15 and sST-2 are also associated with increased risk of HF. The pathways of inflammation, cardiac remodeling, and fibrosis represented by these biomarkers may be important in the pathogenesis of CVD in those with CKD.

Funding: NIDDK Support

TH-PO476 Syndecan-4 is Associated with eGFR and the Incidence of Myocardial Infarction in a General Population: The Tromso Study Mari D. Solbø,1,2 Trine M. Reine,3 Sven T. Kolset,3 Trond G. Jansen,1,4 Østfold Hospital, Oslo, Norway; 2University Hospital of North Norway, Tromsø, Norway; 3University of Oslo, Oslo, Norway; 4Metabolic and Renal Research Group, UiT The Arctic University of Norway, Tromsø, Norway; 5University of Oslo, Oslo, Norway.

Background: Cardiovascular disease (CVD) is a common cause of morbidity and mortality. A link between chronic kidney disease (CKD) and CVD exists, but mechanisms are poorly understood. The endothelial glycocalyx is essential in maintaining vascular integrity. Disruption and shedding of the glycocalyx may be a common pathway in CVD and CKD. Syndecans are components of the glycocalyx. Increased serum levels of syndecan-4 is a marker of glycocalyx change or damage. We studied the cross-sectional association between syndecan-4 and kidney function, and the longitudinal association of these markers with myocardial infarction.

Methods: We used a case-cohort design and included participants from the Tromso 5 Study (2001-02). Syndecan-4 was measured in frozen serum specimens with ELISA-assays. Baseline variables also included age, sex, cardiovascular risk factors, estimated GFR (eGFR) and urinary albumin–creatinine ratio (ACR). We used Spearman correlation, linear regression, and Cox regression models we applied Borgan II weights.

Results: Among the 1496 men and women included, 328 experienced a fatal or non-fatal myocardial infarction between inclusion and the end of 2007. In the subcohort (n=931), mean age was 63.8 (±10.9) years, and 60.3% were women. Mean syndecan-4 was 18.7 (±5.6) nmL, mean eGFR was 87.7 (±13.7) mL/min/1.73 m² and median ACR (IQR) was 0.43 (0.30, 0.77) mg/mmol. In the entire cohort, syndecan-4 was significantly correlated with eGFR (r=0.15; P=0.001), but only borderline significantly with ACR (r=0.10; P=0.045). In multiple linear regression analyses adjusted for age, sex, systolic blood pressure and waist circumference, syndecan-4 was positively associated with eGFR, but not significantly associated with ACR. Adjusted for the same variables plus smoking, glycosylated hemoglobin A1c, eGFR and ACR, syndecan-4 was an independent predictor of myocardial infarction (per 1 ng/mL: HR 1.24 (1.01, 1.52; P=0.04)), but eGFR and ACR were not.

Conclusions: In a general population serum syndecan-4 was positively associated with baseline eGFR and an independent predictor of myocardial infarction. Whether this association partly may be mediated through kidney function, remains to be studied.

Funding: NIDDK Support

TH-PO477 Decreased Serum Sulfatide Level and Hepatic Sulfatide Synthesis Ability in 5/6 Nephrectomy CKD Model Mice Yosuke Yamada,1 Kosuke Yamaka,2 Keita Inui,3 Yuji Kamijo,4 Shinshu University, Matsumoto, Japan; 5Institute of Clinical Medicine, University of Tsukuba, Ibaraki, Japan; 6University of Colorado Denver and Denver Health Medical Center, Denver, CO; 1Osaka University Hospital, Osaka, Japan; 2University of Colorado, Aurora, CO; 3University of Colorado Denver, Aurora, CO; 4University of Colorado Denver Health Science Center, Aurora, CO; 5University of Colorado Denver and Denver Health Medical Center, Denver, CO; 6University of Colorado Denver: Anschutz Medical Campus, Aurora, CO.

Background: Chronic kidney disease (CKD)-associated mineral and bone disorder (MBD) is associated with vascular calcification and accelerated atherosclerosis. Higher uric acid reportedly suppresses 1,25-dihydroxyvitamin D (1,25(OH)2D). It is unknown if lowering serum uric acid improves markers of CKD-MBD, vascular calcification, or atherosclerosis in CKD.

Methods: Post-hoc analysis of a clinical trial randomizing 80 patients with stage 3 CKD and hyperuricemia to placebo vs allopurinol. Serum markers of CKD-MBD were measured. Protein expression of extra-renal 1α-hydroxylase was evaluated from participants’ vascular endothelial cells. Tapo and carotid intima-media thickness (CIMT) were measured as markers of serum calcification and vascular atherosclerosis, respectively. The Wilcoxon two-sample T-test was applied.

Results: Baseline characteristics between both study groups were similar except for significantly higher FGF-23 levels in the placebo group vs allopurinol. Allopurinol lowered serum uric acid levels significantly vs placebo (Table). We found no significant change in vitamin D metabolites or iPTH. Median FGF-23 levels increased slightly with allopurinol vs placebo (6.1 (10.6, 16.7) vs 1.8 (2.3, 7.8), 19.1)), but this was not statistically significant. There was not a significant change in the expression of endothelial 1α-hydroxylase, serum Tapo or CIMT.

Conclusions: These data suggest that factors other than uric acid play a more important role in the regulation of CKD-MBD including vitamin D metabolism and the progression of vascular calcification and atherosclerosis in patients with CKD.

Funding: NIDDK Support

TH-PO478 Uric Acid-Lowering and Markers of CKD-Associated Mineral and Bone Disorder, Vascular Calcification, and Atherosclerosis Emily Andrews,1 Loni J. Perrenoud,2 Kristen L. Nowak,1 Zhijing You,1 Andreas Pasch,2 Michel Chonchol,3 Jessica B. Kendrick,4 Diana J. Jalal,5 UC Denver, Aurora, CO; 1University Hospital Bern, Bern, Switzerland; 2University of Colorado, Aurora, CO; 3University of Colorado Denver, Aurora, CO; 4University of Colorado Denver Health Science Center, Aurora, CO; 5University of Colorado Denver and Denver Health Medical Center, Denver, CO; 1University of Colorado Denver: Anschutz Medical Campus, Aurora, CO.

Background: Chronic kidney disease (CKD)-associated mineral and bone disorder (MBD) is associated with vascular calcification and accelerated atherosclerosis. Higher uric acid reportedly suppresses 1,25-dihydroxyvitamin D (1,25(OH)2D). It is unknown if lowering serum uric acid improves markers of CKD-MBD, vascular calcification, or atherosclerosis in CKD.

Methods: Post-hoc analysis of a clinical trial randomizing 80 patients with stage 3 CKD and hyperuricemia to placebo vs allopurinol. Serum markers of CKD-MBD were measured. Protein expression of extra-renal 1α-hydroxylase was evaluated from participants’ vascular endothelial cells. Tapo and carotid intima-media thickness (CIMT) were measured as markers of serum calcification and vascular atherosclerosis, respectively. The Wilcoxon two-sample T-test was applied.

Results: Baseline characteristics between both study groups were similar except for significantly higher FGF-23 levels in the placebo group vs allopurinol. Allopurinol lowered serum uric acid levels significantly vs placebo (Table). We found no significant change in vitamin D metabolites or iPTH. Median FGF-23 levels increased slightly with allopurinol vs placebo (6.1 (10.6, 16.7) vs 1.8 (2.3, 7.8), 19.1)), but this was not statistically significant. There was not a significant change in the expression of endothelial 1α-hydroxylase, serum Tapo or CIMT.

Conclusions: These data suggest that factors other than uric acid play a more important role in the regulation of CKD-MBD including vitamin D metabolism and the progression of vascular calcification and atherosclerosis in patients with CKD.

Funding: NIDDK Support

Changes in CKD-MBD markers, CIMT, and T50 from baseline to the end of study visit (week 12)

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

TH-PO479 Impact of Renal Function on Association between Uric Acid and All-Cause Mortality in Patients with Chronic Heart Failure Viera Stupan,1,5 Ingrid Os,1 Morten Grundtvig,1 Bård Waldum-Grevbo,1 Finnmark Hospital Trust, Kirkenes, Norway; 2Inlandet Hospital Trust Lillehammer, Lillehammer, Norway; 3Oslo University Hospital, Oslo, Norway; 4Oslo University Hospital, Ullern and University of Oslo, Oslo, Norway; 5Institute of Clinical Medicine, University of Oslo, Oslo, Norway.

Background: Serum uric acid (SUA) is associated with poor prognosis in patients with heart failure (HF). It is still unclear whether there is a causal inference between UA and increased mortality. We investigated if SUA was an independent predictor of all-cause mortality in HF patients using a propensity score matching model to correct for
Possible confounding variables. As SUA is closely related to renal function, we examined if SUA was associated with hypertension and albuminuria. The majority of patients had hypertension (51.2%) and albuminuria (13.4%), and SUA was associated with both conditions (P < 0.001 for both). Using multivariable models, SUA remained an independent predictor of hypertension (odds ratio [OR] 1.05; 95% confidence interval [CI] 1.02-1.08) and albuminuria (OR 1.07; 95% CI 1.05-1.09). Our findings suggest that SUA may play a role in the development of hypertension and albuminuria and may be a marker for future cardiovascular events.

Methods: We conducted a retrospective cohort study of patients with systolic hypertension and albuminuria identified in a large clinical database. The primary outcome was progression to diabetes, defined as a diagnosis of diabetes or a 25% increase in HbA1c level. We used multivariable logistic regression models to examine the association between SUA and diabetes progression. We adjusted for age, sex, race, body mass index, smoking status, and history of cardiovascular disease.

Results: In the cohort of 10,000 patients, 2,500 had hypertension and albuminuria. SUA was associated with diabetes progression (OR 1.2; 95% CI 1.1-1.3; P < 0.001). Additional factors associated with diabetes progression included age, sex, race, and history of cardiovascular disease.

Discussion: Our findings suggest that SUA may be a marker for diabetes risk in patients with hypertension and albuminuria. Further research is needed to determine the underlying mechanisms and explore the potential for reducing SUA levels in order to prevent diabetes progression.

Conclusion: SUA is a marker for diabetes risk in patients with hypertension and albuminuria. Further research is needed to determine the underlying mechanisms and explore the potential for reducing SUA levels in order to prevent diabetes progression.
Methods: This retrospective cohort study included adult patients without prevalent heart failure referred for echocardiography. Patients with serial echocardiograms, left ventricular ejection fraction (LVEF) ≤50% on baseline echocardiogram and estimated glomerular filtration rate (eGFR) ≥90 ml/min/1.73m² were matched 1:1 with patients with eGFR<60 for ≥5 years, sex, history of hypertension or diabetes, use of renin-angiotensin inhibitors, or a Framingham score ≥10%. A secondary analysis included patients with preserved LVEF and normal left ventricular mass index matched for the same parameters except for use of renin-angiotensin inhibitors.

Results: Among 685 matched pairs, those with CKD had higher prevalence of comorbidities and worse left ventricular diameter compared with controls, as well as biochemical abnormalities associated with CKD. 256 admissions for HFPEF were observed. Patients with CKD were at increased risk for HFPEF admission: crude hazard ratio (HR) 1.79 [95% CI (confidence interval) 1.38-2.33, p<0.001] and adjusted HR (for age, sex, hypertension, and left ventricular diameter) 1.66 [95% CI 1.23-2.24, p<0.001]. LVEF and left ventricular diameter decreased over time in both groups (p=0.001 and p=0.001 respectively) but no difference was observed in rate of dropping (p=0.39 and p=0.83 respectively). Results were similar in the secondary analysis that included 289 pairs with preserved LVEF and normal left ventricular mass index (crude HR 1.99 [95% CI 1.31-2.51, p=0.03] and adjusted HR 1.80 [95% CI 1.35-2.43, p=0.001]). Rate of change was similar for LVEF, pulmonary artery pressure, and left ventricular mass index in both groups (p=0.80, p=0.38, and p=0.63 respectively).

Conclusions: The increased risk of HFPEF admission in CKD is independent of baseline cardiovascular disease and occurs despite a similar change in relevant echocardiographic parameters over time in patients with or without CKD.

Funding: NIDDK Support

TH-PO484
Renal and Overall Survival (OS) in Type 5 Cardiorenal Syndrome in Systemic AL Amyloidosis Is Dictated by Cardiac Response at 12 Months Tamer Rezk,1,2 Helen J. Lachmann,2 Carol Whelan,3 Ashutosh Wechalakar,2 Philip N. Hawkins,2 Julian D. Gillmore,2 “Center for Nephrology, UCL Division of Medicine, London, United Kingdom; 2National Amyloidosis Centre, UCL, London, United Kingdom; 3National Amyloidosis Centre, Hull and East Riding Cardiac Trust, Hull, United Kingdom.

Background: Systemic AL amyloidosis is a progressive, fatal disease that is a cause of Type 5 cardiorenal syndrome. Renal involvement leading to ESRD is the main determinant of morbidity and cardiac involvement the main determinant of mortality. Current consensus is that renal progression (reduction in eGFR≥25%) is the main determinant of renal survival. We hypothesize that in patients with systemic AL amyloidosis and type 5 cardiorenal syndrome renal survival is primarily dictated by cardiac organ response as defined by current consensus criteria.

Methods: 1000 patients were prospectively enrolled into the UK ALCHYMY study from 2009-2016; 518 patients were diagnosed with cardiorenal syndrome. We report OS, renal survival and time to the composite endpoint of death and dialysis. Organ responses were defined according to consensus criteria, NTproBNP increase/decrease of >30% (cardiac progression/regression) and reduction in eGFR ≥25% (renal progression). Results: Median age was 66yr, eGFR 55ml/min and NTproBNP 655ng/L. Median systolic BP was 112mmHg. 199 patients died and 50 required RRT with an overall survival of 18.5 months by Kaplan Meier analysis. Factors predictive at baseline of OS, renal survival and composite endpoint were NTproBNP (p=0.001, r=0.0001), systolic BP (p=0.001, r=0.0007) and NTproBNP (p=0.001, r=0.0001). Cardiac progression (NTproBNP increase of 30%) or cardiac regression (NTproBNP decrease of >25%) at 12 months was more predictive of death (HR 5.0 vs 1.3, p=0.01), dialysis (HR 3.7 vs 2.7, p=0.017) and composite endpoint (HR 3.8 vs 1.7, p=0.001). Cardiac response (NTproBNP reduction of >50%) compared to renal response (reduction in proteinuria by 30% without >25% reduction in eGFR) at 12 months was also more predictive of OS (HR 0.3 vs 0.8, p=0.001), renal survival (HR 0.3 vs 0.6, p=0.008) and composite endpoint (HR 0.3 vs 1.0, p=0.001).

Conclusions: OS, renal survival and the composite endpoint of death or dialysis in patients with type 5 cardiorenal syndrome in systemic AL amyloidosis are strongly associated with baseline cGFR, systolic BP and NT proBNP. Cardiac organ response at 12 months, as defined by consensual criteria, is more predictive of both patient and renal survival in this cohort of patients than renal organ response.

TH-PO485
Associations of Cardio-Renal Biomarkers in CKD Patients with Non-Alcoholic Fatty Liver Disease Rajkumar Chinnadurai,1 Helen Alderson,1 Philip A. Kalra,2 1SFORDER ROYAL NHS FOUNDATION TRUST, Manchester, United Kingdom; 2Salford Royal Hospital NHS Trust, Salford, United Kingdom.

Background: Non-Alcoholic Fatty Liver Disease (NAFLD) and Chronic Kidney Disease (CKD) are both associated with increased risk of cardiovascular disease (CVD). Novel biomarkers may aid early diagnosis and guide prognosis. We studied the associations of Cardio-Renal biomarkers in a cohort of non-dialysis dependent CKD (NDD-CKD) patients with NAFLD.

Methods: Patients with and without ultrasound characteristics of NAFLD were identified within the Salford Kidney Study (SKS), a large single-centre NDD-CKD cohort study. Associations of important biomarkers (KIM-1, NGAL, MPO, Anti ApoA1, NTproBNP and hsTNT) with NAFLD and major outcomes (MACE, mortality and ESKD) were studied using Cox-Regression analysis.

Results: Of the 3061 patients registered in SKS, 630 patients (NAFLD-137, Normal-493) had had liver US, complete datasets and analysis of baseline CRBM. Demographics and median values (with IQR) of biomarkers are expressed in the Table. In a Multivariable Cox-Regression Model adjusted for age, gender, NAFLD Status and baseline history of cardiovascular risk factors, Troponin (HR:1.008, P=0.0021), NGAL (HR: 2.261, P<0.001) and KIM-1 (HR: 2.95, P=0.005) showed associations with MACE. All biomarkers except Anti Apo-A1 showed a positive association with mortality with Trop T showing a strong association HR 1.02, P=0.001. Higher KIM-1 and NGAL were associated with progression to ESKD.

Conclusion: The biomarker associations were very much reflective of the renal and cardiac status of the patient group. A strong independent association of biomarkers was observed with outcomes in this cohort, but NAFLD was not independently associated with any particular pattern.

Funding: Commercial Support - Takeda UK Ltd; Hull and East Riding Cardiac Trust Fund and the Hull and East Yorkshire Hospitals NHS Trust R&D; Renal Research Fund (Hull and East Yorkshire), Clinical Revenue Support

TH-PO487
Iron Status and the Risk for Heart Failure Hospitalization in Veterans with CKD Monique E. Cho,1 Jared Hansen,1 Celena B. Peters,2 Brian C. Sauer,2 1Veterans Health Administration, Salt Lake City, UT; 2University of Utah, Salt Lake City, UT.

Background: The risk for heart failure (HF) hospitalization associated with abnormal iron balance has not been evaluated in a large pre-dialysis CKD population.

Methods: We performed a historical cohort study using the national data from the Veterans Affairs Informatics and Computing Infrastructure. We identified a pre-dialysis CKD cohort (MDRD eGFR <60 ml/min/1.73m²) with at least one set of iron indices between 2006-2015. The clinical characteristics were determined from the ICD-9 codes and laboratory data during the baseline period, defined as the year preceding the first available iron indices (index date). Patients with ESRD, genetic and chronic disorders affecting iron metabolism were excluded. The cohort was divided into 4 iron groups based on the joint quartiles (Q) of transferrin saturation (Tsat) and ferritin: functional iron deficiency (FID), 1st Tsat Q, 2nd Tsat Q, 3rd Tsat Q, <25% of normal ferritin (FID), 1st Tsat Q, 2nd Tsat Q, 3rd Tsat Q, ≥25% of normal ferritin. We applied absolute iron deficiency, 1st Tsat-ferritin Qs; High Iron (HI), 4th Tsat-ferritin Qs and Reference
The Association between Neutrophil to Lymphocyte Ratio and Severity of Coronary Artery Disease in Patients with CKD II Young Kim,1

Seong Park,1 Min Jeong Kim,2 Minyoun Han,1 Harin Hee,1 Sang hoon Song,2 Eun Young Seong2, Dong Won Lee,2 Soo Bong Lee,2 Ilm soo Kwak,2

Pusan National University Hospital, Busan, Republic of Korea; 2Pusan National University Yangsan Hospital, Yangsan, Republic of Korea.

Background: Chronic inflammation is associated with increased cardiovascular mortality in patients with chronic kidney disease (CKD). Neutrophil to lymphocyte ratio (NLR) was introduced as a potential marker of inflammation in cardiac disorder. Emerging evidence have suggested that NLR might be a useful marker of cardiovascular disease. This study aimed to investigate the association between NLR and severity of coronary artery disease in patients with CKD.

Methods: A total of 952 pre-dialysis CKD patients [estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m²] who underwent elective coronary angiography (CAG) were studied. Depending on eGFR, study subjects were categorized into 3 groups (stage 3: n = 617, stage 4: n = 240, stage 5: n = 95). NLR values were calculated from complete blood count before CAG. The severity of CAD was determined by Gensini score accounting for the degree of luminal narrowing and location (s) of obstruction in the involved main coronary artery. A significant CAD was defined as lumen narrowing of one or more main coronary artery ≥ 50%.

Results: In univariate analysis, Gensini score correlated with NLR (r = 0.542, P < 0.001), age (r = -0.123, P < 0.001), diabetes mellitus (DM) (r = 0.124, P < 0.001), hypertension (r = -0.133, P < 0.001), smoking (r = -0.088, P = 0.007), eGFR (r = -0.343, P < 0.001), uric acid (r = -0.390, P = 0.001), calcium (r = -0.097, P = 0.003), phosphate (r = -0.107, P < 0.001), total cholesterol (r = -0.115, P < 0.001), CRP (r = -0.292, P < 0.001), and Creatinine (r = -0.465, P < 0.001), age (r = -0.064, P = 0.013), DM (β = -0.079, P = 0.005), hypertension (β = 0.056, P = 0.013), GFR (β = 0.027, P = 0.001), total cholesterol (β = 0.063, P = 0.015), and CRP (β = 0.095, P = 0.001) were independent predictors of Gensini score. In ROC analysis (AUC: 0.791, 95% CI: 0.710-0.772), the best cut-off value of NLR for identifying the significant CAD was 2.26 with associated sensitivity of 70.2% and specificity of 67.2%.

Conclusions: A higher NLR was an independent predictor of the severity of CAD in CKD patients. NLR could be a valuable measure for CAD risk stratification in CKD patients.

TH-PO490

Estimated GFR Variability: A Novel Predictor of Cardiovascular Outcomes in Outpatients with Congestive Heart Failure Tatsuumi Oka,1 Takayuki Hamano,2 Satoshi Yamaguchi,1 Keichi Kubota,1 Masamitsu Sendai,1 Sayoko Yamamoto,1 Yusuke Sakaguchi,1 Isao Matsui,1 Yoshitaka Ishikawa,1
1Nephrology, Osaka University Graduate School of Medicine, Suita, Japan; 2Comprehensive Kidney Disease Research, Osaka University Graduate School of Medicine, Suita, Japan.

Background: Reportedly, variability in renal function is associated with mortality and CKD progression in predialysis patients with CKD. However, its clinical relevance in patients with congestive heart failure (CHF) is uncertain.

Methods: In this retrospective cohort study, we enrolled CHF patients who were discharged from an educational hospital. Using 6-month data just after discharge, we linearly regressed each patient’s eGFR on time and calculated eGFR variability (EGV) as “mean sqrt(residuals of eGFR)” / mean eGFR × 100%”. Exposure of this study was EGV, and outcome was death or hospitalization rates over the follow-up period starting 6 months after discharge. For main analyses, we employed negative binomial regression models. As sensitivity analyses, we used Cox proportional hazards models to estimate the hazard risk of mortality or readmission whichever occurred first. Additionally, we calculated the net reclassification index (NRI) and the integrated discrimination index (IDI) of EGV.

Results: Among the 351 outpatients, median left ventricular ejection fraction, eGFR, and follow-up were period 54%, 57.5 mL/min/1.73 m², 4.4%, and 23.6 months, respectively. Multivariate negative binomial regression analyses showed that higher EGV was associated with an increased incidence rate ratio for the outcome (Figure 1). Excluding the patients with their eGFR measured only 3 times during 6 months after discharge didn’t change the results substantially. Cox regression analyses also showed that EGV of Q3 had significantly higher hazard ratio (HR) than the combined group of Q1 and Q2 (HR, 2.00; 95%CI, 1.27 to 3.15) (Figure 2). The NRI and IDI were 0.283 (P=0.014) and 0.013 (P=0.038), respectively.

Conclusions: Higher EGV variability predicts worse cardiac outcome in outpatients with CHF.

TH-PO491

Assessment of Comorbidities and Pre-Dialysis Adverse Outcomes among Incident Renal Replacement Therapy Patients MinJeong Lee,1,2

Inheec Park,1 Heungsoo Kim,1 Gyu Tae Shin,1 Jong Cheol Jeong,1 Nephrology, Ajou University School of Medicine, Suwon, Republic of Korea; 2Emergency Medicine, Ajou University School of Medicine, Suwon, Republic of Korea.

Background: Several observational studies have shown that initiation of RRT at high estimated glomerular filtration rate(eGFR) was associated with poorer post-RRT patient survival. But, most of previous studies have been based on registry data by patients who survived to initiate RRT. Therefore, we investigated pre-dialysis morbidity and adverse outcome preceding initiation of dialysis as clinical outcomes and the association of pre-dialysis clinical outcomes with eGFR at RRT initiation.

Methods: EMR of incident dialysis patients who started maintenance dialysis between Jan 2010 and Dec 2015 were reviewed. Patients with eGFR<20ml/min were enrolled. Comorbidity indices were calculated for each patient based on the comorbidity at the enrolled time. Patients were classified as “safe RRT” group vs “urgent RRT” group defined as the patients who started the RRT from urgent indication such as uremic encephalopathy, uremic pericarditis, pulmonary edema, or serum potassium 7.0mmol/L.
Results: Among total 1,044 patients, mean cGFR at RRT initiation was 6.7±4.3ml/min/1.73m². Mean eGFR at RRT initiation was higher in larger comorbidity burden(Fig.1). Urgent RRT group had higher modified Charlson score than safe RRT group(4.9±2.1 vs 3.5±2.3, P<0.001). During pre-dialysis period from enroll time to RRT initiation, patients with higher comorbidities experienced more cardiovascular adverse outcome such as MI or angina, and more infection event requiring hospitalization(Fig.2).

Conclusions: Patients with larger comorbidities experienced more adverse events during pre-RRT period. Timing of RRT initiation should be individualized considering burden of comorbidities.

Figure 2. Pre-Dialysis Adverse Outcomes

TH-PO493

The Efficacy of Febuxostat in CKD Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials Dasing Hong.1 Ying Wang.1 *None, Epping, NSW, Australia; *Sichuan Provincial People’s Hospital, CHENGDU, China.

Background: Uric acid is considered as an independent risk factor for kidney disease. Hyperuricemia is associated with progression of renal dysfunction. Febuxostat, a xanthine oxidase (XO) inhibitor, is used to treat hyperuricemia in patients with gout. However, its effects on renal functions remain unclear. We aimed to systematically evaluate the efficacy and safety of febuxostat in patients with chronic kidney disease (CKD).

Methods: Cochrane library, MEDLINE, EMBASE and trial register system were searched for randomized controlled trials to May 18, 2017 with the terms of “febuxostat” and “chronic kidney disease”. The primary outcomes were serum creatinine level, while secondary outcomes included serum uric acid level, eGFR, hsCRP, HDL-C, LDL-C, SBP and DBP. Fixed effects model analysis was used to explore the effect size of febuxostat versus control.

Results: Eight studies involving 981 participants were eventually included in this review. All studies were high quality studies. Compared with the control group, febuxostat significantly reduced the serum uric acid levels (WMD=-2.71, 95% CI: -3.68, -1.73, P<0.01, I²=96%), with a nonsignificant effect on renal functions (a reduction in serum creatinine levels by 0.07mg/dl (WMD, 95% CI: -0.34, 0.20, P=0.60, I²=90%), and an increase in the level of eGFR by 3.15ml/min/1.73 m² (WMD, 95% CI: -1.40, 7.71, P=0.17, I²=83%)). Subgroup analysis show that febuxostat significantly increase in the level of eGFR by 6.58ml/min/1.73m² compared with placebo (WMD, 95% CI: 3.04, 8.13, P=0.01, I²=0%). Fixed effect model analysis showed that febuxostat can significantly reduce cTnT levels by 0.25ng/L (WMD, 95% CI: -0.40, -0.09, P=0.001, I²=31%), reduce HDL-C levels by 0.77mg/dl (WMD, 95% CI: -4.52, 2.98, P=0.69, I²=0%) and reduce LDL-C levels by 5.95mg/dl (WMD, 95% CI: -11.89, -0.01, P=0.05, I²=18%). There was no significant difference in the blood pressure between the febuxostat group and the control group.

Conclusions: Febuxostat can significantly reduce serum uric acid levels in patients with CKD with hyperuricemia with potential beneficial impact on renal function as compare to placebo. Further large RCTs are needed to assess the effect of febuxostat on renal outcomes as compared to other active uric acid lowering treatment.

TH-PO494

The Effect of Uric Acid Lowering on Albuminuria and Renal Function in Type 1 Diabetes: A Randomized Clinical Trial Sascha Pilemann-Lyberg.1 Frederik Persson.1 Jan Frystyk.1 Peter Rossing.2 1Steno Diabetes Center, Gentofte, Denmark; 2Steno Diabetes Center Copenhagen, Gentofte, Denmark; 1Aarhus University, Aarhus, Denmark.

Background: Epidemiological studies indicate that uric acid (UA) is a risk factor for development and progression of CKD. Whether UA lowering with allopurinol changes urinary albumin excretion rate (UAER) or GFR in patients with type 1 diabetes (T1D) suffering from diabetic nephropathy is not known.

Methods: We conducted a randomized, placebo-controlled, double-blinded, cross-over trial enrolling patients with T1D and a plasma uric acid ≥ 4.4 mg/dl, persistent albuminuria (urinary albumin creatinine ratio) ≥ 30 mg/g and an eGFR ≥ 40 ml/min/1.73m² on stable RAS blocking intervention. The participants were randomized to: (1) Allopurinol (400 mg daily) + standard therapy; or (2) placebo + standard therapy for 60 days. Participants underwent a 4 week washout period prior to cross-over. Primary end-point was change in UAER (3×24h collections), secondary endpoint was change in GFR (¹⁵⁴Cr-EDTA-plasma clearance) measured at the end of each treatment period. The effect of UA lowering was tested using a paired t-test, after testing for carryover effects.

Results: We enrolled 30 patients, blood pressure 133(3)/75(2) mmHg and HbA1c 67.3 mmol/mol. UA decreased to 3.6 (1.2) mg/dl with allopurinol compared to 5.8 (1.5) with placebo (p<0.001). The 24h UAER (geometric mean [IQR]) was 221 (131-352) mg/24h after treatment with placebo (p=0.83). Mean (SD) GFR (¹⁵⁴Cr-EDTA) was 74 (20) ml/min/1.73m² after allopurinol treatment compared with 73 (20) ml/min/1.73m² after placebo (p=0.51). Glycemic control 24-h blood pressure and RAS blockade was stable. We found no significant association (p=0.45) between uric acid and UAER. In an unadjusted linear model, UA was significantly associated with the level of GFR (¹⁵⁴Cr-EDTA) in the placebo treatment period (R²=0.2, p=0.017).

Conclusions: Short term UA lowering by allopurinol did not improve UAER or GFR in patients with TID and nephropathy. The clinical significance of long-term UA lowering is currently investigated in a large multicentre clinical trial (the PERL Study), investigating the effect of 3 years of allopurinol treatment on albuminuria and slopes of measured GFR.

Funding: Private Foundation Support
TH-PO495

Effect of Losartan on Uric Acid in Patients with CKD

Komal Patel,1 Jordan L. Rosencstock.1 None, New York, NY.2 Northwell Health Lenox Hill Hospital, Paramus, NJ.

Background: Increased serum uric acid (UA) is a risk factor for end-stage renal disease and agents that lower it such as allopurinol may decrease renal disease progression. Losartan inhibits URAT1 mediated renal tubule urate reabsorption by the proximal tubule, which results in an increase in uric acid excretion. This appears to be an effect that is unique to losartan of all the angiotensin receptor blockers. Losartan has previously been shown to increase UA excretion and decrease serum UA levels in patients without kidney disease. However, the effects of losartan on serum and urine UA in patients with kidney disease is unknown. The purpose of this study was to evaluate the change in serum and urine UA levels among individuals with stage 3 chronic kidney disease (CKD3).

Methods: The study enrolled 15 individual outpatients with CKD 3 that were to be started on losartan as part of standard clinical care indications such as proteinuria or hypertension. Baseline serum UA and 24 hour urine for fractional excretion of uric acid (FeUA) were collected prior to starting losartan and after 30 days. Patients were excluded if they had started other medications affecting UA levels within 30 days or during study period.

Results: Mean baseline GFR was 42.07 ± 6.05, and 60% were males. We found that serum UA 30 days post treatment was significantly lower than baseline (7.39 ± 1.47 to 6.85 ± 1.70) (p = 0.009). The median serum UA percent decrease from pre to post was 6% (p=0.008). However, the FE UA 30 days post treatment was not significantly different from baseline (p = 0.89).

Conclusions: This study did show a statistically significant change in serum UA levels in CKD 3 patients after the initiation of losartan. Though statistically significant, the small change in UA level may not be clinically meaningful. In patients without kidney disease, effects may fall by as much as 20% and the difference suggests that renal disease may compromise the ability to respond to the uricosuric effect of losartan. Furthermore, we did not find a significant change in the FeUA. It has been suggested that the uricosuric effect with losartan is short lived as a new steady state is reached quickly, so 30 days may have been too long to recheck FeUA. This study involved a small cohort of patients, and a larger study is warranted to confirm our finding.

TH-PO496

The Effect of Uric Acid-Lowering via Allopurinol on Markers of Kidney Function and Damage in Stage III CKD Patients: A Prospective Comparative Pilot Study of the Short Term Efficacy and Safety of Xanthine Oxidase Inhibitors

Jon L. Ferreiro,1 Emily Andrews,1 Zhizi You,2 Michel Chonchol,2 Richard J. Johnson,3,4 Diana I. Jalal,1,5 UC Denver, Aurora, CO; 3 University of Colorado, Aurora, CO; 4 University of Colorado Denver, Aurora, CO; 5 University of Colorado Denver Health Science Center, Aurora, CO.

Background: Hyperuricemia associates with kidney disease progression and pilot data suggest that lowering serum uric acid may slow kidney disease progression. It remains unknown if lowering serum uric acid levels improves markers of kidney damage in CKD.

Methods: Post-hoc analysis of a double-blind randomized placebo-controlled clinical study utilizing allopurinol to lower serum UA in 80 subjects with stage III CKD. The following markers of kidney damage were evaluated: urinary albumin/creatinine ratio (ACR), urinary neutrophil gelatinase-associated lipocalin (NGAL), urinary kidney injury molecule-1 (KIM-1), and urinary transforming growth factor (TGF)-β1. Urinary NGAL, KIM-1, and TGF-β1 were normalized to urinary creatinine. The Wilcoxon Two-Sample Test was applied.

Results: No significant differences existed between both groups at baseline. Specifically, serum uric acid levels, CKD-EPI estimated glomerular filtration rate (eGFR), and urinary ACR were similar in the placebo and allopurinol groups. After 12 weeks, allopurinol lowered serum uric acid significantly. CKD-EPI eGFR increased by 1.79 (8.08) mL/min/1.72m² with allopurinol group vs declined by 0.83 (5.2) mL/min/1.72m² in the placebo arm, but this did not achieve statistical significance (p=0.07). There was no significant difference between study groups regarding changes in serum cystatin C, cystatin C-eGFR, urinary ACR, or urinary NGAL, KIM-1, or TGF-β1 (Table). Conclusions: Allopurinol significantly lowers serum uric acid levels in adults with stage III CKD and may increase CKD-EPI eGFR. The mechanism behind the increased eGFR is unclear as uric acid-lowering was not associated with significant change in markers of kidney damage.

Funding: NIDDK Support

Changes in markers of kidney function and kidney damage from baseline to the end of study visit (week 12)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n=40)</th>
<th>Allopurinol (n=40)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>63.9 ± 15.5</td>
<td>68.8 ± 11.3</td>
<td>0.021</td>
</tr>
<tr>
<td>Serum uric acid (mg/dL)</td>
<td>7.2 ± 1.3</td>
<td>5.6 ± 1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cystatin C (mg/l)</td>
<td>1.2 ± 0.3</td>
<td>1.1 ± 0.2</td>
<td>0.018</td>
</tr>
<tr>
<td>Cystatin C-eGFR (mL/min/1.73m²)</td>
<td>49.1 ± 10.8</td>
<td>65.6 ± 11.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACR (mg/d)</td>
<td>26 ± 10</td>
<td>22 ± 9</td>
<td>0.008</td>
</tr>
<tr>
<td>NGAL (ng/mg)</td>
<td>136 ± 100</td>
<td>112 ± 101</td>
<td>0.20</td>
</tr>
<tr>
<td>KIM-1 (ng/mg)</td>
<td>147 ± 142</td>
<td>125 ± 123</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SD or median (IQR)

TH-PO497

Reduction in Uric Acid Correlates with Better eGFR in Patients with Hyperuricemia and CKD Treated with XOIs – A Systematic Meta-Analysis


Background: Hyperuricemia may contribute to worsening of renal function in patients with chronic kidney disease (CKD). Uric acid (UA) lowering xanthine oxidase inhibitors (XOIs) may therefore preserve GFR.

Methods: TrialTrove was queried for studies with results using the terms “+uricosuric agent or xanthine oxidase inhibitor”. Of 660 trials 8 were published randomized clinical trials in patients with hyperuricemia and CKD treated with XOI. The effect of XOIs on renal function was selected to control on eGFR and the impact of reduction in serum uric acid on eGFR was assessed in a random effects meta-analysis model.

Results: Estimated GFR at end of treatment was significantly higher in the XOIs arms (p<0.035) without significant heterogeneity in effect (p-value=0.075, I²- index: 45.7%). Greater reduction in UA correlated with better eGFR at the end of treatment (p<0.002).

Conclusions: Renal function may benefit from intensive UA lowering therapy in CKD. Prospective studies of intensive UA lowering in CKD are warranted.

Funding: Commercial Support - AstraZeneca

Included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up</th>
<th>Experimental Arm</th>
<th>Control Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sicari 2015</td>
<td>6</td>
<td>fruvostat</td>
<td>placebo</td>
</tr>
<tr>
<td>Ten 2015</td>
<td>6</td>
<td>feuvostat</td>
<td>placebo</td>
</tr>
<tr>
<td>Sicari 2015</td>
<td>6</td>
<td>feuvostat</td>
<td>placebo</td>
</tr>
<tr>
<td>Kato 2009</td>
<td>4</td>
<td>allopurinol</td>
<td>placebo</td>
</tr>
<tr>
<td>Gomemba 2010</td>
<td>24</td>
<td>chamilostat</td>
<td>placebo</td>
</tr>
<tr>
<td>Yarla 2015</td>
<td>3</td>
<td>chamilostat</td>
<td>placebo</td>
</tr>
<tr>
<td>Mith 2012</td>
<td>6</td>
<td>allopurinol</td>
<td>placebo</td>
</tr>
<tr>
<td>Remton 2014</td>
<td>5.5</td>
<td>hypouric</td>
<td>placebo</td>
</tr>
<tr>
<td>Total</td>
<td>319</td>
<td>Total</td>
<td>323</td>
</tr>
</tbody>
</table>

TH-PO498

Prospective Comparative Pilot Study of the Short Term Efficacy and Oxidative Stress Effects of Various IV Iron Therapies in Iron Deficient CKD Patients

Ahmed Zeidain,1,2 Academic Renal Department, Hull & East Yorkshire Hospitals, NHS Trust, Hull, United Kingdom; 1Research, Hull & York Medical School, Hull/York, United Kingdom.

Background: Iron deficiency is common in chronic kidney disease (CKD) and usually leads to anaemia which is associated with fatigue, reduced quality of life and poorer clinical outcomes. Treatment with oral iron is often insufficient and guidelines recommend intravenous (i.v.) iron as an option for the treatment of iron deficiency anaemia in certain clinical situations. Reports have raised safety concerns regarding the potential increase in oxidative stress reactions and effects on cardiovascular events related to changes in endothelial function. In this study we hypothesized that CKD patients who receive intravenous iron, although efficacy may be similar, there may be differences in the

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
effects of iron preparation on the acute generation of oxidative stress markers and clinical effects of endothelial dysfunction.

Methods: Patients were randomised in a 1:1:1:1 ratio to intervention with one of 3 iron preparations (Cosmofer, Venoferr 200mg single dose or Monoferr 200mg or high single dose 1000mg). All patients underwent baseline assessments and following iron infusions with 1 week, 1 month and 3 monthly intervals. At each visit, Blood Wave Velocity (PWV) and blood samples for the assessment of renal function, changes in haemoglobin, iron markers, and markers of oxidative stress and endothelial function were collected.

Results: IV iron led to a rise in storage iron within the first 24 hours of administration and by one week a maximal rise with all iron preparations. Monoferr 1000mg produced the most significant rise and reduced over the subsequent period. There was a rise in T8S within hours to levels within a toxic range (>80% for some iron). Venoferr produced the greatest rise, followed by Monoferr at 1 week, and 3-monthly intervals in the first 24 hours. The greatest improvement in SF-36 score over the 3 month follow-up period was seen in patients who received Monoferr. Acutely IV iron did not affect measures of endothelial function, but there was a trend in the reduction in PWV over the 3 month period.

Conclusions: All studied parenteral iron preparations led to a rise in storage and circulating iron. Further studies assessing a saturation approach 100% may cause an iron rise in catalytic iron which may lead to increased oxidative stress (under evaluation). Paradoxically there was a fall in PWV suggesting benefit in endothelial function.

Funding: Commercial Support - Pharmacosmos

TH-PO504

On Top of Standard Treatment Selective Endothelin-A Receptor Antagonism Improves Lipid Profile in CKD

Neeja Dhaun, Cardiovascular Sciences, University of Edinburgh, Edinburgh, United Kingdom.

Background: CKD patients have an increased risk of cardiovascular disease (CVD) that is partly explained by conventional CVD risk factors. Current guidelines recommend the use of angiotensin (AT1) receptor antagonists (AT1R) to improve lipid profile in patients with pre-dialysis CKD. Despite their use many patients continue to have elevated lipids and remain at increased CVD risk. Endothelin-A (ET-A) receptor antagonism is currently being investigated as a novel therapeutic approach to reduce proteinuria and blood pressure (BP), and to improve outcomes in pre-dialysis CKD. Here, we investigated the effects of AT-A antagonism on circulating lipids in these patients.

Methods: In a randomized double-blind, 3-way crossover study, 27 subjects with proteinuric, pre-dialysis CKD received 6 weeks treatment with placebo, sitaxentan 100mg, an AT1 antagonist, and nifedipine 30mg. Those with nephrotic syndrome were excluded. Serum total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides were measured at baseline and week 6 of each treatment period, alongside the primary endpoints of proteinuria, BP, and arterial stiffness.

Results: After 6 weeks of treatment, serum lipids were improved in sitaxentan and nifedipine treated patients compared to placebo.

Conclusions: In addition to currently recognized effects on proteinuria and BP, ET-A antagonism may lower lipid profile and so have broader cardioprotective effects in CKD. Longer and larger trials with this specific endpoint are now warranted.

TH-PO505

Phase I Evaluation of AZD9977, a First in Class Mineralocorticoid Receptor (MR) Modulator Bamber Chialda,1 Rasmus Jansson-Lofmark,1 Linda Nelander,1 Kristina Ihnbom.2

Background: The role of endoplasmic reticulum (ER) stress in the development of renal disease is a relatively recently described, and has been suggested as a cause for the fibrotic response of ER stress. Therefore, modulation of diazoxidic ER stress could be beneficial in end-stage renal disease.

Methods: Phase I development began with a single dose escalation trial from 5mg to 1200mg, followed by a randomized placebo controlled cross over four period clinical trial in 23 healthy volunteers. The treatments administered were fludrocortisone (A), 200mg AZD9977 + fludrocortisone (B), 100mg eprenolone + fludrocortisone (C), and 200mg AZD9977 + 100mg eprenolone + fludrocortisone (D). Treatment D was administered to assess if AZD9977 could ameliorate the nephrotoxicity induced by eprenolone as observed in rodent studies. A baseline session without treatment was performed. Food and fluid intake was controlled and urine collected in 2h intervals. The primary endpoint was log[Na]/[K] in urine collected from 2 to 8h.

Results: In single dose escalation trial all doses were well tolerated. Pharmacokinetic and safety results were comparable with further development. In the cross-over trial 200mg AZD9977 (B) exhibited similar effects on diuresis and urinary electrolytes as 100mg eprenolone (C), and the combination (D) had an additive effect on urinary electrolytes. Fludrocortisone exposure was similar across treatments, and there was no significant pharmacodynamic effect of AZD9977 on diuresis.

Conclusions: The results in man contradict the results in rodent models driven by aldosterone and endothelial dysfunction. Further studies in rodent models driven by fludrocortisone. The effect of MR modulators on electrolyte excretion may depend on the MR agonist. Clinical studies of how AZD9977 or other MR modulators affect urinary electrolytes in the presence of aldosterone are needed.

Funding: Commercial Support - AstraZeneca

Cross-over trial results

<table>
<thead>
<tr>
<th>Dose</th>
<th>Baseline</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>log[Na]/[K]</td>
<td>2.0</td>
<td>2.0</td>
<td>1.8</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Plasma</td>
<td>1.9</td>
<td>1.5</td>
<td>1.7</td>
<td>2.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

TH-PO501

A Phase 2a Trial of DMX-200: Synergistic Blockade of AT1R and CCR2 in Patients with CKD

David A. Power,1 Stephen G. Holt,2 Paul J. Champion de Crespygny,3 Matthew A. Roberts,4 James H. Williams,5 Kathryn M. Harrison,6 David K. Packham.7

Background: The angiotensin II receptor type 1 (AT1R) and chemokine receptor 2 (CCR2), both G protein-coupled receptors, form function homertomers. Simultaneous antagonism of these receptors would have a beneficial effect on proteinuria, podocyte viability and recruitment of inflammatory monocytes to the kidney in the sub-total nephrectomy rat model of nephrotic syndrome.

Methods: Patients (n=27) were enrolled in an open label, Phase 2a, dose escalation study at 4 sites in Australia. The primary objective was to determine the safety and tolerability of the CCR2 antagonist organic germanium added to stable treatment of the AT1 antagonist irbesartan in patients with proteinuria. The secondary objective was to evaluate the effects of organic germanium on various biomarkers including proteinuria. All patients were on a stable dose of irbesartan for ≥3 months prior to enrolment and throughout the study. Patients received escalating doses of organic germanium (10, 20, 40 and 80 mg TID) at 4-week intervals unless proteinuria remained within normal limits. Participants remained on their maximum dose for a further 2 months.

Results: No safety concerns were observed in patients on irbesartan when treated with 10-80 mg TID organic germanium. The average age of patients was 61±13 (SD) years. Primary diagnoses were diabetic nephropathy (n=7), IgA nephropathy (n=5), and other primary diseases (n=15). The baseline eGFR was 32±12 (range 15-59), PCR 255±174 mg/ml (range 70-700), and irbesartan dose 75-300 mg (81% on 300 mg). Three patients withdrew from the study for reasons unlikely to be related to the study drug. There were no clinically relevant changes in blood pressure, eGFR and serum proteinuria. Of the 24 patients that completed dosing, 6 achieved ≥50% reduction in proteinuria during at least one dose level of organic germanium.

Conclusions: No safety concerns were observed in patients on irbesartan when treated with 10-80 mg TID organic germanium. The additive reduction in proteinuria over and above AT1R blockade in some patients warrants additional clinical investigation of DMX-200 for proteinuric CKD.

Funding: Commercial Support - Dimexim Limited

TH-PO502

Stanniocalcin-1 Inhibits ER Stress and Renal Fibrosis via an AMPK-Activated Protein Kinase Kinase-Dependent Pathway in HK2 Cells

David Roberts,1 G. Power,2 M. Packham.3

Background: Stanniocalcin-1 (STC-1) is a multifunctional glycoprotein with antioxidant and anti-inflammatory properties and regulates AMP-activated protein kinase (AMPK) activity in the kidney. Activation of AMPK may reduce fibrosis and recruitment of inflammatory monocytes to the kidney in the sub-total nephrectomy rat model of nephrotic syndrome.

Methods: HK2 cells pretreated with STC-1 (5NG) were cultured with and without 10 ng/ml TGF-β1 for 16 hours. Media was collected for protein, DNA content, and mRNA expression analysis.

Results: TGF-β treatment induced upregulation of glucocorticoid-related protein (GRP)78 and C/EBP homologous protein (CHOP) and STC-1 pretreatment attenuated the rise in GRP 78 and CHOP. TGF-β treatment also induced upregulation of fibronectin and alpha-smooth muscle actin (α-SMA) and STC-1 pretreatment attenuated the TGF-β-induced increase in fibronectin and α-SMA. STC-1 pretreatment significantly blocked TGF-β-induced downregulation of AMPK and decreased level of ROS via upregulate the uncoupling protein (UCP2). On the other hand, compound C pretreatment with STC-1

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

Underline represents presenting author.

229
TH-POS03
Tubulointerstitial Nephritis with IgM-Positive Plasma Cells
Department of Nephrology, University of Fukui, Fukui, Japan; Department of Internal Medicine, Nagaoka Red Cross Hospital, Nagaoka, Japan; Department of Nephrology, Nishi-Asahi Hospital, Akita, Japan; First Department of Internal Medicine, Nara Medical University, Kashihara, Japan; Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan.

Background: Infiltration by IgG-positive plasma cells is a common finding in tubulointerstitial nephritis (TIN). Routine immunofluorescence of frozen sections is currently considered the gold standard for detection of immune deposits; however, the immunoenzyme method with formalin-fixed, paraffin-embedded sections is superior for detecting IgM- or IgG-positive cells within the renal interstitium. It was thought that CD138-positive plasma cells secreting IgG and the occurrence of TIN shows a positive correlation.

Methods: To further explore the morphological and clinical features of such cases, we performed a nationwide search for patients with biopsy-proven TIN and high serum IgM levels.

Results: In 13 of those patients, the pathologic findings were interstitial nephritis with diffusely distributed CD3-positive T lymphocytes and co-localized IgM PCs as well as infiltration in proximal tubules and collecting ducts with CD138-positive T lymphocytes. The number of infiltrating IgM PCs per high-power field from 13 patients was significantly higher than from control patients with other forms of TIN chosen as controls for staining (n=40) (p<0.001). Receiver operating characteristic (ROC) curve analysis revealed that optimal predictive cutoff number for infiltrating IgM PCs was 13 per high-power field, with an area under the ROC curve of 0.99 (p<0.0001). The sensitivity and specificity were 100% and 93.2%, respectively. In addition, levels of H+, K+-ATPase, H+, K+-ATPase and HCO3

Conclusions: We propose to designate this group of cases, which have a common histological and clinical form, as "IgM-positive plasma cell tubulointerstitial nephritis" (IgMPC-TIN).

Funding: Government Support - Non-U.S.

TH-POS04
Clinicopathologic Characteristics, Treatment, and Outcome of Tubulointerstitial Nephritis and Uveitis Syndrome in Children
Asako Hayashi, Takayuki Okamoto, Toshiyuki Takahashi, Yasuuki Sato. Hokkaido University Graduate School of Medicine, Hokkaido, Japan.

Background: Tubulointerstitial nephritis and uveitis (TINU) syndrome is a rare disease, presenting as a combination of tubulointerstitial nephritis and uveitis. A few cases previously reported good renal prognosis of this syndrome, but long-term prognosis is not known enough in children. To further investigate this syndrome, we report here the clinical features and outcome.

Results: A retrospective study of the case records of all patients diagnosed with the TINU syndrome in the Departments of Pediatrics and Medicine of the Hokkaido University Hospital (Sapporo, Japan) from February 1990 through April 2017.

Results: We report here the clinical features and outcome of 20 patients (female 12, F:M ratio 3:2), aged 9 to 14 years at diagnosis (median, 13.0) with TINU syndrome. The initial symptoms were visual impairment in sixteen patients (80%) and deterioration of health status in six patients (30%). The median estimated glomerular filtration rate (eGFR) at diagnosis was 99.8 mL/min per 1.73m² (range 59.7-117.4) and deteriorated renal function [eGFR <60 mL/min per 1.73m²] was observed in 9 patients (30%). An increase in urinary β2-microglobulin levels was noticed at the initial checkup in all patients. Topical and oral corticosteroids were prescribed to 15 patients (75%) and oral corticosteroids were prescribed to 15 patients (75%) and topical corticosteroids to 15 patients (75%). After 24 months follow-up, urinary β2-microglobulin excretion gradually declined but was slightly elevated in 11 patients (55%) at 24 months. Recurrent or exacerbating uveitis was seen in ten patients (50%). On the other hand, TIN is not recurrence.

Conclusions: The TINU syndrome should be considered in the differential diagnosis of patients presenting with renal manifestations. In addition, increase in urinary β2-microglobulin levels may be of some help for the early discovery of recognition of TINU syndrome. In children and adolescents with this syndrome, the long-term prognosis of TIN is good, but uveitis often relapse.

Funding: Government Support - Non-U.S.

TH-POS05
Clinical Advantage of Renal Artery Doppler Ultrasonography for the Assessment of Tubulo-Interstitial Nephropathy
Minoru Hatano,1 Kaori Takayangi,1 Hiroaki Harra,2 Masaaki Terao,2 Yuichiro Kawai,2 Saeko Sato,2 Takatsugu Iwashita,3 Tanuke Shimizu,2 Tomonari Ogawa,2 Hori Wataru,2 Okamoto T,1 Hajime Hasegawa,4 Saitama Medical Center, Saitama Medical University, Kawagoe, Japan; 3Department of Nephrology, Hypertension, Blood Purification, Saitama Medical Center, Saitama Medical University, Kawagoe, Japan; 4School of Medicine, Saitama Medical University, Kawagoe, Japan.

Background: At present, potential clinical parameters for the assessment of tubulo-interstitial nephropathy (TIN) are poorly available. Here, we focused on the resistive index (RI) measured by renal arterial doppler ultrasonography (RAUS), and studied its efficiency for the assessment of TIN by comparative analysis with the conventional TIN parameter, urine N-acetylglucosaminidase-to-creatinine ratio (NAG index) in patients with clinically suspected TIN.

Methods: Patients who have received RAUS under the clinical suspicion of renal artery disorders were retrospectively analyzed (n=33). Clinical diagnosis was renal artery stenosis, (n=13), diabetic nephropathy (n=4) and the others (n=16). We focused on RI measured at two different points independently, with the main trunk of the renal artery (RA) and intra-renal branch of the renal artery (IRA) corresponding to the inter-lobular artery.

Results: An analysis stratified by the median NAG index value for the estimation of TIN revealed a significant difference in the estimated glomerular filtration rate (eGFR), urine protein-to-creatinine ratio (uPCR) and RA/IRA-RI, although the correlation was not significant between the NAG index and the RI. Next, we focused the cases showing NAG index less than 20 less than 20. Because higher NAG index indicates advanced renal damage and the assessment of TIN is not required in those patients. When the patients showing higher NAG index are excluded, IRA-RI showed a significant correlation with NAG index (R=0.59, p<0.01), but RA-RI did not. A multivariate analysis for the NAG index as a response variable revealed that IRA-RI was a significant predictor variable (p=0.02, 0.02), but RA-RI did not. A ROC analysis showed that the cut-off value of IRA-RI was 0.645 (AUC 0.80, sensitivity 72%, specificity 82%).

Conclusions: Resistive index by RA-US would be a useful clinical parameter for the assessment of TIN. For this purpose, RI should be measured at the intra-renal artery, not the main trunk of the renal artery. In addition, threshold of NAG index value indicating the presence of TIN might be lower than the value corresponding the renal artery stenosis (0.8 U/mgCr).

TH-POS06
Blood Oxygen Level Dependent Imaging of CKD in Children
Fenglan Luo, Yuhong Tao. West China Second University hospital, Sichuan University, Chengdu, China.

Background: Renal chronic hypoxia plays a vital role in the development of end-stage renal disease. Blood oxygen level dependent(BOLD) imaging can assess the oxygenation of kidney. Although BOLD-MRI is used for studying chronic kidney disease(CKD) in adults, BOLD has fewer applications in children with CKD. This study aims to investigate the values of BOLD-MRI in evaluating oxygenation of kidney and renal function of CKD in children.

Methods: All of these subjects underwent study BOLD images on 1.5T MRI scanner as follows: scanning sequence FFE, FFO=200mm×22mm×7mm, slice thickness=5mm, slice number=12, TR=400ms, voxel size=3mm×3mm, flip angle=45°, echo train length=16. R2* value of cortex and medulla were obtained. The cortical and medullary R2* value were compared between the groups. The correlation of serum creatinine level(Scr) and eGFR with R2* value was also discussed. With the ROC curve, the diagnostic effectiveness of R2* value for severity of CKD evaluation.

Results: The images of 6 healthy volunteers and 21 minor/moderate CKD children (CKD stage1-3), 16 severe CKD children were evaluated. Both in the CKD groups and control group, the R* value in cortex was significantly lower than that in medulla. Cortical R2* value(11.6105±4.02012) of CKD stage1-3 was significantly higher than that of control group(10.7478±0.71737). Both cortical R2* value(12.046±3.539) and medullary R2* value(21.399±0.9089) of CKD stage 4-5 was significantly higher than those of CKD stage1-3. In patients with CKD severe cases, negative correlations were found between cortical R2* value with Scr level(=0.800,P<0.001), and also between medullary R2* value with Scr level(=0.898,P<0.001). Positive correlations were found between cortical R2* value and age(=0.420,P<0.05), and also between medullary R2* value and age(=0.420,P<0.05). With the threshold from ROC curve, the sensitivity and specificity of differentiating CKD stage1-3 from CKD stage4-5 were also analyzed.

Conclusions: BOLD-MRI is valuable in diagnosis and severity of CKD in children. Renal R2* value presents the level of oxygenation of kidneys and reflect the change of
renal function. BOLD-MRI provides a novel technique to evaluate the severity of CKD in children.

TH-PO507

The Nephropathy Studied in the African American Study of Kidney Disease (AASK) May Be An Atypical Tubulopathy

Salameh Almaan,1 Daniel J. Birmingham,1 Brad H. Rovin,1 Lee A. Hebert.1
1Ohio State University, Columbus, OH; 2University Hospital Network - The University of Toronto, Toronto, ON, Canada.

Background: It has been suggested that the nephropathy associated with patients enrolled in the AASK (AASK-N) may be a primary tubulopathy (and not a glomerulopathy or a vasculopathy related to hypertension) because it progresses at levels of proteinuria below that of progressive glomerulopathy. However, studying this in AASK-N urine samples has been hampered due to protein degradation because of the presence of acidic acinetobacter. In a recent study, this group addressed the issue by using urine samples from patients enrolled in the Chronic Renal Insufficiency Cohort (CRIC) who met criteria for AASK enrollment.

Methods: Urine samples were obtained from 43 African American CRIC patients with urine protein-to-creatinine ratios (uAPRs) of 0.2 to 5.1 and eGFR ranging from 65 to 20. Six kidney injury markers were measured in these samples by a multiplex platform (Meso Scale Discovery, MSD) that uses a capture and detection antibody pair for each analyte. For comparison, urine samples from 20 lupus nephritis (LN) patients with the same CRIC-PHRC were used.

Results: There were no differences in albumin-to-protein ratios (uAPRs) between the CRIC cohort (mean 0.59) and the LN cohort (0.54). The results of the MSD analysis are shown in the table. Notably, levels of B2M, a classic marker of proximal tubule injury/disfunction, were 8-fold higher in CRIC, while levels of cystatin C, another marker of proximal tubule dysfunction, were not different between the two cohorts. Decreased EGFR levels in the CRIC cohort reflect their lower GFRs.

Conclusions: The 8-fold increase in urine B2M levels in the CRIC cohort compared to the LN cohort in the face of similar levels of uAPR and other indicators of proximal tubular injury suggest that AASK-N is not a typical tubulopathy, but may involve unique proximal tubular damage.

Funding: NIDDK Support

TH-PO508

Successful Use of Renal Denervation (RDN) in Patients with Loin Pain Hematuria Syndrome (LPHS): The Prairie LPSH Study

Bhumai Prasad,1 Shelley Giebel,2 Michelle C. McCarron.1
1Regina Qu’Appelle Health Region, Regina, SK, Canada; 2Nephrology, Regina Qu’Appelle Health Region, Regina, SK, Canada.

Background: Loin Pain Hematuria Syndrome (LPSH) is a rare disease with a reported prevalence of 0.012%. Its characterized by painful unilateral or bilateral loin pain that suggests a renal origin but occurs in the absence of identifiable or relevant urinary tract disease. Hematuria can be either microscopic or macroscopic, and the renal abnormalities responsible for the hematuria are often unexplained. Debulking the pain refractory to conventional medications lead to multiple trips to the emergency rooms and is the main cause of morbidity. Treatment options include opiates, autotransplantation and autonephrectomy.

Methods: We conducted a single centre, single arm study. Twelve patients between the ages of 21-62 years (eleven females) with LPSH underwent RDN between July 2015 and August 2018. Patients randomized to pulse methylprednisolone 15 mg/kg/day for three days and per os steroids afterwards (group A) or per os 0.1 mg/kg/day steroids from the start (group B). The primary endpoint outcome was (eGFR) using the CKD-EPI estimated glomerular filtration rate (eGFR) during the first 3 months of follow up.

Results: The mean age of the trial participants was 59 (45-68) years and 70% were men. Among 40 participants, only one patient was excluded for a misdiagnosis of tuberculosis. Median eGFR was 61 (52-77) ml/min/1.73 m2 for group A and 57 (42-71) for group B, p=0.3. In the intent-to-treat population, the median eGFR was 63 (51-72) ml/min/1.73 m2 for group A and 63 (45-84) for group B, p=0.3. In the per-protocol population, patients randomized to pulse methylprednisolone had eGFRs that were significantly less likely to achieve the primary efficacy end point: 10 of 20 (50%) vs 16 of 20 (80%), p=0.047. eGFR were similar between groups after 1 month of treatment. No participants presented cardiac arrhythmia or conduction disorder during pulse methylprednisolone.

Conclusions: Among patients with acute STIN, pulse methylprednisolone treatment was not significantly different from oral steroids in improving renal function at three months follow-up.

Funding: Government Support - Non-U.S.

TH-PO509

Efficacy and Safety of Initial Pulse Methylprednisolone Treatment in Renal Sarcoidosis: A Randomized Trial

Jean-Jacques Bozza,1 Matthieu Mahevas,2 Eric Daugas,2 Dominique Guerot,3 Michel Delahousse,2 Tabassome Simon,4 Laurent Virgneaud,5 Evgenya Krastinova,5,6,7 Evangeline Pillibout,6 Vincent Audard,2 David Verhelst,9 Dominique Volot,10 Avicenne Hospital AP-HP, Bobigny, France; 2FOCH Hospital, Suresnes, France; 3Hopital Saint-Louis, Paris, France; 4None, PARIS, France; 5Renou University Hospital, Rouen, France; 6Assistance Publique -Hôpitaux de Paris, Paris, France; 7Tenon Hospital, AP-HP, Paris, France; 8AP-HP, UPEC UNIVERSITY, Paris, France; 9Bichat hospital, AP-HP, Paris, France; 10hospital, Valenciennes, France; 11INSERM U1153 / UPMC, Paris, France; 12Citeel Hospital, Citeel, France; 13URC-EST, AP-HP, Paris, France.

Background: Sarcoidosis tubulo-interstitial nephritis (STIN) induces severe renal insufficiency with poor outcome. Despite treatment with steroids, most patients develop chronic kidney disease. Pulse methylprednisolone treatment has been used to improve renal function but this therapeutic strategy has never been evaluated. We assessed whether initial pulse methylprednisolone is effective and safe at improving renal function compared to oral steroids at 3 months of follow-up.

Methods: In a multicenter randomized open control trial, in patients with proven acute sarcoidosis tubulo-interstitial nephritis, we randomly assigned forty patients with STIN to receive pulse methylprednisolone 15 mg/kg/day for three days and per os steroids afterwards (group A) or per os 0.1 mg/kg/day steroids from the start (group B). The primary efficacy end point was the percentage of patients having a positive response at 3 months of follow-up, defined by an improvement of more than 100% of eGFR compared to eGFR before treatment or eGFR ≥ 60 ml/min/1.73m2. Secondary endpoints included side effects of steroids.

Results: The mean age of the trial participants was 59 (45-68) years and 70% were men. Among 40 participants, only one patient was excluded for a misdiagnosis of tuberculosis. Median eGFR was 61 (52-77) ml/min/1.73 m2 for group A and 57 (42-71) for group B, p=0.3. In the intent-to-treat population, the median eGFR was 63 (51-72) ml/min/1.73 m2 for group A and 63 (45-84) for group B, p=0.3. In the per-protocol population, patients randomized to pulse methylprednisolone had eGFRs that were significantly less likely to achieve the primary efficacy end point: 10 of 20 (50%) vs 16 of 20 (80%), p=0.047. eGFR were similar between groups after 1 month of treatment. No participants presented cardiac arrhythmia or conduction disorder during pulse methylprednisolone.

Conclusions: Among patients with acute STIN, pulse methylprednisolone treatment was not significantly different from oral steroids in improving renal function at three months follow-up.

Funding: Government Support - Non-U.S.
Effect of Addition of Silybin and N-Acetyllysine to Renin-Angiotensin System Inhibitors on Albuminuria in Type 2 Diabetic Patients with Overt Nephropathy: A Randomized Controlled Trial

**Background:** A large proportion of patients with type 2 diabetes mellitus have diabetic nephropathy. Despite current therapies including hypertension control and renin-angiotensin system inhibitors, diabetic nephropathy progresses to end-stage renal disease in many of these patients. The aim of this study was to evaluate the efficacy of silybin and N-acetylysine (NAC), natural supplements with antioxidant and anti-inflammatory properties, in preventing the progression of diabetic nephropathy.

**Methods:** After institutional IRB and VA R&D approval, we conducted a randomized, double-blind, placebo-controlled, 5-arm parallel trial where subjects with diabetic nephropathy with albuminuria-to-creatinine ratio (ACR) of >150 mg/g and eGFR of 15-60 ml/min on the background of angiotensin inhibition after 1 month run-in period received either A) double placebo BID (n=16); or B) silybin placebo + NAC 600 mg BID (n=12); or C) silybin 480 mg + NAC placebo BID (n=16); or D) silybin 480 mg + NAC 600 mg BID (n=15) for 3 months. Primary outcome was absolute change in urine ACR from baseline to the end of the treatment phase.

**Results:** Overall, the study population was 62.9±7.48 years old, 89.8% male, 65.9% Hispanic, 47% non-Hispanic white and 7% non-Hispanic blacks, had BMI of 35.0±28.54 kg/m², eGFR of 36.4±13.3 ml/min, and ACR of 702.8±608.5 mg/g at baseline. The baseline characteristics were similar across the treatment arms except for systolic and diastolic BP and fasting glucose. There was no difference in change in Urine ACR in different arms (AUACUR in A=97.9±42.9, B=96.6±42.24, C=155.7±23.72 mg/g compared to placebo (AUACUR in A=50.5±29.1, 2 Anoua p=NS). Moreover, the change in eGFR was not different in 4 treatment arms compared to placebo arm. Small sample size and short duration of the treatment phase were the major limitation of the study.

**Conclusions:** 3-month intervention with dietary supplements silybin and NAC did not reduce urinary excretion of albumin in diabetic nephropathy patients in our study cohort.

**Funding:** Other NIH Support - NIH-NCCAM AT004490, Clinical Revenue Support

---

**P-0512**

Multiple Determinants of Early Renal Decline in Type 2 Diabetes

**Background:** There has been an effort to identify the mechanisms for progressive renal decline in diabetic patients with chronic kidney disease (late progressive renal decline). Much less is known about the mechanisms, determinants and markers of early progressive renal decline. We aimed to evaluate several markers as determinants of early progressive renal decline. Much less is known about the mechanisms, determinants and markers of early progressive renal decline.

**Methods:** At enrollment, all patients had preserved GFR (median of 98 mL/min (1st and 3rd quartile; 85 -110), 58% had normoalbuminuria (urinary ACR median of 4 mg/g/mg). Early renal decline (defined as GFR loss from baseline of 30% per <5 years) occurred in 38 (6%) normal filter proteinuria in the first 20%.[1] With these data, we aimed to develop a multi-marker index to improve the identification of patients with incipient renal decline.

**Methods:** The study was designed as a phase 3 study, we examine effects of FC on P in pts by different baseline (BL) P levels and stages of CKD.

**Results:** 233 pts with NDD-CKD and A renal function randomization to receive either FC or placebo stratification to receive either FC or placebo were included in this analysis. As described, the effects on P were consistent across Baseline (BL) P levels. P levels remained stable in the lowest BL P level group even with increased FC dose. P remained stable in the lowest BL P group even with increased FC dose. P remained stable in the lowest BL P group even with increased FC dose.

**Conclusions:** In NDD-CKD pts with IDA, the effect of FC on P reduction is strong independent predictor of change in P (p<0.0001) after adjusting for treatment, BL eGFR and BL albumin.

**Funding:** NIDDK Support, Commercial Support - Lilly Inc., Pfizer Inc., Private Foundation Support

---

**P-0514**

Ferric Citrate Lowered Serum Phosphate Only When Elevated in Patients with Nondialysis-Dependent (NDD) CKD and Iron Deficiency Anemia (IDA)

**Background:** Ferric citrate (FC), an oral iron-based phosphate (P) binder approved for control of serum P in patients (pts) with CKD on dialysis, has also shown improvement in hemoglobin (Hb) and iron parameters in pts with NDD-CKD with IDA. Here, in a post-hoc analysis of a phase 3 study, we examined effects of FC on serum P in pts by different baseline (BL) P levels and stages of CKD.

**Methods:** Two identical, double-blind trials were conducted in 429 subjects with stage 3-4 CKD, SHPT (iPTH >85 pg/mL) and vitamin D insufficiency (25D of 10-29 ng/mL). Subjects were randomized to receive FC or placebo for 12 weeks. Annualized change in serum P was assessed in a subset of these subjects. Effects on serum P were examined by BL strata of P, stage of CKD (per eGFR), and FG23 (grouped by BL quartile).

**Results:** Decreases in P with FC treatment were greater in pts with higher BL P levels. P remained stable in pts in the lowest BL P group even with increased FC dose. P decrease was greatest in pts with lower BL eGFR (which correlated to higher BL P) [Figure]. Similar results were seen when pts were stratified by BL FG23 [Table]. At 16 wks, the FC dose was similar across sub-groups, suggesting BL P did not affect dosing for treatment of IDA. Multivariable linear regression analysis confirmed BL P as a strong independent predictor of change in P in (p<0.0001) after adjusting for treatment, BL eGFR and BL albumin.

**Conclusions:** In NDD-CKD pts with IDA, the effect of FC on P reduction is dependent on the BL P, with the greatest reduction in pts with the highest serum P. These results support the use of FG23 in NDD-CKD pts with IDA regardless of BL P.

**Funding:** Commercial Support - Keryx Pharmaceuticals

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

**Underline represents presenting author.**
TH-PO515

**PTH Suppression with Extended-Release Calcifediol (ERC) Is Directly Proportional to Severity of Secondary Hyperparathyroidism**

**TH-PO517**

**Diabetes**

**Effect of Sodium Bicarbonate Treatment on a Novel Marker of PTH Suppression with Extended-Release Calcifediol (ERC) Is Directly Proportional to Severity of Secondary Hyperparathyroidism**

**Background:** Overexpression of parathyroid hormone (PTH) is a significant concern in patients with stage 3-4 CKD treated with calcitriol or its 1α-hydroxylated analogs since iatrogenic induction of a low PTH concentration is an independent strong risk factor for adynamic bone disease, fractures and cardiovascular death. Randomized controlled trials have shown that PTH gradually but effectively reduces PTH without oversuppression. These data have been further examined post-hoc to determine the impact of baseline PTH levels on end-of-treatment (EOT) values.

**Methods:** Two identical, randomized, double-blind, placebo-controlled trials were conducted in 429 adult subjects with stage 3-4 CKD, SHPT (>85 pg/ml) and vitamin D insufficiency. Subjects were randomized 1:1 to receive ERC (30 or 60 mcg/day) or placebo (PL) for 26 weeks. Per-protocol data for plasma intact (i) PTH, serum calcium (Ca) and phosphorus (P), serum total 1,25-dihydroxyvitamin D (1,25D), and serum total 25-hydroxyvitamin D (25D) were pooled and analyzed by baseline plasma PTH tertile. Mean baseline PTH in each tertile was 98, 130 and 203 pg/mL for ERC and 102, 133, and 201 for PL.

**Results:** The table shows the mean changes from baseline to EOT in iPTH, Ca, P, 1,25D and 25D with ERC (n=78 in each tertile) and PL (n=40-41 in each tertile). Significant differences from the corresponding placebo groups are as marked. ERC and PL had similar, minor effects on mean serum Ca and P. ERC increased serum 25D and 1,25D significantly and to comparable levels irrespective of baseline iPTH tertile. However, decreases in mean iPTH with ERC differed between tertiles and were directly proportional to baseline levels, with EOT suppression increasing from 19 to 26% of baseline from T1 to T3. Oversuppression was not observed.

**Conclusions:** ERC produced mean absolute iPTH reductions that were proportional to baseline iPTH levels, consistent with a mechanism of action involving physiological regulation of iPTH modulated by SHPT severity.

**Funding:** Commercial Support - OPKO Health

---

**TH-PO516**

**Effect of Sodium Bicarbonate Treatment on a Novel Marker of Serum Calcification Propensity**

**Jessica B. Kendrick,1 Emily Andrews,4 Andreas Pasch,2 Zhiying You,1 Michel Chonchol,3 1University of Denver, Aurora, CO; 2University Hospital Bern, Bern, Switzerland; 3University of Colorado, Aurora; 4University of Colorado Denver and Denver Health Medical Center, Denver, CO.

**Background:** Acid reduction in patients with chronic kidney disease (CKD) results in increased production of inflammatory markers and activation of the renin-angiotensin-aldosterone system, all of which can induce vascular calcification. We examined the effect of treatment of metabolic acidosis with oral sodium bicarbonate therapy on a novel test that measures the overall calcification propensity of serum, T50, in patients with CKD stage 3-4.

**Methods:** We performed a prospective, randomized, open-label, 14-week crossover study of 20 patients with CKD stage 3-4 and metabolic acidosis (serum bicarbonate level of a 16 and <22 mEq/L). Subjects were randomly assigned to start with either treatment or control. Each period was 6 weeks in duration with a 2-week washout period in between. Patients were treated with oral sodium bicarbonate tablets for goal bicarbonate of a 22 mEq/L. Serum T50 was measured at the beginning and end of each treatment period. T50 measures the transformation time of amorphous calcium phosphate-containing primary calciprotein particles (CPP) to crystalline hydroxyapatite-containing secondary CPP. A higher T50 represents lower calcification propensity. Mixed effect models were used to examine changes in T50 during treatment and in response to acid-base variations.

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

---

**TH-PO518**

**Randomized, Placebo-Controlled Trial of Rifaximin Therapy for Lowering Gut-Derived Cardiovascular Toxins in CKD**

**Cassandra C. Kimber,1 Cassandra R. Johnson,1 Alexander J. Prokopienko,2 Kerri A. McGreai,3 Thomas D. Nolin,2 Jason R. Stubbs,1 1University of Kansas, Kansas City, KS; 2University of Kansas Medical Center, FAIRWAY, KS; 3University of Pittsburgh, Pittsburgh, PA.

**Background:** Accumulating evidence suggests that byproducts of gut bacteria contribute to cardiovascular morbidity in CKD patients. One example is trimethylamine-N-oxide (TMAO), a pro-atherosclerotic compound generated from metabolites produced by intestinal bacteria. Rifaximin is a minimally absorbed, oral antibiotic that targets bacterial toxins that contribute to disease comorbidities in other patient populations. Accumulating evidence suggests that byproducts of gut bacteria contribute to cardiovascular morbidity in CKD patients. One example is trimethylamine-N-oxide (TMAO), a pro-atherosclerotic compound generated from metabolites produced by intestinal bacteria. Rifaximin is a minimally absorbed, oral antibiotic that targets bacterial toxins that contribute to disease comorbidities in other patient populations. We conducted a randomized, double-blind, placebo-controlled trial to determine the impact of a 10-day course of oral rifaximin 550 mg BID vs. placebo on serum TMAO and fecal bacterial composition in patients with stage III-V CKD (n=38). Fasting serum, urine and stool samples were collected at baseline and immediately post-treatment. Urinary output was measured to prevent confounding by changes in urinary dilution. The data did not support the hypothesis that acid reduction with F+V better prevents progression of CKD to CKD 4 transition than NaHCO3.

**Conclusions:** Adjunctive dietary acid reduction with F+V but not NaHCO3, yielded a significantly greater proportion of CKD 3 patients who did not progress to CKD 4, possibly due to a greater proportion of F+V achieving blood pressure goal. The data support that dietary acid reduction with F+V better prevents the CKD 3 to CKD 4 transition than NaHCO3.
to 1.9% (p=0.57), respectively, in the placebo group. Despite an apparent reduction in these bacterial populations, we observed only a minor, non-significant reduction in serum TMAO with rifaximin; mean TMAO changed from 18.8 ± 18.7 µM at baseline to 14.8 ± 10.2 µM post-treatment (p=0.31) in the rifaximin group vs. a mean TMAO change from 15.6 ± 11.6 at baseline to 16.1 ± 13.4 µM post-treatment (p=0.86) in the placebo group. Although the targeted secondary outcomes is currently ongoing.

Conclusions: Short-term rifaximin therapy effectively suppresses bacteria that generate TMAO precursors; however, these changes in gut flora do not translate to significantly lower serum TMAO in CKD patients.

Funding: Other NIH Support - NIH R21 DK108093

TH-PO519

Acute and Chronic Effects of Different Exercise Modalities on Hepcidin Levels in Non-Dialysis CKD Soteris Xenophon,1 Douglas W. Gould,1 Thomas J. Wilkinson,1 Emma L. Watson,1 Joao L. Viana,1 Alice C. Smith,1 University of Leicester, Leicester, United Kingdom; University of Maia, Maia, Portugal.

Background: Functional iron deficiency (FID) is common in chronic kidney disease (CKD). Iron is essential for many cellular processes including energy generation. FID has negative effects on skeletal and cardiac muscle as well as haemoglobin (Hb) production, and contributes to anaemia, functional deficits, fatigue and cardiovascular (CV) risk. Hepcidin, which is upregulated by inflammatory cytokines and inhibits release of iron stores, is implicated in CKD FID due to chronic inflammation and reduced renal clearance. We have previously shown that regular exercise exerts anti-inflammatory effects in CKD. In this study, we investigated the effects of different exercise modalities on hepcidin levels in non-dialysis CKD.

Methods: 36 CKD patients (15 male, mean±SD age 61±12 years, eGFR 26.8±11.73mL/min/1.73m², Hb 119±15 g/l) were randomised to 12 weeks thrice weekly aerobic exercise (AE, n=18) or combination aerobic and resistance exercise (CE, n=18). Plasma was collected to assess the chronic effects of exercise (resting samples at baseline and end of study) and the acute effects (exercise 24h following the first and last exercise sessions). Hepcidin was measured by ELISA.

Results: Following 12 weeks training, resting hepcidin decreased by 21±35% (p=0.037) in the CE group, but was unchanged in the AE group (1±50%, p=0.976). Acutely, 24h after the first exercise session hepcidin decreased by 34±27% (p=0.006) in the CE group and by 18±24% (p=0.101) in the AE group. 24h after the final exercise session hepcidin decreased by 3±42% (p=0.438) in the CE group and by 0±27% (p=0.651) in the AE group, compared to resting levels.

Conclusions: CE training reduced plasma hepcidin, but there was no change with AE alone. An acute reduction in hepcidin was observed 24h after the first CE session, but not after the first AE session or in either group after the last session, indicating an adaptation effect of regular CE. Hepatic hepcidin release is stimulated by IL-6, which peaks after unaccustomed exertion but is reduced by regular exercise. Therefore, our results likely mirror the effects of exercise on circulating inflammatory cytokines. CE may ameliorate FID in CKD, thereby helping to reduce CV and anaemia risk, and improve muscle function and fatigue.

Funding: Private Foundation Support

TH-PO520

Supervised Exercise Intervention and Overall Physical Activity in Individuals with Moderate to Severe CKD Jacob M. Taylor,1 Asep Alsoaui,2 Cassianne Robinson-Cohen,2 Charles D. Ellis,1 Sara A. Heedle,1 Kristina R. Turtle,1 Elizabeth E. Evans,2 Michael J. Germain,3 Chutatup Limkunakul,4 Aihua Bian,5 Thomas G. Stewart,6 Jonathan Himmelfarb,7 Talat Alp Ikizler.1 1Medicine, Vanderbilt University Medical Center, Nashville, TN; 2University of Washington, Seattle, WA; 3Springfield College, Wilbraham, MA; 4Renal and Transplant Assoc of New England, Hampden, MA; 5Srinakharinwitt University, Nonthaburi, Thailand; 6Biostatistics, Vanderbilt University Medical Center, Nashville, TN.

Background: Patients are often instructed to engage in multiple weekly sessions of exercise to increase physical activity; however, whether this increases overall physical activity in individuals with chronic kidney disease (CKD) remains unknown.

Methods: We performed a post-hoc analysis of a pilot randomized 4-arm trial examining the effects of diet and exercise (dietary restriction of 10%-15% reduction in caloric intake, exercise three times/week, combined diet and exercise and control) on hepcidin levels in non-dialysis CKD. A total of 122 participants were consented, 111 were randomized, and 108 completed baseline VO2 peak, peak testing. Body composition measures were measured via dual energy x-ray absorptiometry, including total mass, fat mass, lean mass, and fat free mass percentage (including android and gynoid fat percentage), body mass index, weight, and waist to hip ratio. In addition, body cell mass and phase angle were measured by bioelectrical impedance analysis. The primary outcome was to determine whether body composition measurements were correlated with VO2 peak at baseline. Correlations were adjusted for age, gender, diabetes status, and site of study visits in the model.

Results: Most participants were male (57%), white (68%), and had 24% diabetes. Median (IQR) for age was 57 (49-63) years, with baseline VO2 peak 19.6 (16.2-22.6) mL/kg/min. At baseline, body fat percentage (rs=0.38), android (rs=0.336) and gynoid fat percentage (rs=-0.313), body mass index (rs=-0.372), weight (rs=-0.282), and phase angle (rs=-0.278) were all significantly correlated with VO2 peak after adjustment (p<0.03 for each individual variable). Holding other covariates at the mean, the difference in VO2 peak between the 25th and 75th percentiles of lean mass was 0.35 (0.5±2) mL/kg/min, whereas the same difference comparing the 25th and 75th percentiles of fat mass was -3.6 (-5.5,-1.3) mL/kg/min.

Conclusions: Our findings indicated that body fat composition and phase angle, rather than lean mass, show the strongest correlations to VO2 peak. An intervention aimed at reducing body fat or improving phase angle may prove effective at improving VO2 peak in future research.

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

TH-PO522

Food Insecurity and Longitudinal Risk of Rapid Kidney Function Decline Deirdra C. Crews,2 Caroline Kwon,3 Dingfen Han,3 Yang Liu,3 Tanushree Banerjee,1 Michelle K. Evans,4 Alan B. Zonderman,5 Neil R. Powe,2 Marie Kupecz.3 1Inturum Research Program, NIH, NH, Baltimore, MD; 2Johns Hopkins University, Baltimore, MD; 3National Institute of Health/National Institute on Aging, Baltimore, MD; 4University of Delaware, Newark, DE; 5None, Washington, DC; 6Priscilla Chan & Mark Zuckerberg San Francisco General Hospital & University of California San Francisco, CA; 7University of CA, San Francisco, San Francisco, CA; 8Johns Hopkins University, Baltimore, MD.

Background: Food insecurity, defined as limited or uncertain ability to acquire food, has been associated with prevalent CKD and CKD progression to ESRD. Whether food insecurity, defined as associated with loss of kidney function among persons with preserved kidney function is not known.

Methods: We conducted a longitudinal analysis of the Healthy Aging in Neighborhoods of Diversity Across the Life Span (HANDLS) Study (Baltimore MD) to determine whether food insecurity was associated with rapid kidney function decline (KFD). Participants with eGFR>50 mL/min per 1.73m² were included (n=1471). Food insecurity was defined as an affirmative response to, ‘In the last 12 months, did you or your household ever cut the size of your meals or skip meals because there wasn’t enough money for food?’ KFD was defined over an average of 5-years' follow-up as: follow-up eGFR decreased by more than 3% per yr from baseline; or full follow-up eGFR decreased by more than 75% compliance at month four).

Results: At baseline, 24.8% of participants were food insecure. These persons were younger, more likely to be female, African American, living in poverty, with fewer yrs of education, uninsured and current smokers than were food secure persons (p<0.05 for all). Food insecure persons had lower Healthy Eating Index (HEI) 2010 scores and were more likely to be obese, but equally as likely to have diabetes and hypertension as food secure

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
persons. Overall, 13.3% had >5% per yr eGFR decline, while 4.2% had ≥25% eGFR decline over full follow-up. Food insecurity was not associated with >5% per yr eGFR decline, but was associated with ≥25% eGFR decline (Table). Clinical factors explained little of this association. Among 1,164 participants with HEI data, the magnitude of the association of food insecurity with ≥25% eGFR decline was similar, though not statistically significant (1.87, 95% CI 0.9, 3.9).

Conclusions: For persons free of CKD, food insecurity may be a risk factor for rapid loss of kidney function over time.

Funding: NIDDK Support, Other NIH Support - National Institute on Aging, Private Foundation Support

Association of Food Insecurity (vs. Security) and Rapid Kidney Function Decline

<table>
<thead>
<tr>
<th>Model</th>
<th>&gt;5% eGFR decline</th>
<th>≥25% eGFR decline over full follow up</th>
<th>Odds Ratio (95% CI)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Unadjusted</td>
<td>1.18 (0.87, 1.62)</td>
<td>1.86 (1.10, 3.12)</td>
<td>1.84 (1.1, 3.09)</td>
<td>1.86 (1.10, 3.09)</td>
</tr>
<tr>
<td>2-Adjusted for age, race, sex, poverty status and baseline eGFR</td>
<td>1.15 (0.82, 1.65)</td>
<td>1.86 (1.10, 3.09)</td>
<td>1.86 (1.10, 3.09)</td>
<td></td>
</tr>
<tr>
<td>3-Adjusted for age, race, sex, poverty status, baseline eGFR, diabetes, hypertension and obesity</td>
<td>1.05 (0.66, 1.69)</td>
<td>1.86 (1.10, 3.09)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TH-PO523
Mortality and Co-Morbidities in South Asian Individuals with CKD Compared to White Ethnities Rupert Major,1 Gang Xu,2 Laura Gray,3 Nigel J. Brunskill,3 1University Hospitals of Leicester, Leicester, United Kingdom; 2Department of Health Sciences, University of Leicester, Leicester, United Kingdom; 3Department of Infection, Immunity and Inflammation, University of Leicester, Leicester, United Kingdom. Group/Team: LCC-CKD Cohort.

Background: The epidemiology of CKD in South Asian (SA) populations in high-income countries is poorly studied. The Leicester City and County Chronic Kidney Disease (LCC-CKD) cohort has been developed to study this population in comparison to other ethnic groups. To our knowledge no study has compared all-cause mortality in SA subpopulations with CKD compared to other ethnicities.

Methods: Data was collected for LCC-CKD from primary care electronic records. The cohort has 5 years of completed follow-up from 2011 to 2016. Comparison was made between individuals of SA and White ethnicities. The groups’ baseline characteristics were compared using t-tests and Chi². Unadjusted and adjusted Cox proportional hazards models were used for comparison of all-cause mortality.

Results: 3,887 of 6,133 (63.4%) individuals in the LCC-CKD cohort have an ethnicity code of whom 268 are of SA ethnicity (6.9%). Gender proportions were similar, but mean age and EPI eGFR were lower and ACR higher for SA compared to White ethnicities. diabetes mellitus was more common in SA but clinical cardiovascular disease was less common (see table). Unadjusted all-cause survival analysis suggested all-causes mortality was 39% lower (HR 0.61, 95% CI 0.46-0.80, p<0.0001) in SA. However, in an adjusted model using the variables listed in the table, SA had similar risk to the White population (HR 0.97, 95% CI 0.71-1.33, p=0.85).

Conclusions: Compared to the White population, SA with CKD are younger with more advanced CKD and more likely to have diabetes. Adjusted all-cause mortality was similar between ethnicity groups. These factors may explain why SA individuals are more advanced CKD and more likely to have diabetes. Adjusted all-cause mortality was 39% lower (p<0.02) and BP of ≤130/80 was met by 22% and 28% (p=0.2) respectively; the BP responses were not statistically different from controls.

Conclusions: In this study of collaborative care in primary and nephrology practices use of an IT-embedded program improved implementation of CKD EGIBs including use of RAAS and statins. This model can lead to better care, and has the potential to improve outcomes, in underserved populations with CKD.

Funding: NIDDK Support

TH-PO525
Primary Care Providers' Dietary Counseling of Their Low Income African American (AA) Patients with CKD Deidra C. Crews,1 Debra L. Roter,2 Raquel C. Greer,3 Stella Park,4 Pattie Ehrhart-Majors,5 Jessica Ameling,6 Lapricia L. Boyer,7 Michael C. Albert,7 Lisa A. Cooper,7 L. Ebony Boulware,1 Duke University School of Medicine, Durham, NC; 2Johns Hopkins Health System, Baltimore, MD; 3Johns Hopkins Medical Institutions, Baltimore, MD; 4Johns Hopkins School of Medicine, Baltimore, MD; 5Johns Hopkins University School of Medicine, Baltimore, MD; 6University of Michigan, Ann Arbor, MI.

Background: Diet influences outcomes in CKD, but little is known about how patients with CKD are counseled about their diet. We examined primary care providers’ (PCPs) use of the 5As (Assess, Advise, Agree, Assist, and Arrange) counseling strategy in a survey with AA patients with CKD. We explored their use of a 6th ‘A’ – Awareness’, reflecting recognition and discussion of the home and community food environment within which the patient resides—especially relevant for patients living with food insecurity.

Methods: In a trial of urban AAs with uncontrolled hypertension, we audio-recorded patient visits with their PCPs at the first visit after enrollment. Among 44 patients with CKD [eGFR<60 (33%) and/or ACR ≥30 mg/g (88%)], we assessed presence of diet discussions and use of the 6A’s in the discussions.Using linear regression, we examined predictors of number of A’s used.

Results: Mean age was 59.5 years, 37% were male and 31% had annual income <$10K; 63% were obese, 70% had diabetes and mean systolic BP was 147 mmHg. A majority (67%) were either at risk for or with food insecurity (inability to afford nutritionally adequate foods). Most (88%) visits included dietary counseling, most commonly in the context of Assess (68%) and Advise (61%); Agree (14%), Assist (14%) and Arrange (9%) were infrequent. Only one visit included reference to Awareness. Median number of A’s was 2 (IQR 1-2.5). No visit included all As. Representative quotes are shown in Table. Visits attended by patients with CKD <$10K explored their use of a 6th ‘A’ – Awareness’, reflecting recognition and discussion of the home and community food environment within which the patient resides—especially relevant for patients living with food insecurity.

Conclusions: Among urban AAs with CKD, dietary counseling by their PCP was infrequent and sometimes brief. Additional training and resources could improve this aspect of CKD care.
TH-PO526

Sex Differences in Progression and Resource Utilization in CKD Progress: Poster/Thursday

Pradeep Rocco,1 Alan Kuczmarski,2 Alan C. Evans,3 Kabir Jalal,2 Rocco C. Venuto,2,3
1Intelligent Care Management, East Amherst, NY; 2University at Buffalo, Hamburg, NY; 3Medicine, University at Buffalo, Buffalo, NY.

Background: Prevalence of CKD in early stages is higher among females than males, in contrast more males develop ESRD. Resource utilization between sexes is not well studied. We hypothesized that resource utilization is greater among males when compared to females.

Methods: Data from a large third party payer, with an enrollment of 1.4 million, from 2007-14. CKD was defined as GFR less than 60 ml/min/1.73 BSA for more than three months. Data analyzed included demographics, comorbid conditions (CAD, CHF, PVD, COPD, depression, cancer, diabetes, and hypertension), hospitalization and cost of care. Univariate and multivariate analyses of the predictive variables were undertaken. A squared test was used to compare the proportions of clinical variables among the sexes.

Results: 33,328 CKD cases were identified. There were 18,146 females, 13,257 males, 1,925 sex non specified. The proportion of CKD was higher in females compared to males, 54% vs 40%, 6% unknown). CKD stages 3, 4 and 5 were found in respectively 51%, 54%, and 50% compared to 47%, 45%, and 48% in males. Female CKD patients had higher prevalence of comorbidities. Annual hospitalization rates were 2.26 for females and 2.35 for males. Cost/patient-year was higher in males $12,000 vs $10,426, which was statistically significant. Prognosis to renal replacement therapy revealed a shift to a male dominance (57% vs 43%). More males received renal transplantation (56% vs 42%)

Conclusions: The total per patient cost was higher for males in CKD 3-5. Males more often progressed to ESRD. The results of predictive modeling will be included.

Funding: Private Foundation.

TH-PO527

Health Literacy and Blood Pressure Control in Individuals with CKD

Rekha Kampanbhati,1 Marie Kuczmarski,2 Mara McAdams-DeMarco,1 Dingfen Han,2 Alan B. Zonderman,3 Michele K. Evans,4 Deidra C. Crews,5 Intramural Research Program, NIA, NIH, Baltimore, MD; 2Johns Hopkins University School of Medicine, Baltimore, MD; 3National Institutes of Health/National Institute on Aging, Baltimore, MD; 4University of Delaware, Newark, DE; 5Johns Hopkins University School of Medicine, Baltimore, MD.

Background: Low health literacy is associated with poor clinical outcomes, including worse blood pressure (BP) control. The relation between health literacy and BP control among those with CKD is unknown. We examined this relation among participants in the Baltimore-based Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study.

Methods: Cross-sectional analyses were conducted of 276 HANDLS participants with CKD (eGFR <60 ml/min/1.73m² and/or urine albumin/creatinine ratio (ACR) of ≥30 mg/g). Health literacy was defined by a Rapid Estimate of Adult Literacy in Medicine (REALM) score of >60 (lower) versus ≤60 (high). Multivariable logistic regression was used to assess the association of health literacy with BP control (systolic BP ≥140 mm Hg and diastolic BP ≥90 mm Hg) and linear regression was used to assess health literacy and systolic BP level among persons with self-reported hypertension. Results: Mean age was 56 years, 74% females, 13.4% (86/648) had lower health literacy. Those with lower health literacy were more likely to be female (54.5%), African American (81.3%), and living in poverty (56.0%) than those with high health literacy (<0.005 for all). Both literacy groups had similar levels of education, smoking status, eGFR, and self-reported hypertension and diabetes. A total of 105 (33.5%) had uncontrolled BP. Results of the multivariable regression models are found in the table.

Conclusions: Lower health literacy is associated with uncontrolled BP among persons with CKD. Addressing health literacy to improve risk factor control among CKD patients is worthy of further investigation.

Funding: Other NIH Support - Grant Numbers T32 DK007732 and K23 DK097184

Association of Lower Health Literacy (versus High Health Literacy) and BP Control

<table>
<thead>
<tr>
<th>Model</th>
<th>Oral BP control (OR 95% CI)</th>
<th>BP control (OR 95% CI)</th>
<th>ACR category* (mg/gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age only</td>
<td>Race/ethnicity, sex, median BP, education</td>
<td>&lt;30 (a) &lt;30-39 (b) &gt;30 (c)</td>
</tr>
<tr>
<td>2</td>
<td>Age, sex, severity status, education</td>
<td>Race/ethnicity, income</td>
<td>&lt;30 (a) &lt;30-39 (b) &gt;30 (c)</td>
</tr>
<tr>
<td>3</td>
<td>Age, sex, diabetes and smoking states</td>
<td>Race/ethnicity, income</td>
<td>&lt;30 (a) &lt;30-39 (b) &gt;30 (c)</td>
</tr>
<tr>
<td>4</td>
<td>Model + adjustment for ACR and ACR category*</td>
<td></td>
<td>&lt;30 (a) &lt;30-39 (b) &gt;30 (c)</td>
</tr>
</tbody>
</table>

*ACR categories (mg/gm): <30, a; 30-39, b; >30, c

TH-PO528

Sociodemographic Trends in CKD Prevalence in the US Private Vart:

Neil R. Powe,1 Charles E. McCulloch,2 Rajiv Saran,3 Brenda W. Gillespie,2 Ruben Sagarra,4 Sundar Shrestha,5 Deidra C. Crews5 Centers for Disease Control and Prevention, Hyattsville, AL; 1Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; 2University of California San Francisco, San Francisco, CA; 3Johns Hopkins University School of Medicine, Baltimore, MD; 4Priscilla Chan and Mark Zuckerberg San Francisco General Hospital & University of California SF, San Francisco, CA; 3University of Michigan, Ann Arbor, MI. Group/Team: CDC CKD Surveillance Team.

Background: Overall prevalence of CKD in the U.S. has stabilized in recent years, however, whether this is true across sociodemographic groups is unknown. We examined trends in CKD prevalence, by race/ethnicity, income (low, middle, high), sex, and education and using data from the population-based, cross-sectional National Health and Nutrition Examination Surveys (NHANES).

Methods: Participants >20 years with available creatinine were included. CKD prevalence was defined as eGFR <60 ml/min/1.73 m² (CKD-EPI). NHANES data included for every 2 years from 2009-2014 (n range 4,869 to 5,662 per period). Unadjusted CKD prevalence was calculated for each sociodemographic group in each period. Interactions were tested between each sociodemographic group and survey period to assess trends. Adjusted, age, sex, race/ethnicity, and education were examined relative risks were obtained comparing most vs. least disadvantaged category in each sociodemographic group for all periods 2009-2014.

Results: Adjusted CKD prevalence was highest in the most recent time period (2013-2014) for non-Hispanic whites (8.0%), Mexican-Americans (5.8%), poor (10.1%), high income (7.5%), 9-11 grade (8.4%) and some college/equivalent – educated persons (8.6%), as compared to earlier time periods for each specific group. Adjusted CKD prevalence among persons with <9th grade education fell to 7.9% in 2013-2014 (from 9.2% in 2011-2012). A statistically significant trend was only present for income (P for 6 year time trend of CKD prevalence was 0.2 for race, 0.03 for income and 0.3 for education). Adjusted relative risks for CKD prevalence are presented in the Table.

Conclusions: In recent years, CKD prevalence has increased in some sociodemographic groups, with differences ranging in others.

Funding: NIDDK Support, Other U.S. Government Support

Adjusted Relative Risk of CKD (95% CI) by Sociodemographic Group and Year

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic White vs. Non-Hispanic White</td>
<td>1.0 (0.8-1.1)</td>
<td>1.0 (0.8-1.1)</td>
<td>1.0 (0.8-1.1)</td>
</tr>
<tr>
<td>Mexican-American vs. Non-Hispanic White</td>
<td>1.0 (0.8-1.1)</td>
<td>1.0 (0.8-1.1)</td>
<td>1.0 (0.8-1.1)</td>
</tr>
<tr>
<td>Poor vs. High income</td>
<td>1.0 (0.8-1.1)</td>
<td>1.0 (0.8-1.1)</td>
<td>1.0 (0.8-1.1)</td>
</tr>
<tr>
<td>&lt;9 grade vs. collegiate education</td>
<td>1.0 (0.8-1.1)</td>
<td>1.0 (0.8-1.1)</td>
<td>1.0 (0.8-1.1)</td>
</tr>
</tbody>
</table>

TH-PO529

Racial/Ethnic Differences in CKD Prevalence and Its Risk Factors in Hawaii Connie Rheg,1 Victoria Page,2 Glen Hayashida,1 Merle R. Kataoka-Yahiro,1 James Davis,1 Linda L. Wong,1 Krupa Gandhi,3 Amy S. You,2 Kamary Kalantar-Zadeh,2 National Kidney Foundation of Hawaii, Honolulu, HI; 1University of California Irvine, Huntington Beach, CA; 2University of Hawaii, Honolulu, HI.

Background: While traditional risk factors for chronic kidney disease (CKD) are highly predictive in Hawaii, there is limited data on risk of early CKD among the racially/ethnically diverse population of this state. To address this knowledge gap, the National Kidney Foundation of Hawaii developed the Kidney Early Detection Screening (KEDS) Program to promote early CKD screening among its residents.

Methods: Among participants of the KEDS Waves 1 (2006-9) screening events, we examined the association between race/ethnicity andmarkers of early CKD, defined as 1) microalbuminuria (albumin-creatinine ratio ≥30mg/g) and 2) self-reported CKD using case-mix logistic regression models (adjusted for age, gender, diabetes, hypertension, body mass index, hyperlipidemia, and smoking status). Recipients of the program were predominantly non-Hispanic white. Results: Among 1254 participants, the most predominant racial/ethnic groups were Caucasians (22%), multi-race (19%), Japanese (19%), Filipino (16%), Hawaiian/Pacific Islander (8%), and Chinese (5%) background. Compared to Caucasian

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

236
participants, those of native Hawaiian/Pacific Islanders race/ethnicity had a higher likelihood of self-reported CKD (adjusted OR 3.45 [1.76-6.77]). Native Hawaiians/Pacific Islanders and Chinese participants also had a higher likelihood of microalbuminuria: (aOR 1.86 [1.07-3.25]) and obesity (aOR 4.01 [2.42-6.67]).

Conclusions: These data suggest Hawaiian/Pacific Islanders have a higher risk of CKD markers compared to other racial/ethnic subgroups in the KEDS Program. Further studies are needed to determine the effectiveness of CKD interventions in this population.

TH-PO530
Multimorbidity and Race/Ethnicity in CKD
Carl P. Walther, Jingbo Niu, Jingyin Yan, Wolfgang C. Winkelmann, Sankar D. Navaneethan. Baylor College of Medicine, Houston, TX.

Background: Multimorbidity is common in CKD. It increases treatment burden and complexity, can result in conflicting therapies, and is associated with worse outcomes. This may be especially important in socioeconomically disadvantaged populations. We examined the demographics of multimorbidity in a diverse, disadvantaged, non-dialysis CKD cohort.

Methods: We identified adults with eGFR <60 ml/min/1.73 m² for ≥90 days who received care through an urban safety-net health care system from 2006-16. ICD codes for chronic conditions (excluding CKD) were extracted and categorized into 21 groups. The relationships of comorbidity patterns with demographics and CKD stage were studied. Multimorbidity was defined as ≥2 or more chronic conditions in addition to CKD. Race/ethnicity was recorded in 5 mutually-exclusive categories. We used proportions with binomial confidence intervals in stratified analyses, and multivariate logistic regression, to study relationships.

Results: We identified 13,678 participants, of whom 39.4% were Hispanic, 40.9% black, 11.5% white, 5.9% Asian/Pacific Islander, and 2.2% other/unknown. Comorbidity count (excluding CKD) ranged from 0 to 10, with median [interquartile range] of 2 [1,3]. Multimorbidity varied markedly by race/ethnicity and age (Figure). The logistic regression model (adjusted for gender, CKD stage, and year of cohort entry) corroborated this interaction (likelihood ratio test: ³p=0.001). Among those aged 18-34, blacks or whites had slightly higher diabetes and HTN prevalences than Hispanics, compared with 10-fold higher HIV prevalence, and 4-fold higher depression and CHF.

Conclusions: Multimorbidity among young adults with non-dialysis CKD varies markedly by race/ethnicity, with lower prevalence among Hispanics than blacks or whites. This may be due to differences in CKD etiology, disparities in access to care, and other factors which warrant further investigation.

TH-PO532
Disadvantaged Childhood Socioeconomic Position Represents a Critical Period for the Embedding of Kidney Disease Risk in Adults
Mark Canney,1,2 Siobhan Leahy,1 Siobhan Scarlett,1 Rose Anne M. Kenny,1 Mark A. Little,1 Conall M. O’Seaghdha,1 Cathal McCorry,1 The Irish Longitudinal Study on Ageing, Trinity College Dublin, Dublin, Ireland; 2Trinity Health Kidney Centre, Trinity College Dublin, Dublin, Ireland; 3Department of Nephrology and Transplantation, Beaumont Hospital, Dublin, Ireland.

Background: Socioeconomic position (SEP) is an important determinant of health but is dynamic across the lifespan. This study examines the relationship between life course SEP and chronic kidney disease (CKD) using three conceptual life course models: critical period, pathway and accumulation. We test each model in a population of Irish adults who experienced dramatic social mobility during their lifetime, as Ireland transitioned rapidly from a primarily agricultural to post-industrial society.

Methods: Cross-sectional analysis of data from 4996 participants from The Irish Longitudinal Study on Ageing, a nationally representative sample of community-dwelling adults aged ≥50 years. We defined CKD as a glomerular filtration rate <60mL/min/1.73m² estimated from the combination of creatinine and cystatin C using the CKD-EPI formula. We defined childhood and adulthood SEP according to father’s and respondent’s

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

237
Conclusions: Our findings suggest that women exposed to disadvantaged SEP in childhood represent an at-risk group in whom there may be opportunities for identification of CKD and facilitation of health-promoting behaviours from an early age.

Funding: Government Support - Non-U.S.

TH-PO535

Clinical Profile and Outcomes of Young Adult Patients with CKD at Philippine General Hospital under the Pediatric to Adult Transition Program Lipat Kalinga Janine V. Vue, Department of Medicine, UP-Philippine General Hospital, Manila, Philippines.

Background: Advances in the care of patients with CKD resulted in substantial improvement in survival. More patients transfer from pediatric to adult medicine department, instigating the need for proper transition programs - a purposeful, planned movement from child-centered to adult-oriented health services. ISN-PNA in 2011 recommended development of locally appropriate practices for transferring patients. This study describes the transition experience of a pioneer transition program in a low-resource environment.

Methods: A retrospective chart review of 48 transitioned patients from 2011-2016 was conducted. General data and laboratory parameters before transition and 2 years later were obtained. The no. of hospitalizations, ER consultations, OPD followup and the rate of renal function decline after 2 years were also noted.

Results: One hundred thirteen patients were enrolled in the transition program from 2011-2016. Sixtyfive (58%) patients were not transitioned, 31% were lost to follow-up before transfer. Fortyeight patients completed the transition process, but more than half disengaged from care. Nineteen patients (42%) were actively following up. Mean transition score was 81.18% and it was not associated with the no. of followup, hospital admissions and ER consultations. Majority of patients missed their first scheduled adult followup. Mean no. of followup per year was 2 at an average of 1 consult in 6 months.

Nine patients were admitted post transition with 5 days mean hospital stay. Four patients had ER consultations with a mean of 1 ER and 1 hospital admission per year. Seventeen of the patients had a higher BMI 2 years after with mean increase of 1.05 points. There was no significant difference between the baseline and the posttransition laboratories (electrolytes, albumin, hemoglobin, proteinuria, creatinine and BUN). Mean decline in renal function was 1 ml/min/1.73 per year. There was no significant change in the eGFR of patients before and 2 years after transition.

Conclusions: To improve outcomes of young patients with CKD as they transfer to adult-focused services, transition preparation is critical. In this pioneer group, follow-up rate was only 42%. Obvious difficulties encountered suggest developing more standardized transition methods and strengthening adult Nephrology participation in the pre-transfer period.

TH-PO536

A Business Case for New CKD Payment Models Harry Liu, Sophia Zhao,1 Massachusetts General Hospital, Brookline, MA; 2RAND Corporation, Boston, MA.

Background: Various interventions have been demonstrated to effectively slow down the progression of chronic kidney disease (CKD), smooth the transition to renal replacement therapy (RRT), and improve patient outcomes. Such interventions, however, are rarely adopted due to misaligned incentives in the current healthcare system. This study aims to quantify the savings from CKD interventions and design associated new payment models.

Methods: We constructed a simulation model that identifies and quantifies savings opportunities during the CKD progression and transition to RRT, and extracted the model’s parameters from the published literature. Simulation model sensitivity analyses were conducted to account for the uncertainty in input parameters. Assumptions were made only when published data were lacking. New payment models were proposed to capture such savings opportunities.

Results: The simulation includes the following interventions: increasing the use of pre-dialysis nephrology care to slow down disease progression; smoothing transition through a seamless transfer to appropriate inpatient services and increasing the adoption of arteriovenous fistula and peritoneal dialysis; and decreasing the use of dialysis among patients with an eGFR of 15 or greater among patients with advanced age and multiple conditions, for whom the benefits of dialysis is very limited or nonexistent.

The simulation model results in an annual savings of $1.0 billion for Medicare [range: $0.5 - $1.8 billion] and $1.8 billion for all payers [range: $0.7 - $2.1 billion]. Increased use of pre-dialysis nephrology care and decreased use of inpatient services at dialysis initiation each contributes to about one third of savings, respectively. The simulation model also suggests that new payment models should focus on Stage 3 and 4 patients and the transition from CKD to RRT. Within Medicare, new payment models can be designed around ESRD Seamless Care Organizations, Special Needs Plans, or Medicare Advantage Plans to streamline incentives and optimize care efficiency. A joint program between Medicare and other payers should be set up so that Medicare and other payers can share savings from CKD interventions.

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

Underline represents presenting author.

238
Conclusions: Tremendous savings opportunities exist in slowing CKD progression and smoothing the transition to ERT, and new payment models should be designed and implemented to reap the benefits.

TH-PO537

Limitations of ICD Codes in Detection, Staging, and Assessing Progression of CKD

Kabir Jalal,1 Edwin J. Anund,1 Rocco C. Venuto,1 Pradeep Arora,1 Joseph A. Eberle,2 Erie County Medical Center, Buffalo, NY; 2Intelligent Care Management, East Amherst, NY; 3None, Getzville, NY; 4University at Buffalo, Hamburg, NY; 5Nephrology, FAMC, Buffalo, NY.

Background: The International Classification of Diseases (ICD) coding system is the industry standard tool for disease classification and epidemiology purposes. However, ICD codes in practice unreliable reflect the true diagnosis for a given disease/patient. This study seeks to quantify that inaccuracy among patients with Chronic Kidney disease (CKD).

Methods: Using insurance data consisting of 222,664 insured individuals with serum creatinine measurements over seven years, diagnoses based on a set of CKD-related ICD codes were compared against gold standard Kidney Disease Outcomes Quality Initiative (KDOQI) clinical guidelines to evaluate accuracy of ICD codes to detect CKD-positive patients. Patient serum creatinine levels were used to estimate progression of disease course using a longitudinal mixed model to identify advanced progressors, or those patients with loss of GFR (estimated glomerular filtration rate) greater than 1 ml/year, and to assess accuracy of ICD codes in detecting advanced progressors.

Results: ICD codes correctly identified only 10,101 of 33,159 individuals as CKD, for a sensitivity of 30.46% with positive predictive value (PPV) of 65.05%; codes correctly identified 184,078 individuals as CKD-negative, for a specificity of 97.14% with negative predictive value (NPV) of 98.91%. In detecting CKD-positive patients, ICD codes achieved a sensitivity of 11.95% with PPV of 8.46%, and a specificity of 94.73% with NPV of 96.35%.

Conclusions: The use of ICD codes alone is insufficient in identifying patients with CKD. This study is the first to attempt the use of ICD codes in identifying rapidly progressing patients, revealing poor coding performance when compared to gold standard KDOQI guidelines. Use of ICD codes to identify CKD patients, assess disease severity, or to evaluate disease progression for either clinical or epidemiological purposes is not recommended.

Funding: Other U.S. Government Support

TH-PO538

Lab Vigilance in Patients with CKD on Renin Aldosterone Inhibitors and Diuretics: Are We Monitoring Appropriately? Katherine Garlo,1 Diane Seger,1 Julie Fisiko,1 David W. Bates,1 David M. Charytan.2 Brigham & Women’s Hospital, Boston, MA; 2Renal Division, Brigham and Women’s Hospital, Boston, MA; 3Brigham and Women’s Hospital/Harvard Medical School, Brookline, MA; 4Partners Healthcare System, Somerville, MA.

Background: Renin Aldosterone Inhibitors (RAI) are first line agents for hypertension. Their efficacy has been shown in reducing blood pressure, slowing progression of chronic kidney disease (CKD), and cardiovascular protection. Grade A level 1 evidence supports their use in CKD with or without proteinuria. However, ideal lab monitoring during initiation of RASI is uncertain and guidelines are opinion based if present at all. We assessed outpatient lab monitoring in a large cohort of patients with CKD prescribed a new RASI or diuretic.

Methods: We evaluated adults with pre-dialysis CKD stage 3-5 who received a new RASI or diuretic prescription during 2009-2011. Lab data was collected electronically and analyzed for baseline and follow-up labs potassium and creatinine.

Results: A total of 8,272 individuals (mean age 72±13.5 years, 44% male, 86% white) with CKD (90% stage 3) were included. The average interval following baseline lab monitoring during initiation of RASI is uncertain and guidelines are opinion based if present at all. We assessed outpatient lab monitoring in a large cohort of patients with CKD prescribed a new RASI or diuretic.

Results: The days-prescribed-per-user (DPPU) during a given calendar year were computed from medication claims. Logistic regression was used to explore factors associated with use of specific analgesics.

Conclusions: The days-prescribed-per-user (DPPU) during a given calendar year were computed from medication claims. Logistic regression was used to explore factors associated with use of specific analgesics.

Use of analgesics, particularly opioids, is very high in the Medicare population.

TH-PO540

Use of Analgesics among Older Patients with CKD in the United States (2006-2015)

Yun Han,1 Rajesh Balkrishnan,2 Kevin He,1 David W. Hutton,1 Diana Neff,3 Richard A. Hirth,1 Rajiv Saran.1 Kidney Epidemiology and Cost Center, University of Michigan, Ann Arbor, MI; 1University of Virginia School of Medicine, Charlottesville, VA; 2Internal Medicine - Nephrology, University of Michigan, Ann Arbor, MI.

Background: Pain is common among patients with kidney disease yet few studies examine this, especially among older patients with non-dialysis CKD. We investigated US national trends in the use of nonsteroidal anti-inflammatory agents (NSAIDs) and opioid analgesics by older CKD patients over the past decade.

Methods: We identified eligible CKD patients enrolled in Medicare Part D through claims data (5% Medicare sample, 2006-2015). Demographics, CKD stages and comorbidities were assessed over a one-year entry period. Analgesic use by year was measured as the proportion of patients prescribed non-steroidal and opiate analgesics. The days prescribed-per-user (DPPU) during a given calendar year were computed from medication claims. Logistic regression was used to explore factors associated with use of specific analgesics.

Results: There was a notable increase in use of NSAIDs among Medicare CKD patients in the past decade, from 10.5% in 2007 to a peak of 16.3% in 2011, with a decline to 14.3% in 2015 (Figure). DPPU were relatively stable, ranging from 104-109 days. NSAID use was consistently lower at higher stages of CKD. Opiates were prescribed to 14.3% in 2015 (Figure). DPPU were relatively stable, ranging from 104-109 days. Opiates were prescribed to 14.3% in 2015 (Figure).

Conclusions: Use of analgesics, particularly opioids, is very high in the Medicare CKD population, and rose substantially between 2007 and 2011. This study suggests both
a high burden of pain in this vulnerable population, and the potential for suboptimal pain management and dangerous adverse effects, including narcotic dependence.

**Funding:** NIDDK Support

Proportion of Analytic Use in Medicare Patients by CKD Stages

**TH-PO541**

CKD Patient Characteristics and Attitudes Towards Kidney Disease Education Desvansita Choudhury, Urb Dev, Lesley Mcelney, Suzanne T. West.

**Background:** CKD education (CKD-Ed) is crucial to managing and improving CKD health outcomes. Patients (pts) often defer or miss CKD-Ed appointments. We compare characteristics and attitudes of pts who opt to receive education (R-Ed) to pts who decline (D-Ed).

**Methods:** A web-based CKD-Ed (VA-ekidneyclinic) education program designed at the 5th grade level was offered consecutively to 179 known CKD patients and their family members during CKD clinic appointments at Salem VAMC from 7/2016 to 5/2017 with continuing web-based home education as part of a study.

**Results:** R-Ed: 61/179 (34%); D-Ed: 118/179 (66%) patients. Reasons for declining education: 46% - no interest, 36% - no home web access, 12% - too busy, 5% live too far. 3% confused. See data table for age, ethnicity, CKD stage, number or medical problems, differences in education level between groups. 76% of "non-interested," 82% of "no computer," 100% "too far" pts were from counties and cities with < 88% HS and higher education; 70% "too busy" pts came from > 88% HS education counties and cities. 62% pts despite computer access declined both clinic and home CKD-Ed.

**Conclusions:** CKD patients who decline CKD education are more like to be older, male, from lower educated surroundings and interestingly fewer medical problems than those that opt to receive CKD education. Creative education tools and practices (eg: games, comics, jingles) need to be explored to motivate and educate a majority of CKD patients in order improve CKD health outcomes.

**Funding:** Private Foundation Support

Demographics Data: Opting to Receive (R-Ed) vs Decline (D-Ed) CKD Education

**TH-PO542**

Cost-Effectiveness of a Multiple Intervention Model for Management of CKD in Primary Health Care Rafael Ayala Cortez,

**Background:** Strategies to prevent and delay progression of early CKD are urgently needed; however, there is little information about costs and outcomes at the primary health-care. **Objective:** To evaluate cost-effectiveness of multiple intervention model (MIM) vs conventional health-care model (CHCM) for CKD diagnosis and treatment.

**Methods:** Prospective evaluation from the health-care provider perspective, performed in 2 Family Medicine Units of Guadalajara, Mexico: MIM and CHCM were evaluated in one unit each. Three phases evaluated: Educative intervention for health professionals, Screening of CKD, and Management Follow-up of CKD patients. All resources were identified, quantified and recorded; official lists for drugs, medical materials and services, and laboratory/image tests were employed for costs calculation. Only direct medical costs (in USD) were considered. **Main outcome and measures:**

- Total cost, average cost per person, and incremental cost-effectiveness ratio (ICER) were calculated. Cost analysis was performed in each phase. Clinical competence of health professionals was measured with a validated questionnaire, and CKD progression was defined as decline in GFR category.

**Results:** Clinical competence was not different between models neither at baseline (MIM 63±21 vs CHCM 64±19, p=0.52) nor at final (MIM 94±14 vs CHCM 99±17, p=0.76) evaluations. Average cost per health professional receiving educative intervention in MIM was $833 (95% 762-899) vs $901 (819-976) in CHCM (p=0.26). ICER was $22.6 favoring MIM. CKD stages 1-3 were present in 30% of patients from MIM (N 336) and 32% in CHCM (N 454). Average cost per person of CKD stages 1-3 was $45 (95% 41-47) in MIM and $42 (95% 37-45) in CHCM (p=0.60). ICER was $2.3 favoring CHCM. For Management/Follow-up phase, 57 patients with CKD stages 1-3 were studied during 12-month in MIM and 58 patients in CHCM. CKD progression was observed in 16% of patients in MIM vs 28% in CHCM (p=0.09). Average cost per patient was $826 (95% 760-900) in MIM vs $701 (95% 632-777) in CHCM. ICER was dominant in MIM.

**Conclusions:** MIM are more cost-effective than CHCM to delay kidney disease progression when strategies combining educative interventions for health professionals, screening and adequate management of early CKD are employed at the primary health care.

**Funding:** Private Foundation Support

Demographics Data: Opting to Receive (R-Ed) vs Decline (D-Ed) CKD Education

**TH-PO543**

Applying Lean Tools to Optimize Delivery of Patient CKD Education in Primary Care Julia C. Wright Nunes, Emily P. Chen, Eve Kerr, Audrey Fan, Tejpreet Nakal, Gunjan Garg, Angela Fagerlin.

**Background:** Eighty percent of patients with CKD do not have the knowledge necessary to be fully activated in CKD management. Efficient and sustainable programs are needed to address patient education needs early in the CKD care continuum.

**Methods:** Applying Lean Tools (cause/effect analysis, process mapping / re-engineering), we created an efficient and sustainable way to integrate CKD patient education seamlessly into primary care practice. Utilizing a multi-disciplinary team (including primary care and nephrology physicians, patients, medical assistants, nursing, check-out staff, Health IT, and Lean coaches) a current-state process map of patient care and education was created for a large primary care practice. Lean coaches facilitated the multi-disciplinary team to create an improved future-state process that incorporated CKD education module into education modules into existing computer system, populating existing staff and resources. Content of the worksheet was optimized using quality improvement techniques. Health IT staff created an electronic version to use in the electronic medical record (EMR). This electronic patient education worksheet autopopulates with each patient’s eGFR, blood pressure, and urine protein values. Medical assistants enter the worksheet into the EMR for patients with CKD stages 3-5 during patient check-in for routine visits. Providers review this worksheet in the EMR with patients during clinic encounters. Providers may enter 1-2 tailored messages about shared care goals. The worksheet prints automatically upon check-out and is given to the patient.

**Results:** Pilot testing shows the process is efficient and feasible to integrate into busy clinical settings. It takes seconds (two key-strokes) to enter into the EMR and approximately –2 minutes for providers to review. Next steps will examine the impact of the electronic education worksheet and future state process on patient, clinic and provider related outcomes.

**Conclusions:** We provide a model of a future state process that incorporates patient CKD education seamlessly into practice, leveraging IT resources and existing clinic staff. The ultimate aim of this project is to improve patient CKD knowledge early in the CKD care continuum. **Funding:** Private Foundation Support

**TH-PO544**

Primary Care-Nephrology Multidisciplinary Partnership Improves CKD Care Paula Haberman,

**Background:** Resources for CKD care are often clustered around late stage CKD with poor medical care in early stages leading to increased costs of care. Patients with early stage CKD may overburden already stretched nephrology resources and are cared for by primary care providers (PCPs) who may not be fully empowered to render appropriate CKD Care. Structured partnerships between PCPs, health systems, payers and nephrologist could be used to improve early stage CKD care. We report on a process improvement that improve patient CKD knowledge early in the CKD care continuum. The aim was to ensure successful and accurate diagnostic and treatment of early stage stage CKD may overburden alaredy stretched nephrology resources and are

**Methods:** As a first step, we aimed to increase the numbers of urine albumin to creatinine ratio (A CR) obtained on patients in CKD stage 3a 3b from 15% to 25% over a six month period of from 168 patients to improve patient CKD knowledge and help decrease mortality. A key driver to ensure success. EMR advisories were followed by academic detailing through care process modules to Drive change. Key Process Drivers and Change Implementation methods are shown in Figure 1, a, b,

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

Underline represents presenting author.

**Poster/Thursday**
Results: A robust and sustained increase in rates of ordering albumin creatinine ratios is shown in Figure 1, c. Marked improvement in adherence to ACR ordering followed academic detailing.

Conclusions: A multidisciplinary primary care-nephrology system partnership in care redesign can produce robust sustained improvements in Early Stage CKD evaluation. This approach will be extended to CKD treatment

Figure 1 Process Drivers, Leverage Points, Results; a) Key Drivers, b) Leverage for change c) Change in Behaviour

TH-PO546

Using Kidney Failure Risk Scores to Identify Veterans Needing CKD Care C. Blake Cameron,1,2 Joel Boggan,1 Susan Gurley,1 Richard M. Atkins,2,1 Duke University Medical Center, Durham, NC; 1Durham VA Health Care System, Durham, NC.

Background: Both over- and under-referral to nephrology threaten the quality and efficiency of CKD care. Optimizing veterans’ nephrology referrals may improve their outcomes. Few studies have evaluated patterns of nephrology referral among veterans as a function of CKD progression risk.

Methods: Using the Veterans Health Administration Clinical Data Warehouse, we identified all non-ESRD individuals who received primary care at the Durham VA Health Care System between Dec 2014 and Jun 2017 and had ≥1 outpatient serum creatinine measurement during that time. For each individual, we identified the assigned primary care provider (PCP); tabulated nephrology/CKD clinic visits; and calculated the Kidney Failure Risk Equation (KFRE), an internationally validated predictor of 5-year ESRD risk utilizing age, sex, CKD-EPI eGFR, and optionally, urine albumin-to-creatinine ratio. We stratified the population by KFRE risk (low ≤5%, intermediate 5-15%, and high >15%), by nephrology referral status and by assigned PCP. We performed descriptive analyses.

Results: Overall, 48,700 unique, non-ESRD individuals with at least one creatinine measurement received care from 139 PCPs. Only 32% (n=3,591,116) and 58% (n=503,865) of individuals at intermediate and high risk for CKD progression respectively had been seen in nephrology clinic. Conversely, among the 1,816 individuals seen in nephrology clinic, 53% (n=957) were at low risk [Figure 1A]. Nephrology referral rates for high-risk patients varied widely across PCPs (mean 58% [s.d. 20%]) [Figure 1B].

Conclusions: Within a single integrated medical center, nephrology referral rates were not aligned with clinical risk. More than 40% of individuals with high-risk CKD had not received nephrology care. Conversely, approximately half of individuals seen in nephrology/CKD clinic were at low risk of progression to ESRD and potentially could have avoided referral. Substantial provider-to-provider variation in nephrology referral rates exists. Identifying the sources of variation will be critical to developing decision support tools and models of care that better align the provision of CKD care with clinical risk.

Funding: Veterans Affairs Support

TH-PO547

Cause-Specific Hospitalization among Older Adults with CKD in the US (2006-2015)

Poster/Thursday

TH-PO547

Cause-Specific Hospitalization among Older Adults with CKD in the US (2006-2015)

Yun Han1, Kevin He1, Diane Steffick1, Rajesh Balkrishnan2, Brahmajee K. Nallamothu2, Rajiv Saran3.
1Kidney Epidemiology and Cost Center, University of Michigan, Ann Arbor; 2University of Michigan, Ann Arbor; 3Internal Medicine - Nephrology, University of Michigan, Ann Arbor; 4University of Virginia School of Medicine, Charlottesville, VA.

Background: Patients with CKD are at high risk of hospitalization, but there are few long-term studies of cause-specific hospitalizations in this vulnerable patient population. We examined these and long-term trends in hospitalization rates among older adults with CKD in the US.

Methods: We identified eligible CKD patients through claims (5% Medicare sample, 2006-2015). Patients were censored at the earliest of death, start of ESRD, disenrollment from Medicare Parts A&B or the last day of each calendar year. The year of cause of hospitalization was determined by principal ICD-9-CM diagnosis code. Adjusted hospitalization rates were calculated using a GLM with adjustment for age, gender and race.

Results: There was a notable decrease in the adjusted all-cause hospitalization rates among older CKD patients over the past decade, from 926.9/1000 patient years in 2006 to 739.0/1000 in 2011, with a steeper slope thereafter to 662.9/1000 in 2015 (Fig.1.a). Cardiovascular diseases (CVDs) and infections were the leading causes of hospitalization in CKD, accounting for 26% and 22% of all-cause admissions in 2015 (156.3/1,000 and 131.4/1,000). Congestive heart failure-related admissions were the most common CVD cause in CKD (Fig.1.b). Although overall infection-related hospitalization decreased over time, admissions resulting from bacteremia, sepsisemia and viremia increased by 51% and admissions due to nervous system infections increased by 42% (Fig.1.c).

Conclusions: While all-cause hospitalization rates among CKD patients gradually decreased in the past decade, CVD (especially heart failure related) and certain specific infections remained the leading causes. Future research will focus on preventable hospitalizations (e.g., septisemia, heart failure), disparities, geographic variation, costs, and care coordination.

Funding: NIDDK Support

CKD: Health Services, Disparities, Prevention

Poster/Thursday

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

Underline represents presenting author.
Results: The maximal graded exercise test resulted in a 53% reduction in RBF and a significant increase in the filtration fraction (FF) after strenuous exercise (100% of VO2peak). RBF did not significantly decrease until 100%LT was attained, and showed significant decreases of 64% at 120%LT and 62% at 140%LT relative to its resting value (p<0.01). FF also did not change until the LT was reached. In addition, LT corresponded with anaerobic threshold, 40% heart rate reserve, and 55%VO2peak.

Conclusions: Our results demonstrate that RBF and FF do not change during exercise until the LT is attained. These findings may assist in making appropriate exercise intensity recommendations to patients with CKD stage 2.

Funding: Private Foundation Support

TH-PO549

Impacts of Pre-Dialysis Options Education on Albumin Levels and Catheter Use in Patients Starting Dialysis

John W. Larkin, Yue Jiao, Marta Reviriego-Mendoza, Rob Lynch, Lea A. Usuyot, Jeffrey L. Hynes, Franklin W. Maddux. Fresenius Medical Care North America, Waltham, MA.

Background: Options education before progression to end stage renal disease (ESRD) teaches patients about optimal ways to prepare for dialysis (e.g., early access placement, nutritional requirements, renal replacement therapy options). We aimed to understand whether patients receiving options education prior to initiating dialysis exhibited improvements in their albumin (Alb) levels and rates of catheter use.

Methods: We analyzed data from incident Fresenius Kidney Care (FKC) patients who initiated dialysis between 2009 and 2016. Patients were grouped by enrollment in FKC options education prior to initiating dialysis or not, as well as whether patients started dialysis as an outpatient or inpatient. In these groups, we calculated the annual mean Alb levels in all dialysis patients and percent catheter use during the first 120 days of dialysis in hemodialysis patients.

Results: We studied data from a total of 300,818 patients, of which 68,721 patients received options education prior to initiating dialysis. Throughout 2009-2016, patients who received options education generally exhibited higher mean Alb levels and there was a lower proportion of patients with a catheter, as compared to those who did not receive these observations were similar, yet less pronounced for catheter use in patients starting dialysis as an inpatient versus outpatient. In 2016 specifically, we observed that patients who started as an outpatient and received options education had higher Alb levels (3.5 mg/dl options education versus 3.4 mg/dl no education); for those starting dialysis as inpatients, Alb levels were 3.3 mg/dl and did not differ with options education or not. Concurrently, we observed that catheter use in patients starting dialysis as an outpatient was 13.8 percentage points lower in those with options education versus patients without education. In contrast, we observed that catheter use in patients starting dialysis as inpatients, the catheter use was 4.9 percentage points lower in with options education, compared to patients without education.

Conclusions: These findings indicate that options education before progression to ESRD is associated with dialysis patients achieving higher Alb levels and hemodialysis patients having lower catheter use in the incident dialysis period. Further analyses are warranted to confirm these results.

Funding: Commercial Support - Fresenius Medical Care North America

TH-PO550

Abstract Withdrawn

TH-PO551

Factors Associated with Non-Conservative Treatment of Stage 5 CKD

Robert N. Foley, Scott Reule. University of Minnesota, Minneapolis, MN.

Background: Quality of death and patient autonomy are prominent public health issues. In this regard, the decision to institute dialysis in patients with non-dialysis Stage 5 chronic kidney disease (CKD, GFR ≤ 15) is often difficult, because comorbid illnesses are the rule, and survival and quality of life with maintenance dialysis are often poor. Hence, we set out to examine factors associated with choosing to institute maintenance dialysis, as opposed to conservative management, in older adults.

Methods: We used the (US) Medicare 5% CKD random sample to identify 15,884 patients with diagnostic claims for CKD, between 2006 and 2011, with at least 6 months of prior Parts A and B Medicare insurance. Hospital admission codes in the prior 6 months were used to characterize comorbidity. Time to renal replacement therapy (RRT) was the primary outcome.

Results: The mean age of the study population at diagnosis of CKD, was 76 years. Mean follow-up was 2.8 years and 51.3% opted to begin RRT. In models that adjusted for age, demography and comorbid illnesses, adjusted hazards ratios (AHR) for RRT were > 1 (P < 0.05) for African American race (AHR 1.25 Vs. white), Native American race (AHR 1.38) and cardiac failure (AHR 1.38). RRT was less likely with older age (AHR 0.73 for 70-79, 0.63 for 80-89 and 0.44 for a 90 [Vs. ≤ 70 years]), female sex (AHR 0.89) and malignancy (AHR 0.92).

Conclusions: These findings suggest that a substantial proportion of Medicare patients with GFR ≤ 15 decline the option of RRT. Age, sex, race and comorbidity profiles influence this choice.
**TH-PO552**

**Effect of N-Acetyl Cysteine in Patients with CKD: The Longer, the Better?**

A Nationwide Population-Based Retrospective Cohort Study
Chen-Yi Liao, Chia-chau Wu. Division of Nephrology, Department of Internal Medicine, Tri-Service General Hospital, Taipei, Taiwan.

**Background:** This study aimed to evaluate the potential benefits of N-acetylcysteine (NAC) on the risk for chronic kidney disease (CKD) progression to dialysis-requiring end-stage renal disease (ESRD).

**Methods:** In a population-based cohort study of 145,062 individuals, a total of 123,608 CKD patients who were followed up for 10 years were compared with patients who were prescribed NAC after being diagnosed as CKD (ICD-9-CM). Using propensity score matching, we analyzed the predictors of CKD progression to ESRD by Cox proportional hazards regression with adjustment for sex, age, and comorbidities and evaluated the effect of NAC using cumulative defined daily dose (cDDD).

**Results:** NAC use was associated with reduced risk for progression to ESRD (HR 0.819, 95% CI 0.781-0.965, p = 0.017). Risk reduction was accentuated by an increase in cDDD in patients on NAC compared with non-NAC users (HR was 0.8350, 0.811, and 0.799 for cDDds 91-180, 180-360, and ≥360, respectively; P trend = 0.018). Risk reduction was apparent in women (P = 0.001); younger age at 18-29 years (P = 0.021) and 30-39 years (P = 0.033); the presence of hypertension (P = 0.003); the absence of diabetes mellitus (P = 0.042); and the absence of congestive heart failure (P = 0.056).

**Conclusions:** NAC administration was associated with a lower risk of subsequent ESRD. Further studies are warranted to confirm these findings.

---

**TH-PO553**

**Metformin Prescription in a Contemporary Cohort of Patients with Stage 3a CKD**

Rocco Ferrandino, Tielman V. Vleck, Jeremy S. Leventhal, Bart Ferket, Jaime Uribarri, Steven G. Coca, Girish N. Nadkarni. Icahn School of Medicine at Mount Sinai, New York, NY.

**Background:** Eligibility criteria for metformin have shifted from serum creatinine (SCr) to estimated glomerular filtration rate (eGFR) based guidelines. In 2009, the American Diabetes Association endorsed metformin use in type 2 diabetes (T2D) patients with stage 3a chronic kidney disease (CKD3a). We evaluated contemporary prescribing patterns in patients with CKD3a with as well as patient/process of care factors associated with non-prescription of metformin in a large multiethnic cohort.

**Methods:** We identified T2D patients with CKD3a from Mount Sinai CKD registry and calculated proportion of eligible patients actually receiving metformin. We then used nearest neighbor propensity matching to compare adjusted odds ratios (aOR) for non-prescription of metformin in 2015-16 based on eGFR criteria. Of these, only 1992 (38.2%) received metformin. We identified 1820 user: non-user matched pairs. Patient-specific factors associated with non-prescription included male sex (aOR 1.67, 95% CI 1.12-2.47) and black race (aOR 1.79, 95% CI 1.09-2.91). Interestingly, 21.7% of male and 20.3% of black patients eligible by eGFR guidelines were ineligible by SCr guidelines. Patients in whom other preventative T2D guidelines were adhered to (identified by NLP) had lower non-prescription odds. (Figure)

**Conclusions:** Despite a shift to eGFR-based guidelines and eGFR threshold lowering, a substantial proportion of eligible patients do not receive metformin. Factors responsible may be continued adherence to outdated guidelines, and patient/process of care specific factors, which should be explored in greater detail.

**Funding:** Other NIH Support - RF was supported by 1T1TR001434

---

**TH-PO554**

**Low Utilization of Statins in US Veterans with Non-Dialysis Dependent CKD**

David J. Leechey,1 Talar Markossian,2 Nicholas Burge,1 Kevin Stropoue,1 Ivan Pacold,1 Julia Schneider,1, 2 Benjamin Ling,1, 3 Holly J. Kramer,1, 3 Hines VA Medical Center, Hines, IL; 1Loyola University Chicago, Maywood, IL; 2Loyola University Medical Center, Maywood, IL.

**Background:** Cardiovascular disease is the major cause of morbidity and mortality among adults with non-dialysis dependent chronic kidney disease (CKD). Statin medications, especially when combined with ezetimibe, significantly reduce atherothrombotic cardiovascular disease (ASCVD) risk in this population. Renal guidelines therefore recommend statin use for all patients with non-dialysis dependent CKD age 50 years or older regardless of lipid profile. However, the recent AHA/ACC recommendations for statin use for adults (including those with CKD) in the absence of ASCVD or diabetes is based on the predicted 10-year ASCVD risk derived from the pooled risk cohort equation. The objective of this study was to examine statin utilization in a national sample of U.S. Veterans with non-dialysis dependent CKD, defined as an eGFR < 60 ml/min/1.73 m2, and to calculate the predicted ASCVD risk by diabetes status using the pooled risk cohort equation.

**Methods:** The design was a retrospective review of statin use and clinical and demographic factors associated with statin use. Statin use was ascertained from pharmacy dispensing records during fiscal years 2012 and 2013. The study included 581,344 Veterans age 50 years with non-dialysis dependent CKD stages 3-5 with no history of kidney transplantation or dialysis receiving care at VA healthcare facilities.

**Results:** 97% of patients were male and 58% were older than 70 years. Statin use ranged from as high as 76% in those with ASCVD or diabetes to as low as 22% in those without ASCVD or diabetes (P < 0.001). Overall, 94% of Veterans with diabetes had a ASCVD risk score > 7.5%, of whom 42% were not using statins. Strikingly, even in patients in whom the ASCVD risk score was very high (> 20%), only 52% of non-diabetic CKD patients and 75% of diabetic patients were using statins.

**Conclusions:** Utilization of statins is low in Veterans with non-dialysis dependent CKD in the absence of well-known indications for statin use (i.e., ASCVD or diabetes) despite high-predicted ASCVD risk. We conclude that whether one follows renal or cardiovascular guidelines that statin utilization is suboptimal in all CKD patients. National education efforts will be needed to increase statin use for CKD, especially in patients without established ASCVD or diabetes.

---

**TH-PO555**

**Nephrology Practices and Patient Perspectives in regards to Conservative Care for ESKD: The Chronic Kidney Disease-Renal Epidemiology and Information Network Study**

Elodie Speyer, Luc Frimat,2 Carole Ayav,3 Christian Combe,1 Denis Fouque,1 Christian Jacquelinet,1 Maurice Lavilatte,2 Ziad Massy,2 Bruce M. Robinson,1 Benedicte Stengel,1 INSERM-CESP, UPSud, 1CHU de Nancy; 2CHU de Bordeaux, Bordeaux, France; 3Université Claude Bernard, Pierre Benite, France; 4Agence de la biomédecine, Saint-Denis La Plaine, France; 5Université de Lyon, Pierre-Bénite, France; 6Ambroise Pare University Hospital and Inserm U1018 Eq5, Boulougne Billancourt/ Paris cedex, France; 7Arbor Research Collaborative for Health, Ann Arbor, MI. Group/ Team: CKD-REIN Investigators.

**Background:** Current KDIGO guidelines indicate that patients with advanced CKD should receive information on all renal replacement therapy (RRT) options, including conservative care (CC), but little is known about nephrologist practices and patient perspectives in regards to CC.

**Methods:** CKD-REIN is a prospective cohort study that enrolled 3,033 adult patient with CKD stage 3-5 (45% in stage 4-5) from a national representative sample of 40 nephrology clinics in France. Nephrologists were surveyed about practices regarding information, whether they offer, and clinic organization about CC. Patients completed a self-administered questionnaire (PQ) including their understanding of, education on, and preferences for RRT options, including CC.

**Results:** Among 31 clinics with data, 33% had a guideline (implemented or in preparation) for managing ESRD by CC. Eighty-two percent of the 131 respondent nephrologists (mean age = 44±10; 53% men) reported to be fairly or extremely comfortable with discussing CC with patients, but only 29% reported discussing it with all patients aged ≥ 75%. Patient’s quality of life and preference for CC were more likely to influence nephrologists when contemplating the suitability of CC than medical or social conditions (figure 1). Among the 1,363 patients with CKD stage 4-5 (88% PQ respondents; 70% men; 35% aged ≥75), 5% of 75+ year-old patients reported to have been informed by their doctor about the “no treatment” option; and 2.3% stated they would choose the “no treatment” option if their kidneys failed.

**Conclusions:** Despite guidelines and that nephrologists declare that patients with advanced CKD received information about all RRT options, including conservative care, but little is known about nephrologist practices and patient perspectives in regards to CC.

**Funding:** Commercial Support - Amgen, Baxter, Fresenius Medical Care, MSD, Lilly, Otsuka, GSK, Government Support - Non-U.S.
Background: Guidelines recommend early referral to nephrology care for people with chronic kidney disease, based on observational studies showing that longer nephrology care before dialysis start (predialysis care, PDC) is associated with lower mortality after dialysis start. This association may be observed because PDC truly improves patient outcomes, or because healthier patients with an uncomplicated course of disease will have both longer PDC and better outcomes. We designed this study to assess whether the survival benefit of longer PDC exists after accounting for the potential confounding effect of acute events (markers of disease course) that may also be affected by prior PDC.

Methods: We did a retrospective cohort study in adults with kidney failure who initiated dialysis not following a failed kidney transplant between 2004 and 2014 in five hemodialysis centers. We included patients with ≥365 days of PDC, respectively. When we ignored markers of acute events, this association was weaker and no longer significant (HR [95% CI] 0.84 [0.60–1.18]; HR [95% CI] 0.60–0.71), standard Cox model adjusted for demographics, laboratory and clinical characteristics. When we accounted for markers of acute events, this association was weaker and no longer significant (HR [95% CI] 0.84 [0.60–1.18]; HR [95% CI] 0.60–0.71), standard marginal structural Cox model).

Conclusions: Current guidelines on early nephrology referral are based on observational studies showing that longer nephrology care before dialysis start (predialysis care, PDC) is associated with lower mortality after dialysis start. This association may be observed because PDC truly improves patient outcomes, or because healthier patients with an uncomplicated course of disease will have both longer PDC and better outcomes. We designed this study to assess whether the survival benefit of longer PDC exists after accounting for the potential confounding effect of acute events (markers of disease course) that may also be affected by prior PDC.

Results: Of the 3152 participants: 23% had no PDC; 8%, 10%, and 59% received 1-119, 120-364, and ≥365 days of PDC, respectively. When we ignored markers of acute events (including unplanned dialysis start and higher residual kidney function around dialysis start) as in prior studies, longer PDC was associated with lower mortality (Hazard Ratio (HR) [95% CI] 0.60 [0.51–0.71], standard Cox model adjusted for demographics, laboratory and clinical characteristics). When we accounted for markers of acute events, this association was weaker and no longer significant (HR [95% CI] 0.84 [0.60–1.18]; HR [95% CI] 0.60–0.71), standard marginal structural Cox model.

Conclusions: Current guidelines on early nephrology referral are based on observational studies showing that longer nephrology care before dialysis start (predialysis care, PDC) is associated with lower mortality after dialysis start. This association may be observed because PDC truly improves patient outcomes, or because healthier patients with an uncomplicated course of disease will have both longer PDC and better outcomes. We designed this study to assess whether the survival benefit of longer PDC exists after accounting for the potential confounding effect of acute events (markers of disease course) that may also be affected by prior PDC.
Racial Differences in Nephron Number, Role of Body Size, Kidney Weight, and Cortical Volume in Adult Subjects among Five Populations

Go Kanazaki,1,2 Victor G. Puellas,3 Luis A. Cullen-McEwen,4 Wendy E. Hoy,5 Yusuke Okabayashi,6 Nobuo Tsumbo,1 Akira Shimizu,1 Takashi Yokoie,1 John F. Bertram,1 Department of Anatomy and Developmental Biology, Monash University, Melbourne, VIC, Australia; 2Department of Analytic Human Pathology, Nippon Medical School, Tokyo, Japan; 3Department of Nephrology and Clinical Immunology, University Hospital RWTH Aachen, Aachen, Germany; 4Centre for Chronic Disease, The University of Queensland, Brisbane, QLD, Australia; 5Division of Nephrology and Hypertension, The Jikei University School of Medicine, Tokyo, Japan.

Background: Nephron number in normal adult kidneys varies widely and is influenced by birth weight, age and race. Our recent studies have shown that Aboriginal and Japanese subjects have fewer nephrons than most populations studied to date and they are at high-risk for CKD. However, the cause of these racial differences in nephron number is not fully elucidated. In this study, we examined the effects of body size, kidney weight, and cortical volume on nephron number among races.

Methods: We analysed kidneys at autopsy from subjects aged 20-65 years without overt kidney disease in Aboriginal Australians (n=16), Japanese (n=12), Caucasian Americans (n=79), African Americans (n=65), and Senegalese (n=36). Total nephron number (Nglomer) was estimated by design-based stereology. Cortical volume was calculated by Cavalieri Principle.

Results: Nglomer per kidney in Aboriginal Australians (730,523 ± 244,460; means±SD) and Japanese subjects (716,256 ± 185,767) was significantly lower than in Caucasian Americans (974,940 ± 304,731), African Americans (943,466 ± 276,017) and Senegalese (987,029 ± 276,210). Although this difference was still present after adjustment for height or kidney weight, Nglomer after adjustment for BMI, BSA, or cortical volume was similar in the five populations.

Conclusions: This study shows there is no difference in nephron number among the five races after adjustment for body size or cortical volume. It indicates that while Aboriginal and Japanese subjects with smaller body size have fewer nephrons than the other races, further nephron loss and/or increased body size would likely increase the risk of CKD.

Nephron number in 20-65 years old subjects among five populations

Nationality | Nglomer (means ±SD) | Nglomer adjusted for BMI (means ±SD) | Nglomer adjusted for BSA (means ±SD) | Nglomer adjusted for cortical volume (means ±SD) | ANOVA (P values)
--- | --- | --- | --- | --- | ---
Aboriginal | 730,523 ± 244,460 | 730,523 ± 244,460 | 730,523 ± 244,460 | 730,523 ± 244,460 | 0.0016
Japanese | 716,256 ± 185,767 | 716,256 ± 185,767 | 716,256 ± 185,767 | 716,256 ± 185,767 | 0.0018
American | 974,940 ± 304,731 | 974,940 ± 304,731 | 974,940 ± 304,731 | 974,940 ± 304,731 | 0.0001
African | 943,466 ± 276,017 | 943,466 ± 276,017 | 943,466 ± 276,017 | 943,466 ± 276,017 | 0.0018
Senegalese | 987,029 ± 276,210 | 987,029 ± 276,210 | 987,029 ± 276,210 | 987,029 ± 276,210 | 0.0018

MeansSD

TH-PO556

Discovery of Novel Treatments for Ciliopathies and Cystic Kidney Disease

Elisa Molinar1, Jacqueline Bond, Julie Higgin, Shalabh Srivastava,2 Simon Ramsbottom,3 Colin A. Johnson,4 John Sayer,5 University of Leeds, Leeds, United Kingdom; 5University of Newcastle, Newcastle upon Tyne, United Kingdom.

Background: Nephronophthisis (NPHP) is an autosomal recessive cystic kidney disease that represents one of the most frequent genetic causes of end-stage kidney disease during childhood and adolescence. NPHP is a genetically heterogeneous disorder with 20 identified causative genes all encoding for proteins with a function in the primary cilium. NPHP is part of a spectrum of disease phenotypes associated with ciliopathies. We have previously generated a Cep290−/− model for NPHP. These animals exhibit renal cysts that originate from collecting duct epithelium from which we derived an immortalised cell culture. In recent work, we have shown that the Hedgehog (Hh) agonist Purmorphamine can rescue the cellular and ciliary phenotype in these cells, indicating that ciliopathies are both reversible and treatable. However, the ciliogenic effects of Hh agonism make it unsuitable as a means of treatment, especially of paediatric patients. We set forth to identify existing compounds which can be repurposed for the treatment of NPHP.

Methods: A PerkinElmer “Operetta” High Content Imager, with an “Harmony” and “Colonies” analysis and data storage system, was used to test 1120 biologically active compounds from the Torescreen Mini drug library on ciliated monolayers of immortalised murine Cep290−/− collecting duct epithelial cells. Measured parameters were cell number, cilia incidence and cell junction integrity.

Results: Through a high-throughput screening approach, we have tested 1120 existing drugs for their efficacy in ameliorating the cellular and ciliary defect of NPHP cells and we identified 33 hits in a primary screen. A secondary screen validated the efficacy of 5 compounds.

Conclusions: Our high-throughput screening revealed that the ciliary phenotype of NPHP cells can be rescued by treatment with selected drugs. Positive hits from our high-throughput screening will be further validated on murine and human NPHP 2D and 3D cell models.

Funding: Private Foundation Support

TH-PO562

Suppressive Effect of RXR Ligand and MEK Inhibitor on RXR Expression and Cellular Proliferation in Immortalized Polycystic Kidney Cells

Masanori Kugita,1 Tamio Yamaguchi,2 Kazuhiro Nishii,3 Mai Sasaki,4 Nohoru Ogiso,1 Harold M. Aikema,1 Shizuko Nagao,2 Laboratory of Experimental animals, National Center for Geriatrics and Gerontology, Obu-city, Aichi, Japan; 2Department of Clinical Nutrition, Suzuka University of Medical Science, Suzuka, Mie, Japan; 3Faculty of Rehabilitation, Fujita Health University, Toyoake, Aichi, Japan; 4Department of Human Nutritional Sciences, University of Manitoba, Winnipeg, MB, Canada; 5Education and Research Facility of Animal Models for Human Diseases, Fujita Health University, Toyoake, Aichi, Japan.

Background: We previously reported that expression of renal retinoid X receptor (RXR) was increased in three animal models of cystic kidney disease (Kugita et al AJP Renal 2011), and presented that treatment with beaxetron, a RXR agonist, significantly decreased renal RXR expression and kidney weight to body weight ratios in Han:SPRD-Cy−/− rats (Kugita et al ASN 2015). In hepatocellular carcinoma, phosphorylated RXR is related to aberrant cell proliferation accompanied by MEK-ERK phosphorylation to inhibit its degradation. RXR ligands may have suppressive effects on cell proliferation by phosphorylation and degradation of RXR (Adachi et al Hepatology 2002). In the current study, we determined the phosphorylation sites of RXR, and elucidated the effects of a RXR ligand and a MEK inhibitor on expression of RXR and ERK, and proliferation of immortalized PKD cells.

Methods: An immortalized PKD cell line, WT9-12 was obtained from ATCC and was maintained in DMEM with 10% FBS. Phosphorylation of RXR was analyzed by Phos-tag SDS-PAGE. To elucidate the effect of RXR ligand and MEK inhibitor, starved WT9-12 cells were treated with 10mM 9-cis retinoid acid (9cRA) and/or 100nM U0126. The expression levels of RXR and phospho-ERK (pERK) were analyzed by western blotting. Cell proliferation activity was measured by the MTT assay.

Results: In WT9-12 cells, RXR ligand and or MEK inhibitor decreased renal RXR expression and kidney weight to body weight ratios in Han:SPRD-Cy−/− rats (Kugita et al ASN 2015). In hepatocellular carcinoma, phosphorylated RXR is related to aberrant cell proliferation accompanied by MEK-ERK phosphorylation to inhibit its degradation. RXR ligands may have suppressive effects on cell proliferation by phosphorylation and degradation of RXR (Adachi et al Hepatology 2002). In the current study, we determined the phosphorylation sites of RXR, and elucidated the effects of a RXR ligand and a MEK inhibitor on expression of RXR and ERK, and proliferation of immortalized PKD cells.

Conclusions: The RXR ligand had a suppressive effect on proliferation of immortalized PKD cells, possibly by reducing expression of RXR and pERK. RXR ligands may have therapeutic potential either alone or in combination with MEK inhibitor to ameliorate PKD progression.

Funding: Government Support - Non-U.S.
TRPP2-Dependent Cellular Metabolism and Transcription
Achis and Hannah Müller, Sebastian Keller, Michael Kottgen. Medical Center - University of Freiburg, Freiburg im Breisgau, Germany.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic cause of chronic kidney disease, accounting for 7–10% of patients with end-stage renal disease. ADPKD is caused by loss of function mutations in PKD1 or PKD2. The gene products of PKD1 and PKD2, Polycystin-1 (PC1) and Transient Receptor Potential ion channel Polycystin-2 (TRPP2), form a receptor-ion channel complex of unknown molecular function. In an unbiased forward genetic screen we have previously identified a Short Ca2+-binding Mitochondrial polycystin Carrier (SCaMC) as a downstream effector of TRPP2. Here we investigate, whether TRPP2-SCaMC associated metabolic fluctuations regulate cellular gene expression – translating transient TRPP2 ion channel activity into lasting cellular responses.

Methods: To correlate changes in metabolite levels with cellular gene expression, we used CRISPR-Cas9 technology to generate multiple clones of HEK293 cell lines with truncated PKHD1 mutations. Whole transcriptome single-cell sequencing was performed on differentiated-type, PKD2- and SCaMC-repelled renal epithelial cell lines.

Results: The quantitative measurement of the dynamic multiparametric metabolic response to the pathophysiological loss of TRPP2 and SCaMC identified significantly changed metabolites in both systems. We found that these metabolites are associated with amino acid metabolism including branched chain amino acids (BCAA) in mitochondria. Similarly, the expression of a large number of genes is affected by loss of TRPP2 and SCaMC. We are now correlating concordant changes in cellular metabolism and gene expression to identify novel molecular entities in the polycystin-signaling cascade.

Conclusions: We have previously shown that loss of the metabolite carrier SCaMC phenocopies loss of TRPP2 in invertebrate and vertebrate model systems. Emerging evidence suggests that metabolite fluctuations regulate cellular signal transduction. We hypothesize that the polycystin model discovered a significant number of metabolites and genes indeed regulated by TRPP2 and SCaMC. It is tempting to speculate that concordantly changed molecular entities may provide mechanistic links between the polycystin-receptor-ion channel complex and the diverse morphological changes observed in ADPKD.

Truncating PKHD1 Mutations Alter Energy Metabolism
Philip H. Chumley,1 Sylvie Mrug,1 Juling Zhou,2 Bradley K. Yoder,2 Michal Mrug.1,3 University of Alabama at Birmingham, Birmingham, AL, USA.

1Department of Veterans Affairs Medical Center, Birmingham, AL, USA.

Background: Polycystin 1 deficiency triggers specific changes in energy metabolism. However, it remained uncertain whether similar changes are caused by relevant defects in other human cystopathies. As our initial step towards identification of novel mechanisms of polycystin-driven energy metabolism, we explored the influence of engineered PKHD1 gene mutations on the metabolic phenotype of human renal epithelial cell lines. Specifically, we investigated whether these mutations result in energy metabolism disorders at an early stage of cyst development.

Methods: We prioritized PKHD1 mutations targeting for based on their reported frequency in the African American population. We performed a panel of metabolic analyses in human papillary renal epithelial cell lines harbouring insertions, deletions, or truncations of the PKHD1 gene. Furthermore, we evaluated the effects of these mutations on the cellular dynamics of the human papillary renal cell line, NRCPC. Finally, we investigated the impact of these mutations on cellular proliferation and cell cycle analysis.

Results: The metabolic analyses revealed significant changes in energy metabolism, including alterations in the tricarboxylic acid cycle, the oxidative phosphorylation pathway, and the pentose phosphate pathway. The cell cycle analysis showed a significant increase in the number of cells in the S phase, indicating an increased proliferation rate.

Conclusions: Our findings suggest that truncating PKHD1 mutations alter energy metabolism, potentially contributing to the pathogenesis of cystic kidney disease. Further studies are needed to elucidate the underlying mechanisms and to evaluate therapeutic strategies for targeting these metabolic changes.

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

Underlines represent presenting author.

Diminished TRPV4 Activity and Glycocalyx Contributes to Compromised [Ca2+]i Homeostasis in Human ADPKD Cells
Viktor N. Tomlin,1 Oleg L. Zaika,2 Gail Reif,1 Darren P. Wallace,1 Oleh Pochynuk.1 University of Kansas Medical Center, Kansas City, KS; University of Texas Health Science Center-Houston, TX.

Background: PKD is a devastating clinical pathology leading to a decline in kidney function due to development of fluid-filled cysts. No effective pharmacological treatments exist for PKD patients. Defective flow-mediated [Ca2+]i responses and disrupted [Ca2+]i homeostasis have been repeatedly associated with the development of PKD. Our previous work in rodents demonstrated that the activity of the Ca2+-permeable TRPV4 channel is imperative for flow-mediated [Ca2+]i responses in the distal renal tubule. TRPV4 function is dramatically decreased in isolated cystic cell monolayers and systemic stimulation of TRPV4 interferes with PKD progression in PCK 453 rats, an ARPKD model.

Methods: Here, we determined the role of TRPV4 in Ca2+ signaling in human ADPKD and normal human kidney (NHK) cells. ADPKD cells failed to respond to flow and had significantly lower basal [Ca2+]i levels compared to NHK cells, consistent with our previous work. Tomlin et al. (Am. J. Physiol. Cell Physiol. 2016). Application of TRPV4 antagonist, HC-067047 significantly reduced basal [Ca2+]i in NHK cells but had no measurable effect in ADPKD cells. TRPV4 agonist, GSK1016790A elicited more than two times higher [Ca2+]i response in NHK than in ADPKD cells. GSK1016790A-
mediated responses were precluded by HC-067047 or a Ca2+-free media. Patch clamp and in vitro, we have shown that the expression of FxATMIN in a cell-permeable form restored [Ca2+]i homeostasis in cyst cells to levels similar to those in normal tubules.

**Results:** The cystic phenotype observed in ADPKD patient-derived cell cultures is characterized by increased [Ca2+]i levels. These elevated [Ca2+]i levels result in enhanced [Ca2+]i release from the endoplasmic reticulum, which leads to increased [Ca2+]i influx through voltage-dependent Ca2+ channels. The activation of these calcium influx pathways is further enhanced by the decreased expression of fibronectin and eGFP, as well as the increased expression of CD8+ T-cells.

**Conclusions:** The increased [Ca2+]i levels observed in ADPKD cells are due to the enhanced expression of CD8+ T-cells, which is associated with increased fibronectin expression and decreased eGFP expression. These findings suggest that the increased [Ca2+]i levels in ADPKD cells are due to the increased expression of CD8+ T-cells and the decrease in fibronectin expression, leading to increased fibronectin turnover and decreased [Ca2+]i homeostasis.

**Funding:** NIDDK Support

**TH-PO568**

**Overexpression of Activated TGFβ1 in Collecting Ducts Induces Cyst-Like Tube Dilatation and Renal Fibrosis in Wildtype Mice and Accelerates the Decline in Renal Function in ADPKD Mice. Yuqiao Dai,1 Yan Zhang,2 Archanan Rama,1 Emily A. Daniel,1 Aditi Khanna,1 Gail Reif,2 Fernando Pierucci-Alves,1 Darren P. Wallace,2 Kansas State University, 1University of Kansas Medical Center, Kansas City, KS.

**Background:** Transforming growth factor β1 (TGFβ1), a master regulator of extracellular matrix production, is involved in autocrine driven polycystic kidney disease (ADPKD). TGFβ1 is also involved in Marfan Syndrome (MFS), a genetic disorder caused by defective connective tissue genes, which leads to increased and formation of renal cysts in approximately 60% of patients. Currently, the role of activated TGFβ1 in renal cyst formation is MFS and the effect of TGFβ1 on cyst growth and disease progression in ADPKD remain unclear.

**Methods:** To determine if activated TGFβ1 is sufficient to induce renal cyst formation and fibrosis, we crossed β1++ (TGFβ1) mice, which conditionally express TGFβ1, with Phkdl-Cre mice to express activated TGFβ1 selectively in collecting ducts (CD; TGFβ1+++). We also overexpressed activated TGFβ1 in CDs of Pkd1++/− mice, a slow-progressing mouse model of ADPKD.

**Results:** CD overexpression of TGFβ1 caused cyst-like tube dilatations and increased kidney weight (% body weight; KW/ID) by 5 wk of age. However, by 10 wk, the kidneys developed focal area of fibrosis and pitting of the surface that was indicative of scarring, and there was a significant reduction in KW/ID of β1+++ mice compared to wildtype (WT) mice. There were increased renal levels of perisin, a marker for PKD progression, phosphorylated SMAD3, α-smooth muscle actin (α-SMA) and vimentin, markers for myofibroblasts. Blood urea nitrogen (BUN) was slightly increased in β1+++ mice compared to WT mice at 20 wk, but this difference was not statistically significant. Similar results were obtained in Pkd1++/− mice, which have one hypomorphic Phkdl allele. Overexpression of TGFβ1 in Pkd1++/− mice did not increase cystic index, but rather caused extensive fibrosis and contraction of the kidneys, leading to decreased KW/ID. This was accompanied by increased levels of perisin, α-SMA and vimentin, and a decline in renal function, evidenced by an elevation of BUN compared to Phkdl++/− mice.

**Conclusions:** Our results demonstrate that expression of activated TGFβ1 is sufficient to induce cyst-like tube dilatations and renal fibrosis in normal mice, and accelerate the decline in kidney function in ADPKD mice.

**Funding:** NIDDK Support

**TH-PO569**

**Increased Wnt/β-Catenin Signaling in Postnatal Mouse Model of ADPKD Yun Joon Jung,1,2 Jordan A. Kreidberg,1,2 Urology, Boston Children’s Hospital, Boston, MA, 1Surgery, Harvard Medical School, Boston, MA.

**Background:** The Wnt signaling pathway has an important role for nephron morphogenesis of the ureteric bud during embryonic renal development. The range of disease severity observed in ARPKD suggests that besides PKHD1 that when mutated causes ARPKD, other genes might also play a role in ARPKD, acting as modifiers of disease severity. Our previous work on ATMIN has shown that it plays a role in kidney morphogenesis by modulating Planar Cell Polarity (PCP) signaling.

**Methods:** Quantitative real-time PCR and immunohistochemistry was employed in age-matched normal and ARPKD human kidneys, to investigate causal (fibrocystin) and PCP (Daam2, ATMIN, NPHSP2/Inversin) effects. Amnio and Phkdl siRNA-mediated knockdowns and Antin-Green Fluorescent Protein (GFP) overexpression studies were conducted in mouse inner medullary collecting duct (IMCD3) cells, to study the mechanistic relationship between ATMIN and Fibrocytin.

**Results:** A 2-fold increase in ATMIN was observed in human ARPKD vs normal kidneys; no significant differences were seen in Daam2 or NPHSP2. In normal human kidneys ATMIN, Inversin and Fibrocystin were expressed in ureteric bud-derived collecting tubules, whereas in age-matched ARPKD tissue, strong ATMIN and Inversin expression was observed, consistent with the role of ATMIN and Inversin in cyst-lining epithelial cells. By flow cytometry, immunofluorescence, qPCR, histopathology, and antibody depletion, we evaluated the role of T-cells in the CD8+ T-cell ratio (1:1 vs C57BL/6 1:1), suggesting selective activation of CD8+ T-cells from 1-3 months in C57BL/6 and BALB/c: 6.6, 17.6). We further observed increases in CD44 to CD4+ T-cells from 1-3 months in C57BL/6 (3m: 21.4; 5m: 27.1; 8m: 35.6) and in BALB/c (87.5%). Importantly, there was an increase in fibrotic area (2.6 vs 1.7).

**Conclusions:** This work suggests that ATMIN interacts with Fibrocytin, proposing ATMIN as a modifier of ARPKD that could in the long term be used as a biomarker of ARPKD severity and progression.

**Funding:** NIDDK Support

**TH-PO571**

**Activation of CD8+ T-Cells Inhibits Cyst Growth in a Murine Model of ADPKD Emily K. Kleczko,1,2 Kenneth H. Marsh, Eric T. Clambey,1,3 Seth B. Furgeson,1 Berenice Y. Gitomer, Michel Chonchol, Raphael A. Nemenoff,1,2 Katharina Hopp,1 University of Colorado Anschutz Medical Campus, Aurora, CO.

**Background:** Phenotypic heterogeneity observed in Autosomal Dominant Polycystic Kidney Disease (ADPKD) cannot be explained solely by genetic factors. As in other diseases, differences in the microenvironment likely contribute to disease variability. In ADPKD, the role of the adaptive immune system, a critical component, is largely unknown. The goal of this study was to determine the function of T-cells in ADPKD progression.

**Methods:** Using flow cytometry, immunofluorescence, qPCR, histopathology, and antibody depletion, we evaluated the role of T-cells in the CD8+ T-cell ratio (1:1 vs C57BL/6 1:1), suggesting selective activation of CD8+ T-cells in our model and a potential correlation of CD8+ T-cell numbers to disease severity. In concordance, antibody depletion of CD8+ T-cells from 1-3 months in C57BL/6 mice versus IgG controls significantly increased kidney weight/body weight ratio (4.2 vs 2.1), average cyst size (18.6 vs 14.2 x10³ µm²), and %fibrotic area (2.6 vs 1.7). However, cyst number did not change (8.4 vs 8.6 per mm²), indicating that CD8+ T-cells slow cyst progression/fibrosis, but not initiation.

**Conclusions:** These data indicate that T-cells are upregulated in ADPKD and are recruited to cystic lesions. Further, CD8+ T-cells play a crucial role in attenuating cyst growth, suggesting that therapeutic compounds designed to activate CD8+ T-cells may be promising ADPKD treatment options.

**Funding:** Foundation Private Support

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
**TH-PO572**

**Effectiveness of MTT in Liver Phenotype in a Model of Autosomal Recessive Polycystic Kidney Disease (ARPKD) Adrian Cordido,1 Olaya Lamas-Gonzalez,2 Ana Barcia de la Iglesia,3 Jesus Bañales,2 Candido Diaz-Rodriguez,2 Miguel A. García-González,3 Biodosmetics Health Research Institute, San Sebastián, Spain; 1Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain; 2Instituto de Investigación Sanitaria Fundación Jiménez Díaz, Madrid, Spain; 3Instituto de Investigación Sanitaria Fundación Jiménez Díaz, Madrid, Spain; 4University Clinic Hospital of Santiago de Compostela (CHUS), Santiago de Compostela, Spain.

**Background:** Polycystic liver disease (PLD) are genetic disorders characterized by progressive bile duct dilatation and cyst development in hepatic parenchyma. PLD are inherited in a dominant or recessive form and can develop alone or in association with polycystic kidney disease (PKD). A number of different mechanisms have been related to the pathogenesis of PLD, including alteration in the extracellular matrix (ECM). MTT is a Metalloproteinases inhibitor. In previous work (ASN2016), we have shown the effectiveness of MTT in models of Autosomal Dominant PKD (ADPKD), both in renal and hepatic phenotype.

**Results:** Here, we examined the effects of MTT in a potential therapy for PLD associated to Autosomal Recessive PKD (ARPKD). In this model, we used a model of ARPKD, Pkd1cko/cko (Pkd1-KO), to test the effectiveness of MTT in hepatic cystogenesis.

**Conclusion:** In our previous work, we showed the benefit effect of MTT in Autosomal Dominant Polycystic Kidney Disease (ADPKD) inhibiting the hepatic cystogenesis and collecting duct cyst (DBA + cyst). Now, we have deeply characterized the liver phenotype in our ARPKD model, identifying a time depending gender effect of disease progression. We have also tested MTT, alone and in combination with Tolvaptan, in different points resulting in a significant inhibition of hepatic cystic progression in ARPKD.

**Conclusions:** In ASN 2016, our group showed the effect of MTT in Autosomal Dominant Polycystic Kidney Disease (ADPKD) inhibiting the hepatic cystogenesis and collecting duct cyst (DBA + cyst). With this work, we have demonstrated the effectiveness of MTT in the inhibition of hepatic phenotype of ARPKD.

**TH-PO573**

**Cytokine TWEAK Promotes Cystogenesis in Autosomal Dominant Polycystic Kidney Disease (ADPKD) in a Time Dependent Manner Adrian Cordido,2 Ana B. Sanz,3 Ana Barcia de la Iglesia,2 Candido Diaz-Rodriguez,2 Alberto Ortiz,4 Miguel A. García-González,3 Fundacion Jimenez Diaz, Madrid, Spain; 1Instituto de Investigacion Sanitaria (IDIS) de Santiago de Compostela, Santiago de Compostela, Spain; 2Instituto de Investigacion Sanitaria Fundacion Jimenez Diaz, Madrid, Spain; 3University Clinical Hospital of Santiago de Compostela (CHUS), Santiago de Compostela, Spain.

**Background:** Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common monogenic disorder in which kidneys develop fluid-filled cyst derived from the tubule epithelial cells. Several mechanisms are associated with cyst initiation and cyst progression, recent findings aim inflammation as one the most important molecular mechanism in the progression of ADPKD. TWEAK (tumor necrosis factor TNF-like weak inducer of apoptosis) binds to the TNF receptor superfamily, TWEAK promotes inflammation, proliferation, cell death and angiogenesis. However, the role of TWEAK in ADPKD is unknown.

**Methods:** We have studied the effect of TWEAK in our ARPKD animal model, Pkd1cko/cko (Pkd1-KO). This model represents a cystogenic strain, which is at the backcross stage of a developmental switch and may converge the inactivation of Pkd1 gene in different points of life determines cystic phenotype. In this study, we analyzed the expression of TWEAK in the ARPKD model and in control animals. We cultured TWEAK and TWEAK knockouts. We measured cystic area, tubular cells proliferation, apoptosis, DNA damage, cystic index, interstitial inflammation and fibrosis was decreased in kidneys of ARPKD mice. We examined the effects of lixivaptan in PKD rats, an orthologous animal model of Autosomal Recessive PKD that develops a phenotype reminiscent of ADPKD. 4-week old PKD rats were randomly assigned to vehicle control, standard dose of lixivaptan or two dose levels of lixivaptan daily and subsequently treated for 8 weeks. At the end of treatment, a comprehensive panel of biochemical and histomorphometric endpoints was evaluated to assess the effect of lixivaptan on disease progression.

**Conclusions:** PKD rats in the control group showed enlarged kidneys and extensive cyst formation, consistent with the development of a polycystic kidney phenotype. Compared to control animals, PKD rats treated with the standard dose of lixivaptan showed a 27% reduction in kidney weight as a percentage of body weight (p=0.006), a 23% reduction in kidney cAMP levels (p=0.014), a small but statistically significant increase in liver weight as a percentage of body weight (6%; p=0.03) and a reduction in cyst burden. As expected, these reductions were associated with statistically significant increases in 24h urine output (179%; p<0.0001) and serum sodium (1.7%; p=0.02). Pharmacological effects of disease manifestations were also observed in animals treated with the two alternative dosing regimens of lixivaptan, however the difference with the control did not reach statistical significance.

**Conclusions:** The beneficial effect of lixivaptan in the PKD rat model of PKD adds to the body of evidence implicating vasopressin V2 receptors in the pathology of ADPKD.

**Funding:** Our results indicate that epithelial innate immunity signaling concurs in maintaining inflammation and fibrosis in the mouse model of NPHP7.

**TH-PO575**

**Targeting Epithelial Innate Immunity Improves Inflammation and Fibrosis in a Mouse Model of Nephronophthisis Heng Jin,1 Shanshan Wang,2 Qiong Ding,3 Dongmei Lu,1 Massimo Attanasio,2 UT Southwestern Medical Center, Dallas, TX; 1University of Iowa, Iowa City, IA.

**Background:** Inactivation of the gene Glis2 causes nephronophthisis type 7 (NPHP7), a kidney disease characterized by progressive interstitial inflammatory infiltration and fibrosis. Recently, we have shown that cell senescence of kidney epithelial cells is a key event in the pathogenesis of NPHP. Senescent cells are known to secrete an array of molecules, referred to as senescence associated secretory phenotype (SASP), that is controlled by the NF-kB pathway and sustain organ inflammation and fibrosis. Toll-like receptors (TLRs) are “surveillance” receptors that recognize microbial particles and endogenous molecules. TLR2 and TLR4 are abundantly expressed on the surface of kidney epithelial cell and, when stimulated, induce activation of the NF-kB pathway through the shared adaptor myeloid differentiation protein 88 (MyD88).

**Methods:** We found that multiple NF-kB genes are overexpressed in Glis2 deficient kidney cells, including TLR4, which is at the backcross stage of a developmental switch and may converge the inactivation of NF-kB, and hypothesized that activation of epithelial innate immune may affect inflammation and fibrosis in Glis2 knockout kidneys. We tested this hypothesis by generating Glis2del3-4/del3-4;Tlr4mut/mut;Ksp-cre mice at 3 months of age. No differences of kidney function and tubular cell senescence were detected.

**Conclusion:** Our results indicate that epithelial innate immunity signaling concurs in maintaining inflammation and fibrosis in the mouse model of NPHP7.

**Funding:** NIDDK Support.
isolation was excluded from the papilla, while the C24 isoform was highly enriched in the islet of Langerhans (IC) kidneys. Western blot analysis, Cytoquant cellular assay, and Firefly-renilla assays were performed on human primary epithelial cells from normal renal cortical tubular epithelium (PKD1+/+) and ADPKD cyst-lining epithelium (PKD1−/−) transfected with control or pcAG-F113A or transfected with control or F113A lentivectors.

**Results:** Phospho 4E-BP1 species were present in cyst lining cells of human ADPKD and Cy renal tissues. F113A resulted in substantially reduced phospho 4E-BP1 T37/46 (0.9±0.8 vs 0.01±0.004DUC, p<0.01) and S65 (0.6±0.3 vs 0.005±0.001DUC, p<0.01) reduced cap-dependent protein translation (37%, p<0.01) and reduced T22K proliferation (50±8 vs 140±50±82Duc, p<0.001) in PKD1−/− cells. Surprisingly, in PKD1−/− cells, F113A resulted in no phospho 4E-BP1 reduction, reduced cap-dependent protein translation (32%, p<0.01), and marginally reduced proliferation (375±5 vs 314±4 480±500Duc, p=0.0001). Acute stimulation with insulin resulted in maintained S65 suppression with F113A transfection in PKD1−/− (2.1±0.3 vs 0.2±0.1AU, p<0.0001).

**Conclusions:** F113A results in a shift towards hypophosphorylated 4E-BP1 species, reduced cap dependent protein translation, and reduced proliferation, with more aggressive effects in PKD1−/− vs PKD1+/+. Utilizing F113A gene therapy to counter the loss of the translationally repressive 4E-BP1 pathway in a murine model of PKD, is the next step in addressing a pathway seemingly integral to the pathology of PKD.

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

**TH-PO579**

**Phosphorylation Insensitive 4E-BP1 Reduces Hypophosphorylative Phenotype**

*A Vira* Holtzclaw,* Carolyn* N. Brown,* Kameswaran Ravichandran,* Charles* L. Edelman,* UC Denver Anschutz Medical Campus, Aurora, CO; *University of Colorado Denver, Aurora, CO; *Hera BioLabs, Lexington, KY.

**Background:** Unchecked proliferation of cystic epithelial cells is a major contributor to cyst growth in PKD. The 4E-BP1 pathway is a crucial checkpoint in protein translation initiation and cellular proliferation. Evidence from oncology supports the malignant potential of 4E-BP1. A recognized oncoagent, 4E-BP1 is associated with worsening progression, metastasis, and morbidity in oncology. The aim of this study was to determine 1) whether PKD patient and animal model kidney tissues have dysregulated phosphorylated 4E-BP1 (F113A) on phospho 4E-BP1 species distribution, cap dependent protein translation, and proliferation in renal epithelial cells.

**Methods:** Immunofluorescence staining of phospho 4E-BP1 species (T70, T37/47, S65) in human (ADPKD) and murine (Pkd1−/−) kidneys. Western blot analysis, Cytoquant cellular assay, and Firefly-renilla assays were performed on human primary epithelial cells from normal renal cortical tubular epithelium (PKD1+/+) and ADPKD cyst-lining epithelium (PKD1−/−) transfected with control or pcAG-F113A or transfected with control or F113A lentivectors.

**Results:** Phospho 4E-BP1 species were present in cyst lining cells of human ADPKD and Cy renal tissues. F113A resulted in substantially reduced phospho 4E-BP1 T37/46 (0.9±0.8 vs 0.01±0.004DUC, p<0.01) and S65 (0.6±0.3 vs 0.005±0.001DUC, p<0.01) reduced cap-dependent protein translation (37%, p<0.01) and reduced T22K proliferation (50±8 vs 140±50±82Duc, p<0.001) in PKD1−/− cells. Surprisingly, in PKD1−/− cells, F113A resulted in no phospho 4E-BP1 reduction, reduced cap-dependent protein translation (32%, p<0.01), and marginally reduced proliferation (375±5 vs 314±4 480±500Duc, p=0.0001). Acute stimulation with insulin resulted in maintained S65 suppression with F113A transfection in PKD1−/− (2.1±0.3 vs 0.2±0.1AU, p<0.0001).

**Conclusions:** F113A results in a shift towards hypophosphorylated 4E-BP1 species, reduced cap dependent protein translation, and reduced proliferation, with more aggressive effects in PKD1−/− vs PKD1+/+. Utilizing F113A gene therapy to counter the loss of the translationally repressive 4E-BP1 pathway in a murine model of PKD, is the next step in addressing a pathway seemingly integral to the pathology of PKD.

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

**TH-PO580**

**PKD1-Deficient Mice Show Increased Susceptibility to Induction of Endoplasmic Reticulum Stress Following Mild Renal Ischemia/Reperfusion**

Andressa* G. Amaral,* Andre* F. Pires,* Elielser* H. Watanabe,* Luiz* F. Onuchic,* Nephrology and Molecular Medicine, University of São Paulo, São Paulo, Brazil; *Sírio Libanes Hospital, São Paulo, Brazil.

**Background:** PKD1 haploinsufficiency has been shown to increase susceptibility to renal ischemia-reperfusion (IR) in mice. IR is a classical cause of endoplasmic reticulum stress (RS) and RS can aggravate renal injury induced by IR. Activation of Xbp1, in turn, has been proposed to amplify the cystic phenotype of Scv6<sup>−/−</sup>−/−<sup>−/−</sup>Ksp-Cre mice by decreasing cystinuria-Polycystin-1 activity. To investigate the effect of mild renal IR on RS in Pkd1−/− mice, we analyzed RS and inflammation markers in Pkd1−/− and controls submitted to mild renal IR and SI. Renal expression of Xbp1s was measured 24h after IR and SI after these procedures. Kidneys were harvested 48h post-IR or SI to evaluate IL6, IL6, IL10, MCP1, TNFα and RANTES by multiplex assay; GRP78 and XPB1s by western blot; Hif1α, Hspa3 and Ddit3 by real time RT-PCR; and Xbp1s/Xbp1a ratio by dual color F/PCR.

**Results:** SUN did not differ between WT and HT mice after IR and SI. Hif1α expression did not significantly increase following renal IR in mice with either genotype, indicating that the induced insult was mild. The levels of IL1β, IL6, IL10, MCP1, TNFα, IL12, IFNγ, IL6, IL10, MCP1, TNFα and RANTES were different between IR and control (mean±SD) at 48h after these procedures. Kidneys were harvested 48h post-IR or SI to evaluate IL6, IL6, IL10, MCP1, TNFα and RANTES by multiplex assay; GRP78 and XPB1s by western blot; Hif1α, Hspa3 and Ddit3 by real time RT-PCR; and Xbp1s/Xbp1a ratio by dual color F/PCR.

**Conclusions:** Our findings support that Pkd1 haploinsufficiency increases the level of RS following mild renal IR in mice, by favoring the activation of the 1REα1-XPB1 branch of UPR. Our data suggest that this effect may possibly modulate polycystin-1 function and pathophysiological changes in the setting of mild IR, potentially limiting the increased susceptibility associated with Pkd1 haploinsufficiency.

**Funding:** Government Support - Non-U.S.
Induced Inactivation of Pkd2 Results in Progressive Tubule Reduction and Loss in New, 3D Model of ADPKD Cystogenesis

Erynn E. Dixon, Owen M. Woodward. University of Maryland School of Medicine, Baltimore, MD.

**Background:** The role of PKD1/PKD2 loss in renal cystogenesis remains both unequivocal and undefined. Many disparate pathways are known to be altered in ADPKD without a definitive mechanistic pathway connecting back to the loss of either polycystin proteins. A long standing roadblock has been the inability to model cystogenesis resulting from the spontaneous loss of PKD1/PKD2 as postulated by the two-hit ADPKD hypothesis.

**Methods:** To better understand the local effects of Pkd2 inactivation on cystogenesis, signaling, and organization of different cell types, we initiated a new, three-dimensional (3D) in vitro model has been developed that employs primary renal cells from an inducible Cre (Pkd2 PAsxRTTA TetoCreERT2+mTmG) mouse line. This 3D culture system combines a unique “sandwich” plating technique with a gel-derived neurotrophic factor (GDNF) growth factor cocktail to increase the yield of differentiated and complex epithelial structures, including spheroids and tubules. In addition, this new model system allows tracking of gross morphological changes of 3D structures and cellular components before and after the inactivation of Pkd2.

**Results:** Characterization of the differentiated tubule structures reveals that the cells of the organoids demonstrate typical apicobasolateral polarization and primary cilia as defined by basolateral Na+/K+ATPase and luminal acetylated tubulin, respectively. Interestingly, the differentiated organoids are positive for collecting duct markers, Dct, Dct-like (Dct-like aquaporin 1 (DRA)), and the apical water channel, aquaporin-2 (AQP2) while negative for proximal tubule markers, Lotus tetragonolobus lectin (LTL) and ATP-binding cassette sub-family G member 2 (ABCG2). Addition of doxycycline induces Cre and mosaic inactivation of Pkd2 with an approximately 50% decrease in the abundance of secondary markers of Pkd2 disruption in a progressive reduction and eventual loss of tracked tubule structures when compared to control organoids.

**Conclusions:** Changes in morphology of differentiated structures following inactivation of Pkd2 in this novel cystogenesis culture system suggest a defect in the 3D organoid culture model that is dependent on the study of cystogenesis. In 3D organoid culture systems may provide novel insights into the pathogenesis of ADPKD.

Funding: NIDDK Support, Other NHI Support - T32 Training Program in Integrative Membrane Biology

---

Kidney Glycosphingolipidomics and Metabolomics Reveal Metabolic Crosstalk between Elevated Glycosphingolipids and Glucose Metabolism in PKD Progression

Kazuki Nakajima,1 Kazuo Takahashi,2 Masanori Kugita,3 Shizuko Nagao,2 Yukio Yuzawa,4 Fujita Academy, Fujita health university, Toyoake, Aichi, Japan; 2Fujita Health University, Toyoake, Aichi, Japan; 3Fujita Health University; School of Medicine, Toyoake, Japan; 4Fujita Health University School of Medicine, Toyoake, Japan.

**Background:** Polycystic kidney diseases (PKDs) are characterized by abnormal proliferation and cyst formation in renal epithelial cells. Particularly, abnormal glucose and lipid metabolism are known therapeutic targets of PKD. We previously reported that a crucial cellular energy sensor, AMP-activated protein kinase, tightly regulates glycosphingolipid (GSL) biosynthesis by reducing nucleotide sugars, suggesting a metabolic crosstalk between GSLs and glucose metabolism (Ishibashi. Y et al. J.Biol. Chem. 2015). Herein, we investigated whether this crosstalk leads to cooperative effects in PKD progression by using lipidomics and metabolomics.

**Methods:** Glycosphingolipidomics and metabolomics in 10-week-old male juvenile cystic kidney (JCK) mice and control mice were performed by four newly developed methods using liquid chromatography electrospray ionization tandem mass spectrometry (LC-ESI-MS/MS). This study included the (1) global analysis of abundant sphyngolipids, (2) quantification of glycosylceramides using an isometric separation system, and (3) acidic GSLs-focused analysis. Moreover, (4) metabolomics included the quantification of nucleotide sugars, the substrate of GSLs. The involvement of the crosstalk in PKD progression was demonstrated by analyzing changes in cell lines treated with several inhibitors.

**Results:** Global analysis of sphingolipids revealed no significant changes in more than 100 species of abundant ceramides and sphingomyelins. However, the second method showed higher levels of major GlcCer species in the PKD mouse kidney. Further, acidic GSL-focused analysis showed a remarkable increase in G3M gangliosides, but not sulfatides. Lipidomics revealed the UGPase level was up-regulated in PKD. The elevated GSLs were abrogated by treatment with 2-deoxy-glucose, an inhibitor of glucose metabolism. Conversely, treatment with Genz-123346, an inhibitor of GSL synthesis, suppressed UDP-glucose levels in a PKD model cell line.

**Conclusions:** The metabolic crosstalk between GSL and lipid metabolism may play a role in PKD progression. Our workflow provides valuable information regarding the molecular mechanisms studied during the search of novel therapeutic targets of PKD.

---

ADAM10-MMP14 Complex Regulates Renal Cystogenesis in Autosomal Dominant Polycystic Kidney Disease

Frank Xu,1 Li-lun Ho,1 Bradley M. Denker,2 Tianqing Kong,1 Joseph V. Bonventre,1 Tongshi Lu,1 Brigham and Women’s Hospital, Harvard Medical School, Boston, MA; 2Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.

**Background:** Autosomal dominant polycystic kidney disease (ADPKD) is associated with mutations in polycystins, alterations in cell-cell junctions and focal adhesions in renal epithelial cells. Polycystin 1 (PC1) forms a large protein complex that includes E-cadherin and cell surface receptors that play key roles in renal cell-cell junctions and cell polarity. We previously reported that deletion of PC1-regulated protein, Gα12, protected kidneys from kidney cystogenesis induced by Pkd1 inactivation, and activation of Gα12 increased the shedding of E-cadherin. However, signaling pathways of PC-induced ADPKD are not fully understood.

**Methods:** We used Madin-Darby canine kidney (MDCK) cells, Pkd1 deletion renal cells and Pkd1 knock out mice kidney tissue. Inducible Pkd1 knock out mice were generated by flanking exons 2 through 6 with two LoxP sites (MxCre; Pkd1fl/fl). Double knockout of Pkd1 and G12-β/γ mice were obtained by crossing MxCre Pkd1floXflo mice with G12-α mice (Pkd1/-;G12-β/γ). MDCK Tet-off inducible G12 and G12QL cell lines were used in 3D cell culture.

**Results:** The conditional deletion of Pkd1 (Pkd1−/−) resulted in multiple kidney cysts forming within 9 weeks, but Pkd1−/-;G12β/γ mice had no structural and functional alterations in renal epithelial cells. Polycystin 1 (PC1) forms a large protein complex that includes E-cadherin and cell surface receptors that play key roles in renal cell-cell junctions and cell polarity. We previously reported that deletion of PC1-regulated protein, Gα12, protected kidneys from kidney cystogenesis induced by Pkd1 inactivation, and activation of Gα12 increased the shedding of E-cadherin. However, signaling pathways of PC-induced ADPKD are not fully understood.

**Methods:** We used Madin-Darby canine kidney (MDCK) cells, Pkd1 deletion renal cells and Pkd1 knock out mice kidney tissue. Inducible Pkd1 knock out mice were generated by flanking exons 2 through 6 with two LoxP sites (MxCre; Pkd1fl/fl). Double knockout of Pkd1 and G12-β/γ mice were obtained by crossing MxCre Pkd1floXflo mice with G12-α mice (Pkd1−/-;G12β/γ). MDCK Tet-off inducible G12 and G12QL cell lines were used in 3D cell culture.

**Results:** The conditional deletion of Pkd1 (Pkd1−/−) resulted in multiple kidney cysts forming within 9 weeks, but Pkd1−/-;G12β/γ mice had no structural and functional abnormalities in the kidneys. Pkd1 deletion promoted increased E-cadherin fragments in renal cystic fluid. No change in cyst E-cadherin fragments in G12-α/- mice. G12 increased the active form of ADAM10, and knock down of ADAM10 blocked the G12 mediated E-cadherin shedding. Our data indicate that ADAM10 is the major sheddase for cleavage of E-cadherin caused by G12 activation. Increased ADAM10/MMP14 complex promotes cystogenesis in renal epithelial cells. ADAM10 activity is dependent on the catalytic and hemopexin domains of MMP14. Inhibition of ADAM10 and MMP14 activity slows cystogenesis induced by G12 activation. The deletion of Pkd1 increases the activation of G12, which subsequently decreases cell-matrix and cell-cell adhesion by affecting focal adhesion and E-cadherin cleavage.

**Conclusions:** G12 is an essential downstream signaling molecule for PC1, and G12 activation increases ADAM10 activity promoting the ectodomain shedding of E-cadherin that plays a key role in renal cystogenesis in Pkd1 deletion induced ADPKD. The ADAM10-MMP14-Ecadherin axis is a potential therapeutic target for ADPKD.

Funding: Private Foundation Support
TH-PO585

Recessive Mutations of MAP7D3 Cause a Renal Ciliopathy

Tilman Jobst-Schwan,1 Joao Goncalves,3 Einat Lahav,2 Deborah R. Stein,1 Benjamin Dekel,3 Laurence Pelletier,2 Friedhelm Hildebrandt,1 1Division of Nephrology, Boston Children's Hospital, Boston, MA; 2Lunenfeld-Tanenbaum Research Institute, Toronto, ON, Canada; 3Sheba Medical Center, Safra Children's Hospital, Division of Pediatric Nephrology, Pediatric Stem Cell Research Institute, Ramat Gan, Israel.

Background: Renal ciliopathies are characterized by dysfunction of the primary cilium and centrosomes. Mutations in one of 95 genes have been discovered to cause these single gene-disorders in ~65% of patients with renal ciliopathies.

Methods: To identify novel ciliopathy genes, we analyzed whole exome sequencing (WES) data in individuals with ciliopathies, who had no mutations in any known ciliopathy genes. We examined the subcellular localization of MAP7D3 using confocal immunofluorescence (IF) analysis in and performed co-immunoprecipitation (co-IP) to test the interactions with other known ciliopathy genes.

Results: The male index patient from a non-consanguineous family presented with polyuria, enuresis, tubular proteinuria, impaired kidney function (GFR 30ml/min) and acidois. Renal ultrasound (US) showed small, echogenic kidneys. By WES trio analysis, we identified the hemizygous truncating mutation c.1284,1285insC (p.Ser429Glnfs) in the X-chromosomal MAP7D3 gene in this patient. In a second unrelated non-consanguineous family, the male patient presented with severe hyperkalemia, small echogenic kidneys upon US and end stage renal disease. Renal biopsy of this patient showed nephronophthisis-like features with additional glomerulosclerosis. By WES, we identified the hemizygous missense mutation c.655G>C, p.Arg22Pro in MAP7D3 introducing a proline residue in a coiled-coil domain that is known to interact with microtubules. By IF, we show that wild type Flag-BiRa-MAP7D3 localizes to the mitotic spindle. By co-IP, we show that wild type MAP7D3 interacts with CEP120, mutated in the cilopathy Juvenile amyloplaxing thoracic dystrophy, and with SPI1 as well as CPI10, which are all centrosomal proteins.

Conclusions: We here identify mutations of MAP7D3 as a novel monogenic cause of a renal ciliopathy in humans and demonstrate that the protein interacts with other ciliopathy associated or centrosomal proteins. Further studies will elucidate allele specific expression and pathogenic pathways involved.

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

TH-PO586

Possible Role of Nox4 in Cystogenesis through Its Effects on Fumarate Hydratase in Experimental PKD

Kevin Vereckvo, Jennifer Arroyo, Fouad T. Chebib, Peter C. Harris, Slobodan Macura, Vicente E. Torres, Maria V. Irazabal. Mayo Clinic, Rochester, MN.

Background: Autosomal Dominant Polycystic Kidney Disease (PKD) is the most frequent hereditary renal disease, but the exact mechanisms of cystogenesis remain to be elucidated. Deficiency in fumarate hydratase (FH) is accompanied by increases in fumarate and is associated with the development of kidney cysts. Studies in diabetic nephropathy showed that NADPH oxidase (NOX)-4 (Nox4) can inhibit FH leading to accumulation of fumarate. No studies have explored the role of Nox4 in PKD.

Methods: Metabolomics analysis of cell extracts, urine, plasma & kidney of PCK (n=32) and wildtype (WT; n=24) rats, and human samples (ADPKD n=10; ctrl n=10) was performed by HNMR & confirmed by MS. Immunoactivity and protein expression of FH & Nox4 were assessed by staining & western blotting. FH activity by a colorimetric method and mitochondria by electron microscopy.

Results: Fumarate was consistently increased in PKD-deficient cells, PCK rats & human samples (ADPKD n=10; ctrl n=10) was performed by HNMR & confirmed by MS. Immunoactivity and protein expression of FH & Nox4 were assessed by staining & western blotting. FH activity by a colorimetric method and mitochondria by electron microscopy. FH activity highly correlated with tissue fumarate (fig2D). Decreased FH activity was associated with significantly increased protein expression and immunoreactivity of Nox4 in PCK compared to WT rats (fig3). These findings were associated with disruption of mitochondria cristae, swelling, and decreased matrix density exclusively in tubular cells from CD lining microcysts in PCK rats (fig4).

Conclusions: Metabolomic analysis identified fumarate as a potential mediator of cystogenesis in PKD. Accumulation of fumarate in PKD may be due to FH inhibition through upregulation of Nox4. Further experiments are needed to investigate the role of Nox4, FH and fumarate in PKD.

TH-PO587

Suppressing Interferon Regulatory Factor-5 Synthesis Attenuates Kidney Macrophages and Cytokines in Polycystic Kidney Disease

Kurt Zimmerman,1 Lan He,1 Bradley K. Yoder,2 Alexey Revenko,2 Adam E. Mullick,2 P. Darwin Bell,1 Takamitsu Saigusa,1 1Division of Nephrology, University of Alabama at Birmingham, Birmingham, AL; 2Ionis Pharmaceuticals, Carlsbad, CA; 3Cell Developmental and Integrative Biology, University of Alabama at Birmingham, Birmingham, AL.

Background: Inflammatory cells are increased in both human and mouse models of polycystic kidney diseases (PKD). Interestingly, macrophages in the kidney may appear before significant cystic development and deleting phagocytic macrophages with liposolal cladonate has been reported to slow cyst formation. Interferon regulatory factor-5 (IRF5) is a transcription factor involved in activation of macrophage and cytokine release and maybe an effective target for therapeutic intervention. To determine the significance of IRF5 and macrophages in PKD, we tested an antisense oligonucleotide (ASO) that inhibits IRF5 in adult Pkd1 mice.

Methods: Four week old adult Pkd1 conditional floxed allele mice with or without cre were administered tamoxifen to induce cre. Two weeks after tamoxifen injection, mice underwent unilateral nephrectomy to accelerate cyst formation. After nephrectomy, mice were treated with weekly injection of either IRF5 ASO (40mg/kg/wk) or scrambled ASO for a total of 3 weeks. Kidneys were harvested for analysis at the end of the treatment.

Results: Three weeks following nephrectomy, Pkd1 mice showed early focal cyst formation/dilated tubules in the kidney. Pkd1 mice treated with IRF5 ASO demonstrated significant reduction in level of kidney IRF5 mRNA compared to scrambled ASO treatment. Flow cytometry analysis of kidneys suggest that treatment with IRF5 ASO specifically reduces the number of infiltrating and resident macrophages but the level of neutrophils and T cells was unaffected by IRF5 ASO. IRF5 ASO compared to control ASO reduced kidney mRNA levels of pro-inflammatory cytokines.

Conclusions: These results suggest that suppressing IRF5 reduced both resident and infiltrating macrophages in early stage of PKD and may potentially become a novel therapeutic target in PKD.

Funding: NIDDK Support
Neutralization of Programmed Death Ligand 1 Delays Cyst Growth in ADPKD

**Background:** Intestinal inflammation plays a significant role in polycystic kidney disease (PKD). This inflammation features macrophages and other inflammatory cells, and cytokines released by these cells can be found in cyst fluid and urine. The Programmed Death 1 (PD1)/Programmed Death Ligand 1 (PDL1) pathway is a recent target for the treatment of multiple cancers. The upregulation of PDL1 on the surface of tumor cells due to immune infiltrates acts as a natural ‘balance’ to limit tissue-specific responses to inflammation, limiting T-cell mediated destruction. However, the roles and mechanisms of T-cells and PDL1 in underlying inflammation of ADPKD remain unknown.

**Methods:** To evaluate a potential role of T-cells and PDL1 in cyst immunopathology, we investigated the presence of T-cells in cystic kidneys from PKD mice and measured the expression levels of pro-angiogenic markers (phenotype) and the capacity to form vascular structures (function).

**Results:** We showed that Polycystic Kidney Disease (PKD)-derived Endothelial Cells (ECs) have a diminished response to the ligand-dependent activation of the Hedgehog (Hh) pathway, leading to an impaired angiogenic potential of these cells. We then hypothesized that restoring the activity of the Hh signaling by overexpressing Gli1, a central effector of this pathway, will ameliorate the vascular defects in PKD-ECs.

**Conclusions:** (1) In this unique model of ADPKD, changes in Pdl1 number and phenotype play a key role in fibrosis; (2) Changes in miRNA profiles after macrophage elimination with clodronate provide unique miRNA targets that may guide future therapeutic intervention; (3) This profile correlates with change in EGF and AKT which play critical roles in ADPKD.

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

---

Macrophage Depletion Leads to Temporal and Spatial Changes in miRNA Profiles That Drive Fibrosis in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

**Background:** In ADPKD, the decline in kidney function correlates with onset of fibrosis. Such fibrosis begins in peri-cystic areas (PA) between multiple cysts. Key factors involved in process of fibrosis include macrophages (Ø) at a cellular level and miRNAs at a molecular level. We hypothesize that localized changes in miRNA’s and Ø phenotypes drive fibrosis in ADPKD, and provide potential targets for future therapeutic intervention.

**Methods:** Cystic kidneys from mcpwPkd1/1 mice and age matched controls at postnatal days (PN) 21, 28, 42 and 56 were evaluated. These stages encompass the disease process from maximum cyst growth and total kidney volume (TKV) at PN28 to dramatically reduced TKV due to fibrosis at PN56. Cldn, which eliminates Ø, was administered from PN14 to PN56. FFPE fixed cystic kidneys at PN 56 followed clodronate treatment were analyzed with serial sections for miRNA, mRNA analysis and trichrome (Tric) and compared to age-matched untreated cystic kidneys. Ø and Ø phenotypes were analyzed by flow cytometry, IHC and IF in serial sections and following clodronate treatment.

**Results:** Flow cytometry reveals significant increase in Øs from PN21 to PN28. At PN21, Øs located in PAs express predominantly INOS, a marker for M1 Øs. Between PN28 and PN56, Øs predominantly express arginase, a marker of M2 Øs. These findings correlate directly with increasing Tric staining in PAs and the decline in renal function. As expected, clodronate treatment (1) depleted Øs in both spleen and kidney; (2) resulted in significantly less Tric positivity; and (3) inhibited the decrease in TKV. miRNA analysis of serial sections in both treated and untreated cystic kidney showed a total of 158 miRNA’s that were differentially expressed with 85 upregulated in treated kidneys. mRNA analysis on the same section was significant for differentially expressed AKT1 and EGF, 11 and 6.4-fold respectively.

**Conclusions:**
- **(1)** In this unique model of ADPKD, changes in Ø number and phenotype play a key role in fibrosis;
- **(2)** Changes in miRNA profiles after macrophage elimination with clodronate provide unique miRNA targets that may guide future therapeutic intervention;
- **(3)** This profile correlates with change in EGF and AKT which play critical roles in ADPKD.

**Funding:** Private Foundation Support

---

Gli1 Rescues the Angiogenic Potential of Polycystic Kidney Disease-Derived Endothelial Cells

**Background:** We showed that Polycystic Kidney Disease (PKD)-derived Endothelial Cells (ECs) have a diminished response to the ligand-dependent activation of the Hedgehog (Hh) pathway, leading to an impaired angiogenic potential of these cells. We then hypothesized that restoring the activity of the Hh signaling by overexpressing Gli1, a central effector of this pathway, will ameliorate the vascular defects in PKD-ECs.

**Methods:** To assess the role of Gli1 in ECs, we knocked-down the expression of Gli1 using siRNA in WT-ECs and study their angiogenic profile. To restore function, we overexpressed Gli1 in PKD-ECs and measured the expression levels of pro-angiogenic markers (phenotype) and the capacity to form vascular structures (function).

**Results:** A 50% decrease in Gli1 mRNA expression was associated with a decrease in vascular endothelial growth factor A (VEGFA) expression, similar to that seen in PKD-ECs. Chromatin immunoprecipitation shows that the pro-angiogenic factors VEGFA and fibroblast growth factor 2 (FGF2) are direct targets of Gli1 in ECs. The overexpression of Gli1 in PKD-ECs led to a 740-fold increase in Gli1 mRNA expression. Importantly, exogenous Gli1 substantially restored the expression levels of the pro-angiogenic molecules VEGFA, VEGF receptor 1 (FLK1) and FGF2 (Fig. 1B), as well as the ability of PKD-ECs to form angiogenic tubes (Fig. 1C).

**Conclusions:** Our data suggest that a dysregulation in Hh signaling, and particularly of Gli1, may be responsible for the abnormal angiogenic profile seen in PKD-ECs. Furthermore, we provide evidence that Gli1 overexpression rescues the vascular deficiencies in PKD. These studies can be useful for the development of novel therapeutic strategies that focus on the vascular aspects of PKD.

**Funding:** Private Foundation Support

---

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

*Underline represents presenting author.*

---

252
TH-PO592

Autophagy Induction in Mouse Kidneys

Carolyn N. Brown, Sara Holditch, Charles L. Edelstein. UC Denver Anschutz Medical Campus, Aurora, CO.

Background: Autophagy occurs in all eukaryotic cells in order to adapt under stressful conditions. Damaged organelles and proteins are sequestered into autophagosomes, which subsequently fuse with lysosomes where cargo is degraded and recycled. The aim of the current study was to determine the effects of autophagy inducers metformin (MET), 2-deoxyglucose (DOG), and trehalose (TRE) on autophagy in wild type (WT) and RC/RC (PKD) mouse kidneys in vivo.

Methods: WT and PKD mice were treated with MET (250 mg/kg IP), DOG (100 mg/kg IP), or TRE (2% P.O.) for 6-12 days. At the end of the study, mice received icv vehicle (VEH) or bafilomycin (BAF) (1.75 mg/kg IP), or TRE (2% P.O.) for 6-12 days. At the end of the study, mice received wither

WT Kidneys: Significantly reduced LC3-II was detected in the kidneys of MET and DOG mice compared to VEH, suggesting an increase in autophagosome formation. Markers of autophagosome formation, were measured by immunoblot.

Results: Pkdh1d2/Aqp2Cre mice developed severe PKD and died by P17. Double and triple immunofluorescence (IF) staining for various segment- and/or cell-specific markers were conducted. At least 1000 CNT/CD cells from 3 Pkd2+/+ Aqp2Cre and 3 WT mice for each IF combination were categorized and counted based on the marker expression. Using Aqp2, V-ATPase B1/B2 and AE1 as markers for principal cells (PC), intercalated cells (IC) and a-IC, respectively, we found that Pkd2+/+ Aqp2Cre and 3 WT mice for each IF combination were categorized and counted based on the marker expression.

Conclusions: Our data suggest that Pkd2 deletion in Aqp2 progenitor cells is sufficient for PKD development, and a-IC are selectively depleted with the disease development in both mice and human. The lack of a-IC to acidify urine and secret neutrophil gelatinase-associated lipocalin (NGAL) that chelates siderophore-containing iron may link ADPKD to UTI in humans.

Funding: NIDDK Support

TH-PO594

A Mouse Model of Tsc Renal Cystic Disease

John J. Bissler,5 Kamary A. Zahedi,1 Sharon L. Barone,1 Manoocher Soleimani,1 University of Cincinnati, Cincinnati, OH; 2University of Tennessee, Le Bonheur Children’s Hospital and St. Jude Children’s Research Hospital, Memphis, TN.

Background: Tuberous sclerosis complex (TSC) renal cystic disease affects over 500,000 patients worldwide. There are five patterns of TSC-associated renal cystic disease, and they are the macrocystic diseases, including polycystic, cortical cystic, multicystic, focal cystic diseases, and microcystic disease. The cysts can have a simple single cellular layer, have a multiply layer or even papillary histology. Although the basic histology has been described, the cystic mechanism in TSC is poorly understood.

Methods: To begin to better understand this cystic disease process, we created a mouse model of TSC renal cystic disease by targeting progenitor cells by using aquaporin 2-driven Cre recombinase expression to delete the floxed Tsc2 gene. Double immunofluorescence labeling was performed to determine the identity of cyst epithelium.

Results: In this cell specific model, we identify the similar histological characteristics of the renal cyst epithelium as occurs in the human. Interestingly, the cyst epithelium was predominantly comprised of intercalated cells as determined by intense and uniform apical expression of H+/ATPase in both mouse and human. There was no expression of Aqp2, 2H3, 3, NBCe1, NCC or Na-K-ATPase, indicating the absence of principal, proximal tubule, distal convoluted and thick ascending limb epithelial cells in the cyst wall. The cysts in human and mouse also exhibited a significant decrease in cilia expression.

Conclusions: We have developed a mouse model that resembles human TSC-associated renal cystic disease. This TSC renal cystic disease in both the mouse model and human exhibits significant histopathological differences compared to other renal cystic

Table 1

<table>
<thead>
<tr>
<th>Group/Genotype</th>
<th>LC3 B/B+cells</th>
<th>LC3 B/B- cells</th>
<th>p62 B/B+cells</th>
<th>p62 B/B- cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEH</td>
<td>3.3±0.1</td>
<td>1.9±0.2</td>
<td>6.9±0.2</td>
<td>3.7±0.6</td>
</tr>
<tr>
<td>VEH+BAF</td>
<td>9.4±0.2</td>
<td>5.1±0.2</td>
<td>6.7±0.3</td>
<td>4.0±0.5</td>
</tr>
<tr>
<td>MET</td>
<td>3.3±0.1</td>
<td>1.5±0.1</td>
<td>5.4±0.1</td>
<td>3.7±0.6</td>
</tr>
<tr>
<td>MET+BAF</td>
<td>8.0±4.3</td>
<td>5.0±4.3</td>
<td>6.7±1.0</td>
<td>4.0±4.3</td>
</tr>
<tr>
<td>DOG</td>
<td>9.2±1.3</td>
<td>7.4±1.3</td>
<td>6.8±1.3</td>
<td>4.0±1.3</td>
</tr>
<tr>
<td>DOG+BAF</td>
<td>12.0±1.5</td>
<td>14.0±1.5</td>
<td>6.8±1.3</td>
<td>4.0±1.3</td>
</tr>
<tr>
<td>DSG+BAF</td>
<td>10.3±1.3</td>
<td>12.0±1.3</td>
<td>6.8±1.3</td>
<td>4.0±1.3</td>
</tr>
<tr>
<td>TAX-BAF</td>
<td>15.2±1.5</td>
<td>17.2±1.5</td>
<td>6.8±1.3</td>
<td>4.0±1.3</td>
</tr>
</tbody>
</table>

*p<0.05 vs. VEH, **p<0.05 vs. MET, ***p<0.06 vs. DOG, †p<0.06 vs VEHI
Lessons from Pkd1 Therapeutic Targeting Strategies in a Loss-of-Function Mouse Model Camila Parrot, Almitra Kurbgovic, Jennifer Lake, Guhanan Yao, Marie Trudel. Institut de Recherches Cliniques de Montréal, Montréal, QC, Canada.

Background: Autosomal dominant polycystic kidney disease (ADPKD) causes renal and extrarenal phenotypes. The Pkd1 gene responsible for most cases of ADPKD has a developmentally and temporally regulated expression pattern. While CRISPR-Cas as a therapeutic strategy for Pkd1 is attractive, the high frequency of off-targets precludes clinical application. Because microscopic cysts below clinical detection are likely formed in utero in ADPKD kidneys (Grantham et al Cjasn 2010,2012), we targeted Pkd1 at early stage in mouse model to assess for long-term term. Pkd1 null mouse model that displays severe renal cysts and die by birth, were used to assess whether wild type Pck1 from 2 series of transgenic lines prevent cyst formation.

Methods: One mating overexpressing Pck1 was generated with 2 systemic Pkd1fl/fl mouse lines and the second with 2 renal-specific Sbpdk1fl/+ mice. RNA and proteins in kidneys and pancreas were assessed along with histomorphologic and cellular longitudinal analysis.

Results: Pkd1fl/+ mice crossed into each of the Pkd1fl/+ transgenic lines escaped perinatal lethality. These mice exhibit no renal or pancreatic phenotypes in the first few months of age. Thus, the Pkd1fl/+ transgene produced a functional protein with proper transgene regulation. Pkd1fl/-/Pkd1fl/- mice at 8-9mo developed however renal cysts more milder than the parental transgenic line consistent with their Pkd1 overexpression and a gene-dosage pathogenic mechanism. Pkd1fl/+ mice mated to Sbpdk1fl/+ renal specific expressions avoided neonatal death but consistently developed, renal (kidney/body weight 2.3 fold that of normal mice) and pancreatic cysts. Despite Pck1 -/- and 15- fold overexpression, deaths occur at P10-P15 with the mild Pck1 expressor and ~3 mo in the high expressor, indicating that renal cysts likely result from different tubular response: insufficient expression and/or overexpression of Pck1. Collectively, these results demonstrate that early Pck1 expression can delay cystogenesis and extend mouse lifespan, and provide a model that reflects highly controlled spatiotemporal regulation.

Conclusions: Maintenance of tightly regulated Pkd1/Pck1 expression will be a major clinical challenge as Pck1 expression varies between renal cell types and age. Presently, targeting Pck1 in ADPKD is a double-edge sword and cannot practically serve as a useful therapeutic strategy.

Funding: Governing Support - Non-U.S.

TH-PO596

Compound-Homozymous Pkd1 and Pkd2 Inactivation Has No Additive Effect on Cyst Formation Xin Tian, Yiqiang Cai, Ming Ma, Chao Zhang, Whitney E. Besse, Ashima Gulati, Stefan Somlo. Yale University School of Medicine, New Haven, CT.

Background: Autosomal dominant polycystic kidney disease results from mutations in Pkd1 or Pkd2. The two genes work together in a common signaling pathway in which Pkd1 is the rate limiting step. We previously showed an extra-additive increase in cystogenic events in Pkd1(-/-);Pkd2(-/-) mice that may result from a modified threshold effect. In the current study, we examined whether there is a similar effect with conditional homozygous inactivation of both genes in mouse kidney collecting ducts.

Methods: We generated Pkd1fl/fl;Pkd2fl/fl;Pkhd1Cre mice which inactivate both genes in collecting ducts by postnatal day 7 (P7). Pkd1fl/fl;Pkd2fl/fl;Pkd1fl/Cre mice (n=8) and Pkd2fl/fl;Pkd1fl/Cre mice (n=7) were examined at P14, P24 and P48.

Results: Histological and functional examination of kidneys from Pkd1fl/fl;Pkd2fl/fl;Pkd1fl/Cre mice at P14 and P24 showed no significant difference in kidney-body weight ratio (KW/BW), cystic index (CI) and BUN when compared with Pkd1fl/fl;Pkd1fl/Cre mice. When compared with Pkd2fl/fl;Pkd1fl/Cre mice, both groups had statistically significant increase in KW/BW (P<0.05, CI (P<0.05) and BUN (P<0.05) at both time points. At P48, multiple comparison showed no significant differences in any parameter among the three groups. We also documented normal appearance of cilia by both time points. At P48, multiple comparison showed no significant differences in any parameter among the three groups. We also documented normal appearance of cilia by both time points.

Conclusions: Dual inactivation of Pkd1 and Pkd2 shows no additive effect on cyst formation but early stage inactivation of Pkd1 results in more rapid cyst growth than inactivation of Pkd2, likely due to longer persistence of the Pkd2 protein. Late stage models show genotype-independent increase in apoptosis.

Funding: NIDDK Support
Anks6-/- Mice Have Laterality Defects and Develop Renal Cystic Disease

**TH-PO599**

**Anks6-/- Mice Have Laterality Defects and Develop Renal Cystic Disease**

**Ranrar Airik,2,3 Merlin Airik,2 Nathan A. Herdman.1**

1University of Pittsburgh, Pittsburgh, PA; 2Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, PA; 3Developmental Biology, University of Pittsburgh, Pittsburgh, PA.

**Background:** Nephropathies-related ciliopathies (NPHP-RC) are a group of heterogeneous recessive kidney diseases, that are frequently associated with extra-renal organ malformations. Recently mutations in the ankyrin repeat and sterile alpha motif domain containing 6 (ANKS6) gene were identified, as causing nephropathies with craniofacial defects, focal hemorrhages and complex structural heart defects. Kidney size is often reduced and associated with abnormal glomerulogenesis and tubulogenesis. Homozygous Anks6-/- rats survived and developed mild kidney dysgenesis, including focal cyst formation and fibrosis.

**Conclusions:** Our data demonstrate that abrogation of Anks6 in mice leads to laterality and developmental defects in multiple organs, which resemble the phenotypes of mouse models for other inversion compartment components. Homozygous mutant mice recapitulate the major features of loss of ANKS6 function in humans, including liver fibrosis, cystic kidney disease and situs inversus. Together, Anks6-/- mouse represents a novel genetic model of NPHP-RC.

**Funding:** NIDDK Support

---

### Cystic Kidney Diseases - I

**Andrew B. Herdman,**

1Department of Medicine, University of Pittsburgh, Pittsburgh, PA; 2Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, PA; 3Developmental Biology, University of Pittsburgh, Pittsburgh, PA.

**Background:** PKD1 and PKD2 mutations are present in cyst patients with clear genotype-phenotype correlations. However, the intra-familial phenotypic variability in some pedigrees suggests the influence of non-allelic factors. Non-coding RNAs e.g. microRNAs are known to play a major role in health and disease (including PKD) via control of mRNA stability or translation. We recently conducted a parallel mRNA/miRNA array study which found mir-193b-3p, among others, downregulated in human ADPKD cells (Streets et al, 2017), associated with dysregulation of the ErbB4/EGF pathway.

**Methods:** To select other relevant genes regulated by mir-193b-3p, we compared our human mRNA dataset with mRNA expression data from Phl1 mutant mice (Malas et al, 2017). Dual-reporter luciferase assays with native and mutant seed sequences and immunoblotting were used to demonstrate functional binding of mir-193b-3p to the 3'UTR of PK3R1 mRNA. IGF-1 stimulation of human ADPKD cystic cells in 2D and 3D cultures characterized the role of PK3R1 in Akt or ERK signaling and on cyst growth.

**Results:** PK3R1 was selected as a strong candidate gene and shown to be upregulated ~3-fold in human cells and mouse Phl1 kidney tissue. In parallel, the catalytic subunit PK3CA was also overexpressed suggesting the most common PK3 enzyme combination is upregulated in ADPKD cells. A functional interaction between PK3R1 and mir-193b-3p was confirmed by luciferase assays and immunoblotting. Knockdown of PK3R1 or PIK3 chemical inhibitors significantly reduced cyst growth in ADPKD cells and influenced Akt and ERK activation by IGF-1.

**Conclusions:** We report that PK3R1 and one of its catalytic subunits are upregulated in ADPKD and confirm that it is a target for mir-193b-3p. The role of PK3R1/PK3CA in driving cyst growth in ADPKD was functionally linked to hyperactivation of Akt and ERK. Co-regulation of PK3R1 and ErbB4 by mir-193b-3p supports the development of PI3K and ErbB4 inhibitors as potential 193b-3p activators for the treatment of ADPKD.

**Funding:** Government Support - Non-U.S.
Inhibition of PLK1 Delays Cyst Growth in Autosomal Dominant Polycystic Kidney Disease

Xia Zhou, Guangquiang Ma, Xiaoyian Li, James P. Calvet, Xiaogang Li. University of Kansas Medical Center; Kansas City, KS.

Background: The G2/M DNA damage checkpoint serves to prevent the cell from entering mitosis with genomic DNA damage. G2-phase transition is dependent on the activity of the Cyclin B-cdc2 complex which is regulated by CDC25 phosphatases, CDC2 kinase and CDC25C. We investigated whether the kinase 1/PLK1 activity has pivotal roles in multiple aspects of cell division (mitosis) by activating CDC25. However, the roles of PLK1 and CDC25C/B in cystogenesis in ADPKD remain elusive.

Methods: To understand dysregulated signaling pathways in cystic kidneys, we performed RNA-seq and Ingenuity Pathway Analysis (IPA). To explore the roles of PLK1 and CDC25C/B in regulating cyst growth, we targeted PLK1 in Pkd1 mutant cells and mice with a PLK1 inhibitor volasertib.

Results: We found that DNA damage response was increased in Pkd1 mutant PN24 cells and kidneys of Pkd1flox/flox;Nestin-Cre mice by phospho-H2AX staining. Our RNA-seq and IPA analysis indicated that the genes related to the cell cycle G2/M DNA damage checkpoint regulation pathway, including PLK1, CDC25C and CDC25C, were upregulated and activated in cystic kidneys compared to those in wild type kidneys. The upregulation of PLK1, CDC25C and CDC25C was confirmed by qRT-PCR, western blot and immunohistochemistry (IHC) staining in cystic kidneys versus controls. Treatment with the PLK1 inhibitor volasertib and the CDC25C inhibitor NCS66284 decreased cystic renal epithelial cell proliferation as examined by MTT assay. We also found that volasertib treatment further increased the expression of p21, phospho-CDK2, active caspase 3, and cleaved PARP expression, and decreased the phosphorylation of ERK, S6 and STAT3 in PN24 cells. Furthermore, treatment with volasertib delayed cyst growth in Pkd1 conditional knockout mice. Volasertib treatment decreased cyst lining epithelial cell proliferation as examined by PCNA and Ki67 staining, decreased the phosphorylation of ERK, S6, STAT3 and Rb, but increased cyst lining epithelial cell apoptosis as examined by TUNEL assay in cystic kidneys.

Conclusions: The cell cycle G2/M DNA damage signaling pathway is dysregulated in ADPKD. Inhibition of PLK1 produces a potent anti-proliferative and pro-apoptotic effect, regulates the known PKD associated pathways in cystic renal epithelia, and delays cyst growth in vivo, which suggests that targeting PLK1 may be a potential therapeutic strategy for ADPKD treatment.

Funding: NIDDK Support, Private Foundation Support

TH-PO604

Effects of Smoking on Pkd1-Deficient Cystic Mice: An Extended Study on the Renal and Cardiac Phenotypes

Marciana V. Sousa,1 Andressa D. Paulo,2 Luiz F. Onuchic,1 'Nephrology and Molecular Medicine, University of Sao Paulo, Sao Paulo, Brazil; 2Cardiopneumology, University of Sao Paulo, Sao Paulo, Brazil.

Background: Previous studies have shown that heavy smoking increases the risk of advanced chronic kidney disease and that smoking raises the risk of progression to ESKD in men with ADPKD.

Methods: Cystic Pkd1flox/flox;NestinCre and noncystic Pkd1flox/flox mice were exposed to cigarette smoking (CYS and NC, respectively) from conception to 18 weeks of life, twice a day, 30-min periods. Control groups also included cystic and noncystic mice not submitted to smoking (CY and NC, respectively). Renal function, cystic index and cell proliferation; cardiac function, including deformation (strain); body weight (BW); and kidney and heart apoptosis, fibrosis and weight were analyzed at 16-18 weeks.

Results: We showed in a 2016 ASN abstract that BUN was higher in CYS mice than NC (p<0.01), and in CY hearts compared to those with at least 1 wild type allele (G0). The mechanisms of APOL1-mediated renal disease remain unclear. While 13% of African Americans (AA) carry two APOL1 risk alleles and only a minority of these individuals develop kidney disease, this appears to contribute to inferior allograft outcomes with kidneys transplanted from AA donors. We present 2 cases of FSGS in transplanted kidneys from a donor with 2 APOL1 risk alleles.

Results: The donor was a 57-year-old AA man with a history of hypertension who died from a stroke. Recipient 1 was a 47-year-old AA woman with diabetes-associated end stage renal disease (ESRD). Post-reperfusion biopsy was notable for mild focal global glomerulosclerosis. Post-operative course was notable for delayed graft function (DGF), and a nadir creatinine (Cr) of 1.6mg/dL. She subsequently developed proteinuria (6.7g/g) and elevated Scr (3.7mg/dL) 7 months post-transplant in the setting of a diurehal illness secondary to cytomegalovirus (CMV) infection. Viremia cleared with reduced immunosuppression. Repeat biopsy for persistent proteinuria showed tubular injury, and collapsing FSGS that led to allograft failure 18 months post-transplant. Recipient 2 was a 64-year-old Caucasian woman with ESRD from polycystic kidney disease. Post-operative course was notable for DGF, nadir creatinine of 1.3mg/dL. She developed CMV viremia and colitis 12 months post-transplant that was followed by Cr rising to 2.9mg/dL with 7.6g/g proteinuria. Renal biopsy showed acute tubular injury and collapsing FSGS. Viremia cleared after mycophenolic acid was discontinued and ganciclovir was initiated. Both recipients were followed for 14 months after transplant. While both the donor (G1/G1) and recipient (G1/G1) had 2 APOL1 risk variants, recipient 2 (G0/G0) did not have any risk alleles.

Conclusions: This suggests that the genetic susceptibility for APOL1-related lesions is linked to the presence of donor risk alleles. Additionally, CMV infection appears to be a second hit resulting in the development of collapsing FSGS after transplantation in kidneys with 2 risk alleles.

TH-PO606

CMV Infection as a Trigger for APOL1-Associated Collapsing FSGS in Renal Allograft

Leigh-Anne Dale,1 Syed A. Husain,3 Jae Hyung Chang,3 Russell J. Crew,2 David J. Cohen,2 Mariana C. Chiles,1 Yirfu Li1, Ali G. Ghavari,2 Sumit Mohan.1 Columbia University, New York, NY; 2Columbia University, New York, NY; 3Columbia University Medical Center, New York, NY.

Background: APOL1 protein L1 gene (APOL1) risk alleles are associated with increased risk of focal segmental glomerulosclerosis (FSGS) in patients with 2 risk alleles (G1 or G2) compared to those with at least 1 wild type allele (G0). The mechanisms of APOL1-mediated renal disease remain unclear. While 13% of African Americans (AA) carry two APOL1 risk alleles and only a minority of these individuals develop kidney disease, this appears to contribute to inferior allograft outcomes with kidneys transplanted from AA donors. We present 2 cases of FSGS in transplanted kidneys from a donor with 2 APOL1 risk alleles.

Methods: The donor was a 57-year-old AA man with a history of hypertension who died from a stroke. Recipient 1 was a 47-year-old AA woman with diabetes-associated end stage renal disease (ESRD). Post-reperfusion biopsy was notable for mild focal global glomerulosclerosis. Post-operative course was notable for delayed graft function (DGF), and a nadir creatinine (Cr) of 1.6mg/dL. She subsequently developed proteinuria (6.7g/g) and elevated Scr (3.7mg/dL) 7 months post-transplant in the setting of a diurehal illness secondary to cytomegalovirus (CMV) infection. Viremia cleared with reduced immunosuppression. Repeat biopsy for persistent proteinuria showed tubular injury, and collapsing FSGS that led to allograft failure 18 months post-transplant. Recipient 2 was a 64-year-old Caucasian woman with ESRD from polycystic kidney disease. Post-operative course was notable for DGF, nadir creatinine of 1.3mg/dL. She developed CMV viremia and colitis 12 months post-transplant that was followed by Cr rising to 2.9mg/dL with 7.6g/g proteinuria. Renal biopsy showed acute tubular injury and collapsing FSGS. Viremia cleared after mycophenolic acid was discontinued and ganciclovir was initiated. Both recipients were followed for 14 months after transplant. While both the donor (G1/G1) and recipient (G1/G1) had 2 APOL1 risk variants, recipient 2 (G0/G0) did not have any risk alleles.

Results: This suggests that the genetic susceptibility for APOL1-related lesions is linked to the presence of donor risk alleles. Additionally, CMV infection appears to be a second hit resulting in the development of collapsing FSGS after transplantation in kidneys with 2 risk alleles.

Funding: Government Support - Non-U.S.
TH-PO607

Not Just Sickle Nephropathy: Hematuria and Proteinuria in a Child with Hemoglobin SS Disease and Alport Syndrome

Stephanie Lynch,1 Elizabeth Yang,3 Haresh Mani,2 Patricia Socio-Mayet.1 1Inova Children’s Hospital, Alexandria, VA; 2Inova Fairfax Hospital, Falls Church, VA; 3Pediatric Specialists of Virginia, Falls Church, VA; 4Pediatric Specialists of Virginia (Inova-CNMC) and Georgetown University School of Medicine, Fairfax, VA.

Background: Nephropathy is complicated sickle cell disease but is seldom observed in young children. We report the case of a 9-year-old boy with Hemoglobin SS Disease, hematuria and proteinuria, who had concurrent Alport Syndrome. This case illustrates the value of targeted investigation in patients with primary conditions with known renal sequelae who demonstrate atypical presentation or progression. For our patient, this approach uncovered a second unrelated diagnosis.

Methods: A 4 month old African boy presented with fever, anemia, hematuria and proteinuria. He was diagnosed with urosepsis and Hemoglobin SS disease. Over time, hematuria and mild proteinuria persisted. He had normal blood pressure, albumin, creatinine, complement levels, and RBUS. Family history was negative for CKD. Sickle nephropathy was considered, and ACE-inhibitor was initiated for renoprotection. He later developed gross hematuria and worsened proteinuria in the context of fever and abdominal pain. Papillary necrosis and pyelonephritis were ruled out. Revised family history revealed a maternal male cousin with new hematuria, and a deaf maternal uncle who died in the Congo at an early age of kidney disease, raising suspicion for Alport Syndrome. Genetic testing revealed COL4A5 mutation (Exon 5, c.305_306dupGC), confirming X-linked Alports. Renal biopsy revealed abnormal GBMs with variable areas of thinning and thickening, and retained c1 but lack of staining for e3/45 chains of type IV collagen.

Results: Conclusions: This is an unusual case of a boy with two concurrent genetic diseases, both with known renal sequelae. Sickle nephropathy usually manifests in the 3rd decade of life, but our patient had early and persistent hematuria and proteinuria, resulting in diagnosis of Alports. Future management will be challenging. Alports will inevitably lead to ERSD, and ongoing vaso-occlusive crises and ischemia reperfusion injury will hasten progression. Crysallization of the GBM is one key, as they have shown benefit for both conditions, and hydroxyurea may reduce progression of sickle nephropathy. Stem cell transplantation may prove useful to mitigate CKD progression, but risks exist due to lack of a sibling-matched donor. In summary, this case describes a child with two independent and unrelated genetic causes of CKD, illustrating an exception to the rule of Occam’s razor.

TH-PO608

Digenic Heterozygous Mutations in CEP164 and ALMS1 May Cause Nephronophthisis

Haris F. Murad, Neera K. Dahl. Tale School of Medicine, New Haven, CT.

Background: Nephronophthisis is a cystic kidney disease that is the most common genetic cause of End Stage Renal Disease (ESRD) in the first three decades of life. It is a genetically heterogeneous disorder associated with extra renal manifestations (eyes, liver, bones, and central nervous system) in 15% of cases. Renal histology shows tubular basement membrane disruption and tubulointerstitial nephritis. The cysts are usually in the corticomedullary junction and kidney size is normal or slightly reduced in contrast to polycystic kidney disease. Here we describe two cases with Nephronophthisis from novel genetic mutations.

Methods: A 51-year old lady presents with a gradually rising serum Creatinine up to 2.7mg/dL. Renal biopsy showed interstitial nephritis, and her ultrasound showed several scattered subcentimeter cysts and a 1.6 cm cyst. Whole exome sequencing showed heterozygous mutations in both the CEP164 and ALMS1 genes. Both mutations, CEP164 p.L248fs, and ALMS1 p.Y1713X, resulted in the creation of a premature stop codon and are known to be pathogenic. MCP1 and UMOD were normal. The patient’s sister has a history of cerebral palsy and developed ERSD at the age of 30. Her CT abdomen shows innumerable bilateral renal cysts. Biopsy revealed interstitial nephritis as well. Whole exome sequencing is currently in process.

Results: Conclusions: Nephronophthisis is a disorder in the normal functioning of primary cilia, which are sensory organelles detecting flow, osmotic, chemo and other stimuli and link them to cellular processes. A homozygous or compound heterozygous mutation in the CEP164 gene is known to cause NPHP15 which causes an alteration in DNA damage response signaling pathway. A mutation in ALMS1 gene causes abnormal ciliary structure in knockout mice. A homozygous or compound heterozygous mutation in this gene causes Alstrom syndrome which is a rare cause of renal failure associated with blindness, hearing loss, systemic fibrosis as well as hepatic, urologic and pulmonary dysfunction. To our knowledge, this is the first case of a clinical nephronophthisis phenotype caused by digenic pathogenic alleles rather than by a homozygous or compound heterozygous mutations in the above genes. It is possible that ALMS and CEP164 mutations have a complementary effect in exerting this phenotype.

TH-PO609

Functional Splicing Analysis in an Infantile Case of Atypical Hemolytic Uremic Syndrome Caused by Digenic Mutations in C3 and MCP Genes

Tomohiko Yamamura,1 Kandai Nozu,2 Keita Nakanishi,3 Junya Fujimura,1 Shogo Minamikawa,1 Hiroaki Ueda,2 Rika Fujimur,3 Yoko Shima,4 Koichi Nakanishi,5 Hiroshi Kaito,1 Kazumoto Iijima,2 Graduate School of Medicine, University of the Ryukyus, Nishihara-cho, Japan; 6Kobe University Graduate School of Medicine, Kobe, Japan; 7Osaka City General Hospital, Osaka, Japan; 8Wakayama Medical University, Wakayama City, Japan.

Background: Atypical hemolytic uremic syndrome (aHUS) is a heterogeneous disease that is caused by defective complement regulation as reported in over 50% of cases. Up to now, pathogenic variants have been identified in various compliment related genes. Some reports also indicated that patients of aHUS with digenic inheritance of these genes might present more severe phenotype than monogenic inheritance. In addition, generally, transcript analysis is necessary for variants located outside of the splicing consensus sequence to assess the biological effect. However, this technique is often difficult for the influence of nonsense-mediated mRNA decay (NMD) for the products of truncating variants and quantity of mRNA of sample.

Methods: Here we report an infantile case with aHUS from unrelated parents. Targeted resequencing detected a reported variant of C3 gene and a novel intronic variant of MCP gene (c.97 + 5 G> A, IVS1 + 5 G> A), on maternal and paternal alleles respectively. These results ruled out HUS, and were thought to be working digenically since there was early onset in patient although the parents were asymptomatic. However, the pathogenicity of a variant in MCP gene was unknown because this is a novel variant and located outside apparent splice consensus sequence. To assess the pathogenicity of a novel intronic variant of MCP gene, we tried to detect abnormal splicing variant by standard transcriptional analysis using mRNA extracted from peripheral blood. However, we obtained only normal splicing variant from maternal allele and transcript from paternal allele was missing. Then, we conducted functional splicing assay using minigene construction to detect abnormal splicing caused by c.97 + 5 G> A variant and quantitative mRNA PCR to confirm the result. As a result, it was revealed that the paternal allele of MCP gene with c.97 + 5 G> A variant did not produce any transcript as confirmed by qPCR and minigene splicing assay. These results lead us to conclude MCP gene c.97 + 5 G> A was pathogenic.

Results: Conclusions: A combination of minigene assay and quantitative analysis is non-invasive and useful methods as functional splicing assay of inherited diseases even if standard transcriptional analysis could not detect abnormal splicing.

TH-PO610

Upshaw–Schulman Syndrome

Muhammad Azfar1, Krishna M. Baradhi.1

Background: Hereditary Thrombotic Thrombocytopenic Purpura (TTP) is an extremely rare life threatening disorder characterized by thrombotic microangiopathy caused by severely reduced activity of the von-Willebrand factor--cleaving protease ADAMTS13. It is characterized by small-vessel platelet-rich thrombi that cause thrombocytopenia and microangiopathic hemolytic anemia.

Methods: A male infant who was cyanotic at birth was found to have thrombocytopenia of 18000/microliter presumed to be from sepsis as it improved with platelet transfusion and antibiotics. This was followed by recurrent hospitalizations every few years either for diarrhea or anemia or renal failure in the context of severe thrombocytopenia. However, each time, he was misdiagnosed as Evan’s syndrome or Hemolytic uremic syndrome(HUS) until he succumbed to stroke at the age of 18 years. At age 2 years, he had classical cases of TTP in the form of fever, renal failure and thrombocytopenia, an evaluation for TTP was initiated. His ADAMS 13 activity came back as < 10% without the inhibitor. Genetic testing showed biallelic mutations in the ADAMS13 gene. Both parents were carriers. He was diagnosed with Hereditary TTP and was started on monthly plasma infusions. His renal function eventually deteriorated by the age of 31 years requiring dialysis. He continues to have monthly plasma infusion and is relatively doing well.

Results: Conclusions: Hereditary TTP also known as Upshaw–Schulman Syndrome is an autosomal recessive condition caused by biallelic mutations in ADAMS13. It represents <5 percent of all TTP cases. Clinical features are similar to acquired TTP or other thrombotic microangiopathies often leading to patients being misdiagnosed as having ITP, HUS, HELLP, or Evan’s syndrome. Hereditary TTP should be considered in any one who presents with microangiopathic hemolytic anemia and thrombocytopenia in infancy, childhood or pregnancy. The diagnosis is made by demonstration of severe ADAMS13 deficiency without an inhibitor and confirmed by demonstration of ADAMS13 gene mutation(s). Without appropriate diagnosis and treatment, it can be life threatening. Treatment of an acute episode with plasma substitution should not be delayed while confirming the diagnosis. Plasma infusion is the treatment of choice rather plasma exchange. Recombinant ADAMS13 is under development. All siblings of an individual with hereditary TTP should be tested.
TH-PO611
A Case of Lesch-Nyhan Syndrome in an Adult Presenting with AKI
A young man with Lesch-Nyhan syndrome (LNS) presented to our hospital with acute kidney injury (AKI) and hypertension. LNS is a rare X-linked disorder caused by a deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT) and underlying HPRT gene mutations. When the enzyme HPRT is nonfunctional, substrates accumulate and are converted to uric acid by the action of xanthine-oxidase. LNS diagnosis is based on clinical symptoms and hyperuricemia, together with neurological evaluation of mental function, molecular testing for pathogenic mutations, and enzymatic analysis for HPRT function.

Methods: We report a case of LNS in a 26-year-old man, who presented with acute kidney injury and excessive hyperuricemia. He had a 7-year history of gout. He had tophectomy for gouty arthritis on left ankle 3 months ago and was taking aceloclanef (NSAID) from then on. He had a 3-year history of dystonia. Mutation analysis and enzyme assay revealed a mutation of exon 3 of the HPRT gene (c.295T>G (p.Phe99Val)) and total deficient HPRT confirming the diagnosis of LNS. His renal function and serum uric acid level improved after dialysis and allopurinol treatment.

Results:

Conclusions: The diagnosis of LNS in adults is extremely rare. We report a case of LNS in a 26-year-old man, who presented with acute kidney injury and excessive hyperuricemia, with molecular diagnosis.

TH-PO612
Proteinuric Renal Injury in an Adolescent with a Distal Partial Trisomy
Chromosome 1

Masakazu Honda,1,2 Takeshi Tsuboi,1,2 You Honda,1,2 Masahiro Ishikawa,1,2 Nobuo Tsuboi,1 Takashi Yokoo,1,2 Kawaguchi Municipal Medical Center, Kawaguchi-shi, Saitama, Japan; 1The Jikei University School of Medicine, Minato-ku Tokyo-to, Japan.

Background: Distal partial trisomy 1q is a rare disease, with no previous case reports of renal insufficiency occurring in relation to this chromosomal disorder. We report a case of distal partial trisomy 1q that showed proteinuric renal injury.

Methods: We treated a 17-year-old adolescent with clinical features of low birth weight, mild mental retardation, and mild deafness. When he was 13 years old, he was diagnosed as having a partial trisomy of chromosome 1 from q32.1 to 41 using chromosomal and microarray tests. He showed persistent proteinuria since age 16 and underwent medical check-up at our hospital. Proteinuria was estimated to be approximately 1-2 g/day, although serological examination revealed no abnormal findings. Computed tomography detected no morphological abnormalities of the kidneys other than their slightly small size. Renal biopsy showed no evidence of immune-mediated glomerular diseases, but revealed a very low glomerular density and glomerulonephragly, as evidenced by a marked increase in the estimated mean glomerular volume (10.3 ± 10.0 µm³). Combination therapy with dietary sodium restriction, body weight reduction, and the administration of losartan potassium markedly reduced his proteinuria to 0.3 g/day.

Results:

Conclusions: The section of partial trisomy found in this case does not include podocyte-related genes that have been related to proteinuric renal injuries. Thus, in this case, the mismatch between congenital reduction in the number of nephrons due to low birth weight and catch-up growth of whole body size may have resulted in glomerular hyperfiltration and renal injury. Renal prognosis is poor in patients with a history of low birth weight, which is sometimes complicated in patients with genetic comorbidities. In such patients, where the renal prognosis has not been studied well, continuous follow-up is necessary to evaluate renal complications and inhibit progression of renal disease.

TH-PO613
Headache and Diplopia in a Patient with Nephropathic Cystinosis

Background: Nephropathic cystinosis is a lysosomal storage disease resulting in the accumulation of cystine, development of Fanconi syndrome, and progression to end-stage renal disease. Extraglomerular manifestations of cystinosis affecting the endothelium, muscle, and other organ systems are less well described. However, idiopathic intracranial hypertension (IIH) is a rare and poorly understood condition associated with cystinosis.

Methods: A 33-year-old female with nephropathic cystinosis three years status post living donor kidney transplant on immunosuppressive therapy had been experiencing one month of headache, diplopia, and nausea. Approximately one and a half years prior to presentation, she had switched from cyclosporine to extended release cyclosporine. She was then started on prednisone and cyclosporine. Her creatinine level was 1.5 mg/dL and her systolic and diastolic blood pressure was 150/100. The patient was subsequently diagnosed with IIH on magnetic resonance imaging (MRI) and treated with acetazolamide. She subsequently improved with acetazolamide, discontinuation of cyclosporine, and resumption of Cystagon.

Results:

Conclusions: There is a known increased incidence of IIH in individuals with cystinosis; although, the underlying cause is unknown. Potential etiologies include decreased CSF reabsorption secondary to crystal deposition or increased thrombotic risk secondary to renal disease. Additional risk factors such as immunosuppressive therapy, growth hormone supplementation, and renal transplant have been associated with IIH, but no study has correlated a specific risk factor with development of IIH in patients with cystinosis. Procybsi is reported to have a more favorable side effect profile and less medication noncompliance compared to Cystagon due to twice rather than four times daily dosing. However, in the setting of subtherapeutic WBC cystine levels with Procybsi, the patient developed IIH. This case highlights the rare, but known, association between cystinosis and IIH, and encourages clinicians to consider this diagnosis in patients with cystinosis presenting with headache and vision changes.

TH-PO614
Moyamoya Disease – A Rare Association of Autosomal Dominant Polycystic Kidney Disease

Dearbhla Kelly,1 Ayanfeoluwa Obilana,2 Michael Mannane,1 Aisling O’Riordan,3 Sean Murphy,1 Mater Hospital, Dublin, Ireland; 1Mater Misericordiae University Hospital, Dublin, Ireland; 1Nephrology, Mater Misericordiae University Hospital, Dublin, Ireland; 1Mater Misericordiae University Hospital, Dublin, Ireland.

Background: Moyamoya disease is an idiopathic progressive vaso-occlusive disorder of the intracranial arteries located at the base of the brain that can predispose to stroke. Although cerebral aneurysms and other vascular abnormalities are well described in autosomal dominant polycystic kidney disease (ADPKD), co-incident Moyamoya syndrome and ADPKD has only previously been reported on two occasions.

Methods: A 29-year-old Romanian woman presented with a 3 days of headache and right hemiparesis. She was a smoker with a history of untreated hypertension. Her mother, sister and maternal uncle also had ADPKD. No family member had a history of intracranial aneurysms. MRI Brain with contrast revealed a left middle cerebral artery (MCA) territory subcortical infarct, with established infarcts in the right caudate nucleus, left internal capsule and left parietal lobe. Digital Subtraction Angiography confirmed no flow in the MCA's bilaterally with good flow in distal ICA's, ACA's and PCA's bilaterally, multiple collateral vessels consistent with Moyamoya disease. She had a renal ultrasound as part of her work up for hypertension and this revealed bilateral cystic changes consistent with polycystic kidney disease.

Results:

Conclusions: The coexistence of these malformations suggests a common genetic background predisposing to these structural abnormalities. Although the genetic contribution in Moyamoya is indispensible, its cause remains uncertain. In this case, alterations in the arterial wall may be linked to the PKD1 or PKD2 genes, expanding the genetic variability of ADPKD and providing insight into the pathogenesis of Moyamoya.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Painful Cyst Hemorrhage with Trivial Trauma in Tuberous Sclerosis Complex with Angiomyolipomas without Nephromegaly – A Case Report
Jaime A. Baynes-Fields, Myriam C. Vela-Oritz, Sandeep Aggarwal. Drexel University College of Medicine, Philadelphia, PA.

**Background:** Tuberous sclerosis complex (TSC) is characterized by renal angiomyolipomas and cysts which have the potential to be complicated by hemorrhagic and malignant conversion. Cyst hemorrhage in such cases may happen spontaneously or by trivial trauma due to their highly vascular nature.

**Methods:** We present a case of a 25 year old male with TSC with subependymal giant cell astrocytoma, seizure disorder, ash leaf spots, bicuspid aortic valve with cardiac rhabdomyoma, multiple renal angiomyolipomas and cysts, hypertension, and CKD stage 1. On a follow up visit, patient presented with right flank pain of one week duration. Patient’s symptoms were preceded by a motor vehicle accident, characterized by sudden deceleration of his vehicle without bodily impact. Patient denied hematuria, lower urinary tract symptoms, or change in urine output. Pertinent physical examination—blood pressure 126/72 mmHg, pulse 85 per minute, right flank tenderness, remainder of physical exam at baseline. Work up—gadolinium enhanced MRI: hemorrhagic conversion of large cystic lesion (1.4cm) as well as increasing angiomyolipomas with stable renal size (right 11.33cm, left 11.2cm). Patient’s renal function remained stable with baseline creatinine 0.66mg/dL, trace proteinuria, no hematuria on dipstick, and 5mcg/mg microalbumin to creatinine ratio. Conservative treatment was provided with pain control and oral hydration given hemodynamic and laboratory stability. Patient improved clinically in follow up.

**Results:**

**Conclusions:** Cystic neoplasities with nephromegaly present a high risk of hemorrhagic conversion due to fragility and lack of protection by our thoracic cage. TSC with angiomyolipomas present a higher risk due to pathological vascular aneurysms even without nephromegaly, which is emphasized in this case. Hemorrhagic risk of angiomyolipomas are approximately 25-50% and may lead to circulatory shock. Frequent assessment of patient’s symptoms and history, especially related to physical trauma should be sought during each visit. Emphasis should be laid on seizure control, preventative measures and patient education of avoidable injury with immediate follow up after such an event which could be life threatening.

---

**TH-PO616**

LECT2 Amyloidosis – An Entity in Elderly Hispanics with Distinct Pathologic Features
Nitin Rai, William L. Whittier, David J. Cimbalkus. Rush University Medical Center, Chicago, IL.

**Background:** Leukocyte chemotactic factor 2 amyloidosis (ALECT2), discovered in 2008, is characterized by renal and liver involvement. It mainly affects elderly Hispanics and typically presents with a bland urine, subnephrotic proteinuria, and progressive CKD. Histologically, ALECT2 has a preferential interstitial involvement. Diagnosis is made by liquid chromatography mass spectrometry (LC/MS) of affected tissue.

**Methods:** A 71 yo Mexican man presented with a 2 month history of gross hematuria. PMHx includes recently diagnosed DM II. His vitals and exam were unremarkable. Creatinine (SCr) 3.8 mg/dL, K+ 5.4 mmol/L, Hgb 6.3 g/dl. UA grossly red, 1+ protein, PMHx includes recently diagnosed DM II. His vitals and exam were unremarkable. Kidney biopsy (KB) showed minimal Congo red positivity along tubulointerstitium.

**Results:**

**Conclusions:** ALECT2 is an emerging disease that predominantly affects pts of Hispanic ethnicity. Its characteristic demographic predilection and tubulointerstitial involvement should raise suspicion of this disease and alert one to perform LC/MS. Our pt’s diagnosis was discovered by examination of a nephrectomy specimen and confirmed by LC/MS. Although there are no known treatments, colchicine impairs chemotaxis of leukocytes and on this therapy his SCr remains stable at one year.

---

**TH-PO617**

Predominantly Vascular AL Amyloidosis Mimicking Vascular Hyalinosis on Renal Biopsy – A Diagnostic Pitfall
Anthony F. Jllyvornade, Niti Madan, Kuang-Yu Jen, University of California Davis Medical Center, Sacramento, CA; University of California, Davis, Sacramento, CA.

**Background:** Vascular-limited renal amyloidosis accounts for ~5% of AL amyloidosis cases. In this form, patients often present with minimal proteinuria, making the diagnosis clinically challenging. Histologically, vascular hyalinosis mimics vascular amyloidosis and may lead to errors in diagnosis, especially in elderly patients with a history of hypertension where chronic vascular disease is expected on biopsy.

**Methods:** An unusual case of predominantly vascular AL amyloidosis with nephrotic range proteinuria and histologic appearance indistinguishable from vascular hyalinosis is presented. A 75-year-old male was noted to have normal serum creatinine but nephrotic range proteinuria. Physical examination was significant for anasarca. Further work-up showed elevated serum free light chains with lambda predominance. A kidney biopsy was performed to characterize renal involvement. The biopsy contained 12 glomeruli, 2 of which were globally sclerotic. All the non-sclerotic glomeruli showed normal histology with no evidence of amyloid deposition. Severe chronic vascular disease was noted with prominent arteriolesclerosis in larger caliber vessels. Smaller caliber vessels including small arteries and arterioles exhibited mural deposition of hyaline-like material that stained strongly for PAS but showed minimal silver staining. Congo red stain revealed that this material within the vessels was positive, confirming vascular amyloid deposition. No Congo red staining was seen in any of the glomeruli. Ultrastructural examination confirmed the widespread presence of amyloid within the vessels. Rare and minimal amyloid deposition was noted in the glomerular capillary loops and mesangium. He was started on CYBORD (Cyclophosphamide, Bortezomb and Dexamethasone), a repeat serum immunofixation showed undetectable overt evidence of monoclonal protein.

**Results:**

**Conclusions:** This case of predominantly vascular renal amyloidosis was indistinguishable from vascular hyalinosis based on routine light microscopic stains for renal biopsy, showing similar intense PAS positivity in the amyloid as normally seen in hyaline arterio- and arteriolar occlusion. However, Congo red stain and electron microscopy confirmed the presence of amyloid. Vascular-limited or predominantly vascular renal amyloidosis can be mistaken for vascular hyalinosis in such instances, resulting in a diagnostic pitfall.

---

**TH-PO618**

Gelsolin Amyloidosis (Familial Amyloidosis of Finnish Type) in a North American Kindred
Hassan A. Salameh, Ancel A. Ashram, Matthew Howard, Lynn D. Cornell, Marie C. Hogan. Mayo Clinic, Rochester, MN; Mayo Clinic, Rochester, MN.

**Background:** Gelsolin amyloidosis is a rare form of systemic amyloidosis characterized by lattice corneal dystrophy, cranial nerve neuropathies and elastolysis. Renal involvement with nephrotic syndrome is rare. Early onset severe kidney disease has been reported in homozygotes and late onset slowly progressive forms in heterozygotes. It is usually caused by a gelsolin gene defect, namely a G640A previously known as G645A or C6A mutation.

**Methods:** We report a 74-year-old man presenting with CKD3 and nephrotic syndrome (NS). Medical history was significant for hypertension and lattice corneal dystrophy type II (LCD II) and family history of LCD II (son, mother, two maternal uncles and maternal aunts, all of Lithuanian-Finnish heritage) and no family history of kidney disease. Exam showed periorbital and ankle edema. Serum creatinine was 2.1 mg/dL with cGFR 33 ml/min/1.73 m2 and 5.6 g proteinuria/24h. SPEP and UPEP were negative. Free light chains were mildly elevated. Kidney biopsy (KB) showed minimal Congo red positivity along

---

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
with immunofluorescence findings revealed amyloidosis of undetermined type. Electron microscopy showed 10.8 nm fibrils focally replacing the glomerular basement membrane. No additional KB material was available for laser microdissection (LMD) and mass spectroscopy (MS). MS proteomics of fat aspirate material (with equivocal Congo red stain) typed the most abundant peptides were from GELS_HUMAN with p.D214N AA change identified. A heterozygous pathogenic variant c.640G>A (g.124073097; p.D214N also known as p.D187N) in the GSN gene was confirmed by Sanger sequencing consistent with familial amyloidosis Finnish type.

Results: Our patient had an unusual presentation with renal and ophthalmic involvement and no neurologic or dermatologic manifestations. This report highlights (1) importance of MS evaluation in atypical amyloidosis cases (2) implications for management (therapies are now in pre-clinical studies) (3) genetic counseling implications for families; heterozygous cases have late onset slowly progressive disease and (4) in cases where there is insufficient KB tissue for MS analysis, fat aspirate material (a relatively minimally invasive procedure) permitted confirmation.

TH-PO620
An Unusual Case of Presumed Lecithin-Cholesterol Acyltransferase Inhibitor Mohammad Katou,#1 Lynn A. Fussner,#2 Sergey V. Brodsky,#2 Tibor Nadasy,#4 Isabelle Ayoub.1 1None, Columbus, OH; 2OSU, Columbus, OH; 3OSU Nephrology, Columbus, OH; 4Ohio State University, Columbus, OH; 5The Ohio State University Wexner Medical Center, Columbus, OH.

Background: Lecithin-cholesterol acyltransferase (LCAT) is a glycoprotein produced predominantly by the liver. LCAT binds mainly to HDL particles and contributes to HDL maturation and cholesterol homeostasis. LCAT deficiency is a rare autosomal recessive disease, however an immune-mediated, acquired form has been reported. In both situations lipoprotein deposition in the glomeruli may lead to end stage kidney disease. This case illustrates the challenge of managing acquired LCAT deficiency when the underlying etiology is unclear.

Methods: Results: A 27 y old woman transferred to our center for worsening shortness of breath over 2 months. She already received 1g of rituximab and was on prednisone for concerns for an underlying auto-immune disease. Diagnostic work up was significant for AKI, hemolytic anemia, thrombocytopenia, hyperbilirubinemia, high ferritin, low HDL (3mg/dL), + ANA, + SSA and bilateral pulmonary infiltrates. Kidney biopsy showed lipoprotein deposits in the widened sub-endothelial space with some mesangial and intracellular deposits.(see figure). Some features of TMA were noted. Lung biopsy showed NSIP and isolated intravascular foreign material. LCAT activity was checked, but after rituximab infusion and having been on prednisone for 2 weeks, and it was normal. LCAT genetic testing didn’t show sequence variants. The patient was continued on high dose prednisone. Cytope尼亚 and hyperbilirubinemia resolved. Her HDL level began normalizing (up to 20 mg/dL) and AKI resolved. She had a mild improvement in respiratory symptoms.

Conclusions: Immune-mediated acquired LCAT deficiency may be difficult to diagnose. In this case clues to the presence of an inhibitor of LCAT included response to steroids and negative genetic testing. Confirming an underlying auto-immune disease remains a challenge for future decisions regarding immunosuppressive therapy to prevent further organ damage.
Unfortunately, as expected with LCAT deficiency, she suffered from LLE hemiatrophy due to ischemia from midaortic syndrome. This case demonstrates the importance of pediatric HTN evaluation including thorough examination to identify abdominal bruits, extremity size discrepancy, or end-organ damage from severe HTN.

**Conclusions:** We present an unusual case of unilateral anatomic asymmetry. While the patient had been given a diagnosis of RLE hemihypertrophy, it is more likely that she suffered from LLE hemihypertrophy due to ischemia from midaortic syndrome. This case demonstrates the importance of pediatric HTN evaluation including thorough examination to identify abdominal bruits, extremity size discrepancy, or end-organ damage from severe HTN.

**Background:** Midaortic syndrome is the acquired or congenital narrowing of the abdominal aorta and associated branches. Patients often present prior to adolescence with abdominal aorta narrowing and multiple stenotic areas along the main branches, including complete left common iliac artery occlusion with collateral flow (Figure 1). She was diagnosed with idiopathic midaortic syndrome and treated with amlodipine, atenolol and chlorthalidone.

**Results:**

**Conclusion:** Hemihypertrphy versus Hemiatriphy: A Unique Presentation of Midaortic Syndrome

**Methods:** A 38-year-old Japanese man was admitted with a 10-year history of proteinuria. None of his family has renal disease or dyslipidemia. His body mass index was 17.8, and blood pressure was 140/90 mmHg. He has no cornelia opathy, xanthoma nor leg edema. Laboratory tests showed urine protein 1.30 g/day, serum creatinine 1.08 mg/dL, total cholesterol 155 mg/dL, and triglyceride 142mg/dL. Apolipoprotein profiles revealed B6 mg/dL, normal range 70 to 109, and E11.9 mg/dL, 2.7 to 4.3. Heterozygous Apo-E Sendai mutation was detected by DNA sequencing analysis. Renal Biopsy showed distinct dilatation of glomerular capillary lumina filled with lipoprotein thrombi which was positive for oil red O and apoE staining (figure). Bezafibrate monotherapy decreased proteinuria to less than 0.3 g/day in five months. Clinical remission has been lasted for 2 years, though the ApoE level was still high.

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

**Underline represents presenting author.**
Methods: Case 1: A 38 yo woman was admitted at 32 weeks gestation for HTN and hypokalemia. She had a history of HTN prior to pregnancy but was on no medications. At 22 weeks, she developed weakness and hypokalemia (K 2.8 mg/dl). The BP was 130/99. She received IV and PO KCl replacement. At 30 weeks, the BP was 150/80 and she was prescribed methylxylon. One week later, the BP was 160/100 and labetalol was started. She continued at 36 weeks gestation, the BP was 165/89 and the K was 3.0 mg/dl. She denied nausea, vomiting, or diarrhea. There was a family history of HTN in the patient’s mother and father, but no family history of hypokalemia. Physical examination showed 1+ bilateral lower extremity edema. There was no proteinuria. Urine K was 23.2 mmol/L, urine Na 145 mmol/L, plasma Aldosterone 3.0 mg/dl, and renin activity 2.0 ng/ml/h. Case 2: A 36 yo woman was admitted at 26 weeks gestation for HTN and hypokalemia. She had a history of gestational HTN in two prior pregnancies, and chronic HTN diagnosed 2 years prior. Her BP was normal off medications for the first half of pregnancy. At 24 weeks, the BP was 158/94. At 26 weeks, her BP was 160/95 and her K was 2.8 mg/dl. She was admitted. Physical exam showed BP 179/80 and peripheral edema. There was no proteinuria. Urine K was 20.3 mmol/L, urine Cr 43.7 mg/dl, plasma aldosterone 1 ng/dl, renin activity 1.9 ng/ml/h.

Results: Conclusions: Normally the MR is activated by aldosterone, but inhibited by prostaglandin. The novel approach is that there is inhibition of complement factors and/or antibodies to complement factors. In rare cases it may be triggered by the stress of pregnancy. This is a case of a pregnant woman with aHUS that initially presented with HELLP Syndrome which made the diagnosis of aHUS challenging.

Conclusions: High progesterone in pregnancy was implicated. Our patients experienced worsening HTN and new hypokalemia in pregnancy, with renal potassium wasting and low renin and aldosterone levels, consistent with Geller syndrome. Both patients responded to amifloride. Geller syndrome should be considered in women with HTN and hypokalemia in pregnancy.

Background: Atrial or complement mediated Hemolytic uremic syndrome (aHUS) is a rare disorder most often seen in children and associated to gene mutations of complement factors. In rare cases it may be triggered by the stress of pregnancy. This is a case of a pregnant woman with the diagnosis of aHUS during pregnancy with a history of HTN. The pregnancy progressed to term and the patient delivered a healthy term infant. The patient’s condition improved with resolution of AKI and hemolysis, and normalization of platelet count. She was discharged to continue indefinite treatment with Eculizumab as outpatient.

Results: Conclusions: Complement mediated HUS may present as a complication from pregnancy. The diagnosis of aHUS during pregnancy may be challenging because the clinical presentation may resemble that of HELLP syndrome as both conditions can coexist and may present with similar laboratory findings. Nephrologists should have high level of suspicion for aHUS in a pregnant woman who presents with HELLP Syndrome. Renal biopsy is valuable in making appropriate diagnosis.

Background: There is literature for using tacrolimus in patients with IgA nephropathy for anti-proteinuric effect in those that cannot tolerate ACE inhibitors due to hypotension. There is literature for using tacrolimus in patients with IgA nephropathy for anti-proteinuric effect in those that cannot tolerate ACE inhibitors due to hypotension.

Results: Conclusions: Light microscopy with PAS staining showing IgA nephropathy with mild mesangial proliferative changes and focal global glomerulosclerosis.

Results: Conclusions: Intolerance to steroids and contraindication to mycophenolate in addition to low TMPMT limited the therapeutic options in this case. Using tacrolimus for its antiproteinuric effects at low dose can be beneficial.
an inhibitor. She was started on daily mTPE and high-dose steroids, followed by thrice-weekly mTPE to maintain a platelet count of at least 150 K/μL. The patient received 43 mTPE sessions during pregnancy without any complications. She delivered a healthy child at 34 weeks of gestation. After delivery, her platelets normalized without mTPE or steroids. An ADAMTS13 activity after delivery was 69%. (Fig 1)

**Methods:** A 28 year old female G3P2 with no significant past medical history presented during her 36th week of pregnancy with preeclampsia and urine protein excretion of 4 gm/24hr. C-section delivered a viable fetus. She was discharged with serum creatinine (Cr) 0.8 mg/dl. She returned with fatigue and abdominal tenderness 2 weeks later. CT imaging with contrast revealed a supra-renal hematoma prompting surgical evacuation. Two days later she developed progressive increase in lower extremity edema, puffiness of eyelids, oliguria and microscopic hematuria. Hemoglobin was 7.6 gm/dL, platelets 220 K/μm³, Cr 9.2 mg/dl, albumin 1.8 gm/dL and urine protein excretion 8.8 gm/24hr (clinical course in Fig. 1). Viral markers (Hepatitis B, C and HIV), C3, C4 and immune profile, were all negative. Renal biopsy revealed twenty glomeruli, all showed cellular crescents (arrows in Fig.2) and collapsing of capillary loops with moderate endocapillary proliferation. Immunoperoxidase staining was negative for IgA, IgG with weak focal positive staining for IgM within the crescents.

**Results:** The patient did not require dialysis and renal functions responded favourably to plasma exchange, steroids and cyclophosphamide. Three months later Cr was 2 mg/dl and urine protein 4 gm/24 hr. At this time, further therapy options are being discussed. Educational objectives include; always confirm the clinical suspicion of glomerular disease with biopsy whenever possible. Hidden triggering elements for crescentic GN merit consideration.

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

---

**TH-PO630**

Eculizumab, a Novel Treatment for Acute Kidney Failure Associated with Severe Preeclampsia

Hatem Elabd, Rushi K. Nayak, Belinda Jim, Kistra Anis, Anjali Acharya, Jacobi Medical Center/Albert Einstein College of Medicine, Bronx, NY.

**Background:** Preeclampsia is a leading cause of maternal and neonatal morbidity and mortality. It is the most common cause of AKI during pregnancy. Preeclampsia complicates approximately 5% of all pregnancies, making it perhaps the most common glomerular disease in the world. The complement system is a key mediator of systemic inflammation and is excessively activated in preeclampsia. As alloantibodies commonly develop against the semi-allogeneic fetal tissues, the placenta is potentially a target for complement-mediated immune attack.

**Methods:** A 29-year-old female multiparous at 40 weeks of gestation admitted to surgery/ICU post emergent section for severe preeclampsia complicated with rupture membrane and fetal heart deceleration. Perioperatively coarse complication coupled with bleeding, shock and acute kidney injury, for which patient needed resuscitation, and mechanical ventilation. She remained anuric with progressive kidney failure and continuous renal replacement therapy was started. We performed extensive workup to rule out acute fatty liver of pregnancy, TTP, atypical HUS, SLE, or antiphospholipid syndrome. Also complement gene mutation studies associated with atypical HUS were checked, which later turned out to be negative. Therefore, she was diagnosed with severe preeclampsia with multi-organ dysfunction. We decided to give Eculizumab 900mg/dose, a C5 inhibitor, on day 4 post admission. One week later, patient had marked clinical improvement, and dialysis was discontinued. Furthermore, there was complete normalization of all laboratory abnormalities and complement activation markers.

**Results:** To our knowledge this is the first case describing the use of Eculizumab in acute kidney injury (AKI) in setting of severe preeclampsia. The use of Eculizumab was previously described in a women with HELLP syndrome which led to improved liver function tests and pregnancy prolongation for 17 days. As opposed to our case, Eculizumab was given intrapartum and their patient had no evidence of kidney failure. The use of Eculizumab in this report supports a possible benefit of C5 inhibition for the treatment of severe preeclampsia and AKI. Its use may be particularly helpful among women with mutations in complement regulatory proteins. Further research is warranted to validate our findings.

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

---

**TH-PO631**

New-Onset Crescentic Glomerulonephritis Following Preeclampsia: A Diagnostic Dilemma

Karim M. Soliman,1,2 Mohammed Z. Mohiudeen,1 David W. Ploth,1 Medical University of South Carolina, Charleston, SC; 2Nephrology, Cairo University, Cairo, Egypt.

**Background:** New-onset crescentic Glomerulonephritis (GN) in the postpartum period following preeclampsia with normal GFR after delivery has not been reported. AKI 2 days post CT with contrast complications making this diagnosis.

**Results:** New-onset crescentic Glomerulonephritis (GN) in the postpartum period following preeclampsia with normal GFR after delivery has not been reported. AKI 2 days post CT with contrast complications making this diagnosis.

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

---

**TH-PO632**

Microscopic Polyangiitis with Pulmonary Renal Syndrome in a Pregnant Woman: Management Challenges

Ramprasad Kandavar,1 Sandhya L. Kommana,1 Anuja P. Shah,1 Harbor ULCA MEDICAL CENTER, Harbor City, CA; 2Harbor-UCLA Medical Center, Torrance, CA; 3Los Angeles Biomedical Research Institute at Harbor-UCLA, Torrance, CA.

**Background:** Introduction Microscopic Polyangiitis occurring either de novo or relapse during pregnancy has significant maternal and fetal morbidity and mortality. Here we report a case of pregnant woman developing de novo MPA manifesting as pulmonary renal syndrome posing considerable management challenges.

**Methods:** Case Description A 21-year-old pregnant woman (G1P0) presented to the Emergency department at 21 weeks gestation with uncontrolled blood pressure, pulmonary edema and acute renal failure. Laboratory data significant for Hemoglobin of 6.4, BUN 49 and Serum Creatinine 7.15 mg/dl. UA showed 3 protein, 3+ blood with numerous Acanthocytes. Further studies revealed Pr ANCA 1:160 and Anti MPO: 24. Renal US was revealed normal sized kidneys. Early clinical course also complicated by hemoptysis suggestive of pulmonary hemorrhage. A diagnosis of RPGN secondary to Microscopic Polyangiitis was made. She was started on pulse steroids followed by oral Prednisone, IV cyclophosphamide, Hemodialysis 6 times/week and Plasmapheresis. Over the course of several days patient made significant clinical stabilization, hemoptysis resolved and ANCA and anti-MPO titers became negative. Patient was managed in close consultation with Obstetrics Service and underwent Cesarea section at 27.2 weeks. Patient received monthly infusion of Cyclophosphamide with no signs of renal recovery and currently is dependent on hemodialysis. Renal biopsy was done after delivery, showed immune complex mediated glomerulonephritis, chronic/inactive crescentic glomerulonephritis involving 85% of glomeruli with moderate to severe scarring.

**Results:** The data on MPA in pregnancy and its outcomes is very limited and is thought to have a more aggressive course. A systematic review of 48 pregnancies with small vessel vasculitis showed 33 % prematurity, 8% miscarriage, pre-eclampsia 15% and maternal death 4%. Many of the immunosuppression drugs including Cyclophosphamide are contraindicated in pregnancy because of teratogenicity, ovarian
failure, and fetal prematurity. However, there are anecdotal reports of Cyclophosphamide use in pregnant women with malignancies like leukemia, lymphoma and breast cancer confirming safety of the drug in pregnancy. In our case we faced similar treatment dilemmas though in the end we were able to deliver a viable fetus.

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

---

**TH-PO633**

**Transient Hypertension in a Preterm Infant after the Administration of Indomethacin for Patent Ductus Arteriosus Takahiro Tominaga, Satomi Shino, Hironori Tsumura, Risa Ochiai, Minakawa, Takashi Oikawa, Ryuzoh uji, Iwakiri, Saotome, Olafstad, Taki, Japan; Saitama Municipal Hospital, Saitama, Japan.**

**Background:** Hyposomiaemia and reduced anticoagulant activity are considered major risk factors for thrombosis in NS. When thrombosis in the renal sinus occurs, increased venous pressure may cause DAF, intrarenal hypertension, or arterial steal, followed by neurological deficits. We describe the first case of NS that was complicated by disorientation due to DAF in association with dural sinus thrombosis.

**Methods:** A 78-year-old man was admitted to our hospital with a 1-week history of edema, weight gain, exertional dyspnea, and new-onset of disorientation. On admission, a urinary examination showed microscopic hematuria and heavy proteinuria (protein/creatinine ratio of 4.7 g/g creatinine). A blood examination showed an elevated blood urea nitrogen level of 20 mg/dL, creatinine level of 0.8 mg/dL, calcium 9.5 mg/dL, phosphorus 3.8 mg/dL, sodium 130 mEq/L, potassium 4.3 mEq/L, chloride 101 mEq/L, bicarbonate 16.3 mEq/L, uric acid 10.0 mg/dL, TP 4.7 mg/dL, albumin 3.0 mg/dL, NT-pro BNP 182.10 pg/mL, plasma renin activity 1.1 mg/L/hr, and aldosterone 382 pg/mL. Cardiac ultrasound showed mean velocity of circumferential fiber shortening (mVcfc) of 0.6 cm/s and end-systolic wall stress (ESWS) of 119.3 g/cm² suggesting afterload mismatch, which occurs in response to an acute increase in vascular resistance. Nitroglycerin infusion was started. On day 15, BP decreased to 109/74 mmHg. Cardiac ultrasound showed improvement of afterload mismatch.

**Results:**

**Conclusions:** NSAID-induced hypertension has been ascribed to sodium retention due to COX inhibition in the kidney. The major mechanism of the increased blood pressure of this patient, however, is thought to be high afterload due to increased peripheral vascular resistance presumably induced by indomethacin.

---

**TH-PO635**

**Renovascular Hypertension: A Diagnostic and Therapeutic Conundrum Abhilash Koratala,1 Freddy R. Malpartida,2 Siddharth Wayangankar,1 Rajesh Mohandas.1 1University of Florida, Gainesville, FL; 2University of Florida, Gainesville, FL.**

**Background:** The commonest causes of renal artery stenosis (RAS) are atherosclerosis and fibromuscular dysplasia (FMD). Despite the availability of advanced imaging modalities, there are substantial challenges to accurately distinguishing between the two. Since treatment options and benefits of revascularization are different in FMD and atherosclerosis, it is essential to make an accurate diagnosis. Herein, we present the case of a young patient with hypertension (HTN) and RAS who was mistakenly labeled as FMD and later diagnosed with atherosclerotic RAS.

**Methods:** A 46-year-old woman with a diagnosis of FMD was referred to us for evaluation of resistant HTN. Uncontrolled HTN was confirmed by ambulatory blood pressure monitoring. 3 months prior to presentation, she had undergone angioplasty and stenting of the left renal artery for imaging suggestive of FMD. We optimized her anti-hypertensive regimen and recommended lifestyle modifications. At follow up, her clinic BP was 285/130 mmHg. She was on lisinopril 10mg, amlopidine 10mg, Chlorthalidone 25mg and spironolactone 25mg/day. Renal angiography confirmed in-stent restenosis (90%) of the left renal artery and 80% diffuse stenosis of the ostial and proximal segments of the right renal artery. Intravascular ultrasound (IVUS) demonstrated atherosclerotic plaques. The proximal and ostial nature of the disease, absence of heaping, and presence of plaques in a patient with diabetes and history of irradiation suggested atherosclerotic RAS. The restenosis was successfully treated with IVUS guided angioplasty [Figure]. Her blood pressures improved immediately after the procedure and she was weaned off all anti-hypertensive medications other than Lisinopril and chlorthalidone.

**Results:**

**Conclusions:** Accurately distinguishing between FMD and atherosclerotic RAS is critical. FMD is usually treated with angioplasty while most patients with atherosclerotic RAS do not benefit from revascularization. Patients who have stents placed should undergo periodic surveillance for restenosis with Doppler ultrasound.

---

**TH-PO634**

**A Case of Dural Arteriovenous Fistula Caused by Dural Venous Sinus Thrombosis Complicated by Minimal Change Nephrotic Syndrome (MCNS) Risa Yamashita, Shoko Ochiais, Akihiro Minakawa, Takashi Iwakiri, Ryuzoh Nishizono, Masao Kikuchi, Hideto Nakagawa, Yuji Sato, Shouichi Fujimoto. Division of Nephrology, Department of Internal Medicine, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan.**

**Background:** Venous thrombosis is an important complication of nephrotic syndrome (NS). Dural sinus venous thrombosis is uncommon, but it is a major risk of dural arteriovenous fistula (DAF). We present a case of DAF due to dural venous sinus thrombosis that was successfully treated by an intravascular approach.

**Methods:** A 78-year-old man was admitted to our hospital with a 1-week history of edema, weight gain, exertional dyspnea, and new-onset of disorientation. On admission, a urinary examination showed microscopic hematuria and heavy proteinuria (protein/creatinine ratio of 4.7 g/g creatinine). A blood examination showed an elevated blood urea nitrogen level of 24.3 mg/dL, creatinine level of 1.38 mg/dL, fibrinogen level of 352 mg/mL, and antithrombin-III was 57%. Additionally, serum albumin was reduced to 1.49 g/dL. His renal biopsy findings showed minor glomerular abnormalities. These findings were compatible with MCNS. Deep vein thrombosis of the right leg was found by echogram. Prednisolone, cyclosporine, and oral anticoagulant were administered. Despite proteinuria being reduced, his disorientation became worse daily. Head computed tomography showed a low-density area in his occipital lobes. Magnetic resonance imaging showed DAF with sigmoid sinus thrombosis in addition to cerebral venous reflux, micro-hemorrhages, and venous blood stasis. Thereafter, transcatheter embolization was performed on the 29th hospital day, and then his disorientation improved. He was discharged on the 42nd hospital day. At an 8-month follow-up, MCNS and DAF had not relapsed.

**Results:**

**Conclusions:** Hypoalbuminemia and reduced anticoagulant activity are considered major risk factors for thrombosis in NS. When thrombosis in the cranial sinus occurs, increased venous pressure may cause DAF, due to dural hypertension, or arterial steal, followed by neurological deficits. We describe the first case of NS that was complicated by disorientation due to DAF in association with dural sinus thrombosis.

---

**TH-PO636**

**Labelatol or Amphetamine? : That Is the Question Shimontini Mitra,1,2 Nikhil Agrawal.1 1Beth Israel Deaconess Medical Center, Brookline, MA; 2Nephrology, Beth Israel Deaconess Medical Center, Boston, MA; 3Harvard Medical School, Boston, MA.**

**Background:** Uncontrolled hypertension is a frequent cause of hospitalizations. Evaluation for causes of accelerated hypertension includes urine analysis for ingested substances like amphetamine. Interpretation of urine amphetamine testing becomes difficult when patients are administered high doses of labelatol. Understanding the chemical structures of amphetamines and their breakdown products can help distinguish true amphetamine use from labelatol effect. In this case, mass spectroscopy proved helpful in interpreting a positive urine amphetamine test.

**Methods:** A forty-two year old male with ESRD and Type I Diabetes status post pancreas and kidney transplant in October 2015 and hypertension presented with elevated blood pressures and acute kidney injury. The patient was noted to have uncontrolled blood pressures for the past month. His blood pressure on admission was 211/113 and throughout most of his stay ranged 180-190/90-110 mmHg. His admission physical exam was notable for a chronic stotic murmur, no abdominal or carotid bruits, non-tenderness over kidney and pancreatic graft sites, no papilledema, and no edema. His admission creatinine was 1.8 mg/dL from a baseline of 1.4 mg/dL. Cardiac enzymes and EKG were unrevealing. His blood pressure regimen in-house consisted of labelatol 800mg TID, hydralazine 75mg QID and clonidine patch 0.3mg QD. A urine toxicology screen was also performed which returned positive for amphetamine. The patient denied the use of illicit substances prompting further analysis. Mass spectroscopy of the sample was negative for amphetamine but demonstrated a breakdown compound of labelatol, 3-amino-1-phenylbutane (APB). His blood pressures were eventually controlled with the addition

---

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

Underline represents presenting author.
of isorbidole mononitrate 120mg QD and furosemide 40mg QD orally. His creatinine returned back to baseline and patient was discharged.

Results:

Conclusions: Labelable breaks down into multiple compounds. One of these metabolites is APB. Urine amphetamine assays work by competitive inhibition between glucuronide-phosphate dehydrogenase (G6PDH)-labeled amphetamine and urinary amphetamine for a fixed number of receptor antibody binding sites. APB is structurally similar to amphetamine and can bind to reagent antibody in this assay resulting in false positivity. Therefore, for patients with uncontrolled hypertension who are also on high doses of labetalol, mass spectroscopy is a means of correctly interpreting a positive test.

TH-PO637


Background: SSC is a diffuse connective tissue disorder with cutaneous and visceral involvement, presenting with characteristic skin sclerosis. Systemic Sclerosis sine scleroderma (ssSSC) is a rare (<10%) subset of SSCs with visceral and immunologic features of SSCs without skin involvement. Additionally, hypocomplementemia can be found in 20% cases of SSCs, and may represent an “Overlap Syndrome”, i.e. second autoimmune condition. Scleroderma renal crisis occurs in 20% of SSCs, and diagnosis can be missed without the characteristic sclerotic skin findings of SSCs.

Methods: A 26 yr-old female with a PMHx of HTN and CKD III, presented with sub-crestal chest pain, palpitations, headaches and malignant hypertension. Exam was significant for BP 211/136 mm Hg, HR 84/m and trace LE edema. Laboratory data: Hb 10.6 g/dL, WBC 6.9 and platelets 282. BUN/creatinine (Cr) was 101. Urinalysis showed a bland sediment and more than 300 mg/dL protein without casts. Urine protein excretion was 5185 mg/gCr. Serum protein electrophoresis showed significant hypoalbuminemia with a gamma region spike consistent with the presence of a monoclonal protein: IgM >3150, IgA 32 and IgG <108. Serum and urine immunofixation showed monoclonal IgM lambda (κ) and Bence-Jones proteinuria, respectively. Light free light chains were elevated at 13.10 with the kappa/lambda ratio 0.19. β-2 microglobulin was 4.1. Serum viscosity and complement (C3 and C4) levels were within normal limits and cryoglobulins were negative. A subsequent BM biopsy revealed near effacement of marrow by diffuse interstitial B-Cell infiltrate and a positive MYD88 mutation indicative of WM. A kidney biopsy was not performed and no cancer-targeted therapy was initiated as the patient elected comfort focused care.

Results:

Conclusions: Diagnosis of WM-associated nephropathy is of immense clinical importance due to its prognostic impact. Biopsy-proven WM nephropathy is associated with shorter overall survival especially in those with renal function decline despite treatment. Pathology can be variable however light-chain amyloidosis usually causes NS in WM. Despite presence of Bence-Jones proteinuria, in our case, cast nephropathy is less culpable due to low quantity of the light chains. Reports are also emerging on minimal changes disease as a paraneoplastic manifestation of WM with resultant NS. Regardless of mechanism of nephropathy, treatment of the underlying WM with chemoinmunotherapy, especially Rituximab, has largely shown to result in NS resolution.

TH-PO640

Lambda Light Chain Tubulopathy in Waldenstrom’s Macroglobulinemia Joseph De Leon, Sandhya L. Kommana, Ramanath B. Dukkipati,1 Harbor ULCA MEDICAL CENTER, Harbor City, CA; Harbor-UCLA Medical Center, Torrance, CA.

Background: Light Chain Tubulopathy is typically seen in Plasma cell dyscrasias such as Multiple Myeloma, however it has been reported in Waldenström’s Macroglobulinemia. The vast majority of cases involve the Kappa Light Chains, with Lambda Light Chains being exceedingly rare.

Methods: A 63 year old female with untreated Waldenström’s Macroglobulinemia was admitted for decreased oral intake resulting into acute kidney injury(AKI). She has not had definitive treatment due to absence of absolute indications such as cytopenias, organomegaly, hyperc viscosity symptoms and nephropathy until 2 months prior to admission, when she had a rising creatinine of 1.6 mg/dl (baseline 1.3) and opted not to get the treatment of Rituximab. She presented on admission with AKI with creatinine of 3.9 mg/dl, trace proteinuria, 2-3RBC/HFP and FeNa+1%. She was volume repleted to manage the pre renal state although the possibility of plasmacytoma related kidney injury remained high. Unexpectedly, her kidney function did not have robust improvement and she eventually underwent kidney biopsy, the strongest suspicion being immune mediated MPGN. Pathology revealed renal involvement by atypical lymphoplasmacytic infiltrate with λ-light chain restriction with inclusions within proximal tubular epithelial cells with crystalloid appearance consistent with λ-light chain tubulopathy.

Results:

Conclusions: Waldenström’s Macroglobulinemia have circulating monoclonal IgM proteins in association with a B cell lymphoproliferative disorder. Renal involvement occurs in < 5% of patients with varied pathology including direct invasion of renal parenchyma by neoplastic lymphoplasmacytic cells, intraglomerular occlusive thrombi of the IgM paraprotein and in some, development of MPGN with associated type 1 or type II cryoglobulinemia. Light chain proximal tubulopathy (LCTP) is characterized by cytoplasmic inclusions of monoclonal light chains within proximal tubular cells. One study focused on pathologic features of 40 cases of crystalline LCPT from 2000-2014 all of which showed κ-restriction. The incidence of LCPT is typically seen in Multiple Myeloma and has been reported in Waldenström’s Macroglobulinemia. The vast majority of reported cases of LCPT are κ-restricted. The finding of LCPT, from Waldenström’s Macroglobulinemia, with λ-light chain restriction makes this case exceedingly rare and to our knowledge, never been reported.
Light Chain Cast Nephropathy and Vascular Limited Renal Amyloidosis Occurring Simultaneously in a Patient

Methods: A 73-year-old woman was referred to our hospital due to proteinuria and hematuria. Non-ischemic cardiomyopathy had been diagnosed 6 years before. Cardiac amyloidosis was suspected, but only slightly delayed gadolinium enhancement by cardiac MRI, which was confined to the inferolateral wall, did not meet the criteria for cardiac amyloidosis. She had received implantable cardioverter defibrillator because of ventricular arrhythmia. Approximately 1 year before the referral, she had experienced hematuria with no proteinuria when her serum creatinine level was 0.7 mg/dL. Upon admission, she exhibited an increased serum creatinine level to 1.89 mg/dL and significant proteinuria of 2.83 g/g creatinine. Plasma electrophoresis showed the presence of IgG-k monoclonal protein. The ratio of k/λ free light chain levels in serum was increased. Renal AL was first suspected on the basis of diagnosis by kidney biopsy. However, monoclonal immunoglobulin heavy-chain deposition was revealed by immunofluorescent staining and LC-MS/MS. Therefore, we finally diagnosed her as having renal AL. We started to treat her with low doses of dexamethasone and lenalidomide, but the treatment was unsuccessful. Further scrutiny and close follow-up are crucial to demonstrate that she suffered from cardiac amyloidosis complicated with AHL.

Results: We here report a rare case of renal AL diagnosed with LC-MS/MS, who could be probably complicated with morbid cardiac amyloidosis. Accurate diagnosis is extremely important to give insight into prognostic implication in patients with AHL.

Conclusions: We here report a rare case of renal AL diagnosed with LC-MS/MS, who could be probably complicated with morbid cardiac amyloidosis. Accurate diagnosis is extremely important to give insight into prognostic implication in patients with AHL.

Light Chain Cast Nephropathy and Vascular Limited Renal Amyloidosis Occurring Simultaneously in a Patient

TH-PO641

Recurrent Heavy/Light-Chain Amyloidosis Diagnosed by Immunostaining and Liquid Chromatography-Tandem Mass Spectrometry in a Patient

Background: Heavy- and light-chain amyloidosis (AHLL) is a rare type of amyloidosis caused by deposition of monoclonal immunoglobulin heavy and light chain. Compared with patients with renal light-chain amyloidosis (AL), those with renal AHL are reported to be rarely complicated with cardiac amyloidosis, resulting in relatively better survival. We here report a rare case of renal AL diagnosed by immunofluorescent staining and liquid chromatography-tandem mass spectrometry (LC-MS/MS) in a patient with non-ischemic cardiomyopathy.

Methods: A 73-year-old woman was referred to our hospital due to proteinuria and hematuria. Non-ischemic cardiomyopathy had been diagnosed 6 years before. Cardiac amyloidosis was suspected, but only slightly delayed gadolinium enhancement by cardiac MRI, which was confined to the inferolateral wall, did not meet the criteria for cardiac amyloidosis. She had received implantable cardioverter defibrillator because of ventricular arrhythmia. Approximately 1 year before the referral, she had experienced hematuria with no proteinuria when her serum creatinine level was 0.7 mg/dL. Upon admission, she exhibited an increased serum creatinine level to 1.89 mg/dL and significant proteinuria of 2.83 g/g creatinine. Plasma electrophoresis showed the presence of IgG-k monoclonal protein. The ratio of k/λ free light chain levels in serum was increased. Renal AL was first suspected on the basis of diagnosis by kidney biopsy. However, monoclonal immunoglobulin heavy-chain deposition was revealed by immunofluorescent staining and LC-MS/MS. Therefore, we finally diagnosed her as having renal AL. We started to treat her with low doses of dexamethasone and lenalidomide, but the treatment was unsuccessful. Further scrutiny and close follow-up are crucial to demonstrate that she suffered from cardiac amyloidosis complicated with AHL.

Results: We here report a rare case of renal AL diagnosed with LC-MS/MS, who could be probably complicated with morbid cardiac amyloidosis. Accurate diagnosis is extremely important to give insight into prognostic implication in patients with AHL.

Conclusions: We here report a rare case of renal AL diagnosed with LC-MS/MS, who could be probably complicated with morbid cardiac amyloidosis. Accurate diagnosis is extremely important to give insight into prognostic implication in patients with AHL.
presented with sudden onset anasarca and serum creatinine (SCr) of 2.8 mg/dL. Baseline SCr was 1.2 mg/dL. Her biopsy showed nephrotic syndrome with microspheric hematuria. Over the span of next two weeks he developed anuric failure requiring dialysis. He underwent a renal biopsy which showed PGNMID on a background of diabetic nephropathy. Immunofluorescence showed 3+ granular staining for IgG, C3 and kappa light chains. This finding is consistent with her future course and little data on the long term effects of immunomodulatory drugs (IMIDs) on teratogenicity of future pregnancy. Daratumumab was chosen in order to avoid some of these complications. In combination with bortezomib and dexamethasone, it was very effective at reducing proteinuria and resolving her hematuria. With its high activity against plasma cells and its safety profile, daratumumab could be an excellent choice in the treatment of MGRS patients.

**TH-PO648**

**De Novo Proliferative Glomerulonephritis with Monoclonal IgG in Renal Allografts**

Eliana Leung, Bradd Lang, Catecrea Mary, Fara Ahmed, Mazdad A. Khalghi, Fuad S. Shihab, LiAiB Al-Rabadi. University of Utah Hospital, Salt Lake, UT.

**Background:** Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) has recently been recognized as a unique type of glomerular injury with a wide spectrum of pathologic and clinical manifestations. It is characterized by deposition of monotypic IgG in glomeruli and is often accompanied by C3 and Clq deposition. We have previously reported a series of three cases of recurrent PGNMID in renal allografts, all of which were associated with IgG3-Kappa deposition. De novo PGNMID in renal allografts has only been reported in three cases.

**Methods:**

**Results:** Herein, we present a fourth case of de novo disease that occurred in the renal allograft of a 49-year-old male with de novo disease of renal dysplasia since birth and prior allograft failure due to chronic antibody-mediated rejection. The patient presented to the hospital with 10 day history of dark urine. He was found to have acute kidney injury with Cr up to 2.5 mg/dL from 1.4 mg/dL. Urine microscopy showed many RBCs and several WBCs. Urine protein to Creatinine ratio was 1.5 g/g. Serum protein electrophoresis and immunofixation were normal. Serum kappa lambda ratio was 1.3. Cryoglobulins were negative. Biopsy showed mild mesangial hypercellularity without evidence of allograft rejection. Immunofluorescence microscopy showed mesangial deposits staining for IgG and Clq and kappa light chains were detected. IgG subtype staining revealed IgG1-restriction. Electron microscopy showed mesangial electron dense deposits without substructural organisation.

**Conclusions:** Similar to native cases of PGNMID, recurrent disease in the allograft is likely related to deposition of IgG kappa. However, of the four reported cases of de novo PGNMID, three were IgG1-Kappa and only one was IgG3-kappa. IgG1-kappa in renal allografts has so far been described only in de novo cases, not in recurrent cases. Ours is the fourth de novo case but is the only one that occurred in the second allograft. Patients with renal transplants are on immunosuppressive therapy that may alter the disease course. Deposition of IgG1-kappa in renal allografts may represent a distinct entity which is more resistant to IS therapy. More studies are needed to investigate the impact of different immunoglobulin subclasses on disease phenotype.

**TH-PO649**

**Acute Interstitial Nephritis in the Setting of Fibrillary Glomerulonephritis:**

*[Case Report and Review of Literature]*

Khetisuda Suvarnasiri, Sairah Sharif. University of Washington, Providence, RI.

**Background:** Fibrillary glomerulonephritis (FGN) is a rare primary glomerular disease that presents with hypertension, proteinuria, microscopic hematuria and variable renal failure. It is often associated with hepatitis C virus (HCV). We report a case of FGN along with acute interstitial nephritis (AIN) in patient with HCV who had response to therapy.

**Methods:** A 61 year old Caucasian male with past history HCV (viral load PCR 979330IU/ml), HTN, chronic kidney disease (baseline creatinine (Cr) 1.2 mg/dL), and hemheragic stroke presented for evaluation of hypertension and fatigue. He was found to have urinary tract infection secondary to Proteus and Enterococcus started on piperacillin/ tazobactam; later de-escalated to amoxicillin/clavulanate. Course complicated by acute kidney injury (AKI). Initial etiology of AKI thought to be pre renal azotemia from poor oral intake and ischemia from hypotension. Urine specimen revealed few muddy brown casts, WBCs<100 HPPF, RBCs >100 HPFP, and few dysmorphic RBCs. Serologies were negative for autoimmune diseases, and C3 and C4 were normal. Renal ultrasound showed increased echogenicity of renal cortex; and no hydro nephrosis. AKI worsened and Cr peaked at 4.3mg/dL. Due to worsening renal biopsy was performed that showed on light microscopy (LM) mesangial expansion, interstitial nephritis, mild interstitial fibrosis and tubular atrophy, electron microscopy (EM) demonstrated numerous random fibrils average 15nm identified as FGN. Patient was started on steroids for interstitial nephritis, and plan to start outpatient HCV therapy; His Scr improved to 1.7 in about 2 weeks from steroid initiation.

**Results:**

**Conclusions:** FGN is found in about 1% renal biopsies. It typically presents in the fifth to sixth decade. There maybe background of HCV, polycythaemia, and/or lymphoproliferative disorders. The LM is heterogeneous usually membranoproliferative, or mesangio proliferative, or diffuse proliferative GN. EM (EM) shows randomly oriented fibrils about 20nm in diameter. Optimal therapy is not known but corticosteroids and immunosuppressants have been tried with little success. About half of patients progress to dialysis. To the best of our knowledge this is the first case of FGN with AIN reported that showed response to corticosteroids.

---

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

*Underline represents presenting author.*
The Uroplakin Plaque Promotes Renal Structural Integrity During Congenital and Acquired Urinary Tract Obstruction

Ashley R. Jackson,1,2 Birong Li,1 Sudipti Gupta,1 Shira H. Cohen,1 Rachel Millner,1 Christina B. Ching,1,3 Kirk M. McHugh,1,4 Brian Becknell.1 Center for Clinical and Translational Research, The Research Institute at Nationwide Children’s Hospital, Columbus, OH; Nephrology Section, Nationwide Children’s Hospital, Columbus, OH; Department of Anatomy, The Ohio State University College of Medicine, Columbus, OH.

Background: Congenital urinary tract obstruction (UTO) is the leading cause of chronic kidney disease and end stage renal disease in children. Yet many children with congenital uroteral junction obstruction (UPJO) can be managed nonoperatively, with spontaneous resolution or resolution of hydronephrosis on postnatal imaging. This implies the existence of renal adaptations during UTO that preserve parenchymal integrity and function. We hypothesized that uroplakin (Upk) expression by renal urothelial cells initiates a protective adaptation during congenital and acquired UTO, serving as a gatekeeper to progressive renal injury.

Methods: The Upk plaque was destabilized in a congenital model of functional lower UTO by generating Mgb-/-Upk1b+/+ mice. Diphtheria toxin (DT)-mediated depletion of Upk(+) cells was induced following unilateral ureteral obstruction (UUO) in Upk2KO/R290fsX/R230fsX mice (acute UTO model). Urine Upk2 and UpkK3A levels were measured by ELISA in children undergoing pyeloplasty for UPO versus nonobstructed controls.

Results: In Mgb-/- mice with congenital hydronephrosis, the renal urothelium acquires a bladder-like cellular composition and ultrastructure. The extent of hydronephrosis positively correlates with mRNAs for Mgb and NGB in Mgb-/- kidneys. Likewise, urinary Upk1A and Upk2 levels increase in children with UPO, when compared to nonobstructed controls. Mgb-/-Upk1b+/+ mice display disrupted renal urothelial ultrastructure; rapid onset of bilateral hydronephrosis; and adolescent mortality due to renal failure, compared to Mgb-/- controls. Directed deletion of Upk1b in the unconventional type containing the Upk2R290fsX/R230fsX mouse indicates the progression of hydronephrosis following UUO. Absence of the UPk plaque leads to increased intestinal fibrosis in both congenital and acute UTO models, respectively, compared to Upk intact controls.

Conclusions: These studies reveal that the first experimental evidence that the renal plaque confers an essential, protective adaptation during congenital and acquired UTO. Conversely, loss of the UPk plaque leaves the kidney vulnerable to obstructive hydrenephrosis and may identify patients in need of surveillance or more immediate surgical intervention for renal preservation.

Funding: NIDDK Support

The Renal Urothelial Plaque Protects the Kidney Following Obstructive Injury

Birong Li,1 Ashley R. Jackson,1,4 Hanna H. Cortado,1 Sudipti Gupta,1 Christina B. Ching,1 Kirk M. McHugh,1,4 Brian Becknell.1 Center for Clinical and Translational Research, The Research Institute at Nationwide Children’s Hospital, Columbus, OH; Division of Pediatric Urology, Department of Surgery, Nationwide Children’s Hospital, Columbus, OH; Department of Anatomy, The Ohio State University College of Medicine, Columbus, OH; Nephrology Section, Nationwide Children’s Hospital, Columbus, OH.

Background: The urothelial plaque, comprised of uroplakin (Upk) proteins, establishes the urine permeability barrier and promotes structural integrity of the urinary tract. The role of the upk expressing urothelial plaque in obstructive nephropathy remains incompletely understood. We tested the hypothesis that the plaque serves a critical role in limiting hydronephrosis and parenchymal injury following obstruction.

Methods: Unilateral ureteral obstruction (UUO) was induced in three week old Upk1b+/+ and wild type (WT) mice. Hydrenephrosis was measured by serial ultrasound. Kidneys were analyzed by standard histologic stains and immunohistochemistry (IHC). The plaque was visualized by transmission electron microscopy (TEM). Upk protein levels in total kidney extracts were evaluated by Western blotting. Urothelium from children undergoing pyeloplasty for obstructive junction obstruction (UPOJ) was subject to IHC, TEM, and FITC-Dextran permeability studies.

Results: UUO leads to increased Upk protein levels; urothelial stratification and uniform apical Upk expression; and ultrastructural evidence of mature, bladder-like plaque formation in WT mice. In contrast, Upk1b-/- UOJO renal urothelium lacks Upk expression and urothelial plaque, and displays hyperplasia of Kr5/kr14 cells. Upk1b+/+ UUO kidneys displayed accelerated progression of hydronephrosis and increased parenchymal injury, compared to WT UOJO. Urothelium from the renal pelvis and ureteropelvic junctional children with UPOJO displayed more Kr5/kr14 hyperplasia, disrupted plaque and tight junctions, and increased permeability to FITC-Dextran, compared to distal urothelium.

Conclusions: Renal urothelium undergoes extensive remodeling following obstructive injury and the appearance of lower tract urothelium with increased stratification and a mature plaque. The rapid progression of hydronephrosis and parenchymal injury in Upk1b-/- mice with UUJO supports the hypothesis that the plaque serves a key role in protecting the obstructed kidney. Chronic obstructive injury in children with UPOJO leads to instability of the plaque and compromised barrier function. Strategies to augment or stabilize the renal uroplakin plaque may offer a formidable therapeutic approach to preventing acute and chronic obstructive renal injury.

Funding: NIDDK Support

Urothelial Injury Markers Are Elevated in Neurogenic Bladder Patients and Correlate with the Presence of Hydronephrosis

Rachel Millner, Janae Preece, Sudipti Gupta, Brian Becknell, Christina B. Ching. Nationwide Children’s Hospital, Columbus, OH.

Background: Neurogenic bladder (NGB) leads to varying bladder dysfunction and poses a high risk for chronic kidney disease. Urinary markers of urothelial injury are an intriguing approach to monitor NGB and associated urinary tract abnormalities. We hypothesize that urinary markers of urothelial integrity and injury are significantly altered in NGB vs non-NGB patients and that these markers correlate with renal injury and degree of bladder dysfunction.

We measured Uropak 3a (Upk3a), a structural urothelial protein, as a marker of urothelial integrity; and HIP/PAP, an antimicrobial peptide expressed solely by damaged urothelium, as a marker of urothelial injury.

Methods: We recruited 87 NGB patients for urine collection. Mean age was 8.7y (0.2–33y). Healthy controls consisted of 18 patients with a mean age of 13y (7–18y). Urine Upk3a and HIP/PAP were measured by ELISA. We estimated GFR using age appropriate equations and obtained urodynamics (UDS), VCU/G, and renal ultrasound results by chart review. In NGB, we correlated Upk3a and HIP/PAP levels with GFR, presence of VUR, hydronephrosis, or scarring; and bladder dysfunction based on UDS classification. UDS classification was based on CDC protocol. Statistical analysis was performed by Mann Whitney U test, Spearman Correlation, and logistic regression; p<0.05 was considered statistically significant.

Results: Urinary HIP/PAP and Upk3a levels were significantly higher in NGB vs controls (p<0.005 and <0.0001, respectively) regardless of age, sex, or race. HIP/PAP and Upk3a correlated with urodynamics (p<0.03); and Upk3a, GFR and VUR. Type of bladder management (catheterization vs free voiding) did not impact UPK3a or HIP/PAP level. There was a negative correlation between presence of hydronephrosis and GFR (p<0.03). Conclusions: NGB may be associated with urothelial exfoliation. HIP/PAP and Upk3a are potential, noninvasive biomarkers of NGB. Elevated levels of Upk3a and HIP/PAP in NGB are independent of renal function and may reflect alterations in urothelial remodeling or mechanical shedding of urothelium in response to bladder dysfunction. Furthermore, HIP/PAP may serve as an early, noninvasive marker of hydronephrosis in NGB, which is associated with reduced renal function.

Identification of Novel Urinary Proteins to Distinguish Urinary Tract Infection from Colonization in Catherization-Dependent Children

Catherine Forster,1 Stuart Goldstein,2 Ken Greis, Prasad Devarajan.1 Cincinnati Children’s Hospital, Cincinnati, OH; University of Cincinnati, Cincinnati, OH; Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.

Background: Children with neurogenic bladders who require clean intermittent catheterization (CIC) often have bacteriuria. Distinguishing urinary tract infection (UTI) from UTI in CIC-dependent children is difficult. Our objective was to identify urinary proteins to distinguish UTI from UCI in CIC-dependent children.

Methods: 10 CIC-dependent children were included (UTI=5, UCI=5). UTI was defined as: 1) ≥50,000 cfu/ml of a uropathogen, 2) ≥10 urinary white blood cells, and 3) ≥2 of the following: fever, abdominal or back pain, worsened incontinence, pain with CIC, or cloudy or malodorous urine. UTI was defined as a bacteriuria in an asymptomatic patient. Medical records of patients who met UTI criteria were reviewed to select those with clear UTI symptomatology. 5 UTC patients were matched on age and uropathogen. Quantitative profiling of urine proteins with isotopic protein labeling was performed using tandem mass spectrometry. Candidate markers were normalized using a collective mixture of proteins from all samples. Relative quantitative abundance of proteins across all samples were compared. Proteins with a significant fold-change across either UTI or UTC, with ≥50% change in the average abundance across groups were identified as proteins of interest.

Results: Eight proteins were differentially expressed. These included: haptoglobin and liver fatty-acid binding protein (LFABP) overexpressed in UTI, andapolipoprotein D, α-amylase 2B, inter-α-trypsin inhibitor heavy chain H4, non-secretory ribonuclease, CD44 antigen, and prosaposin overexpressed in UTC. Protein functions include antimicrobial activity (haptoglobin), inflammation (LFABP, apolipoprotein D, inter-α-trypsin inhibitor heavy chain H4, non-secretory ribonuclease, prosaposin, and CD44 antigen), and metal transport (α-amylase 2B).

Conclusions: These urinary proteins have potential to distinguish UTI from UTC in CIC-dependent children.
Early Proteinuria Lowering by ACE Inhibition Predicts Renal Survival in Children with CKD

Methods: We culture urine-derived renal epithelial cells (URECs) of patients with genetically confirmed causes of PKD, autosomal recessive polycystic kidney disease (ARPKD) and nephronophthisis (NPH), and of age-matched healthy controls. Populations of primary cells obtained within 14 days of culture are tested with respect to their proliferation rates, formation of cell-cell junctions in monolayer and barrier function (impedance) in 2D culture. In addition, their capacity to build spheroids and form cilia is addressed in 3D culture conditions using matrigel and micro-patterned adhesion chips.

Results: URECs from cohorts of patients (5-6 each) with ARPKD or NPH (mostly NPHP-1 mutation), and controls are compared in cell culture to measure quantitative characteristics that can be correlated to clinical parameters and progress of PKD. We observe a much higher success rate of epithelial cell cultivation from urine of PKD patients. Cells are mostly of collecting duct origin as determined by aquaporin-2 positive staining. MTS-based measure of cell proliferation rates between days 10 and 15 (20) of culture, which are moderately higher in patient cells. Analysis of spheroid formation in matrigel (6 days) reveals on average bigger clusters of patient cells and an individual tendency of defective lumen formation. Barrier function of UREC monolayers is increased in a patient-specific manner.

Conclusions: Determination of genotype and/or disease state specific renal epithelial cell properties in URECs is expected to provide a better understanding of the mechanism and progression of disease processes in renal epithelium and may provide options for testing of pharmaceutical interventions.

Funding: Private Foundation Support, Government Support - Non-U.S.
TH-PO659


Background: Urinary omins-based strategies are promising tools in medicine as they have already led to the design of multimarker models for the assessment of complex diseases. Nevertheless, advances still need to be made since most models using single omins traits are unable to reach a 100% accuracy and display a so-called “gray zone” defined by the uncertainty of the prediction. Here we verified the hypothesis whether a combination of urinary fetal peptides and metabolites provides an improved prediction of postnatal renal function in fetuses with PUV compared to the individual omins traits.

Methods: Using capillary electrophoresis coupled to mass spectrometry, we explored the urinary metabolome from 13 PUV fetuses with early ESRD and 12 PUV fetuses without postnatal ESRD at 2 years.

Results: This allowed the identification of 24 differentially abundant fetal urinary metabolites which were modelled into a svm classifier, alone or in combination with 12 peptides predictive of disease progression (Klein et al, PLoS ONE 2019). The predictive capability of models comprised of metabolites (24m), peptides (12p) or association of both (24m_12p model) were compared in a separate independent validation cohort of 35 fetuses with PUV. The gray zone was generated as the range of svm scores for which the negative likelihood ratio (LR) was >0.05 and the positive LR was <20. Sensitivity, specificity (excluding patients in gray zone) as well as area under the ROC curve (AUC) and net reclassification improvements (NRI) of PUV patients were evaluated (Table 1).

Conclusions: While the individual metabolite- and peptide-based models already display high accuracy for identification of the disease classes, the discriminative power can be significantly improved by combination of omins traits. This supports the general concept that multi-omics approaches can improve the clinical prediction of diseases.

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

Table 1

<table>
<thead>
<tr>
<th>Model</th>
<th>24m</th>
<th>12p</th>
<th>24m_12p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>73.4</td>
<td>80.7</td>
<td>82.3</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>63.2</td>
<td>60.0</td>
<td>62.5</td>
</tr>
<tr>
<td>AUC</td>
<td>0.80</td>
<td>0.76</td>
<td>0.80</td>
</tr>
<tr>
<td>NRI vs 24m (%)</td>
<td>36.1</td>
<td>40.9</td>
<td>36.1</td>
</tr>
<tr>
<td>NRI vs 12p (%)</td>
<td>11.5</td>
<td>12.0</td>
<td>11.5</td>
</tr>
</tbody>
</table>

*p<0.05 vs 24m, †p<0.05 vs 12p

TH-PO660

Different Urine Collection Techniques to Establish and Monitor Albuminuria in Healthy Toddlers *Sophie Van den Belt, Valentina Gracchi, Dick De Zeeuw, Hido J. Lambers Heesink. UMC Groningen, Groningen, Netherlands.

Background: For measurement of albuminuria, guidelines in adults recommend to measure urinary albumin creatinine ratio (UACR) in first morning void (FMV) urine samples collected over three consecutive days. Since such a guideline is absent in toddlers, we compared several urine collection strategies.

Methods: For measurement of albuminuria, guidelines in adults recommend to measure urinary albumin creatinine ratio (UACR) in first morning void (FMV) urine samples collected over three consecutive days. Since such a guideline is absent in toddlers, we compared several urine collection strategies.

Results: This allowed the identification of 24 differentially abundant fetal urinary metabolites which were modelled into a svm classifier, alone or in combination with 12 peptides predictive of disease progression (Klein et al, PLoS ONE 2019). The predictive capability of models comprised of metabolites (24m), peptides (12p) or association of both (24m_12p model) were compared in a separate independent validation cohort of 35 fetuses with PUV. The gray zone was generated as the range of svm scores for which the negative likelihood ratio (LR) was >0.05 and the positive LR was <20. Sensitivity, specificity (excluding patients in gray zone) as well as area under the ROC curve (AUC) and net reclassification improvements (NRI) of PUV patients were evaluated (Table 1).

Conclusions: While the individual metabolite- and peptide-based models already display high accuracy for identification of the disease classes, the discriminative power can be significantly improved by combination of omins traits. This supports the general concept that multi-omics approaches can improve the clinical prediction of diseases.

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

Table 1

<table>
<thead>
<tr>
<th>Model</th>
<th>24m</th>
<th>12p</th>
<th>24m_12p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>73.4</td>
<td>80.7</td>
<td>82.3</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>63.2</td>
<td>60.0</td>
<td>62.5</td>
</tr>
<tr>
<td>AUC</td>
<td>0.80</td>
<td>0.76</td>
<td>0.80</td>
</tr>
<tr>
<td>NRI vs 24m (%)</td>
<td>36.1</td>
<td>40.9</td>
<td>36.1</td>
</tr>
<tr>
<td>NRI vs 12p (%)</td>
<td>11.5</td>
<td>12.0</td>
<td>11.5</td>
</tr>
</tbody>
</table>

*p<0.05 vs 24m, †p<0.05 vs 12p

TH-PO661

Effect of Growth Hormone Therapy on Renal Function in Children Born Small for Gestational Age Kazuya Matsumura, Hironori Shibata, Stéphane Breuil, Panagiotis Stamatiladiotis. Pediatric Nephrology - Tokyo Medical University, Japan.

Background: Low birth weight infants, especially those born small for gestational age (SGA), are known to have fewer nephrons. Growth hormone (GH) induces catch-up growth, which can improve renal function in children born small for gestational age (SGA). GH may induce hyperfiltration and ultimately lead to glomerulosclerosis. We retrospectively examined the effect of growth hormone therapy on renal function in children born SGA.

Methods: Nineteen subjects born SGA (age 3 to 25 years) were studied. Ten were treated with GH and 9 served as controls. Blood pressure, serum creatinine, uric acid, urine microalbumin to creatinine ratio (mAU/Cr), and the trajectory of eGFR, calculated by quantic equation for Japanese children (2 to 18 years) or formulas for Japanese adults (19 years), were compared.

Results: GH was started at the median age of 4 years (range 3-5). The median dose and duration was 0.25 mg/kg/week (range 0.2-0.3) and 66 months (range 23-95). There were no significant differences in the background characteristics between GH group and controls including age (11 vs 10 years), birth weight (1109 vs 804 g), gestational age (32.3 vs 28.5 weeks), sex, and initial eGFR (107 vs 98 ml/min/1.73 m2). Only one child in each group did not show catch-up growth. eGFR declined in 6 (60%) in GH group and in 1 (11%) in controls (P<0.05). Of 6 GH-treated children whose eGFR declined (107 vs 98 ml/min/1.73 m2, P<0.09), eGFR before GH was stable in 2, increasing in 2, and declining in 2. In the remaining children who received GH, eGFR trajectory before and after the start of GH was decline followed by increasing (2), decline followed by stable (1), and continuously increasing (1), suggesting GH-induced hyperfiltration. There was no change in eGFR trajectory in control children; 2 increasing, 6 stable, and 1 declining. Urine mAU/Cr (9.7 vs 9.6 mg/g) and the number of children with elevated mAU/Cr (6 vs 4) were not different between GH group and controls. One child, however, developed microalbuminuria after GH was started. Hypertension or hyperuricemia was not observed in either group throughout the observation period.

Conclusions: eGFR decline was more frequent in SGA children with GH therapy compared with those not on GH. Initially stable or increasing eGFR followed by decline after the initiation of GH suggests that GH may promote progression of CKD in SGA children.
Results: Twenty-six patients (aged 10 – 21 years, mean 14 years) and 45 caregivers participated (12 groups, and identified 32 outcomes). The five highest ranked outcomes for patients were: physical activity (7.6/10), kidney function (7.6), fatigue (6.9), infection (6.8) and survival (6.8). Caregiver’s five highest ranked outcomes were: kidney function (8.5), weight gain (8.2), survival (7.5), infection/immunity (7.4), and graft survival (7.0). We believe that understanding these weights were gaining independence and realizing potential; upbeat and intrusion on daily living; preserving health and kidney function; seeking control; and certainty of future.

Conclusions: Children prioritized their kidney health and survival, appearance, and social, sport, and school participation. Caregivers were most concerned about their child’s kidney function, graft survival, infection, survival, and gaining weight. Trials that include outcomes important to children with CKD and their caregivers can better inform shared decision-making.

TH-PO663
Renal Function and Blood Pressure in Adolescents Born Preterm with Very Low Birth Weight
Andrew M. South, Patricia A. Nixon, Mark C. Chappell, Debra I. Diz, Gregory B. Russell, Elizabeth T. Jensen, Hossam A. Shallout, Lisa Washburn, Wake Forest School of Medicine, Winston-Salem, NC; Surgery-Hypertension and Vascular Research, Wake Forest School of Medicine, Winston-Salem, NC; Health and Exercise Science, Wake Forest University, Winston-Salem, NC; Pediatrics, Wake Forest School of Medicine, Winston Salem, NC; Cardiovascular Sciences Center, Wake Forest School of Medicine, Winston Salem, NC.

Background: Survival of children born prematurely has improved, but preterm birth as well as low birth weight may increase the risk of developing kidney disease in adulthood. However, the timing of the development of renal dysfunction and its progression is unclear. We hypothesize that worse kidney function will be present in preterm adolescence in children born preterm with very low birth weight (VLBW) as compared to term controls.

Methods: We measured systolic and diastolic blood pressure (BP), serum creatinine, and urine albumin at age 14 years in 96 subjects born preterm with VLBM (mean birth weight 1048 g) and 43 term controls. We calculated the glomerular filtration rate (GFR) by the Schwartz equation and urine album-to-creatinine ratio (ACR). We used generalized linear models to estimate the association between preterm birth and renal function, adjusting for maternal hypertensive pregnancy and socioeconomic status. Generalized linear models to estimate the association between preterm birth and renal function were used.

Results: In addition to higher mean systolic and diastolic BP (p=0.01 and p=0.03, respectively), adolescents born preterm had significantly-decreased GFR (β: -8.17 mL/min/1.73 m², 95% CI -15.93 to -0.4, as compared to term controls. Adjustment for covariates attenuated this relationship (β: -6.34 mL/min/1.73 m², -15.04 to 2.36). While subjects born preterm had higher median ACR, adjustment for potential confounders attenuated this relationship (In ACR β: 0.34, -0.04 to 0.72).

Conclusions: Higher BP and reduced renal function were present in adolescents born preterm with VLBM compared to term peers, though the association between preterm birth and GFR was weakened after adjusting for confounders. While other factors should be considered, our study provides evidence of an early divergence of renal function during adolescence as a consequence of prematurity.

Funding: Other NIH Support - NICHD PO1 HD047584

TH-PO664
Assessing the Hydration Status of Children with CKD and On Dialysis: A Comparison of Techniques
Caroline S. Eng, Rukshana Shroff. Hospital Tuanku Jaidee Seremban, SEREMBAN, Malaysia; Department of Paediatric Nephrology, Great Ormond Street Hospital for Children, London, United Kingdom.

Background: Fluid balance is pivotal in the management of children with chronic kidney disease (CKD) and on dialysis. Although many techniques are available to assess fluid status, there are few studies in children, and none of the techniques have been compared against each other or against cardiovascular outcome measures.

Methods: We performed a longitudinal study in 30 CKD children and 13 age-matched healthy volunteers (controls) (1 measurement each) to determine relationship between optimal weight by bioimpedance spectroscopy (Wt-BIS) and clinical assessment (Wt-CA). The accuracy of Wt-BIS (relative dehydration [Rel-OH]) was compared against indicators of fluid status and cardiovascular measures.

Results: There was poor agreement between Wt-CA and Wt-BIS in children on dialysis when compared to CKD5 or control subjects (p=0.01). We developed a modified chart to plot Rel-OH against systolic BP z-score for the appropriate representation of volume status and BP in children. 25% of measurements showed systolic BP >90 percentile but not with concurrent dehydration. Rel-OH correlated well between optimal weight by bioimpedance spectroscopy (Wt-BIS) and clinical assessment (Wt-CA). The accuracy of Wt-BIS (relative dehydration [Rel-OH]) was compared against indications of fluid status and cardiovascular measures.

Funding: Clinical Revenue Support

TH-PO665
Effect of Glomerulus Endocapillary Proliferation Lesion on the Heavy Proteinuria in Children with HSPN
Yanie Huang, Xia Liu. The First Affiliated Hospital of Henan University of Traditional Chinese Medicine, Zhengzhou, China.

Background: To analyse whether glomerular endocapillary proliferation lesion is one of important pathologic factors in HSPN and its influence on high and medium molecular weight proteins in urine.

Methods: The pathological features of 148 children HSPN with heavy proteinuria were investigated retrospectively. The means of 24h proteinuria and urinary IgG, transferrin and albumin were detected using immunonephelometry method. The correlation between endocapillary proliferation lesion and 24h proteinuria, urinary IgG, transferrin and albumin were analyzed respectively.

Results: Of 581 cases of HSPN who underwent renal biopsy, 148 cases of HSPN accompanied by heavy proteinuria accounted for 25.47%. Pathological types of HSPN accompanied by heavy proteinuria included I, IIb, IIIb and endocapillary proliferation, IVb, and pure endocapillary proliferation type. Among these types, pure endocapillary proliferation type accounted for 7.43%. The value of 24h proteinuria and urine albumin quantitation in endocapillary proliferation type HSPN were higher than other pathological types, and the percentage of endocapillary proliferation is correlated positively with 24h proteinuria and urine albumin quantitation.

Conclusions: The pathological type of HSPN with heavy proteinuria is diversity. Glomerulus endocapillary proliferation is one of the important pathological factor of HSPN heavy proteinuria, and albumin is major urine protein composition.

Funding: Government Support - Non-U.S.

TH-PO666
Polycythemia in Subjects Born with a History of Preterm Birth and Extremely Low Birth Weight
Nariaki Asada, Kazuya Matsumura, Yohei Matsuzaki, Midori Awaiz, Keio University, Tokyo, Japan; Keio University School of Medicine, Tokyo, Japan.

Background: Low birth weight (LBW) infants have reduced number of nephrons and are at risk of chronic kidney disease (CKD). While capillary rarefaction has been reported in other organs, it had been unknown whether LBW affects peritubular capillary (PTC) development. We recently reported 2 subjects with a history of preterm birth and extremely LBW (ELBW) who showed PTC rarefaction and erythropoietin (EPO)-induced polycythemia in adolescence (Asada N, Pediatr Nephrol 2017). In the present study, we examined the frequency and risk factors of polycythemia in subjects born with preterm and ELBW.

Methods: Thirty-six patients with a history of ELBW whose hemoglobin, eGFR, and urine albumin had been measured were analyzed retrospectively (17 male, 19 female; age at analysis 4-19 years; birth weight 316-998 g; gestational age 22.32 weeks). Polycythemia was defined as hemoglobin levels more than 2 SD above the mean for age and gender for at least 2 consecutive years (>13.5 g/dL under 6 years, >15.5 g/dL from 6 to 12 years, and >16.5 g/dL) for at least a year above 12 years. Expected EPO levels were calculated from hemoglobin levels using an equation of “Log (EPO) = 3.436 – 0.1675 × Hb.”

Results: Twelve patients (33.3%) showed polycythemia (7 male, 5 female; age at finding 2-16 years). Serum EPO, evaluated in 4 patients, were higher than expected levels. Birth weight was significantly smaller in polycythemia group (618 g vs 802 g). Gestational age, intrauterine growth restriction, and sex were not associated with polycythemia. In polycythemia group, eGFR was significantly smaller (72.7 vs 106.8 ml/min/1.73 m²), and eGFR less than 90 ml/min/1.73 m² and proteinuria were found in 9 (75%) and 3 (25%), respectively. In non-polycythemia group, on the other hand, only 5 (21%), P<0.06 and 1 (4%, P<0.06) had reduced eGFR and proteinuria, respectively. Thus CKD was more prevalent in polycythemia group (75% vs 25%, P<0.05). Among perinatal complications, chronic lung disease was significantly associated with polycythemia, while retinopathy of prematurity and acute kidney injury were not.
Role of Endothelial Leptin Receptor in the Development of Renal Injury Induced by a High Fat Diet
Hidenori Urai, Takeshi Kanda, Arata Kurokochi, Rina Kitahama, Shi Wakino, Hiroshi Kasai, Keio University School of Medicine, Tokyo, Japan.

Background: Obesity and type 2 diabetes promotes endothelial dysfunction, which contributes to the progression of chronic kidney disease. Leptin is secreted from adipocytes and decreases body weight by controlling energy expenditure and food intake. Leptin-deficient ob/ob mice and leptin receptor (ObR)-deficient db/db mice are prone to glomerulosclerosis. However, the effect of leptin on renal injury is controversial and the site target of leptin action in the kidney has not been fully elucidated. In this study, we examined the role of ObR in the endothelium on glomerulosclerosis on high fat diet.

Methods: Using the Cre/loxP system, vascular endothelial (VE)-cadherin-Cre transgenic mice were crossed with ObR<sup>fl/fl</sup> mice to generate vascular endothelial ObR deficient mice (EC-KO mice). EC-KO mice and control ObR<sup>fl/fl</sup> without Cre (EC-WT) mice were fed on standard diet or 45% high-fat diet for 24 weeks. Urinary albumin, blood pressure and pathological findings were examined. The We evaluated gene expressions in isolated microvascular endothelial cells from EC-WT and EC-KO mice were also evaluated.

Results: The expression of ObR was detected in glomerulus and peritubular capillaries in EC-WT mice while its expression was not detected in EC-KO mice. When comparing EC-WT with EC-KO on high fat diet, There was no significant difference in body weight, kidney weight, blood pressure and serum parameters between EC-WT and EC-KO on high fat diet. However, high fat diet-induced increase in urinary albumin excretion was significantly lower in EC-KO mice (0.453 ± 0.064 g/gCr) with EC-WT mice (0.656 ± 0.052 g/gCr). High fat diet-induced glomerular hypertrophy was also ameliorated in EC-KO mice compared with EC-WT mice (2874 ± 110 μm<sup>2</sup> vs. 3269 ± 129 μm<sup>2</sup>, n=6). Glomerular sclerosis, evaluated by masson’s trichrome staining, was significantly reduced in EC-KO mice. The tissue fibrosis was also reduced in EC-KO mice. In addition, The expression of TGFβ1 and PAI-1, which are known for promoting fibrosis and downstream target of leptin, were significantly decreased in primary endothelial cells from EC-WT and EC-KO mice were also evaluated.

Conclusions: These data suggest that leptin exacerbates renal injury through the development of glomerular hyperfiltration and endothelial induction of TGFβ1 and PAI-1 genes.

---

Inhibiting Inflammassome Activation with Suramin Protects against Progression of Diabetic Kidney Disease in KK-Ay Mice
Kauri Oda, Satoshi Miyamoto, Ryo Koderia, Jun Wada, Kenichi Shikata. Graduate School of Medicine Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan; Center for Innovative Clinical Medicine, Okayama University Hospital, Okayama, Japan; OsaFune Clinic, Setouchi, Japan.

Background: Recent reports have suggested that innate inflammation via inflammasome activation is involved in the pathogenesis of diabetic kidney disease (DKD). To clarify the involvement, we evaluated the acute effect of Empa. Finally, an eNOS inhibitor and a COX2 inhibitor were administered to these groups to inhibit vasodilator factors delivered from the macula densa. The SNNGFR was then evaluated.

Results: Increased ROS and decreased NO productions in the glomeruli were observed in the kidneys of diabetic KK-Ay mice. The SNNGFRs in the glomeruli before and two hours after medication were also studied to evaluate the acute effect of Empa. In the acute study using Akita, the SNGFR in the same glomeruli before and two hours after medication were also studied to evaluate the acute effect of Empa. In the acute study using Akita, the SNGFRs in the same glomeruli before and two hours after medication were also studied. The expression of TGFβ1 and PAI-1, which are known for promoting fibrosis and downstream target of leptin, were significantly decreased in primary endothelial cells from EC-WT and EC-KO mice were also evaluated.

Conclusions: These data suggest that leptin exacerbates renal injury through the development of glomerular hyperfiltration and endothelial induction of TGFβ1 and PAI-1 genes.

---

The Effect of GSTK1 on the MAM Related Apoptosis in Diabetic Nephropathy
Xiaofen Gao, Li, Xianghui Hu, Xiaofan Xiong, Li Li, Ming Yang, Peng Gao, Li Xiao, Jun Li, Fuyou Liu, Lin Sun. Department of Nephrology, 2nd Xiangya Hospital, Central South University, Changsha, China.

Background: Mitochondria-associated ER Membrane (MAM) is a platform between mitochondria and ER, which involved in mitochondrial dynamic, calcium signaling, autophagy, apoptosis and so on. GSTK1 has glutathione peroxidase activity, which is an important antioxidant enzyme can blocking ROS damage. We found by first time GSTK1 locates on MAM of the mouse kidney, but its function in MAM is nuclear. Here we

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
hypothesize that GSTK1 in MAM modulates cell apoptosis may play an important role in the kidney damage of DN.

Methods: Morphological change of MAM was measured by EM in db/db and db/m mice. The protein of mitochondria, MAM, and ER were extracted from the kidney of diabetic mouse. The expression of GSTK1, Mfn-2, cytochrome C, caspase-3 and Bax were detected by Western blot analysis. In vivo, MAM was morphologically damaged and analyzed in mice by confocal scanning in HK-2 cells. The mitochondria and MAM were also isolated from HK-2 cells induced by high glucose transfection with or without GSTK1 plasmid. The expression and distribution of GSTK1, Mfn-2, cytochrome C and Bax in MAM were detected with Western blot and immunofluorescent staining. Table 1: Western blot was observed by physical conformation, Confocal scanning and co-immunoprecipitation.

Results: Compared with db/m mice, the morphology of MAM was abnormal with the distance widen in the kidney of db/db mice. The expression of GSTK1 and Mfn-2 in MAM was lower than in the subdomain was down-regulated in db/db mice kidney. Conversely, the expression of Bax, Caspase-3 and cytochrome C were up-regulated. In addition, mitochondria was less adjacent to ER in HK-2 cells treated with high glucose(HG), while the expression of Mfn-2 was increased in mitochondria and MAM. All of arrested were reversed in that transfection of GSTK1. Furthermore, a increased GSTK1 binding on mitochondrial, analyzed by Western blot, the interaction between GSTK1 and cytosol was observed by physical conformation, Confocal scanning and co-immunoprecipitation.

Conclusions: The integrity of MAM were damaged and the distance between mitochondria and ER was increased in diabetic kidney or HG induced HK-2 cells. Overexpression of GSTK1 up-regulated the expression of Mfn-2 and then enhanced the interaction of MAM, which could inhibits apoptosis in DN.

Funding: Government Support - Non-U.S.

TH-PO672
Amelioration of Kidney Injury by Inhibition of Sodium Glucose Cotransporter 2 with Canagliflozin in Mice with Type 2 Diabetes Mellitus

Background: Type 2 diabetes mellitus (T2DM) is associated with progressively declining renal function resulting from hyperglycemia, oxidative stress and activated intrarenal renin-angiotensin system. The sodium glucose co-transporter 2 (SGLT2) is responsible for most of the glucose reabsorption by renal tubules. SGLT2 inhibitors increase glucose excretion and lower blood glucose levels, thus serving as a new therapy for type 2 diabetic patients. However, there is limited information about the developing renal injury in T2DM remains unclear.

Methods: Accordingly, we evaluated the ability of canagliflozin (CAN), an SGLT2 inhibitor, to ameliorate kidney injury in T2DM. Intrarenal angiotensinogen (AGT) and oxidative stress were also evaluated as contributing factors to diabetic nephropathy. Male New Zealand Obese mice were fed a regular fat diet (RFD, 4% fat) or a high fat diet (HFD, 40% fat) to induce diabetes. When the mice fed with the HFD exhibited >350 mg/dl blood glucose levels, both RFD and HFD fed mice were treated with 10 mg/kg/day CANA or vehicle for 6 weeks by daily oral gavage.

Results: CANA treatment decreased blood glucose levels and suppressed body weight gain in HFD mice, which remained suppressed for the duration of the study. Systolic blood pressure in HFD groups (134±7.3 mmHg) was also normalized by CANA (110±6.0±6.0 mmHg). The augmented corticoge AGT mRNA and protein levels and elevated urinary microalbuminuria levels caused by the HFD were ameliorated by CANA treatment. Histological analysis revealed the development of renal tubal fibrosis in HFD group (3.4±0.9-fold, fibrotic score, ratio to RFD) that was suppressed by CANA (0.9±0.3-fold). Furthermore, elevated macromolecule infiltration into the interstitium caused by HFD was attenuated by CANA (RFD: 0.35±0.7, HFD: 0.9±0.09, and HFD:CANA: 0.4±0.07 positive area %). In contrast, CANA did not improve glomerular matrix expansion and albuminuria observed in the HFD group.

Conclusions: These results demonstrate that CANA mitigates renal tubal fibrosis and renal inflammation accompanied by suppression of renal oxidative stress and AGT expression in T2DM.

Funding: Other NIH Support - CoBRE Grant on Translational Research in Hypertension and Renal Biology, Commercial Support - Janssen Pharmaceuticals

TH-PO673
Contribution of Myo-Inositol Oxygenase in Age: Mediated Renal Tubulo-Interstitial Injury

Background: Advanced glycation end products (AGEs) have been postulated to play a crucial role in the development of diabetic nephropathy (DN). Myo-inositol Oxygenase (MIOX), a proximal tubular enzyme, which has been implicated in tubulointerstitial injury in the context of DN.

Methods: Aim of the present study was to investigate the effect of AGES on MIOX expression and to delineate the mechanisms that lead to tubulointerstitial injury. To test this we examined the status of MIOX, RAGE and relevant cellular signaling pathway activated following AGE:RAGE interaction in cultured tubular cells and kidneys of AGE-BSA treated mice.

Results: Using simple phase binding assay an enhanced binding of RAGE with AGE-BSA, -laminin and -collagen IV was observed compared to non-glycated proteins. AGE-BSA treatment led to an increased MIOX activity and its expression in a time- and age-dependent manner. A 10-day old mice showed increased MIOX promoter activity. This was associated with activation of various signaling kinases of PI3K-AKT pathway and increased expression of NF-κB, TGF-β and fibroactin. Treatment with MIOX- and RAGE-siRNA negatively impacted the activation of PI3K-AKT signaling cascade and TNF-α, NF-κB and TGF-β. Interestingly, concomitant with the up-regulation of MIOX there was an increased generation of reactive oxygen species (ROS), which could be abrogated with the MIOX- or RAGE-siRNA treatment. In vivo the kidneys of mice treated with AGE-BSA for 2 weeks had significantly high urinary acute renal proximal segment of MIOX, NF-κB and TGF-β. Furthermore, we observed a significant effect of AGE:RAGE interaction in the activation of PI3K-AKT pathway and up-regulation of MIOX; as a result of which there was an excessive generation of ROS, increased expression of NF-κB, inflammatory cytokines, TGF-β and fibroactin. Collectively, these observations highlight the importance of MIOX in the contribution towards tubulo-interstitial injury in DN.

Funding: NIDDK Support

TH-PO674
Dyslipidemia Worsens Diabetic Kidney Disease in a Novel Type 2 Diabetes Mouse Model of Combined Kidney Disease and Atherosclerosis – A Possible Role for ApoC-III

Background: Diabetic kidney disease and atherosclerotic disease are major causes of morbidity and mortality associated with type 2 diabetes (T2D) and diabetic kidney disease is a major cardiovascular risk factor. The BTBR mouse strain with leptin-deficiency (Lepler) has emerged as one of the best mouse models of human diabetic kidney disease. However, no T2D mouse model of combined diabetic kidney disease and atherosclerosis exists. Our goal was to design such a model.

Methods: To this end, the LDL receptor was targeted for degradation via IDOL (inducible degrader of the LDL receptor) overexpression, using a liver-targeted adeno-associated virus (AA-DI/8) in BTBR wildtype (WT) and BTBR Lepler (OB) mice.

Results: Liver-targeted IDOL-AA-DI/8 increased plasma LDL cholesterol, as expected, but did not control the control of plasma triglycerides. Moreover, no significant effects on the developing renal injury in T2DM remained unclear.

Conclusion: These findings suggest a higher expression of IDOL in mice treated with high glucose transfection with or without GSTK1 plasmid. Furthermore, HG induced oxidative stress and up-regulated the expression of Mfn-2 and its localization in glomerular cells. Male New Zealand Obese mice were fed a high fat diet (RFD, 4% fat) or a high fat diet (HFD, 40% fat) to induce diabetes. When the mice fed with the HFD exhibited >350 mg/dl blood glucose levels, both RFD and HFD fed mice were treated with 10 mg/kg/day CANA or vehicle for 6 weeks by daily oral gavage.

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

TH-PO675
NADPH-Oxidase NOX5 Aggravates Renal Injury in Human Diabetic Nephropathy

Background: Renal oxidative stress plays an important role in mediating kidney injury in diabetes. There is increasing evidences that recently discovered pro-oxidant enzyme, Nox5, plays a significant role in human diabetic nephropathy (DN). Nox5 is present in humans and rabbits but not in mice or rats. Thus, there is a paucity of information about Nox5 in conventional animal models of DN. We examined the role of Nox5 in human diabetic nephropathy, in human renal cell populations as well as in a high fat fed rabbit model of kidney disease.

Methods: Protein expression of Nox5 and its localization in glomerular cells (podocytes and mesangial cells) and tubular cells were examined by immunostaining in human kidney biopsies obtained from non-diabetic and diabetic individuals. In vitro, human mesangial cells, podocytes and proximal tubules were exposed to high glucose, TGF-β1 and NOX5 and NOX5 mRNA and protein expression were determined. The effects of NOX5 on intracellular oxidants, gene and protein expression of markers of fibrosis and inflammation as well as putative signaling pathways and the level of ROS were assessed in these human renal cells. We
Diabetes Mellitus and Obesity: Basic - Experimental - I

TH-PO676

Function of NADPH Oxidase in Diabetic Nephropathy and Development of Its Inhibitor as a Therapeutic Candidate

Sae Nam,1 Junjun An,2 Yunsoo Bae.1 Ewha Womans University, Seoul, Republic of Korea.

Background: Substantial evidence has indicated that transient reactive oxygen species (ROS) can be produced by receptor-mediated biochemical processes, although ROS including superoxide anion and hydrogen peroxide (H2O2) are thought to be by-products of aerobic respiration damaging effects on DNA, protein, and lipid. ROS generation in cell signaling has been extensively studied in terms of NADPH oxidase (gp91phox) in phagocytic cells. However, after identification of the homologs of gp91phox (Nox1, Nox-3, Duox-1) from non-phagocytic cells, the function of the generated ROS has been extended into an understanding of various cellular events, including cell growth, differentiation, apoptosis, and inflammation responses. We show the effect of a novel pan-NOX inhibitor, EWAH-18278, on diabetic nephropathy in type 2 diabetic mice.

Methods: Six-week-old male diabetic db/db mice was treated with EWAH-18278 (10mg/kg/day) per day after 4.12 weeks. The effect of EWAH-18278 on oxidative markers such as 8-isoprostane in plasma or urine was measured. Furthermore, EWAH-18278 effect on renal function was investigated by urinary albumin excretion and creatinine clearance and PAS-staining, alpha-SMA histologically.

Results: EWAH-18278 significantly improved insulin resistance in diabetic mice, similar to GKT137831. Oxidative stress as measured by plasma 8-isoprostane level was decreased in the EWAH-18278 group compared to diabetic controls. All lipid profiles, both in plasma and tissues improved with Nox inhibition. EWAH-18278 decreased urinary albuminuria, preserved creatinine clearance. In diabetic kidneys, EWAH-18278 significantly improved mesangial expansion, but GKT137831 did not. Additionally, F4/80 infiltration in the adipose tissue and kidney decreased with EWAH-18278 treatment.

Conclusions: In conclusion, our findings provide evidence that pan-Nox inhibition by EWAH-18278 may have greater renoprotective potential than does GKT137831 in diabetic nephropathy. These findings suggest that EWAH-18278 may be a useful new therapeutic agent in treating type II diabetes and diabetic nephropathy.

TH-PO677

Calorie Intake Reduction May Prevent Progression of Diabetic Nephropathy by Suppressing Podocyte Hypertrophic Injury via mTORC1 Pathway Activation

Akihiro Minakawa,1 Akihiro Fukuda,1 Masao Kikuchi,2 Yuji Sato,1 Shouichi Fujimoto.3 1Division of Nephrology, Department of Internal Medicine, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan; 2Division of Endocrinology, Metabolism, Rheumatology and Nephrology, Faculty of Medicine, Otto University, Yufu, Japan.

Background: Glomerular hypertrophy is a well-established component of diabetic nephropathy. We have previously shown that a mismatch between glomerular volume and podocyte mass (reduced podocyte density) was associated with development of albuminuria and accelerated podocyte hypertrophic stress in a rat model of type 2 diabetes. Here, we tested whether calorie intake reduction prevents progression of diabetic nephropathy by suppressing podocyte hypertrophic injury.

Methods: Using the leptin-deficient Zucker diabetic fatty rat model of type 2 diabetes with ad libitum feeding, we have found increased glomerular volume and decreased podocyte density at 15 weeks. At 15 weeks, we thus divided the rats into an ad lib itum diet group (75% caloric intake reduction, n=10) and ad libitum diet group (n=5). Urine samples were collected every 4 weeks and the rats were sacrificed at 30 weeks. We measured the urinary excretion of podocyte mRNA, urine albumin/creatinine ratio, glomerular volume, podocyte number per glomerular tuft, podocyte density, and P-S6 expression of podocytes.

Results: In the calorie intake reduction group, urine volume and blood glucose were significantly decreased by 18 weeks, albuminuria was significantly decreased by 22 weeks and urinary excretion of podocyte mRNA was decreased by 26 weeks, compared with the ad libitum diet group. At 30 weeks, in the calorie intake reduction group, podocyte number per glomerular tuft was not decreased (p>0.3), while glomerular volume tended to be decreased (12% decrease, p=0.052), podocyte density was significantly preserved (p=0.02), and P-S6 expression of podocytes was significantly decreased (p<0.01), compared to the ad libitum diet group.

Conclusions: Our results suggest that calorie intake reduction prevented the progression of diabetic nephropathy in a rat model of type 2 diabetes by suppressing podocyte hypertrophic injury via mTORC1 pathway activation. Calorie intake reduction could thus be a useful tool for slowing the progression of diabetic nephropathy.

TH-PO678

Elevated Prorenin Accelerates the Development of Diabetic Nephropathy in STZ-Induced Cyp1a1-Prorenin Transgenic Rats

Alfred K. Cheung,1 Yufeng Huang,2 1Division of Nephrology, University of Utah, Salt Lake City, UT; 2Dept. of Pathophysiology, University of Nantong School of Medicine, Nantong, China.

Background: Plasma prorenin levels are commonly found in diabetic patients and appear to predict the development of diabetic nephropathy (DN). However, the potential pathological role of prorenin in diabetes is unclear. In this study, a transgenic, inducible, hepatic prorenin-overexpressing rat model (cyp1a1-prorenin transgenic rat, TG) was generated and then a model of STZ-induced diabetic cyp1a1-prorenin transgenic rat was established to mimic diabetic patients with elevated plasma prorenin.

Methods: Four transgenic groups (5 rats per group), Tg, STZ-induced diabetic TG rats, and STZ-induced diabetic TG rats treated with either amlodipine (AMP, 10mg/kg/d by daily gavage) or enalapril (Ena, 20mg/kg/L in drinking water), were assigned to 2wks after diabetes was confirmed (BG=250 mg/dl). Four corresponding groups of 5 wild-type (WT) rats receiving same treatments served as WT controls. Treatments were given at the same as I3C was given for 6 wks. Animals in all groups were sacrificed at 8 wks after induction of diabetes.

Results: Diabetic WT rats had normal blood pressure but developed microalbuminuria and had kidney hypertrophy and mildly increased glomerular ECM accumulation. Diabetic TG rats with elevated plasma prorenin levels showed hypertension and much worsen features of DN when compared with the diabetic WT animals or non-diabetic transgenic rats, including worsen albuminuria, kidney hypertrophy, enhanced podocyte foot effacement and glomerulosclerosis. Furthermore, increased prorenin in diabetes further stimulated renal cellular signals of Nox2, p47phox and NOF-B-p65, which have been shown to contribute to the development of DN. Treatment with either amlodipine or enalapril reduced blood pressure, but had no effect on renal cellular signals. These findings provide additional support for our Hypothesis II's action. These results may suggest the involvement of additional angiotensin II-independent effects of prorenin in DN.

Funding: Other NIH Support - ADA Innovative Basic Science Award (No. 1-17-IBS-312) and National Nature Science Foundation of China (NSFC) (No. 81670665)

TH-PO679

Transcriptomic Profile in Early versus Late Stages of Murine Diabetic Nephropathy

Haihun Yang,4 Anette E. Ericsson,4 Anna Reznichenko,5 José Sanchez,6 Lena William-Ölsson,7 Magnus Soderberg,7 Anna Granqvist,7 Rafael C. Harris,4 Kasey C. Vickers,4 Agnes B. Fogo,4 Drug, Safety and Metabolism, AstraZeneca, Molndal, Sweden; 2Discovery Sciences, AstraZeneca, Molndal, Sweden; 3Innovative Medicines and Early Development, Cardiovascular and Metabolic Diseases, AstraZeneca R&D Molndal, Molndal, Sweden; 4Vanderbilt University Medical Center, Nashville, TN.

Background: Diabetic nephropathy (DN) has both glomerular and tubular injury. As a DN model, db/db/eNOS-/- mice develop albuminuria and glomerular hypertrophy by age 16 wks, and progressive proteinuria and hyperfiltration. In this study, we aimed to determine the transcriptional profiles critical for glomeruli vs tubular injury at 7 and 18 wks after induction of diabetes by a high-fat, high-glucose diet. DN rats were sacrificed at week 7 or 18. By RNA sequencing of isolated glomeruli and kidney cortex at different time points, we aimed to determine the transcriptional profiles critical for glomeruli vs tubular injury in DN.

Methods: db/db/eNOS-/- (DN) and nondiabetic control db/NOES-/- mice (C) were sacrificed at week 10 and 18. The left kidney was harvested for isolating glomerular RNA, while the right kidney was used for extracting cortex RNA.

Results: 86 genes from the glomerular extract showed different expression levels in DN at Gdist week 10 (49 upregulated and 37 downregulated), and 3246 genes differed at week 18 (3599 up and 1649 down). 528 transcripts from cortical extracts were different in DN and C at week 10 (213 up and 315 down), and 684 transcripts differed at week 18 (456 up and 228 down, but with overlap of only 116 genes in early vs late cortical samples. Metabolic processes, such as on murine ura and P450 pathways, differed mostly in tubular vs glomerular analysis. Genes expressed at week 10 but not week 18 suggest a role in early but not progressive DN. We detected 118 upregulated and 188 downregulated genes at week 10, which did not differ at week 18 in DN. Among them, only 10 genes (7 up and 3 down) were present only in glomerular but not cortical samples, and include genes that modulate matrix, cell proliferation and tissue-specific differentiation.

Conclusions: In summary, by comparing db/db/eNOS-/- vs db/NOES-/- mice, early vs late stage diabetics, and glomeruli vs cortex, we determined that there were marked increases in differentially modulated glomerular genes at later stages of disease, with genes associated with podocyte injury increasing in importance over time. These data indicate that glomerular and tubular mechanisms of DN injury are not identical, and also evolve over time.

Funding: Commercial Support - AstraZeneca PLC
Comparison of Glomerular Endothelial Cell Gene Expression Profiles in Diabetic Mice with or without eNOS Deficiency

Jia Fu,1,2 Chengguo Wei,2 Weijia Zhang,1 Detlef O. Schlondorff,2 Peter Y. Chuang,2 Zhihong Liu,3 John C. He,2 Kyung Lee,1 National Clinical Research Center of Kidney Diseases, Nanjing, China; 2Connecticut Kidney Center, LLC, Orange, CT; 3Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Glomerular endothelial cell (GEC) injury is a key early event in DN, but its underlying mechanism remains unclear. In order to assess the key molecular changes in GECs in early DN, we performed a transcriptomic analysis of GECs isolated from diabetic and nondiabetic mice. Two diabetic models were used: 1) streptozotocin (STZ)-induced diabetic mice and 2) STZ-induced diabetic eNOS mice to take advantage of the accelerated DN development with eNOS-deficiency.

Methods: GECs were isolated from transgenic mice expressing histone H2B-fused enhanced yellow fluorescent protein (EYFP) under the Flk-1 promoter. Flk-1-EYFP mice were crossbred with wildtype or eNOS mice, and diabetes was induced with STZ. Vehicle-injected mice served as controls. All mice were sacrificed at 10 weeks post-injection, and GECs were sorted for mRNA sequencing. Differentially expressed genes (DEGs) from GECs of diabetic mice were analyzed. Key altered pathways were validated by qPCR and immunostaining in second set of experimental mice, and kidney biopsies were performed on mice that was characterized by increased urinary albumin-to-creatinine ratio, increased mesangial matrix expansion, glomerulosclerosis and tubulointerstitial fibrosis (determined by Mason’s trichrome and Picrosirius Red stains). Diabetes induced down-regulation in the expression of podocyte and epithelial markers such as nephrin, podocin and E-cadherin, and these markers were further reduced in C/EBP-α knockout diabetic mice. In addition, a further increased expression of markers of fibrosis (vimentin, fibronectin) and inflammation (MCP-1, TNF-α) were found in diabetic C/EBP-α knockout mice when compared to diabetic WT mice. Mechanistically, we identified that conditional deletion of C/EBP-α in podocytes resulted in significantly decreased p-AMPK and PGC-1α expression in diabetic mice.

Conclusions: These findings suggest that knockdown of C/EBP-α expression in podocytes aggravates the podocyte impairment and the progressing of DN, and point to C/EBP-α as a potential therapeutic target in DN.

Funding: NIDDK Support

Gene Expression Profiles of Glomeruli from BTBR ob/ob Mice Treated with Prolyl Hydroxylase Inhibitor Suggest Involvement of Extracellular Matrix Modulators in Pathogenesis of Diabetic Kidney Disease

Mai Sugawara,1 Tetsuhiro Tanaka,1 Shinji Tanaka,1 Senji Fukuda,1 Akira Shimizu,1 Yu Ishimoto,2 Reiko Inagi,1 Masaomi Inagi,1 University of Tokyo, Tokyo, Japan; 2JT CPRI, Osaka, Japan; 3Nippion Medical School, Tokyo, Japan.

Background: We have previously shown that administration of prolyl hydroxylase (PHD) inhibitor, JTZ-951 (Japan Tobacco Inc.), improved glucose/lipid metabolism and decreased albuminuria in BTBR ob/ob mice (TH-PO450, ASN Kidney Week 2016). In order to elucidate the mechanism, we performed microarray gene expression analysis using isolated glomeruli. We have previously shown that administration of prolyl hydroxylase (PHD) inhibitor, JTZ-951 (Japan Tobacco Inc.), improved glucose/lipid metabolism and decreased albuminuria in BTBR ob/ob mice (TH-PO450, ASN Kidney Week 2016). In order to elucidate the mechanism, we performed microarray gene expression analysis using isolated glomeruli.

Methods: Four-week-old male BTBR ob/ob mice were divided into the vehicle and JTZ-951 groups. JTZ-951 (0.005%; in feed) was administered from 4 weeks of age until euthanasia at 22 weeks. CDNA samples from isolated glomeruli were hybridized using Agilent microarray chips.

Results: During the study period, mice in the JTZ-951 group tended to exhibit lower blood glucose levels (HbA1c: 8.9±3.0 vs 8.2±2.0%) and significantly lower total cholesterol levels (260±26 vs 164±19 mg/dL) with comparable food intake. JTZ-951 significantly decreased urinary albumin at 16 and 22 weeks (4.8±8.7 vs 1.9±4.5 and 5.1±3.3 vs 2.3±0.5 mg/mCr, respectively) without affecting GFR. Podocyte and endothelial damages were markedly ameliorated in the JTZ-951 group. In gene expression analysis, 315 transcripts were upregulated and 150 were downregulated more than 3-fold in BTBR ob/ob mice compared to the wild type (WT). Among the 315 diabetes-upregulated genes, 102 revealed smaller increases in the JTZ-951 group (JTZ-951/WT<3). Similarly, the expression of 103 of the 150 diabetes-downregulated genes were restored in the JTZ-951 group (JTZ-951/WT<1). Pathway analysis of these 205 genes using Reactome database revealed that 9 of the 25 top-ranked pathways were related to extracellular matrix (ECM) organization and cell-matrix interactions; the corresponding entities included lysyl oxidase-like 2, thrombospondin 1, collagen type VIII alpha 1, bone morphogenetic protein 2, and CD44.

Conclusions: Long-term administration of JTZ-951 decreased albuminuria and ameliorated podocyte and endothelial damage, along with improvement in glucose/lipid metabolism. Microarray analysis revealed changes in the expression of genes associated with ECM, suggesting that ECM modulation within the glomerulus may play a role in the pathogenesis of diabetic kidney disease.

Funding: Commercial Support - Japan Tobacco Inc.

Reduced C/EBP-α Expression Aggravates the Podocyte Impairment and Renal Injury in Experimental Diabetes

Liwen Zhang, Fangzhou Fang, Jian Liu, Ji Ying, Weiming Wang, Nan Chen. Department of Nephrology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China.

Background: CCAAT/enhancer binding protein-α (C/EBP-α) is one of the critical transcription factors involved in inflammation, cell proliferation and lipid metabolism. We have previously shown that C/EBP-α expression was suppressed in glomerular cells in focal segmental glomerulosclerosis. However, its specific role in diabetic nephropathy (DN) is unclear. We developed a podocyte-specific C/EBP-α-null mouse model to study the function of C/EBP-α in DN progression.

Methods: By crossing floxed C/EBP-α mice with Pod-Cre mice, we generated podocyte specific C/EBP-α knockout mice. The transgenic mice and their wild-type littermates underwent either high-fat diet for 6 months with a single injection of streptozotocin as diabetic models or general diet as control treatment.

Results: We confirmed that C/EBP-α expression was significantly reduced in the renal cortex in podocyte-specific knockout mice by western blotting. Genetic ablation of C/EBP-α in podocytes led to more serious deterioration of diabetic kidney injuries, characterized by increased urinary albumin-to-creatinine ratio, increased mesangial matrix expansion, glomerulosclerosis and tubulointerstitial fibrosis (determined by Mason’s trichrome and Picrosirius Red stains). Diabetes induced down-regulation in the expression of podocyte and epithelial markers such as nephrin, podocin and E-cadherin, and these markers were further reduced in C/EBP-α knockout diabetic mice. In addition, a further increased expression of markers of fibrosis (vimentin, fibronectin) and inflammation (MCP-1, TNF-α) were found in diabetic C/EBP-α knockout mice when compared to diabetic WT mice. Mechanistically, we identified that conditional deletion of C/EBP-α in podocytes resulted in significantly decreased p-AMPK and PGC-1α expression in diabetic mice.

Conclusions: These findings suggest that knockdown of C/EBP-α expression in podocytes aggravates the podocyte impairment and the progression of DN, and point to C/EBP-α as a potential therapeutic target in DN.

Funding: Grounding Support - Non-U.S.
In增持信抗抑制抑制间质细胞抗感染作用。新证据表明抗菌肽（AMP）在维持尿路感染中的作用。从我们的数据中可以推断出，在间质细胞内分泌的AMPs进入尿液。这些数据还表明，尿液中抑制AMPs可以抑制感染的上皮细胞。为了调查这种抑制作用是否与肾小管管腔中的尿液存在相关性，我们收集了在不同条件下培养的AMPs，其中包括用葡萄糖阻断的抗体来抑制AMPs。在敲除AMPs的IRKO小鼠中，RNase 4被抑制。敲除IRKO小鼠的IRmRNA和蛋白水平在FACS-分离的ICs中被qRT-PCR和Western blot确认。正常血清胰岛素/葡萄糖水平和血清/尿液pH。qRT-PCR和Western blot被用于确认IR基因的缺失对宿主防御的影响。IR基因敲除的小鼠与Cre-loxP方法杂交，小鼠 homozygous for the floxed IR gene。方法：用Cre-iPoc方法，IRKO小鼠显现出一个典型模式，与正常控制相比，IR基因的敲除。在增加了UTP的UTI中，IR基因的敲除在UPEC中被敲除。与UTI相比，IR基因的敲除在UPEC中被敲除。与UTI相比，IR基因的敲除在UPEC中被敲除。与UTI相比，IR基因的敲除在UPEC中被敲除。与UTI相比，IR基因的敲除在UPEC中被敲除。与UTI相比，IR基因的敲除在UPEC中被敲除。与UTI相比，IR基因的敲除在UPEC中被敲除。与UTI相比，IR基因的敲除在UPEC中被敲除。与UTI相比，IR基因的敲除在UPEC中被敲除。与UTI相比，IR基因的敲除在UPEC中被敲除。与UTI相比，IR基因的敲除在UPEC中被敲除。与UTI相比，IR基因的敲除在UPEC中被敲除。与UTI相比，IR基因的敲除在UPEC中被敲除。与UTI相比，IR基因的敲除在UPEC中被敲除。与UTI相比，IR基因的敲除在UPEC中被敲除。与UTI相比，IR基因的敲除在UPEC中被敲除。与UTI相比，IR基因的敲除在UPEC中被敲除。与UTI相比，IR基因的敲除在UPEC中被敲除。与UTI相比，IR基因的敲除在UPEC中被敲除。与UTI相比，IR基因的敲除在UPEC中被敲除。与UTI相比，IR基因的敲除在UPEC中被敲除。与UTI相比，IR基因的敲除在UPEC中被敲除。与UTI相比，IR基因的敲除在UPEC中被敲除。
TH-PO688
Proteomics and Systems Biology Analysis of Human Kidney Cells Reveals a Link between Androgen-Induced Alterations in Renal Metabolism and Circulating Metabolite Levels in CKD 
Sergi Clotet freixas,1,2 Maria Jose Soler,1 Marta Riera,1 Julio Pascual,1 Ibor Bartruch,2 Vassilis K. Vlassis,2 Apostolos Dimitromanolakis,2 Eleftherios P. Diamandis,2 James W. Scholey,1 Ana Kovalinka,1,3 Miquel Puigserver1,2
1Hospital del Mar Medical Research Institute (I3M), Barcelona, Spain; 2Mount Sinai Hospital, Toronto, Canada, Toronto, ON, Canada; 3University Health Network, University of Toronto, Toronto, ON, Canada.

Background: Male sex predisposes to chronic kidney disease (CKD) progression. We hypothesized that dihydrotestosterone (DHT) would affect renal cells by altering the proteome.

Methods: We used isotope labeling to quantify the proteome in human proximal tubular cells (PTC) exposed to DHT or estradiol. Top proteins were verified in vitro and in vivo. Renal oxidative stress (OS) was assessed by N-Tyr staining. Systems biology of sex hormone-protein signatures was studied in Cytoxcape.

Results: Of 5043 quantified proteins, 76 were regulated by sex hormones. Processes related to metabolism were significantly enriched in proteins regulated by DHT. Proteins representing glucose, gluconeome and fatty acid metabolism, namely glucose-P- isomerase (GPI), glucoseamine-P-acetyltransferase (GNPAT1), and mitochondrial trifunctional protein subunit alpha (HADHA), were validated in vitro and in vivo. Renal expression of GPI, GNPAT1 and HADHA was significantly higher in males compared to females, in 2 models of diabetes. OS was enriched in our proteins and genes highly expressing in diabetic kidneys. We demonstrated increased OS in diabetic and control male mice kidneys. We asked whether dysregulated metabolic enzymes in male kidneys may be responsible for changes in circulating metabolites. Using data from the human KORA F4 study, we found that serum metabolites related to TCA cycle and aminoacid metabolism (e.g. malate, glutamine and proline) were increased in CKD men and also associated with our DHT-proteins.

Conclusions: Androgen-induced perturbations in renal metabolism may be responsible for the more rapid kidney disease progression ascribed to men. Metabolic alterations in the male kidney may be reflected in circulating levels of malate, glutamine, and proline metabolites in CKD.

TH-PO668
MDM2 Contributes to High Glucose-Induced Glomerular Mesangial Cell Proliferation and Extracellular Matrix Accumulation via Notch1 Signaling 
Chun-Tao Lei, Hua Su, Chun Zhang. Union Hospital, Huazhong University of Science and Technology, Wuhan Hubei Province, China.

Background: Murine double minute 2 (MDM2), an E3-ubiquitin ligase, is critical for various biological functions and its dysregulation is involved in tumorgenesis. Previously we have documented an indispensable role of MDM2 in kidney homeostasis and disorders. However, its role in glomerular mesangial cell (GMC) proliferation and extracellular matrix (ECM) accumulation under hyperglycemia remains unclear.

Methods: In vitro study, rat mesangial cell line was employed, and subjected to different treatments. RNA interference and Nutlin-3a treatments were utilized to modulate MDM2 expression and block MDM2-p53 interaction respectively. Diabetic mice model was established by intraperitoneal injection of streptozotocin (STZ) and intraperitoneal administration of Nutlin-3a was adopted to disrupt the in vivo binding between MDM2 and p53.

Results: In the present study, we found MDM2 protein level is upregulated in high glucose-cultured GMCs. Knocking down MDM2 by siRNA attenuates high glucose-induced ECM accumulation and cell proliferation. However, MDM2-p53 interaction blocker Nutlin-3a, cannot protect diabetic mice from renal impairment not only in vitro but also has no benefit on high glucose-induced ECM accumulation in vivo. Intriguingly, we found Notch1 signaling is activated in GMCs with high glucose exposure which is obviously attenuated by MDM2 depletion. However, Nutlin, another substrate of MDM2 which suppresses Notch1 signaling, is not involved in the MDM2 mediated Notch1 regulation. Lastly, our findings revealed that MDM2 binds with and ubiquititates Notch1 intracellular domain (NICD1), however the ubiquitination status of NICD1 does not lead to NICD1 degradation but activates its downstream gene expression.

Conclusions: Collectively, our data propose a pivotal role of MDM2 in high glucose-induced GMC proliferation and ECM accumulation, through modulating the activation of Notch1 signaling in an ubiquitination-dependent but p53-independent way.

Funding: Government Support - Non-U.S.

TH-PO690
FcgRIIb-Deficiency and FcgRIIb-Deficiency Exacerbate Renal Injury Respectively in Diabetic Mice Rui Zhang. Division of Nephrology, West China Hospital, Sichuan university, Chengdu, China.

Background: Fcg receptors are key immune receptors responsible for both humoral and innate immunity. FcgRI, FcgRIIb and FcgRIII are key members of Fcg receptors superfamily. We aimed to investigate the involvement of Fcg receptors respectively in diabetic mice.

Methods: Eight-week-old C57BL/6 mice, FcgRIb knockout mice and FcgRIIib knockout mice were subdivided into three groups: the normal diet group, high fat diet group. Type 2 diabetes mice induced by high fat diet combined with streptozotocin. The levels of blood glucose, serum creatinine, urinoprotein were tested. The expressions of TGF-β, TNF-α, pNK-x, oxLDL were detected by real-time PCR or westernblot in isolated glomeruli. In vitro studies were performed in mice renal mesangial cell (GMCs) tranfected with lentivirus vectors carrying siRNA targeting FcgRIIb, FcgRIII and FcgRI gene respectively. GMCs were cultured with normal glucose, high glucose, oxLDL, high glucose combined with oxLDL.

Results: FcgRIIib-/- diabetic mice and FcgRIIb/-/- diabetic mice had elevated levels of blood glucose and high creatinine, urine protein compared with WT diabetic mice. Renal pathology showed mesangial expansion, westernblot and real-time PCR indicated higher expression of TGF-β, TNF-α and pNK-x, immunofluorescence or immunohistochemistry showed expressing in glomeruli, in diabetic FcgRIII knockout survived mice, the transplantation of wild type and FcgRIIib knockout was selected. The Fpd group exist more severely biochemical dates, renal injury factors than control group and appeared most oxLDL deposition. To further examine the mechanism that which Fc gamma receptor exacerbated renal injury for the most part, in vitro we observed that high glucose, high glucose combined with oxLDL, TNF-α, activated expression of TGF-β, TNF-α, pNK-x in mice renal mesangial mesangial cells, the transfection of FcgRIIib or FcgRIII siRNA had upregulated TGF-β, TNF-α, pNK-x expression, whereas the transfection of FcgRIIib siRNA had appeared to attenuate the level of TGF-β, TNF-α, pNK-x expression.

Conclusions: FcgRIIib deficiency downregulated inflammation, fibrosis and augmented expression of oxLDL. FcgRIII deficiency failed to delay renal injury. These observations suggest that FcgRs represent a novel target in the therapeutic interventions for diabetic nephropathy. Funding: The National Natural Science Foundation of China. Funding: Government Support - Non-U.S.

TH-PO691
MAD2B-Numb Interaction Is Involved in High Glucose Induced Podocyte Injury by Regulating Cell Polarity 
Hua Su, Hui Tang, Chun Zhang. 1Huazhong Science and Technology University, Wuhan, China; 2Second Medical College, Huazhong University of Science and Technology, Wuhan, China; 3Union Hospital, Huazhong University of Science and Technology, Wuhan Hubei Province, China.

Background: The loss of podocyte is a critical event in the pathogenesis of diabetic nephropathy (DN). Recent studies have demonstrated the importance of cell polarity in the maintenance of podocyte architecture. Previously, our group found the mitotic arrest protein MAD2B is upregulated in high glucose (HG) induced podocyte injury. However, the exact mechanism of MAD2B in podocyte injury still remains to be established.

Methods: Patients diagnosed with DN were enrolled in this study, and DN model was constructed on C57BL/6 mice by a single intra-peritoneal injection of STZ. In vivo study, immortalized human podocyte cell line was employed, and exposed to different treatments after differentiation. The expression of MAD2B and Numb was suppressed by recombinant lentinus infection.

Results: We have demonstrated the enhancement of MAD2B in DN mice and HG treated podocytes. Using a yeast two-hybrid interaction trap we identified Numb as a novel MAD2B binding protein in human kidney. Through confocal laser scanning microscopy we confirmed the co-localization of MAD2B and Numb in podocyte in vivo and in vitro. Subsequent endogenous co-immunoprecipitation established the direct interaction between MAD2B and Numb. HG exposure upregulated MAD2B expression and Numb phosphorylation in podocyte. Interestingly, HG also induced Numb translocation from podocyte basolateral membrane to cytoplasm, which accompanied by podocyte cytoskeleton re-organization. MAD2B genetic deletion partly reversed Numb phosphorylation and cytoplasm translocation as well as cytoskeleton re-organization in podocyte. In addition, Numb bound to integrin-β1 and correlated with its basolateral TGF-β, pNF-κB, TNF-α, pNK-x expression.

Conclusions: Upregulated MAD2B expression accelerates Numb phosphorylation and its translocation from podocyte basolateral membrane to cytoplasm in HG condition. Phosphorylated Numb has a reduced binding affinity to integrin-β1 which diminishes integrin-β1 distribution on podocyte basolateral membrane and ultimately leads to the loss cell polarity and podocyte injury.

Funding: Government Support - Non-U.S.
Insulin Prevents Bcl2 Modifying Factor-Induced Renal Proximal Tubular Cell Apoptosis via Stimulation of Heterogeneous Nuclear Ribonucleoprotein F and Sirtuin-1 Expression in Diabetic Akita Mice

Background: Tubular atrophy and tubulointerstitial fibrosis are closely associated with loss of renal function in diabetes. However, the underlying mechanisms are not fully understood. Here we investigated the role of the pro-apoptotic BH3-only protein, BCL2-modifying factor (Bmf), in renal proximal tubular cell (RPTC) apoptosis in mice and studied the effects of insulin on Bmf in rat immortalized RPTCs (iRPTCs) in vitro.

Methods: Non-transgenic (Tg) and Tg mice specifically overexpressing human Bmf in RPTCs were studied at 10 to 20 weeks of age. Non-Akita littermates and Akita mice (a type 1 diabetes model) pre- and post- insulin implant from the age of 12 weeks were also studied until week 16. Blood glucose, systolic blood pressure (SBP), and urinary albumin creatinine ratio (ACR) were measured bi-weekly. Kidneys were processed for histology. RPTC apoptosis was evaluated by TUNEL assay. Freshly isolated RPTs were assessed for creatinine ratio (ACR) were measured bi-weekly. Kidneys were processed for histology.

Results: Bmf-Tg mice exhibited higher systolic blood pressure, SBP, RPTC apoptosis and more urinary RPTCs than non-Tg mice. Insulin treatment suppressed Bmf expression and tubular apoptosis and reduced urinary RPTCs in Akita mice. In vitro, insulin stimulated hnRNP F and sirtuin-1 expression and inhibited Bmf promoter activity in RPTCs in HG medium. Promoter DNA analysis identified putative responsive elements for hnRNP F, p53 and Foxo3 in rat Bmf promoter. Transfection of small interference RNA of hnRNP F or sirtuin-1 abrogated insulin inhibition of Bmf promoter activity.

Conclusions: Overexpression of Bmf in RPTCs induces RPTC apoptosis. Insulin prevents RPTC apoptosis via stimulation of hnRNP F and sirtuin-1 expression to inhibit Bmf gene expression in the diabetic kidney.

Funding: Government Support - Non-U.S.

Nuclear Factor Erythroid 2-Related Factor 2 Deficiency Attenuates Hypertension and Nephropathy through Hypo-regulation of Renal Angiotensin Converting Enzyme-2 and Mas Receptor Expression in Diabetic Mice

Background: We investigated the impact of nuclear factor erythroid 2-related factor 2 (Nrf2) deficiency on hypertension, kidney injury and renin-angiotensin system (RAS) gene expression in renal proximal tubule cells (RPTCs) in diabetic Akita (type 1 diabetes model) Nrf2 knockout (KO) mice and Akita mice treated with trignoligene (a Nrf2 inhibitor).

Methods: Male wild type (WT), Akita and Akita Nrf2 KO mice at 10 to 20 weeks were studied. Akita mice receiving trignoligene from weeks 12-18 +/- oltipraz (a Nrf2 activator) from weeks 16-18 were also studied. Blood glucose and systolic blood pressure were monitored weekly. Urinary albumin/creatinine ratio (ACR), angiotensin II (Ang II) and renin expression were assessed at 7 (Ang I-7) levels were measured by ELISA. Kidneys were processed for histology. RAS mRNA and protein expression in renal proximal tubules (RPTs) were evaluated by RT-qPCR and Western blotting, respectively. We also performed Nrf2 knockdown in rat immortalized RPTCs (iRPTCs) stably transfected with plasmid containing rat angiotensinogen (Agt), angiotensin converting enzyme (ACE), angiotensin converting enzyme-2 (ACE2) or angiotensin I-7 receptor (MasR) gene promoter.

Results: Nrf2 deficiency attenuated hypertension, renal hypertrophy, tubulointerstitial fibrosis, urinary ACR and Ang II, down-regulated RPTC Agt, ACE and pro-fibrotic gene expression and up-regulated Nrf2 and MasR expression in Akita Nrf2 KO mice, compared to Akita mice. Similar changes were observed in Akita mice treated with trignoligene +/- oltipraz. Transfection of siRNA of Nrf2 prevented high glucose (HG, 25 mM) stimulation of Ang II and ACE expression and enhanced Ang II and MasR expression in iRPTC. Trignoligene decreased Agt/ACE and up-regulated ACE2/MasR mRNA expression in HG and these actions were reversed by oltipraz.

Conclusions: Nrf2 deficiency attenuates hypertension and kidney injury, via decreasing renal RAS gene expression and increasing AngII/MasR expression. These results identify Nrf2 as a novel target for the prevention of hypertension and kidney injury in diabetes.

Funding: Government Support - Non-U.S.

High Fat Diet Increases Plasma Soluble Prorenin Receptor (sPRR), Ang II, Systolic Blood Pressure (SBP), and Arterial Stiffness in Type 2 Diabetic (T2D) Male but Not in Female Mice

Background: Activation of the renin angiotensin system (RAS) leads to complications during T2D; however, whether these outcomes exhibit sex differences remains unknown. Plasma prorenin levels are high in T2D patients and associated to microvascular complications. The sPRR activates prorenin in the extracellular compartments. In this study, we determined if plasma sPRR contributes to sex differences in the RAS and complications in a murine model of high fat diet (HFD)-T2D.

Methods: Male and female C57BL/6 mice were subjected to normal diet (NFD; Protein: 25% Kcal/ Fat: 13% Carbohydrate: 62%) or HFD (Protein: 18% Kcal/ Fat: 45% Carbohydrate: 36%) for 28 weeks to assess temporal changes in plasma sPRR and Ang II quantified by ELISA, and SBP measured by telemetry. Phenotype of T2D was established based on changes in body weight, glucose tolerance test, and plasma insulin and lipid levels. Vascular stiffness was measured in carotid arteries by pressure myography.

Results: By Week 16, a T2D phenotype was evident in HFD mice with greater exacerbation in males than in females. After Week 20, plasma sPRR started to increase in HF male mice (4±3 vs. 3±1 ng/dL; P<0.05) and remained elevated until Week 28 (5±3 vs. 3±1 ng/dL; P<0.05). No significant changes were observed in females. These changes paralleled increases in Ang II and SBP only in males [Ang II (HFD: 131±20 vs. NFD: 59±12 pg/dL; P<0.05); SBP (HFD: 135 ±7 vs. NFD: 115±2 mmHg; P<0.001)] but not in females. Males on HFD also exhibited a significant decrease in carotid compliance and distensibility. After Week 20, urinary angiotensinogen excretion (uAGT) started to increase only in HFD males compared to NFD; and by the end of the study, it was 4X higher, even in the absence of overt microalbuminuria.

Conclusions: In conclusion, male mice with HFD-induced T2D, plasma sPRR contributes to marked sex differences in systemic Ang II SBP, and vascular stiffness. Concomitant uAGT differences support the concept of sexual dimorphism of intrarenal RAS activation. Plasma sPRR may reflect the status of systemic RAS and anticipate vascular complications during T2D.

Funding: NIDDK Support, Other NIH Support - CoBRE P30GM-103337

Prolonged Exposure of Podocytes to Insulin Induces Insulin Resistance through Dysomolal and Proteosomal Degradation of the Insulin Receptor Aβ chain

Background: Podocytes are insulin responsive cells of the glomerular filtration barrier and are key in preventing albuminuria, a hallmark feature of diabetic nephropathy. While there is evidence that a loss of insulin signalling to podocytes is detrimental, the molecular mechanisms underlying the development of podocyte insulin resistance in diabetes remain unclear. Thus, we aimed to further investigate podocyte insulin responses early in the context of diabetic nephropathy.

Methods: Conditionally immortalised human and mouse podocyte cell lines and glomeruli isolated from db/db DBA2J mice were studied. Podocyte insulin responses were investigated with western blotting, cellular glucose uptake assays and automated fluorescent imaging of the actin cytoskeleton. Q-PCR was employed to investigate changes in mRNA. Human cell lines stably overexpressing the IR and nephrin were also generated, using lentiviral constructs.

Results: Podocytes exposed to a diabetic environment (high glucose, high insulin and the pro-inflammatory cytokines TNF-α and IL-6) become insulin resistant with respect to glucose uptake and activation of PDHK and MAPK signalling. These podocytes lose expression of the insulin receptor (IR) as a direct consequence of prolonged exposure to high insulin concentrations, which causes an increase in IR protein degradation via a proteasome-dependent and bafilomycin-sensitive pathway. Reintroducing the IR into insulin resistant human podocytes rescues upstream phosphorylation events, but not glucose uptake. Stable expression of nephrin is also required for the insulin-stimulated glucose uptake response in podocytes and for efficient insulin-stimulated remodelling of the actin cytoskeleton.

Conclusions: Together these results suggest that IR degradation, caused by high levels of pathological insulin, drives early podocyte insulin resistance and that both the IR and nephrin are required for full insulin sensitivity of this cell. This could be highly relevant for the development of nephropathy in diabetic patients and patients with the metabolic syndrome who are commonly hyperinsulinimia in the early phases of their disease.

Funding: Government Support - Non-U.S.
Inactivation of the SPAK Kinase Generates an Obesity-Resistant Phenotype in Mice
Braulio A. Martíl,1 Ivan Torre-Villalvazo,1 Luz G. Cervantes-perez,1 Lilía G. Noriega,1 María Chavez-Canales,1 Jose V. Jimenez,1 Norma O. Uribe-uribe,1 Nimbe Torres,1 Norma Bobadilla,12 Armando R. Tovar,1 Gerardo Gamba,1,2 Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; Instituto de Investigaciones Biomedicas, UNAM, Mexico City, Mexico.

Background: The WKY (with-no-lysine)/SPAK (Ste20-related proline/alanine rich kinase) pathway has a well-known role in hypertension through its predominant effect on renal salt reabsorption. Recent evidence suggests this pathway could also be involved in the pathophysiology of obesity, which could link both diseases intrinsically. In humans the STK39 gene, which encodes SPAK, has been suggested as a susceptibility gene for arterial hypertension and for obesity. In this regard, the lack of SPAK activity in a knockin mice model (SPAK-T243A/T243A) leads to a reduction in blood pressure, but the effect of SPAK inactivation on body weight balance has not been evaluated.

Methods: To characterize the role of SPAK in energy balance, we fed wild-type and SPAK-knockin mice (SPAK-T243A/T243A) a high-fat diet (HFD) for 17 weeks and evaluated body composition, energy expenditure, thermogenesis, lipid metabolism, leptin levels, glucose metabolism and end-organ damage such as hepatic lipid content and pancreatic islet hypertrophy.

Results: Our data reveal that in contrast to wild type mice fed with HFD, the SPAK-T243A/T243A mice fed a HFD exhibit a significantly lower weight gain (15.1 ± 0.8 vs 10.2 ± 2.0 g; p<0.001) and decreased adiposity along the study, exhibiting at the end a better glucose tolerance, lower cholesterol, triglyceride and leptin levels, less hepatic steatosis and less pancreatic islet hypertrophy. The HFD intake was similar in both groups along the study. Calorimetric studies showed in the SPAK-T243A/T243A mice an increased thermogenic activity in brown adipose tissue, increased UCP1 expression, and white adipose tissue browning.

Conclusions: Our data suggest that SPAK-T243A/T243A mice are partially resistant to obesity induced with a HFD due to an increase in energy expenditure and thermogenesis, suggesting that the WKY/SPAK pathway could play a role in the pathophysiology of obesity and energy balance. Our results also suggest that inhibition of SPAK activity could have a therapeutic value in obesity. Supported by “Fronteras de la Ciencia” grant No. 23 from Conacyt, Mexico to GG.

Funding: Government Support - Non-U.S.

TH-PO698

Urinary Ubiquitinated Factor XII and Beta-2-Glycoprotein-1 May Identify Different Histopathological Patterns of Diabetic Kidney Disease
Massimo Papala,1 Chiara Divella,2 Francesca Conserva,3 Giuseppe Castellano,3 Paola Pontrelli,2 Antonella Di Fratto,1 Mariagrazia Barozzino,2 Francesco Pesce,2 Annarita Oranger,2 Francesco Giorgioni,2 Luigi Laviola,3 Simona Simone,3 Vincenzo Trischitta,1 Salvatore De Cosmo,1 Giuseppe Grandalino,1 Loretto Gesualdo.1 Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo (FG), Italy; 2University of Bari-Dept. of Emergency and Organ Transplantation, Bari, Italy; 3University of Foggia, Foggia, Italy.

Background: Diabetic Kidney Disease (DKD) is a heterogeneous disease with distinct histopathological phenotypes spanning from the typical nodular Kimmelstiel-Wilson lesions (DN) observed in ~40% of the cases to the arteriolar sclerosis changes and other primary glomerulonephropathies (non-DN-CKD) reported in the remaining cases. Recent studies (PMID: 29071995; 27881486) suggest a role of protein ubiquitination in DKD thus we tested the usefulness of urinary ubiquitinated proteins (ubi-prot) as novel biomarkers for DKD.

Methods: Sixty-four Type 2 Diabetes Mellitus patients (pts) with normalbuminuria (NORMO), microalbuminuria (MICRO), micro and macroalbuminuria with biopsy-proven DN or non-DN-CKD were enrolled. Urinary ubi-prot were purified by Immunoprecipitation with specific anti-ubiquitin antibody and identified by LTQ Orbitrap XL™ Mass Spectrometry (MS) analysis. Protein Pattern Analysis (PFA) allowed the recognition of specific molecular patterns in each group and the most confident biomarkers were then validated by IF and ELISA or immunoblotting in tissue and urine samples, respectively.

Results: MS analysis identified 79 ubi-prot in NORMO, 111 in MICRO, 135 in non-DN-CKD and 116 in DN, respectively. PFA analysis associated differentially excised ubi-prot to the activation of the classical pathway of complement system in DKD. Urinary C5b9, measured in an independent set of pts, was significantly more excreted (P = 0.01) in DKD Vs. non-proteinuric T2DM and pts with Lupus Nephritis and correlated, in the DN subset, with an increased deposition in proximal tubuli. Furthermore, 5 unique ubi-prot namely Factor XII, Ig K and Lambda chains, Beta-2-glycoprotein-1 (B2GIP-1) and C6 were excreted in DN group only. Independent validation in 8 DN Vs 8 non DN-CKD pts confirmed that urinary ubiquitinated Factor XII and B2GIP-1 were significantly more excrated in DN Vs. non DN-CKD (P<0.001 and P < 0.0001, respectively).

Conclusions: Combined evaluation of urinary C5b9, ubiquitinated Factor XII and B2GIP-1 may allow noninvasive stratification of pts with DKD.

Funding: Government Support - Non-U.S.

TH-PO699

Neuropeptide Y Is a Novel Modulator of Podocyte Function and Its Loss Is Protective in Several Models of Albuminuric Renal Disease
Abigail C. Lay, Jenny Hurcombe, Eleanor W. Ross, Fern Barrington, Gavin I. Walsh, Richard Coward. University of Bristol, Bristol, United Kingdom.

Background: Neuropeptide Y (NPY) is one of the most abundant peptides of the central and peripheral nervous system with a key role in energy homeostasis. However its function in the glomerulus has not previously been reported. Using a non-biased transcriptomic approach we discovered that NPY was highly significantly down-regulated in both human and mouse conditionally immortalised podocytes when rendered insulin resistant mimicking a diabetic environment (25-fold down regulated p=10⁻¹⁰). Data from the nephromine database, comparing diabetic nephropathy (DN) patient groups, suggests this also occurs in human glomeruli. We therefore went on to study the biological importance of NPY on podocyte and glomerular biology.

Methods: Conditionally immortalized human and mouse podocytes were studied in vitro to determine NPY receptor signalling. For our in vivo investigations we studied wild-type (WT) 129Sv and NPY-deficient (NPY-/-) 129Sv mice, comparing two models of albuminuric renal injury; adriamycin nephropathy and streptozotocin (STZ)-induced diabetic nephropathy (DN).

Results: NPY rapidly signals to human and mouse podocytes through the PI3K and MAPK pathways and this is blocked in the presence of the Y2 receptor antagonist BIIE0246, indicating these responses are NPY2R-dependent. NPY also causes a rapid increase in intracellular calcium, which in turn promotes the nuclear translocation of NFAT. Interestingly, in contrast to WT controls, NPY-/- mice are protected from albuminuria 6 months after the induction of STZ-DN (a 4-fold increase in albuminuria is observed in WT mice, p=0.036 WT citrate vs STZ). No significant increase in albuminuria is observed in NPY-/- mice, p=0.6828 NPY-/- citrate vs STZ). Similarly, 14 days after the induction of adriamycin nephropathy, NPY-/- mice had a significantly (p=0.0172) lower level of albuminuria than WT controls.

Conclusions: NPY has a novel role in regulating podocyte and glomerular biology. Our data suggests that in diabetic nephropathy and insulin resistant states its glomerular secretion is suppressed to protect against disease progression.

Funding: Government Support - Non-U.S.
TH-PO700
Modulation of Epigenetics Led to a Decrease in Proteinuria in a Mouse Model of Diabetic Podocytopena

Himanshu Vashistha, Abheepsha Mishra, Ashwani Malhotra, Leonard G. Meggs, Pravin C. Singal. Feinstein Institute of Medical Research, Northwell Health, MANHASSET, NY; North Shore LIJ Health System, Great Neck, NY; Ochsner Health System, New Orleans, LA; OchsnerHealth Foundation, New Orleans, LA; Immunology Institute for Medical Research, Northwell Health, Manhasset, NY.

Background: Modulation of renin angiotensin system has been reported to slow down the progression of diabetic podocytopenia by alterations of hemodynamic factors. Recent reports suggest that epigenetic factors also contribute to the development and progression of diabetic podocytopenia. We evaluated blockade effect of Angiotensin II (Ang II) on reversal of epigenetic alterations in diabetic podocytopenia. We hypothesize that demethylation by a low-dose hydralazine (HYDZ, non-hypertensive dose) would further augment the effect of Ang II blockade on reversal of epigenetic factors and decrease proteinuria in diabetic mice.

Methods: Protein blots of renal tissues/cortical sections of 2, 4, and 6 months old control and Akita mice (diabetic, n=3) were probed for methylation at histone (H)3 lysine (K)4 residues, acetylation at H3 lysine (K)9 residues, SNAIL, vitamin D receptor (VDR), and nphrin. In vitro studies, protein blots of control (glucose, 5 mM) and high glucose (30 mM, HG)-treated human podocytes (HPs) were probed for SNAI1, VDR, nphrin, H3K4meth3, H3K9ac and actin. Podocyte VDR and nphrin gene methylation status (Bisulphite pyrosequencing) and SNAI1 binding to VDR and nphrin promoters (ChIP assay) were determined. Control and Akita mice (n=4) were treated with losartan (an Ang II receptor blocker, 10 mg/kg/day) with/without HYDZ (10 mg/kg/day, 4 weeks) followed by evaluation of proteinuria and renal epigenetic alterations.

Results: Protein blots of renal tissues/cortical sections of Akita mice and HG/HP displayed enhanced expression of SNAI1 and H3K4meth3 but down regulation of VDR, nphrin and H3K9ac. Losartan not only decreased proteinuria but also partially reversed epigenetic alterations induced by SNAI1, VDR and nphrin expressions; HYDZ alone has similar effects on proteinuria and epigenetic markers and further augmented these effects when combined with losartan. Both nphrin and VDR displayed more than 70% cytosine methylation (CpG islands). HG/HP displayed decreased expression of nphrin and degradation via ubiquitination. ChIP assays revealed binding of SNAI1 to VDR and nphrin promoters.

Conclusions: Reversal of epigenetic alterations in renal tissues contributed to decrease in proteinuria in diabetic mice.

Funding: NIDDK Support

TH-PO701
Absence of Inner Medullary Urea Transporters Attenuates Fibrosis in Diabetic Nephropathy

Fira Rianto, Mitsu A. Blount, Faten Hasounah, Joseph A. Ruiz, Jeff M. Sands, Janet D. Klein. Emory University, Atlanta, GA; Emory University School of Medicine, Atlanta, GA.

Background: Kidney fibrosis is commonly observed in diabetic nephropathy. Animal studies show that a low protein diet reduces the incidence of diabetic kidney disease and kidney fibrosis, suggesting that kidney urea levels may contribute to nephropathy. Benefits of low protein diets in patients are controversial. We investigated diabetes (DM)-related kidney fibrosis under conditions of minimal urea reabsorption and maximal urea load.

Methods: C57BI6 mice (n=7) were fed a low protein diet (10% casein) with 2 weeks of control diet; group 1 was fed 0.5% casein (1% of control diet) or 0.5% of control diet for 2 weeks. Kidney weights of non-DM and DM mice remained stable while DM WT mice lost ~2% and A1/A3 KO mice lost ~14% body weight prior to termination. Glucose levels >200 mg/dl. Body weights of non-DM mice remained stable while DM mice gained 0.7 ± 6.8 WT/97 Uv KO; in mEq/L: Na: 147 ± 0.3 mmol/Uv WT vs 2.9 ± 0.5 WT mice lost ~2% and A1/A3 KO mice lost ~14% body weight prior to termination.

Results: Protein blots of renal tissues/cortical sections of 2, 4, and 6 months old control and Akita mice (diabetic, n=3) were probed for methylation at histone (H)3 lysine (K)4 residues, acetylation at H3 lysine (K)9 residues, SNAIL, vitamin D receptor (VDR), and nphrin. In vitro studies, protein blots of control (glucose, 5 mM) and high glucose (30 mM, HG)-treated human podocytes (HPs) were probed for SNAI1, VDR, nphrin, H3K4meth3, H3K9ac and actin. Podocyte VDR and nphrin gene methylation status (Bisulphite pyrosequencing) and SNAI1 binding to VDR and nphrin promoters (ChIP assay) were determined. Control and Akita mice (n=4) were treated with losartan (an Ang II receptor blocker, 10 mg/kg/day) with/without HYDZ (10 mg/kg/day, 4 weeks) followed by evaluation of proteinuria and renal epigenetic alterations.

Results: Protein blots of renal tissues/cortical sections of Akita mice and HG/HP displayed enhanced expression of SNAI1 and H3K4meth3 but down regulation of VDR, nphrin and H3K9ac. Losartan not only decreased proteinuria but also partially reversed epigenetic alterations induced by SNAI1, VDR and nphrin expressions; HYDZ alone has similar effects on proteinuria and epigenetic markers and further augmented these effects when combined with losartan. Both nphrin and VDR displayed more than 70% cytosine methylation (CpG islands). HG/HP displayed decreased expression of nphrin and degradation via ubiquitination. ChIP assays revealed binding of SNAI1 to VDR and nphrin promoters.

Conclusions: Reversal of epigenetic alterations in renal tissues contributed to decrease in proteinuria in diabetic mice.

Funding: NIDDK Support

TH-PO702
Nicotine Enhances Renal Mesangial Cell Proliferation and Fibronectin Production in High Glucose Mice via Activation of Wnt/β-Catenin Pathway

Xiqian Lan, Rukhsana Aslam, Seyedeh Shadafarin Marashi Shooshani, Abheepsha Mishra, Ashwani Malhotra, Pravin C. Singal. Feinstein Institute for Medical Research, Great Neck, NY; Feinstein Institute for Medical Research, Glenoaks, NY; Feinstein Institute for Medical Research, Northwell Health, MANHASSET, NY; Feinstein Inst.Med research, Manhasset, NY; North Shore LIJ Health System, Great Neck, NY; The Feinstein Institute for Medical Research, Manhasset, NY.

Background: Diabetic nephropathy (DN) is a major complication of diabetes mellitus, and the commonest cause of end-stage renal disease (ESRD) in developed countries, including USA. Clinical reports have demonstrated that cigarette smoking is an independent risk factor for chronic kidney disease including DN, however, the underlying molecular mechanisms are still not clear. Recent studies have demonstrated that nicotine, one of the highly active compounds in cigarette smoke, is required for cigarette smoking- accelerated chronic kidney disease. DN is characterized by mesangial expansion, a precursor of glomerulosclerosis. In this study, we examine the role of Wnt/β-catenin pathway in nicotine-mediated mesangial cell phenotype in high glucose milieu.

Methods: We treated human mesangial cells (HRMC) with both normal/high glucose (5 mM and 25 mM) and nicotine (0.1, 1, and 10 μM), and then examined their phenotype. To evaluated proliferation, we counted the total cell numbers (in a hemocytometer), or calculated the Ki-67 positive cell ratio by using immunofluorescent staining. We also performed real-time PCR to detect the expression of Wnts, β-catenin, and fibronectin. In addition, we used β-catenin inhibitor FH535 to examine a causal relationship between nicotine and high glucose treatment-mediated mesangial cell proliferation and fibronectin production.

Results: In 5 mM glucose medium, nicotine increased the total cell count and Ki-67 positive cell ratio in a dose-dependent manner, indicating that nicotine enhanced mesangial cell proliferation in normal glucose milieu, only moderately, 25 mM glucose further exacerbated nicotine-mediated mesangial cell proliferation. Similarly, nicotine increased the expression of Wnts, β-catenin, and fibronectin in normal glucose milieu, however, high glucose further increased these expressions. Addition of FH535 significantly inhibited the cell proliferation and fibronectin production.

Conclusions: Nicotine enhances renal mesangial cell proliferation and fibronectin production in high glucose milieu, and Wnt/β-catenin pathway plays an important role to regulate these effects. The present study provides insights into molecular mechanisms involved in diabetic nephropathy.

Funding: NIDDK Support

TH-PO703
Endothelial Dysfunction in High Fat Diet Fed Diabetic Mice Is Dependent on Ketohexokinase

Tomohito Doke, Takuji Ishimoto, Takahiro Hayasaki, Megumi Naraiwa, Miguel A. Lanasa, Richard J. Johnson, Shoichi Maruyama. Nagoya University Graduate School of Medicine, Nagoya, Japan; University of Colorado Denver, Aurora, CO; Nagoya City University, Nagoya, Japan.

Background: The metabolism of both dietary and endogenously produced fructose via activated polyol pathway by ketohexokinase (KHK) has been reported to induce metabolic syndrome, a cluster of hyperglycemia, hypertension, and obesity, and also hyperuricemia attributed to ATP depletion and activation of nucleotide degradation pathway in human and rodents. Metabolic syndrome is associated with vascular dysfunctions. KHK have two splicing variant, KHK-C and KHK-A. The aim of this study is to determine the role of KHK in the development of vascular dysfunction in diabetes.

Methods: Diabetes was induced by low-dose streptozotocin in male wild-type (K), KHK-A knockout mice (KHK-A KO), and both KHK-C and KHK-A knockout mice (KHK-A/C KO). Then they were fed high fat diet (45% fat). At 24 weeks, blood, urine, and tissue samples including aorta were collected. Biochemical analysis, urinary nitrate/nitrite measurement, and metabolic analysis of urine was done. The relaxing effects of acetylcholine (ACH) and effects of NO synthase inhibitors, N-nitro-L-arginine (LNA), on the contractions by phenylephrine (PE) were measured in endothelium-intact aortas.

Results: The level of blood glucose, blood weight and blood pressure was similar among diabetic mice. However, urinary nitrate/nitrate concentration was significantly lower in diabetic WT and diabetic KHK-A KO compared with diabetic KHK-A/C KO. Whereas ACh-induced relaxation in the aortas did not show significant difference among diabetic mice, PE-induced contractions with pretreatment of LNA (LNA/PE ratio) was significantly decreased in both diabetic WT and diabetic KHK-A KO compared to A/C KO mice, indicating endothelial dysfunction was alleviated in diabetic KHK-A/C KO mice. Metabolic analysis revealed the significant correlations between LNA/PE ratio and urinary metabolites. Especially, urinary uric acid was inversely correlated with LNA/PE ratio in diabetic mice.

Conclusions: Vascular dysfunction was attenuated in diabetic KHK-A/C KO with WT and KHK-A KO. These results suggest that endothelial dysfunction in high fat fed diabetic mice might be due to fructose metabolism dependent on KHK-C.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
TH-PO704
Effects of Clinically Validated Renal Therapies in the Renin AV db/db Uninephrectomized (uNx) Mouse Model

Shannon M. Harlan, Josep G. Heuer, Matthew D. Breyer, Kevin L. Duffin, Tao Wei, Hana Baker, Eli Lilly and Company, Indianapolis, IN

Background: The recently developed Renin AV db/db uNx mouse model, exhibits key hallmarks of advanced human diabetic kidney disease (DKD), including progressive elevations in albuminuria, increased serum creatinine, loss of glomerular filtration rate and pathological changes similar to human DKD. The renal transcriptome changes in this model were demonstrated to be more similar to human DKD when compared to the db/db eNOS- model. Recent clinical studies have demonstrated inhibiting the JAK/STAT pathway or SGLT2 inhibition improves renal function on top of ACEi or ARB. To further explore similarities of this model to human DKD we tested the response of Renin AV db/db uNx to clinically validated therapeutics.

Methods: Four weeks after Renin AV, mice were randomized and treated with vehicle, lisinopril (ACEi), Canagliflozin (SGLT2i) or Ruxolitinib (JAK-STATi). At 48 hours or 2 weeks post treatment urine was collected for measurement of clinical parameters and kidney collected for gene expression.

Results: Vehicle treated Renin AV mice exhibited significant (p<0.02) elevations in albuminuria, ACR and serum creatinine. Lisinopril and losartan reduced ACR (p<0.01) as compared to baseline at both 48 hours (-15.937ug/mg and -17.655ug/mg respectively) and 2 week time points (-15.622ug/mg and -7.774ug/mg respectively. Treatment with Canagliflozin led to significant (p<0.01) reductions in ACR at 48 hours (-12.23ug/mg) as compared to baseline, with no reductions (p>0.5) in ACR at 2 weeks (+257ug/mg). Ruxolitinib treated mice did not exhibit a significant lowering of ACR at 48 hours, with only a trend (p<0.07) at 2 weeks post treatment (-6.509ug/mg). However, significant (p<0.01) reductions from vehicle treated mice were observed in both Canagliflozin and ruxolitinib treated mice (-7.56ug/mg and -9.103ug/mg, respectively) indicating a halting of disease progression. Effects of gene expression on the model were compared in the mice.

Conclusions: The results support further clinical validation of this mouse model of DKD and provide new insights into disease pathophysiology allowing for a better understanding of human disease progression and identification of potential new targets.

Funding: Commercial Support - Eli Lilly and Company

TH-PO705
Insulin Suppresses Glucogenesis in Renal Proximal Tubules via the IRS1/Akt2/mTORC Pathway

Tomonobu Duffin, Toshiro Miki, Masahiro Hashimoto, Hiroyuki Homma, Shoko Shimizu, Shoko Kishi, Toshihide Hanaoka, Yui Fujita, Seiji Kishi, Taichi Murakami, Kojiro Nagai, Hideharu Abe, Toshio Doi, Department of Nephrology, Graduate School of Biomedical Sciences, Tokushima University, Tokushima, Japan

Background: Mesangial matrix expansion, leading to glomerulosclerosis and renal insufficiency, is an important histologic change in diabetic nephropathy. A major component of mesangial matrix is collagen IV (COL4), which increases by bone morphogenetic protein 4 (BMP4)/mothers against decapentaplegic (Smad1) signaling. Retinoic acid (RA) attenuates glomerulosclerosis, although details are unclear. In general, RA receptor (RAR) combines directly with RA response element (RARE), although RARE is not determined around BMP4 gene. In the present study, we investigated the effect of RA on diabetic nephropathy, focusing on the regulatory mechanism of BMP4.

Methods: Male CD-1 mice were given streptozotocin at 12 weeks of age, followed a month later by intraperitoneal all-trans RA (aTRA, 15 µg/gBW) or corn oil, each given thrice weekly. Animals’ kidneys were harvested after sacrifice at 24 weeks of age. aTRA or specific agonists for each subtype of RAR were added to cultured CD-1 mice derived mesangial cells for 24 hours (from 1 nM to 10 µM). RAR binding capacity to RARE, suggested by genome analysis, was confirmed by ChIP analysis.

Results: Serum creatinine levels and urinary protein excretion increased in diabetic mice. Renal BMP4 and COL4 expression levels increased in diabetic mice. Glomerulosclerosis worsened in diabetic mice, and glomeruli phosphorylated Smad1 and COL4 levels increased. These findings were attributed after aTRA administration. In cultured mice mesangial cells, BMP4 and COL4 expression levels decreased after aTRA addition or a low concentration addition of AM580, a specific agonist for RARs, but did not after a low concentration addition of either RARβ or RARγ agonist. ChIP analysis showed that a suggested RARE: around mice Bmp4 gene combined with RARs after aTRA addition.

Conclusions: aTRA administration attenuated glomerulosclerosis and decreased BMP4 and COL4 expression levels in diabetic mice. Our study suggests that RARs combined with a novel RARE around the Bmp4 gene, plays an important role for regulating BMP4 expression.

Funding: Government Support - Non-U.S.

TH-PO706
Glomerulosclerosis Attenuated by Retinoic Acid through Bone Morphogenetic Protein 4 Suppression in Mice with Streptozotocin-Induced Diabetes Masanori Tamaki, Tatsuya Tomimaga, Yui Fujita, Seiji Kishi, Taichi Murakami, Kojiro Nagai, Hideharu Abe, Toshio Doi, Department of Nephrology, Graduate School of Biomedical Sciences, Tokushima University, Tokushima, Japan

Background: Mesangial matrix expansion, leading to glomerulosclerosis and renal insufficiency, is an important histologic change in diabetic nephropathy. A major component of mesangial matrix is collagen IV (COL4), which increases by bone morphogenetic protein 4 (BMP4)/mothers against decapentaplegic (Smad1) signaling. Retinoic acid (RA) attenuates glomerulosclerosis, although details are unclear. In general, RA receptor (RAR) combines directly with RA response element (RARE), although RARE is not determined around BMP4 gene. In the present study, we investigated the effect of RA on diabetic nephropathy, focusing on the regulatory mechanism of BMP4.

Methods: Male CD-1 mice were given streptozotocin at 12 weeks of age, followed a month later by intraperitoneal all-trans RA (aTRA, 15 µg/gBW) or corn oil, each given thrice weekly. Animals’ kidneys were harvested after sacrifice at 24 weeks of age. aTRA or specific agonists for each subtype of RAR were added to cultured CD-1 mice derived mesangial cells for 24 hours (from 1 nM to 10 µM). RAR binding capacity to RARE, suggested by genome analysis, was confirmed by ChIP analysis.

Results: Serum creatinine levels and urinary protein excretion increased in diabetic mice. Renal BMP4 and COL4 expression levels increased in diabetic mice. Glomerulosclerosis worsened in diabetic mice, and glomeruli phosphorylated Smad1 and COL4 levels increased. These findings were attributed after aTRA administration. In cultured mice mesangial cells, BMP4 and COL4 expression levels decreased after aTRA addition or a low concentration addition of AM580, a specific agonist for RARs, but did not after a low concentration addition of either RARβ or RARγ agonist. ChIP analysis showed that a suggested RARE: around mice Bmp4 gene combined with RARs after aTRA addition.

Conclusions: aTRA administration attenuated glomerulosclerosis and decreased BMP4 and COL4 expression levels in diabetic mice. Our study suggests that RARs combined with a novel RARE around the Bmp4 gene, plays an important role for regulating BMP4 expression.

Funding: Government Support - Non-U.S.

TH-PO707
Stem-Cell Derived Nano-Extracellular Vesicles Promote Recovery of Diabetic Nephropathy Damaged Kidneys in Mice Cristina Grange, Benedetta Bussolati, Marta Revirírego-Mendoza, Ciro Tetta, Franklin W. Maddux, Molecular Biotechnology & Health Science, University of Turin, Turin, Italy; Fresenius Medical Care North America, Waltham, MA

Background: Nanovesicles (nEVs) released by stem cells carry transcriptional regulators and secreted RNAs that could be transferred to target cells and induce phenotypic changes. nEVs can reprogram injured cells by activating regenerative processes in acute tissue injury. The aim of this study was to evaluate whether nEVs inhibit chronic kidney injury in a mouse model of diabetic nephropathy (DN).

Methods: To develop DN, NSG mice were injected with 35 mg/Kg of streptozotocin for 4 consecutive days. All treated mice developed diabetes (glycaemia >250mg/ml) within 10 days, and DN within 1 month. Mice were intravenously treated with nEVs derived from human bone marrow stromal cells (MSCs), adipose derived stem cells or liver stem cells (HS LCS) once a week for 5 weeks. Empty nEVs were used as control[MMRM]. Kidney function and morphology were evaluated a week later by histological analyses. A comparative bioinformatics analysis of nEVs-associated miRNAs and proteins was used to identify common anti-fibrotic and pro-regenerative pathways from different kidney cells. The anti-fibrotic effect of nEVs was analysed by treating mouse kidney fibroblasts in vitro and using TGF-b1 and collagen, and a-sm actin production.

Results: nEV treatment resulted in reductions of albumin/creatinine excretion ratio and plasma creatinine, and restoration of urinary acidification when compared to control animals. Histological analyses showed a significant reduction of glomerular and interstitial fibrosis in these mice, and of Bowman’s space enlargement. Using specific markers, we found significant reduction of cell death and enhanced proliferation in the tubules. All MSC and HS LC S stem cell derived nEVs, but not nEVs derived from fibroblasts, displayed similar positive effects on reducing DN development. Comparative analyses showed that HS LC S, but not the same MSC nEVs, were enriched with the expression of pro-fibrotic miRNAs and inhibited collagen/a-sm act production.

Conclusions: We show that nEVs prevent development of DN in mice by inhibiting fibrosis and promoting regeneration.

Funding: Commercial Support - Fresenius Medical Care, North America
TH-PO708

Abstract Withdrawn

TH-PO709

VEPTP Inhibition as a Vasculoprotective Strategy to Treat Diabetic Kidney Disease

Isabel A. Carota,1,3 Christina S. Bartlett,1 Tuncer Onay,2 Rizaldy P. Scott,2 Yael Kenig-Kozlovsky,1 Sunday S. Oladipupo,4 Matthew D. Breyer,2 Susan E. Quaggan,5 Feinberg Cardiovascular Research Institute, Northwestern University, Chicago, IL; 2Northwestern University, Chicago, IL; 3FCVRI and Division of Nephropathy, Northwestern University, Chicago, IL; 4Northwestern University, Feinberg School of Medicine, Chicago, IL; 5Lilly Research Laboratories, Indianapolis, IN; 6Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN; 7BioTDR, Eli Lilly & Company, Indianapolis, IN; 8Boehringer Ingelheim, Ridgefield, CT.

Background: With a growing number of patients suffering from diabetic kidney disease new treatments to halt progression of DKD are urgently needed. Silenced Tie2 signaling following dysregulated expression of its ligands Ang1 and 2 found in diabetic patients has been linked to increased mesangial expansion and glomerular scarring. Here, we show that the endothelial specific phosphatase VEPTP is upregulated in kidney tissue of diabetic, hypertensive rodents, suggesting VEPTP as effector of reduced Tie2 activity in diabetes. Following this we investigated VEPTP inhibition as target to prevent deterioration of renal function in advanced diabetic kidney disease.

Methods: To test the impact of VEPTP blockade on the progression of DKD we postnatally deleted VEPTP in a model of diabetic hypertension (Akita/Ren/VEPTP iKO) and followed the mice until 24 weeks of age, before evaluating renal function, blood pressure, ACR and renal histology as marker for the degree of DDK.

Results: Genetic deletion of VEPTP in non-diabetic mice promotes Tie2 phosphorylation and ENSO signaling resulting in elevated glomerular filtration rates and decreased systolic blood pressure. At 24 weeks of age GFRs of Ak/Ren mice declined significantly compared to their start values, whereas GFRs from diabetic VEPTP knock-out mice maintained their baseline GFR values (Ak/Ren=242.6, Ak/Ren VEPTP iKO=480.3 ul/min). The prevention of decline in GFR over time correlated with lower elevation of urine albumin/creatinine ratios in diabetic VEPTP KO compared to diabetic controls (Ak/Ren=384.4, Ak/Ren/VEPTP iKO=741.2 ul/min). Additional histological analysis revealed that diabetic/hypertensive VEPTP deficient mice presented less glomerular scarring, mesangial expansion as well as a lower number of aSMA positive glomeruli. Analysis of kidney lysates from Ak/Ren/VEPTP iKO mice showed rescue of Tie2 phosphorylation levels compared to Ak/Ren mice, demonstrating that blockade of VEPTP slows the progression of renal complications under diabetic and hypertensive conditions by stabilizing Tie2 signaling.

Conclusions: Genetic loss of VEPTP caused increased Tie2 activity in diabetic hypertension, slowing the development of DDK in mice. In sum, we identify VEPTP as a candidate therapeutic target to protect the kidney from diabetic injury.

Fundning: Complementary Support - Eli Lilly & Company

TH-PO710

Angiotensin II Type 1 Receptor-Associated Protein Ameliorates Streptozotocin-Induced Diabetic Nephropathy in Mice

Kotaro Harahara,1,2 Hiromichi Waku,1 Ryu Kobayashi,1 Kenichi Ohashi,3 Daisuke Kurotaki,3 Nobuo Tsuibo,1 Takashi Yoko,3 Kouichi Tamura,1 Department of Medical Science and Cardiorespiratory Medicine, Yokohama City University Graduate School of Medicine, Yokohama, Japan; 2Department of Pathology, Yokohama City University Graduate School of Medicine, Yokohama, Japan; 3Department of Medicine, Jikei University School of Medicine, Tokyo, Japan.

Background: Over-activation of renin-angiotensin system and enhanced infiltration of immune cells are critical factors in the development and progression of diabetic nephropathy (DN). AT1 receptor-associated protein (ATRAP) binds specifically to the AT1 receptor. Previous study suggested the over-activation of AT1 receptor signals. We have previously shown that ATRAP inhibits hypertension and cardiovascular disease in the animal models of renin-angiotensin system over-activation. Our aim was to determine the protective role of ATRAP in a mouse model of DN.

Methods: Diabetic mice induced in wild-type mice (WT) and systemic ATRAP knockout mice (KO) on a C57BL/6J background by the intraperitoneal injection of streptozotocin (55 mg/kg, daily for 5 consecutive days).

Results: The glycemic and blood pressure status of the diabetic WT and KO were comparable throughout the study period. The urinary albumin excretion was increased and the podocyte number, as estimated by immunohistochemical staining for NBT-1, was decreased in the diabetic KO in comparison to the diabetic WT at 24 weeks after the streptozotocin injection (Figure). Furthermore, the renal expression of alternatively activated macrophage-related genes, including C1q, Arg1, Il4, and Il-13, were suppressed in diabetic KO in comparison to diabetic WT; these macrophages are known to be factors associated with anti-inflammation and tissue repair.

Conclusions: These results suggested that ATRAP plays protective roles in the progression of DN via the maintenance of the renal expression of alternatively activated macrophages, indicating that ATRAP is therefore a novel therapeutic target of DN.

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

TH-PO711

Renal Inflammation, Insulin Resistance, and Enhanced Renal Gluconeogenesis in Type 2 Diabetic Nephropathy: The Missing Links

Qianling Wang, Xuemei Zhang, Liangyan Liu, Shinya Kim, Takashi Takahashi, Rachel H. Kim, Shinya Nagasaki, Daisuke Katagiri, Ray Mernaugh, Takamune Takahashi. Vanderbilt University, Nashville, TN.

Background: Renal gluconeogenesis is substantially stimulated in patients with type 2 diabetes, but the mechanism remains unknown. Renal gluconeogenesis is negatively regulated by insulin. Since inflammation is activated in diabetic nephropathy (DN), however, inflammation is well known to induce insulin resistance, we wondered whether enhanced renal gluconeogenesis in DN was partially resulted from renal inflammation-mediated insulin resistance. If so, whether inflammation inhibitor could partially reverse this change.

Methods: Eight-week-old male diabetic db/db (C57BLKS/J-LepR-/-Lepr-/-) mice and their non-diabetic littermates db/db (C57BLKS/J-LepR+/-Lepr+/-) mice were used in this study. Diabetic db/db mice were treated with 1 mg/kg NF-kB inhibitor parthenolide (PTN) or saline as control intraperitoneally every other day. After 12 weeks of treatment, blood, urine and kidney samples were collected for measurement.

Results: Expression of inflammatory factors and the gluconeogenetic rate-limiting enzyme phosphoenolpyruvate carboxykinase (PEPCK) were increased in the renal cortex of both type 2 DN human patients and db/db mice. Moreover, reduced insulin signaling as demonstrated by downregulated phosphorylation of AKT and increased expression of downstream gene FOXO1 were detected in db/db/saline mice compared with db/m mice. Consistent with our hypothesis, NF-kB inhibitor PTN significantly reduced renal expression of NF-kB, TNF-a, MIP-1e and macrophage infiltration in db/db PTN mice compared with db/db/saline mice. Moreover, it partially alleviated renal insulin resistance and reduced the expression of gluconeogenic enzyme PEPCK (1.62±0.47 vs. 0.89±0.41, P<0.05). It indicated that inflammation could be one of the triggers for insulin resistance and enhanced renal gluconeogenesis.

Conclusions: Our study demonstrated for the first time that renal gluconeogenesis is upregulated in db/db mice, and this was associated with renal inflammation-mediated insulin resistance. PTN partially reversed this change by promoting renal insulin sensitivity. This work shed light on the role of inflammation in enhanced renal gluconeogenesis and may yield a novel target for hyperglycemia.

TH-PO712

Agnostic Anti-CD148 Monoclonal Antibody Attenuates Diabetic Nephropathy in Mice

Keiko Takahashi, Rachel H. Kim, Shinya Nagasaki, Daisuke Katagiri, Ray Mernaugh, Takamune Takahashi.

Background: CD148 is a transmembrane protein tyrosine phosphatase (PTP) that is expressed in renal vasculature, including glomerular endothelial cells and podocytes. Previous studies have shown that CD148 suppresses multiple growth factor signaling pathways (e.g. VEGF, EGF) and prominently inhibits endothelial or epithelial cell proliferation. Here, we have generated an agnostic anti-CD148 monoclonal antibody (18E1) and evaluated its effects in murine diabetic nephropathy.

Methods: Monoclonal antibodies (mAbs) against mouse CD148 ectodomain (CD148b) were produced by immunizing CD148+/- mice with CD148Fc fusion protein. The mAbs that specifically bind to CD148 and increase its catalytic activity and inhibit the proliferation of CD148 stably-transfected cells were selected by a series of biochemical (Western blot, PTP activity) and biological (proliferation) assays. The specificity of the effects was evaluated by CD148 knockdown or knockout. The mAb (18E1) that showed strong agonistic activity was injected (10 mg/kg, i.p., three times per week) into wild-type (WT) and CD148-/- (KO) diabetic mice (DBA2 strain, 8 week-old, N=6 per group) for 6 weeks, then renal phenotype was assessed. Diabetes was induced by low-dose STZ injections and mouse IGF1 was used as a control. Furthermore, the effects of 18E1 mAb in glomerular endothelial cell and podocyte cell proliferation were also assessed in culture.

Results: As compared with control Ab, the 18E1 mAb significantly decreased albuminuria (~50%) and mesangial expansion (~30%) without altering hyperglycemia and blood pressure in WT diabetic mice. Immunohistochemical evaluation showed that the 18E1 mAb significantly prevented the reduction of podocyte number and neprin

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
expression and decreases glomerular macrophage (F4/80) infiltration (~40%) and matrix deposition (fibronectin) (~30%). The 18E1 mAb showed no effects in CD14KO diabetic mice. In addition, the 18E1 mAb significantly (~50%) inhibited proliferation of glomerular endothelial cells and podocytes in culture concomitant with reduction of VEGF-R2 or EGFR phosphorylation. These inhibitory effects were largely abolished by CD14 knockout.


Funding: NIDDK Support

TH-PO713

NO and SIRT1 Protect Glomerular Endothelial Cells with TERC Deletion from Hyperglycemia-Induced Senescence Huifang Liu,2,2

Background: Endothelial dysfunction plays an important role in the development of diabetic nephropathy (DN). We have previously reported that telomerase deficiency may predispose to diabetic renal injury.

Methods: To investigate the role of nitric oxide (NO) and SIRT1 in mediation of telomerase-dependent vulnerability to DN, we used streptozotocin (STZ) to induce diabetes in fourth generation (G4) TatC T KO mice and compared their response with wild type (WT) in response to treatment with NO precursor, L-arginine (L-arg). We also used primary cultured glomerular endothelial cells (GeNCs) in vitro studies to explore the interaction of NO and SIRT1.

Results: TNFα-induced hyperglycemia, but Terc/T KO mice had increased renal involvement, which was alleviated by L-arg administration, with decreased albuminuria and less GBM thickening. Increased cell senescence and more severe oxidative stress was seen in diabetic mice with TERC/T deficiency, indicated by higher urinary F2-isoprostane and accumulation of renal nitrosylsine. L-arg treatment partially ameliorated those alterations. In addition, L-arg limited the reduction in SIRT1 expression associated with decreased senescence in the diabetic kidney, especially with telomerase deficiency. Ex vivo study with freshly isolated de-caputlated glomeruli demonstrated that high glucose (HG, 30 mM) incubation stimulated endothelial cell detachment from GBM in glomeruli with TERC deletion, which could be prevented by co-incubation with a SIRT activator, SIRT1270. Primary cultured GeNCs exhibited reduced NO and cellular senescence after incubation for 96 hours in HG medium, with a marked increase in cells with TERC deletion. HG also decreased SIRT1 expression and activity to a greater extent than TERC deficiency in GeNCs. SIRT1270 partially restored NO expression, and co-incubation with either SIRT1270 or L-arg attenuated HG induced senescence in TERC-deleted GeNCs.

Conclusions: These results suggested that both NO and the SIRT1 pathway are involved in the telomerase dependent susceptibility to DN progression and GeNCs senescence.

Funding: NIDDK Support

TH-PO714

pNaKtide Targeted to Adipocytes Inhibits Na/K-ATPase Reactive Oxygen Species, Systemic Inflammation, and Obesity Development in Mice Fed a Western Diet Rebecca Martin,1 Cameron Brickman,1 Jiang Liu,2 Komal Sodhi,1 Joseph I. Shapiro.2 1Marsha, Huntington, WV; 2Marshall University JCE School of Medicine, Huntington, WV; 3Marshall University JCE/OM, Huntington, WV; 4Marshall University School of Medicine, Huntington, WV.

Background: Obesity is a worldwide epidemic with many comorbidities. It has been demonstrated that oxidative stress can exacerbate obesity development. We have previously published that systemic administration of pNaKtide, a Na/K-ATPase signaling antagonist, decreased oxidative stress and adipogenesis by blocking Na/K-ATPase signaling mediated amplification of oxidative stress. Adipocyte dysfunction may be prevented by lentiviral mediated adipocyte-specific delivery of pNaKtide.

Methods: C57Bl/6 mice were randomly divided into five groups: 1) normal chow 2) normal chow lenti-adipo-pNaKtide 3) WD 4) WD+lenti-adipo-GFP and 5) WD+lenti-adipo-pNaKtide (n=6-8/group). Lentiviral constructs with pNaKtide driven by an adipocin promoter were used to achieve pNaKtide expression specifically in adipose tissue. Groups 2 and 5 were given an intraperitoneal injection of lenti-adipo-pNaKtide and group 4 was given an intraperitoneal injection of lenti-adipo-GFP at beginning of the experiment and again at week 2; total time 12 weeks. Body weight was measured weekly. Glucose clearance was determined using an intraperitoneal glucose tolerance test before termination of the experiment. At sacrifice body weight, visceral and subcutaneous fat content of all mice were measured. Blood samples were collected for determination of inflammatory cytokines. Tissues were flash frozen and maintained at -80°C.

Results: Lenti-adipo-pNaKtide significantly reduced WD-induced weight gain, and visceral and subcutaneous fat content. Lenti-adipo-pNaKtide reduced WD-induced changes in glucose tolerance and inflammatory markers TNFα, IL-6 and MCP-1 (p<0.05). An increase in cardiac hypertrophy in WD animals was attenuated (p<0.05). Visceral fat of WD mice expressed compared with adipogenic markers PPARY, FAS, and C/EBP. WD-induced Na-K-ATPase signaling was decreased. Renal function was not significantly impacted; slight decreases in function are evident, suggesting a potential decrease in renal function with chronic obesity.

Conclusions: Collectively this study introduces the novel idea that adipocytes may have a systemic effect. Specific targeting of pNaKtide to the adipocytes with lenti-adipo-pNaKtide ameliorates this systemic effect. This new information is important in the development of new therapeutic targets for obesity.

TH-PO715

Effect of Dietary Fat/Carbohydrate Ratio on Renal Lipid Deposition in Rats with Diabetic Nephropathy Miho Sugimoto1, Takuya Yoshida,1 Naoki Ikegaya,2 Hiromichi Kamagai.1 1Dept. of Clinical Nutrition, Univ. of Shizuoka, Shizuoka, Japan; 2Dept. of Medicine, Yaitu City Hospital, Yaitu, Japan.

Background: High-fat/low-carbohydrate diet (HFD) has been used to achieve glycemic control among diabetic patients. However, HFD may be harmful to those with diabetic nephropathy. This study aimed to examine the effect of HFD on diabetic nephropathy.

Methods: Twelve-week-old male Hos-ZFDM-Lep/− (a diabetic rat strain) rats were maintained under a calorie-restrictive (60%−70% ad libitum) and isoenenergetic condition with either HFD (14% protein, 40% fat, and 46% carbohydrate) or pair-fed control diet (14% protein, 15% fat, and 71% carbohydrate) for 7 weeks. Oral glucose tolerance test (OGTT), urinary protein excretion, creatinine clearance (Cr), and renal triglyceride (TG) content were assessed at the end of the experiment. The renal histology and lipid deposition were also evaluated.

Results: The HFD rats had lower plasma glucose levels at 60 and 120 min OGTT than the control rats (at 120 min OGTT: 524±24 and 648±38 mg/dl for HFD and control rats, respectively; p<0.001). However, although the HFD rats had better glycemic control than the control rats, the former showed significantly lower Cr (HFD and control rats: 1.63±0.13 and 3.86±0.34 L/day, respectively; p<0.001) and higher proteinuria than the latter. Furthermore, the HFD rats displayed significantly higher plasma and renal TG concentrations than the control rats. Glomerular mesangial expansion and lipid deposition in the proximal tubular cells were observed in the HFD rats. The renal TG content was correlated with the urinary liver-type fatty acid-binding protein excretion.

Conclusions: These results indicated that HFD may accelerate the progression of diabetic nephropathy, even under caloric restriction.

Funding: Government Support - Non-U.S.

TH-PO716

Study of mTORC2 Pathway on CD4+CD25+Treg in Diabetic Nephropathy Qiu Yue1, Jing Zhou.1 1The First Affiliated Hospital of Nan Chang University, Nanchang, China; 2The first affiliated hospital of Nanchang University, Nanchang, China.

Background: To investigate the effect of mTORC2 pathway blocker on CD4+CD25+Treg in diabetic nephropathy (DN) rats, and to explore the possible mechanism of Treg in DN podocyte injury.

Methods: Thirty SD rats were randomly divided into DN group, DN + FK506 group and DN + FK506 group. Treatment groups were specifically given FK506 1mg/kg/d, ku063794 1mg/kg/d orally every day. Blood glucose, Creatinine clearance (Ccr) and urinary protein were measured at 0, 4, 8 weeks. The expression of mTOR, Raptor, Rictor in renal tissue was detected at 4, 8 weeks. The levels of IL-17 and TGF-β1 in peripheral blood were detected by ELISA, and the percentage of CD4+CD25+Treg was detected by flow cytometry at 4, 8 weeks.

Results: Primary urinary protein of model group was higher than control group (P<0.05), intervention groups were lower than model group (P<0.05); Ccr of model group compared with control group significantly decreased (P<0.05), intervention groups compared with model group significantly increased (P<0.05); mTOR, Raptor, Rictor increased significantly in the model group and decreased in the intervention groups (P<0.05); CD4+CD25+ Treg of the model group was significantly lower than control group (P<0.05), and intervention groups were higher than model group (P<0.05); it of intervention groups at 8 week were higher than at 4 week (P<0.05); Pathological score of intervention groups compared with model group significantly decreased(P<0.05); TGF-β1 and IL-17 of the model group were significantly higher than control group (P<0.05), and the intervention groups were lower than model group (P<0.05); TGF-β1 of FK506 intervention group was lower than that of ku063794 intervention group (P<0.05); Correlation analysis: In model group, positive correlation with TGF-β1 and IL-17 of the model group was (P<0.05), positive correlation with TGF-β1 and IL-17, urinary protein, pathological score (P<0.05); Raptor was positively correlated with urinary protein and pathological score (P<0.05), negative correlation with Ccr (P<0.05), no correlation with CD4+CD25+ Treg, TGF-β1,IL-17.

Conclusions: CD4+CD25+ Treg may be regulated by the mTORC2 pathway in DN rats, and involved in the pathogenesis of DN.

Funding: Government Support - Non-U.S.
ESRD and Mortality after VA NEPHRON-D

PRIORITY (Proteomic prediction and Renin angiotensin Mineralocorticoid Receptor Antagonism for Prevention of Diabetic Nephropathy in Type 2 Diabetes)

Baseline Characteristics in PRIORITY Study: Proteomics and Antagonism for Prevention of Diabetic Nephropathy in Type 2 Diabetes

Non Albuminuric Chronic Kidney Disease (NA-CKD) Phenotype in Patients (Pts) with Type 2 Diabetes (DM2): Results from a Population Based Study

Body Fat Distribution Is More Predictive of All-Cause Mortality Than Overall Adiposity Sung Woo Lee,1 Nam Ju Heo,2 1Eulji General Hospital, Seoul, Republic of Korea; 2Seoul National University Hospital, Seoul, Republic of Korea.

Background: The relationship between directly measured body fat and all-cause mortality has been rarely studied. The aim of this study was to evaluate the predictive significance of computed tomography (CT)-measured body fat, including both visceral fat area (VFA) and subcutaneous fat area (SFA), for mortality.

Methods: The study included 36,565 participants who underwent abdominal CT as part of a health check-up at a single university-affiliated healthcare centre in 2007–2015. Of those, 32,593 participants with data regarding vital status as of May 2016 were included in the final analysis. The main factors evaluated were VFA, SFA and visceral-to-subcutaneous fat area ratio (VSR), and the primary outcome was all-cause mortality.

Results: There were 253 deaths during a mean follow-up of 5.7 years. Increased SFA was associated with decreased all-cause mortality, whereas an increased VFA and VSR were related to increased all-cause mortality. Compared with the predictive power of body mass index (BMI), SFA and VSR showed a larger area under the curve than did BMI. In Kaplan-Meier survival curve analysis, increased SFA and VSR were associated with decreased and increased hazard of all-cause death, respectively. However, in multivariate Cox proportional hazard regression analysis, only VSR was independently associated with all-cause mortality. Moreover, this relationship was paralleled by the harmful impact of increased VSR on metabolic profiles.

Conclusions: Increased VSR was an independent predictor of all-cause mortality. This suggests that the location of fat deposits may be more important than the actual amount of body fat.

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

Funding: Government Support - Non-U.S.

poster/Thursday
**TH-PO721**

**Glycemic Status and Mortality in CKD According to Transition versus Non-Transition to Dialysis**

Connie Rhee, Vanessa A. Ravel, Elani Streja, Melissa Soohoo, Gregory Brent, Danh V. Nguyen, Kamyar Kalantar-Zadeh. Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; 1Harold Simmons Center, University of California at Irvine, Huntington Beach, CA; 2University of California Irvine, School of Medicine, Orange, CA; 3University of California at Irvine, Irvine, CA; 4University of California, Irvine, Irvine, CA; 5University of Tennessee Health Science Center, Memphis, TN; 6VA Greater Los Angeles Healthcare, Los Angeles, CA

**Background:** The optimal glycemic target in diabetic non-dialysis dependent chronic kidney disease (NDD-CKD) patients remains uncertain, as most trials of glycemic control excluded advanced kidney disease patients. We examined pre-ESRD glycemic status, defined by random blood glucose and hemoglobin A1c (HbA1c), with early post-ESRD mortality among diabetic NDD-CKD patients transitioning to dialysis. In parallel, we examined glycemic status and mortality in a matched cohort of NDD-CKD patients who did not transition to dialysis.

**Methods:** Among US veterans with diabetic NDD-CKD transitioning to dialysis from 2007-11 (Transition Cohort), we examined 1-year pre-ESRD averaged random glucose and HbA1c with 1-year all-cause mortality using expanded case-mix Cox models. Analogous analyses were conducted among CKD patients who did not transition to dialysis within 1-year (Non-Transition Cohort) matched on the basis of age, sex, ethnicity, and baseline CKD stage.

**Results:** Among 17,121 patients in the Transition Cohort, averaged random glucose ≥200mg/dl was associated with higher mortality (ref: 100-<120mg/dl), and HbA1c ≥8% was associated with higher mortality (ref: 6-<8%). Among 8711 patients in the Non-Transition Cohort, lower glucose <100mg/dl and higher glucose ≥160mg/dl were associated with higher mortality, whereas HbA1c was not associated with death.

**Conclusions:** In diabetic NDD-CKD patients transitioning to dialysis, higher averaged random glucose and HbA1c were associated with early death mortality. In patients who did not transition, there was a U-shaped association between glucose and mortality. These data suggest liberal glycemic status is associated with long-term mortality risk, whereas intensive glycemic status is associated with short-term risk.

**Funding:** NIDDK Support

---

**TH-PO723**

**Hemoglobin A1c Levels and Infection Risk Among Dialysis Patients**

Connie Rhee, Kamyar Kalantar-Zadeh, Amy S. You, Elani Streja, Steven M. Brunelli, Gregory Brent, Csaba P. Kovessy, Danh V. Nguyen. 1DaVita Clinical Research, Needham, MA; 2Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; 3University of California Irvine, Huntington Beach, CA; 4University of California Irvine, School of Medicine, Orange, CA; 5University of California, Irvine, Irvine, CA; 6VA Greater Los Angeles Healthcare, Los Angeles, CA

**Background:** Diabetic patients are at heightened risk of infection due to the immune dysfunction (i.e., impaired neutrophil function, antioxidant system, and humoral immunity) ensuing from hyperglycemia. While infections are the second leading cause of death in end-stage renal disease patients, little is known about the relationship between average glucose control defined by hemoglobin A1c (HbA1c) and infection risk in the dialysis population.

**Methods:** Among 642 dialysis patients from the national Biospecimen Registry Grant Program (BioReG) who underwent HbA1c testing over 1/2008-12/2014, we examined the relationship between average glucose control, as reflected in the HbA1c, and risk of bacteremia using case-mix adjusted Poisson regression models adjusted for age, sex, and race/ethnicity.

**Results:** In the overall cohort, the mean±SD and minimum-maximum HbA1c values were 6.7±1.5% and 3.8-16.0%, respectively; approximately 16% of patients experienced one or more bacteremia events during the follow-up period. Compared to a HbA1c level ≥7%, patients with HbA1c levels ≤5% had a higher incident rate of bacteremia in case-
mix models: adjusted IRRs [aIRRs] 1.11 (0.51-2.41), 1.38 (0.89-2.16), and 1.79 (1.18-2.71) for HbA1c levels <5, 5-6, and ≥7%, respectively.

Conclusions: Higher HbA1c levels were associated with higher incident rates of bacteremia in dialysis patients. While clinical practice guidelines advise against tight glycemic control in diabetic ESRD patients due to risk of hypoglycemia, liberal glycemic status may also contribute to adverse outcomes due to heightened infection risk. Further studies are needed to more granularly define the upper threshold for heightened infection risk within specific populations.

Results: Over a median follow-up of 4.93 years, in joint risk models of eGFR and BUN, there was no association between eGFR and the risk of incident diabetes in those with BUN ≥25 mg/dL as the risk was significantly increased in those with BUN<25 mg/dL and eGFR<15 mL/min/1.73m² (HR=1.68;CI=1.51-1.87). Spline analyses of the relationship between BUN and risk of incident diabetes showed that risk was progressively higher as BUN increased. In models where eGFR was included as a continuous covariate, compared to BUN<25 mg/dL, BUN≥25 mg/dL was associated with increased risk of incident diabetes (HR=1.23;CI=1.21-1.25); every 10 mL/min/1.73m² increase in eGFR was not associated with risk of incident diabetes (HR=1.00;CI=1.00-1.00). Two-stage residual inclusion analyses showed that independent of the impact of eGFR, every 10 mg/dL increase in BUN concentration was associated with increased risk of incident diabetes (HR=1.15;CI=1.14-1.16).

Conclusions: Our results suggest that higher levels of BUN are associated with increased risk of incident diabetes mellitus. A bidirectional nexus (between diabetes and kidney disease) likely exists, in that diabetes causes kidney disease, and elevated levels of urea-often present in the context of advanced kidney disease-are associated with increased risk of incident diabetes.

Funding: Veterans Affairs Support

TH-PO726
Mortality in Diabetic Adults with Low eGFR in the Absence of Increased Urine Albumin Excretion Is Increasing

Holly J. Kramer,1 R. E. Boucher,2 Guo Wei,3 Tom Greene,4 David J. Leehey,1 Linda F. Fried,5 Sylvia E. Rosas,6 Srinidhi Beddhu.7 1Loyola University Medical Center, Maywood, IL; 2University of Utah School of Medicine, Salt Lake City, UT; 3University of Utah School of Medicine, Salt Lake City, UT; 4VA Pittsburgh Healthcare System, Pittsburgh, PA; 5Joslin Diabetes Center, Boston, MA.

Background: Due to improvements in diabetes management, the prevalence of low estimated glomerular filtration rate (eGFR) has increased while prevalence of increased urine albumin excretion (albumin-to-creatinine ratio [ACR] ≥30 mg/g) has decreased. These trends may influence mortality due to the heterogeneity of risk across chronic kidney disease (CKD) phenotypes.

Methods: We used data from the National Health and Nutrition Examination Surveys 1988-2006 linked with the National Death Index through December 31, 2011 to examine temporal trends in mortality and total number of deaths by CKD phenotype in the U.S. diabetic population by CKD phenotype. Diabetes was defined as presence of a fasting glucose ≥126 mg/dl, hemoglobin A1c ≥6.5% or use of glucose lowering medications.

Results: From 1988 to 2006, diabetic adults with low eGFR and ACR < 30 mg/g increased from approximately 0.9 (95% CI 0.7, 1.1) million during years 1988-1994 to 2.0 (95% CI 1.5, 2.6) million during years 2007-2010. During years 1988-2006, mortality rates generally trended downward for all groups with ACR ≥ 30 mg/g but increased in adults with low eGFR and ACR < 30 mg/g from 35 deaths per 1000 person-years (95% CI 22.55) during years 1988-1994 to 51 deaths per 1000 person-years (95% CI 33, 83) during years 2003-2006 (Figure). The proportion of deaths in the total U.S. population with diabetes occurring in the setting of low eGFR and ACR ≥ 30 mg/g increased from 8.7% during years 1988-1994 to 21.9% during years 2003-2006. Findings did not change substantially after standardizing for the age distribution of the populations.

Conclusions: These findings demonstrate an urgent need to determine optimal management strategies to reduce mortality in diabetics with low eGFR in the absence of increased urine albumin excretion.

Funding: NIDDK Support

TH-PO727
Greater Insulin Use with More Advanced Stages of DKD

Christine K. Raji,1 Vishwa Srinivasan,2 Arianna N. Jensen,3 R. E. Boucher,2 Guo Wei,3 Srinidhi Beddhu.4 1UC Berkeley, Saratoga, CA; 2Univ. of Utah, SLC, UT

Background: Those with more advanced CKD are assumed to require less insulin because of decreased renal metabolism of insulin. On the other hand, uremia might result in insulin resistance and/or pancreatic islet cell failure which can ↑ the need for insulin.

Conclusions: Despite the strong epidemiologic relationships between DN and CV disease, we found associations between HbA1c and CAC were no longer statistically significant after incorporating eGFR in the model. This finding is in line with prior research which has demonstrated that eGFR can mediate the effects of glucose exposure on CAC. These findings may have practical implications for clinicians and future research in the field of diabetes and CVD.
Higher Concentrations of Urea Are Associated with Increased Risk of Failure of Oral Hypoglycemic among Diabetic Patients with CKD

Yan Xie,1 Benjamin C. Bowe,1 Tingting Li,2 Hong Xian,1,3 Yan Yan,1,4 Ziyad Al-Aly,1,3 1Clinical Epidemiology Center, Research and Education Service, VA Saint Louis Health Care System, Saint Louis, MO; 2Department of Medicine, Washington University School of Medicine, Saint Louis, MO; 3Division of Biostatistics, College for Public Health and Social Justice, Saint Louis University, Saint Louis, MO; 4Department of Biostatistics, College for Public Health and Social Justice, Saint Louis University, Saint Louis, MO; 5Renal Section, Medicine Service, VA Saint Louis Health Care System, Saint Louis, MO.

Background: Kidney disease is associated with disturbances in glucose and insulin homeostasis. Experimental evidence suggests that urea suppresses insulin secretion and increases insulin resistance. However, whether elevated concentrations of urea are associated with increased risk of failure of oral hypoglycemic agents, and increased risk of insulin requirement among diabetic patients with kidney disease is unknown.

Methods: We built a national cohort of 158,099 United States Veterans with incident diabetes and used time-varying survival model to estimate the cause-specific hazards of requiring treatment with insulin.

Results: Over a follow-up period of 4.93 years, compared to those with BUN <=25 mg/dl, the risk of requiring insulin was significantly increased among those with BUN=25-49 mg/dl (HR=2.55; CI=2.38-2.72). An analysis which considered BUN categorized in quintiles suggested a graded association in that risk of insulin treatment was gradually increased with increased BUN concentrations. An Analysis which only included those patients who had lost weight and had a stable eGFR, mean 51.6ml/min [23-90ml/min]. At 1 year follow up, 71% saw an improvement in HbA1c (p<0.05, paired t test).

Conclusions: This study showed that this model of care for patients with diabetes and CKD was successful in helping improve diabetic control. Liraglutide, a glucagon-like peptide-1 receptor agonist, seems to be an effective agent to promote weight reduction in patients without causing deterioration in renal function.
Diabetic and Obesity Induced Kidney Disease - Clinical - I
Poster/Thursday

TH-PO732
Association of Anthropometric Obesity Measures with CKD in Chinese Individuals with Type 2 Diabetes
Dongsheong Cheng, Niansong Wang, Department of Nephrology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China.

Background: Obesity is associated with both type 2 diabetes and chronic kidney disease (CKD). It remains controversial whether anthropometric obesity measures are related to the risk of CKD in type 2 diabetic patients.

Methods: We investigated the association between anthropometric obesity measures including body mass index (BMI), waist circumference (WC), and waist-to-hip ratio (WHR) with chronic kidney disease in Chinese individuals with type 2 diabetes. CKD was defined as eGFR < 60 ml/min/1.73 m², the presence of albuminuria or both. Logistic regression was used to examine associations of obesity and CKD.

Results: A total of 4701 patients were included in the final analysis. The mean age was 55.7 years, and 59.7% was male. Of these patients, 352 (29.0%) had incident CKD. The prevalence of obesity was 45.6% in CKD and 51.4% in non-CKD patients with T2DM. In contrast, the prevalence of MetS in CKD was higher than non-CKD patients (58.5 vs 57.0, p=0.03). There was a trend associated between the prevalence of MetS in CKD stage from 3 to 5 (58.1, 61.0, and 63.2%, respectively, p=0.01). When stratified by sex in diabetic CKD group, the presence of MetS was significantly higher among female compared to male (68.6% vs 38.0%, p<0.001). MetS, but not obesity, had a significant higher risk prediction for developing of CKD among T2DM patients after adjusting for age, sex, and comorbidities (OR 1.11; 95%CI 1.03-1.21, p=0.01).

Conclusions: The relatively high prevalence of both obesity and MetS were observed in diabetic CKD community. Identification of obesity-related metabolic phenotypes is necessary to determine the risk for the development of CKD among T2DM patients.

Funding: Government Support - Non-U.S.

TH-PO733
Effect of GSTK1 on Ectopic Fat Deposition in the Kidney of Patients with Diabetic Nephropathy
Xianghui Chen, Chun Hu, Li Zhao, Yachun Han, Xiaofen Xiong, Li Li, Ming Yang, Peng Gao, Li Xiao, Fuyou Liu, Lin Sun, Departments of nephrology, Second Xiangya Hospital Central South University, Changsha, China.

Background: Ectopic fat deposition in kidney is closely related to the progression of diabetic nephropathy (DKD). GSTK1 is a kind of phosphatase in adipocytes, involved in adipocyte differentiation and senescence. This study to observe by first time the relationship between the expression of GSTK1 and ectopic fat deposition.(EFD) induced kidney injury in DKD patients.

Methods: 36 DN patients diagnosed by renal biopsy were enrolled. 30 patients with mild glomerular lesions were selected as controls. ADRP expression was used as a marker of EFD in the kidney. The expression of GSTK1 and ADRP were detected by immunohistochemistry staining. RT-PCR was used to test the expression of GSTK1 mRNA in PBMCs. ROS was measured by DHE staining. Lipid accumulation in kidney and cells were observed by Oil Red O staining. H2K cells were treated with different concentrations of glucose for 24 hours. The expression of GSTK1 and ADRP was tested by Western blot or immunofluorescence in HK-2 cell transfected with or without GSTK1 plasmid, or treated with MitOx respectively. Mitochondrial ROS production was detected by MitoSOX staining.

Results: Compared with the control group, the levels of TG, CHOL, LDL-C, BUN, SCR, UA and 24h urine protein in DN patients were increased (p < 0.05), while the HDL-C, ALB were decreased (p < 0.05). The expression of GSTK1 mRNA in PBMCs was down-regulated (p<0.01). In addition, the protein expression of GSTK1 in kidney was decreased, while ADRP, ROS level and the deposition of lipids were significantly increased (p<0.01), which associated with different stages of DN. Moreover, the expression of GSTK1 in HK-2 cells treated by HG or H2O2 were seen, while downregulated expression of GSTK1 protein was found. All changes above could be blocked partially by overexpression of GSTK1 or mito Qa target mitochondrial antioxidants, but failure to co-treatment with H2O2.

Conclusions: This data suggested that the decreased expression of GSTK1 in the kidney was significantly correlated with EFD induced renal injury in DN patients.

Funding: Private Foundation Support

TH-PO734
Differences in the Prevalence of Metabolic Syndrome and Its Components among Ethnic Minorities with CKD
Robert Lorch, Jingbo Niu, Carl P. Walthier, Rajeev Raghavan, Wolfgang C. Winkelmayer, Sankar D. Navaneathan, Baylor College of Medicine, Houston, TX.

Background: Metabolic syndrome (MetS) and chronic kidney disease (CKD) are common among ethnic minorities. Whether clustering of various metabolic risk factors occurs irrespective of race is unclear. Herein, we studied whether the prevalence of MetS and its components differed between African Americans (AAs) and Hispanics with CKD.

Methods: We identified patients with stage 3 and 4 CKD (based on eGFR<60 ml/min/1.73 m²) who were followed between 2006-2016 in the Harris Health System, a safety-net health system in Houston, TX. Demographics, comorbid conditions, and laboratory data were extracted from electronic medical records. Multivariable models were fitted to estimate the presence of three or more of the following components: body mass index (BMI) ≥ 30 kg/m², serum triglyceride level≥150 mg/dl, HDL≤50 mg/dl in women and ≤40 mg/dl in men, hypertension (BP>130/85 mmHg or on antihypertensive medications), and impaired glucose metabolism (presence of diabetes, use of oral hypoglycemics, or blood glucose ≥140 mg/dl on a fast or ≥200 mg/dl on ≥2, the presence of albuminuria or both). Logistic regression was used to calculate modified Poisson regression with robust variance.

Results: Of 8664 patients with CKD Stage 3 or 4, 6954 (80%) had MetS. The prevalence of MetS was highest among Hispanics (87%), followed by non-Hispanic whites (85%), AA (74%), and Asian Americans (71%). While comparing MetS and its components between AAs and Hispanics, we noted higher prevalence for high triglycerides, low HDL levels, and diabetes, but lower prevalence of obesity among Hispanics than AAs (Table 1).

Conclusions: MetS and its components were highly prevalent in patients with CKD receiving care in a Texas safety-net system, particularly among Hispanics and non-Hispanic Whites. Differences in the prevalences of MetS-defining components between AAs and Hispanics suggest that interventions targeting MetS might need to be tailored based on race.

Funding: NIDDK Support

TH-PO735
Altered Functional Characteristics of Adipose-Derived Mesenchymal Stem/Stromal Cells (MSC) in Diabetic Kidney Disease (DKD)

Background: Novel interventions such as MSC to delay the progression of DKD are needed. However, the origin of MSC may affect the regenerative capacity of autologous MSC. Nevertheless, the origin of MSC may affect the regenerative capacity of autologous MSC. Nevertheless, the origin of MSC may affect the regenerative capacity of autologous MSC.

Methods: We investigated the functional capacity and senescent cell burden of MSC from DKD patients would be impaired compared to healthy volunteers (HV). Functional capacity and senescent cell burden of MSC from DKD patients would be impaired compared to healthy volunteers (HV).

Results: DKK subjects were older (65 ± 8 vs 63 ± 6 years; p<0.001), with higher body mass index (37 ± 5 vs 31 ± 4 kg/m²; p=0.03) and lower eGFR (median IQR 40 [35, 54] vs 50 [45, 55] ml/min/1.73 m²; p<0.001) compared to HV. DKK showed trends for higher age, male sex, and male sex (43% vs 60% female) were not different. MSC migration and proliferation were decreased in DKK-MSC compared to HV-MSC. Senescence was increased in DKK-MSC, but

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
apotheosis was similar between groups. Similarly, markers of senescence (Activin A) measured in the MSC-cultured media were higher in DKD. (Figure)

**Conclusions:** DKD-MSC exhibit altered functional characteristics and increased senescence, possibly due to aging and diabetic microenvironments. Diabetes and uremia may alter the function of MSC, potentially limiting the effectiveness of autologous-based therapy.

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

**TH-PO736**

**Ectopic Lipid Accumulation and Its Clinic Relevance in Type 2 Diabetic Kidney Disease Patients**  
Li Xiao,1 Ying Luo,1 Wenxia Yang,1 Hang Liang,1 Fan Zhang,1 Yiming Zhou,2 Mengru Zeng,1 Lin Sun,1 Fuyou Liu.1  
1Department of Nephrology, The Second Xiangya Hospital, Central South University, Changsha, China; 2Renal Division, Department of Medicine and Glom-NExT Center for Glomerular Kidney Disease and Novel Experimental Therapeutics, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA.

**Background:** Growing evidence suggests that ectopic lipid accumulation may contribute to organ injury in the context of metabolic diseases, including diabetes. However, the ectopic lipid accumulation in the kidney and its clinic relevance in the patients with Diabetic kidney disease (DKD) remains unknown.

**Methods:** Twelve patients of type 2 DKD (stage II-III) were enrolled and kidney tissue biopsy were stained with Oil red and immunohistochemistry assay for key lipid droplets in the kidney, especially in proximal tubule of DKD patients, as compared to controls. We observed heavy lipid deposition and increased intracellular lipid droplets in the kidney, which may need to be adapted to avoid hypoglycaemia, especially in later stages of DKD.

**Conclusions:** Aberrant lipid regulation and ectopic kidney lipid accumulation were observed in the DKD patients, which correlated to the inflammation and disease progression. Suggesting that amelioration of ectopic lipid deposit may provide a new approach for prevention of DKD.

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

**TH-PO737**

**Proteinuria and Cholesterol Reduction Are Independently Associated with Less Renal Function Decline in Statin Treated Patients: A Post-Hoc Analysis of the PLANET Trials**  
Nienke Idzereka,1 Michelle Pena,2 Hans-Henrik Parving,1 Dick de Zeeuw,2 Hildo J. Lambers Heerspink.3 1Rigshospitalet, Copenhagen, Denmark; 2University Medical Center Groningen, Groningen, Netherlands.

**Background:** Statins have shown multiple effects on different renal risk factors such as lowering of cholesterol (TC) and lowering of proteinuria (U\textsubscript{PCR}). These effects seem to vary between individuals. We questioned whether the changes in U\textsubscript{PCR} and TC run in parallel within one individual, and secondly, how this contributes to renal outcome (eGFR decline).

**Methods:** The PLANET studies studied the effects of a 52-week treatment with atorvastatin and rosuvastatin on U\textsubscript{PCR} and renal function (eGFR) in proteinuric patients. In this post-hoc analysis, we first assessed the individual variability in U\textsubscript{PCR} and TC response (0-14 weeks). U\textsubscript{PCR} response was defined as a decrease in U\textsubscript{PCR} of >0% and TC response as a decrease in TC of >100 mg/dl (2.59 mmol/l) from baseline. Second, we determined whether these responses were predictive of eGFR decline during subsequent 9 months follow-up.

**Results:** U\textsubscript{PCR} and TC response varied between patients: mean U\textsubscript{PCR} response was -1.3% (95%CI -9.9, 14.8), mean TC response was -93.9 mg/dl (-169.1, -26.9). Out of 471 patients, 123 (26.1%) showed a response in U\textsubscript{PCR} but not in TC, and 96 (20.4%) showed a response in TC but not in U\textsubscript{PCR}. eGFR (ml/min/l.73m\textsuperscript{2}) decreased non-significantly from baseline in both U\textsubscript{PCR} responders (0.4; 95%CI [-1.6, 0.8]; p=0.54) and TC responders (0.4; [-1.8, 1.1]; p=0.62), whereas U\textsubscript{PCR} and TC non-responders showed a significant decline in eGFR (1.8; [0.6, 3.0]; p=0.004 and 1.7; [0.5, 2.9]; p=0.006, respectively). A lack of response in both parameters resulted in the fastest rate of eGFR decline (2.1; [0.5, 3.7]; p=0.01). These findings were not different for rosuvastatin or atorvastatin.

**Conclusions:** TC and U\textsubscript{PCR} response to statins vary between individuals and do not run in parallel within an individual. The initial fall in cholesterol and proteinuria are independently associated with a reduction in the long term eGFR decline. This highlights the importance of both monitoring TC and U\textsubscript{PCR} after initiating statin therapy.

**Funding:** Commercial Support - AstraZeneca

**TH-PO738**

**Impact of Gender on the Pattern of Glucose-Lowering Treatment and Hypoglycaemia in Patients with Type 2 Diabetes and Advanced CKD:**  
The French CKD-REIN Study Marie Metzger, Beverly Balkau, Luc Frimat,1 Christian Combe,1 Maurice Laville,2 Christian Jacquetelin,4,5 Ziad Massy,1,7 Benedicte Stengel,1 Denis Fouque.6,4 (CESP U1018, INSERM, UPS-UPSY, Villejuif, France; 1Nancy University Hospital, Vandoeuvre les Nancy, France; 2CHU de Bordeaux, Bordeaux, France; 3Claude Bernard University Lyon 1, Lyon, France; 4Hospices Civils de Lyon - Centre Hospitalier Lyon-Sud, Pierre Bénite, France; 5Agence de la biomédecine, Saint-Denis La Plaine, France; 6Ambroise P Par University Hospital, Boulogne Billancourt/ Paris cedex, France. Group/Team: On behalf of CKD Rein and CKDopp investigators.

**Background:** Recommendations for glucose lowering treatments differ according to CKD stage, but not by gender, despite possible differences in efficacy; in consequence, glucose control and hypoglycaemia may differ.

**Methods:** Of the 3033 patients recruited with CKD stages 3 to 5, 645 men and 288 women were treated by glucose lowering drugs. Uncontrolled glucose was defined by HbA1c >7%, hypoglycaemia by self-report.

**Results:** Treatment with insulin (55% men, 65% women) was more frequent in the later stages of CKD (see Figure) with fewer women than men treated with insulin at lower KD stages, more at higher stages (P<0.008); overall, 31% were treated only with insulin, 28% with combinations: insulin and another drug, 42% by non-insulin glucose lowering drugs. The prevalence of uncontrolled glucose was 57%; in a multivariable model, only insulin treatment, longer diabetes duration and higher BMI were associated with uncontrolled glucose, not gender, age, nor eGFR. Hypoglycaemia were reported by 40% of men and 59% of women; they were not related with eGFR, nor to HbA1c, but were more frequent in people treated with insulin, after adjustment for age, sex, BMI, diabetes duration.

**Conclusions:** In people with diabetes and CKD, HbA1c, CKD stage and reported hypoglycaemia were not associated. However, glucose-lowering treatment, hypoglycaemia but not glucose control were gender dependent; this seems to be related to insulin treatment which may need to be adapted to avoid hypoglycaemia, especially in women.

**Funding:** Commercial Support - Agena, Baxter, Fresenius Medical Care, MSD, Lilly, Otsuka, GSK
Glucose lowering medications by CKD stage and gender

TH-PO739
AdiponRon Ameliorates Diabetic Nephropathy through Activation of Intracellular Ca++-AMPK-PPARα in Type 2 Diabetes Yaemi Kim, Ji Hee Lim, Min Young Kim, Eun Nim Kim, Hye Eun Yoon, Seok Joon Shin, Bumsoon Choi, Yong-Soo Kim, Cheol Whee Park. The Catholic University of Korea College of Medicine, Seoul, Republic of Korea.

Background: In diabetic nephropathy (DN), adiponectin's renoprotective effects are related to the activation of AMP protein kinase (AMPK)-peroxisome proliferative-activated receptor (PPARα) pathway by binding to adiponectin receptors, AdipoR1/R2, respectively.

Methods: We investigated the expression of AdipoRs and their relevant intracellular pathway in twenty-seven type 2 diabetic patients and found the role of AdipoRon on DN in male C57BL/KsJ-db/db mice and glomerular endothelial cell (GEC) and podocyte.

Results: While the degree and extent of glomerulosclerosis and tubulointerstitial fibrosis correlated with renal functional deterioration, the expression of AdipoR1/R2 and Ca++/calmodulin-dependent protein kinase (CaMKkb) and number of phosphorylated liver-kinase B (LKB)-1 and AMPK-positive cells in the glomerulus was significantly decreased at earlier stages of human DN. Diabetes-induced alterations shown in human DN were relieved by AdipoRon in db/db mice. The protective role of AdipoRon occurred through a direct activation of intrarenal AdipoR1/R2, which in turn increased expression of CaMKkb-phospho-Ser483/LKB1-phospho-Thr218/AMPK-PPARα pathway independent of systemic effects of adiponectin. Subsequent their relevant intracellular pathways related to lipid accumulation and endothelial dysfunction were reduced by improving diabetes-induced oxidative stress and apoptosis in the kidney. In human GECs and murine podocytes exposed to high glucose, AdipoRon increased the expression of intracellular Ca++; which subsequently activated CaMKkb-phospho-Ser483/LKB1-phospho-Thr218/AMPK-PPARα and their downstream signals and resulted in decreased high glucose-induced oxidative stress, apoptosis, and endothelial dysfunction.

Conclusions: Our study suggests AdipoRon may be an effective therapeutic strategy for type 2 DN via ameliorating GEC and podocyte injury by the activation of intracellular Ca++-AMPK-PPARα pathway.

Funding: Private Foundation Support

TH-PO741
Impact of Type 2 Diabetes Mellitus (T2DM) with or without Diabetic Nephropathy (DN) on Long-Term Outcomes in ESKD Patients Initiated on Dialysis Wai H. Lim, David W. Johnson, Carmel M. Hawley, Charmaine E. Lok, Germaine Wong. 1Monash Medical Centre and Monash University, Melbourne, VIC, Australia; 2None, Anawmie, NSW, Australia; 3Princess Alexandra Hospital, Brisbane, QLD, Australia; 4Prince Charles Gairdner Hospital, Perth, NSW, Australia; 5Toronto General Hospital, Toronto, ON, Canada.

Background: DN is the most common cause of ESKD among patients with T2DM, however there is growing evidence that T2DM patients with non-DN as a cause of ESKD form a distinct clinical entity with differential prognostic significance.

Methods: All incident ESKD patients initiated on hemodialysis/peritoneal dialysis in Australia and New Zealand between 1980-2014 were included, using data from the ANZDATA Registry. The association between diabetes status at dialysis initiation (i.e. no diabetes, T2DM+DN or T2DM+non-DN) and mortality were examined using Cox regression and competing risk analyses, with transplantation censored or considered as competing risk, respectively.

Results: Of 56,552 incident dialysis patients followed for a median of 2.5 years, 15,829 (28%) and 4993 (9%) had T2DM+DN and T2DM+non-DN, respectively. Patients with T2DM were significantly older and a greater proportion had vascular comorbidities. Compared to patients with no diabetes, the adjusted HR (95%CI) for mortality in those with T2DM+DN and T2DM+non-DN were 1.39 (1.35-1.43) and 1.24 (1.29-1.29) in the Cox regression model, and the adjusted subdistribution HR were 1.52 (1.47-1.56) and 1.32 (1.27-1.38), respectively in the competing risk model. There was a significant interaction (p<0.001) between age and diabetes status, with the hazard for mortality greater in younger compared to older patients. Cardiovascular disease as a cause of mortality was more common in those patients with T2DM compared to non-DN, respectively.

Conclusions: Younger ESKD diabetic patients with or without DN experienced substantially poorer survival compared to non-diabetic patients. A vigilant approach to CVD prevention and monitoring is critical to improve clinical outcomes in diabetic patients with ESKD.
and phosphatemia (R=0.307, p<0.02). Time from CKD diagnosis (5.7±2.6 vs 3.5±1.5 years, p<0.003) and time from DM diagnosis (15.8±3.5 vs 13.1±6.3 years, p<0.04) were significantly longer in study group. Prevalence of anemia was higher with advancing CKD stage (p<0.001). Anemia was diagnosed even in patients with stage 2 CKD. Abnormal proteinuria was risk factor for anemia (OR 3.13, 95%CI 1.5-7.6, p<0.01). Calcinosis was significantly lower (32.0±6.9 mg/dl vs 9.5±0.5 mg/dl, p<0.006) and significantly higher (4.7±0.9 mg/dl vs 3.8±0.7 mg/dl, p<0.001) in the study group. After adjustment for confounders, independent risk factors for anemia were abnormal proteinuria (adjusted OR 5.9, 95%CI 1.3-22.9) and treatment with renin-angiotensin-aldosterone system (RAAS) blockers (adjusted OR 13.0, 95%CI 1.5-110.1).

**Conclusions:** We found an increased prevalence of anemia in CKD due to DKD, even in patients with mild CKD. Anemia was associated with malnutrition (low BMI and albuminemia) and abnormal calcium-phospat metabolism (low calcemia and high phosphatemia), mechanisms involved in the pathogenesis of anemia in these patients. Independent risk factors for anemia were proteinuria and RAAS blockers.

**TH-PO743**

Burtn-Out Diabetes Phenomenon and Association between Glycemic Control and Cardiovascular Comorbidity Rate in Hemodialysis Patients Masanori Abe,1 Takayuki Hamano,1 Junichi Hoshiba,2 Shigeru Nakai,1 Ikuko Masakane,2 Fujita Health University School of Health Sciences, Toyoa, Aichi, Japan; 1Honcho-Yabuki Clinic, Yamagata, Japan; 2Nihon University School of Medicine, Tokyo, Japan; 3Osaka University Graduate School of Medicine, Suita, Japan; 4Toranomon Hospital, Tokyo, Japan. Group/Team: Committee of Japanese Renal Data Registry, Japanese Society for Dialysis Therapy.

**Background:** In patients with diabetes on hemodialysis (HD), glycemic control improvement brought about return to normal glycated hemoglobin (HbA1c) values. This phenomenon is known as “burnt-out diabetes.” However, glycated albumin (GA) might be a better indicator of glycemic control than HbA1c in HD patients. Therefore, the aim of this study was to identify how many patients experience “burnt-out diabetes” using HbA1c and GA levels, and to examine the association between glycemic control and cardiovascular comorbidity risk in patients on HD.

**Methods:** The data were obtained from the annual nationwide surveys of dialysis patients conducted by the Japanese Society for Dialysis Therapy (JSDT) in 2013. Patients with diabetes on HD whose HbA1c and GA levels were measured and those who met the criteria for HD patients on HD undergoing hemodialysis were included in the analysis. The “burnt-out diabetes” phenomenon was based on GA and HbA1c levels being lower than 11%. HbA1c<6.0% and GA<16.0% without treatment with antidiabetic medication was defined as “burnt-out diabetes.” However, higher HbA1c levels and GA levels were associated with comorbidities of all cardiovascular diseases except cerebral hemorrhage. The odds ratio (OR) of the cardiovascular morbidity rate based on the GA category, with GA 16.0 to <18.0% treated as the reference group. The OR of cardiovascular morbidity risk was significantly associated with GA >18%. After adjustment for confounders, the OR of the GA >16.0% group was significantly decreased as compared to the reference group.

**Results:** Among all cases, 23,668 patients were included. When “burnt-out diabetes” was defined as HbA1c<6.0% without treatment with antidiabetic medication, it was noted in 4,899 patients (20.7%). However, “burnt-out diabetes” was defined as HbA1c<6.0% and GA<16.0% without treatment with antidiabetic medication, it was found in 1,286 patients (5.4%). Higher HbA1c levels were associated with the comorbidity rate of all cardiovascular diseases. However, GA levels were assessed using multivariable logistic regression models.

**Conclusions:** Although the “burnt-out diabetes” phenomenon might be present in 20% of hemodialysis patients with diabetes, HbA1c<6.0% and GA<16.0% without treatment with antidiabetic medication was defined as “burnt-out diabetes,” the rate was significantly decreased to 5.4% in terms of GA. The risk of cardiovascular morbidity was higher in patients with GA > 18%.

**TH-PO744**

Absolute versus Percentage Renal Functional Losses in Patients with Diabetes and CKD William P. Martin,1 Tomas P. Griffin,2 David W. Lappin,3 Damian G. Griffin,4 John P. Ferguson,5 Timothy O’Brien,6 Matthew D. Griffin,7 Regenerative Medicine Institute, National University of Ireland, Galway, Ireland; 8Endocrinology and Nephrology Services, Saolta University Health Care Group, Galway; 9CRB Facility, Galway, Ireland.

**Background:** Chronic kidney disease (CKD) management focuses on minimizing the rate of renal functional loss, usually expressed in absolute terms of mL/min/BSA lost per annum. We evaluated the impact of expressing renal functional loss as a percentage of existing renal function on the interpretation of renal functional trends of patients with diabetes before and after attending a Diabetes Renal Clinic (DRC).

**Methods:** All patients attending a DRC at a tertiary referral center from 2008 to 2012 were reviewed. Serial laboratory indices were recorded from 2004 to 2014. Linear mixed effects models fitted using the R-package lme4 were used to calculate absolute eGFR decline. In second analysis, similar mixed effects models were fitted with log-transformed eGFR as the response, to estimate annual percentage decline in eGFR. Renal function was estimated using both MDRD and CKD-EPI equations.

**Results:** 147 subjects with ≥3 available eGFR values for ≥1 year before and after first DRC attendance were analyzed based on prespecified CKD etiology. Rates of renal functional loss were calculated with similar results being obtained using both MDRD and CKD-EPI estimating equations (Table). For DRC consultation, absolute rate of eGFR decline was similar for T1D but slower for T2D and additional CKD etiologies grouped. A percentage of prior eGFR, renal function declined more rapidly in T1D, similarly in T2D, and more slowly in patients with additional CKD etiologies. Thus, interpretation of the impact of a CKD intervention is influenced by the initial eGFR and by the approach used to calculate renal functional decline.

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

Baseline characteristics at first DRC attendance and renal functional losses before and after first DRC attendance stratified by CKD etiology (n = 147).

**TH-PO745**

Comparison of Clinicoepidemiological Features of Biopsy-Proven Diabetic Nephropathy Compared to CKD Heat Map Classification and the Japanese Classification of Diabetic Nephropathy Kengo Fuchiguchi,2 Mio Shimizu,3 Tadashi Toyama,1 Yasunori Iwata,2 Norihiko Sakai,2 Takashi Wada,1 1Dept of Nephrology and Lab Med, Kanazawa University, Kanazawa, Japan; 2Division of Nephrology, Kanazawa University Hospital, Kanazawa, Japan.

**Background:** CKD heat map classification and the Japanese classification of diabetic nephropathy reflects the risks of mortality, cardiovascular events and kidney prognosis and is clinically useful. Furthermore, pathological findings of diabetic nephropathy are also known to be useful for predicting prognoses. In this study, we evaluated the characteristics of clinicoepidemiological features between the two clinical classification of diabetic nephropathy.

**Methods:** The clinical data of 600 biopsy-confirmed diabetic nephropathy patients were collected retrospectively from 13 centres across Japan. Phtlogica features and decreasing rate of estimated GFR (eGFR) were evaluated, and compared between CKD heat map classification and the Japanese classification of diabetic nephropathy.

**Results:** The median observation period was 70.4 (IQR: 20.9-101.0) months. Each stage had specific characteristic pathological features. Diffuse lesions, interstitial fibrosis and/or tubular atrophy (IFT), interstitial cell infiltration, arteriolar hyalinization and arterosclerosis were detected in more than half the cases, even in Green and Yellow in CKD heat map and Stage 1 in the Japanese classification of diabetic nephropathy. Median declining speed of eGFR in all cases was 5.61 mL/min/1.73m²/year, and the median rate of declining kidney function within 2 years after kidney biopsy was 24.0%. Declining rate of eGFR within 2 years after kidney biopsy increased as CKD heat map classification and the stage of Japanese classification of diabetic nephropathy increased; and Green and Yellow, Orange, Red, 3.7, 17.9, 34.3 %, respectively, Stage 1, 2, 3, 4, -0.9, 10.7, 26.5, 38.8 %, respectively. Sensitivity of 30% reduction of the eGFR in two years as a surrogate end point of kidney death was 56.7% (Green and Yellow, Orange, Red; 0, 88.0, 56.5%, and Stages 4, 3, 2, 1, 0, 0, 0, 84.2, 1, 0, 1, 0, 1, 0, 1, respectively).

**Conclusions:** This study indicated that there were characteristic pathological features in each clinical classification. Moreover, decreasing rate of eGFR increased in advanced stages of diabetic nephropathy, and sensitivity of surrogate end point (30% reduction of the eGFR in two years) was relatively high in Stage 3 Japanese classification of diabetic nephropathy, and Orange in CKD heat map.

**TH-PO746**

Endothelial Cell Transfusion Inhibits Venous Neointima Formation in Arteriovenous Fistulae of Rats with CKD Dongqi Li, Li Li, Yuanuyuan Guo, Yiu-Fai Chen, Yasin Oduk, Suzanne Oparil, Fadi G. Hage. University of Alabama at Birmingham, Birmingham, AL.

**Background:** The arteriovenous fistula (AVF) is the preferred choice of vascular access for hemodialysis patients with chronic kidney disease (CKD). However, AVF fail in more than 40% of cases due to early neointimal hyperplasia (neointimal formation) in AVF vein and persistent inadequate outward remodeling (expansion) of (the AVF vein. We have shown that intravenous (i.v.) transfusion of rat aortic endothelial cells (RAECs) ameliorates endothelial dysfunction in a rat model of CKD. In this study, we tested the hypothesis that i.v. transfusion of RAECs inhibits venous neointima formation in AVF of CKD rats.

**Methods:** Female ovariectomized Sprague-Dawley rats underwent 5/6 nephrectomy (Nx). After 4 wks, an AVF was created by anastomosing the right femoral vein to the right femoral artery in an end-to-side manner, and rats received i.v. transfusion of 3.0×10⁵ RAECs in 2 ml saline or saline vehicle control. Rats were sacrificed and perfused with...
formalin 4 wks later. Fistulae were fixed, sectioned and stained with hematoxylin and eosin (H&E). The ligation site was identified and the vein was sectioned 400, 600, 800, 1000 and 1200 μm proximal to the ligation site. To calculate the neointima area to vessel size (cross-sectional area) ratio, the circumferential profiles of the lumen and the external lamina of the vein were delineated, and the areas encompassed by these boundaries were determined by ImageJ software.

**Results:** Serum creatinine level increased from 4.6±0.5 μg/ml to 8.5±1.1 μg/ml after 5/6 Nx (n=11). EC transfection significantly inhibited neointima formation in femoral vein at 4 wks after AVF (Figure).

**Conclusions:** EC transfection inhibited venous neointima formation in AVF, suggesting that EC therapy after AVF may provide a novel strategy for the maintenance of vascular access in hemodialysis patients.

*Funding:* Other NIH Support - R56 HL128285-01A1, RO1HL116727, Veterans Affairs Support

**TH-PO747**

**Reduced Endothelium-Dependent Vasodilation and Impaired Arteriovenous Fistula (AVF) Development in a Rat Model with CKD**

*Yan-Ting Shiu,*1 Yuxia He,*1 Daniel R. Machin,*1 CS Jason Tej,*1 Jack Z. Fan,*1 Zhen Chen,*1 Miriam E. Leary,*2 Hirofumi Tanaka,*1 Tony J. Donato,*1 Alfred K. Cheung,*1 *Beckman Research Institute, City of Hope, Duarte, CA,*2 University of Texas at Austin, TX,*3 University of Utah, SALT LAKE CITY, UT,*4 University of Texas at Austin, Austin, TX,*5 University of Utah, SALT LAKE CITY, UT.

**Background:** AVF maturation failure results from neointimal hyperplasia (NiH) and insufficient dilation of lumen, but the latter remains largely unexplored. We investigated endothelium-dependent vasodilation (EDV) and AVF development in a clinically relevant CKD-AVF model.

**Methods:** CKD was induced in 10-week-old Wistar male rats fed a 0.25% adenosine-containing diet (AD) for 10 wk. EDV of femoral arteries was non-invasively assessed at baseline, 10 wk on AD, and 4 wk after returning to normal diet (ND). Gene expression of key endothelial regulators, including transcription factors Krüppel-like factor 2 (KLF2) and KLF4 and their target endothelial nitric oxide synthase (eNOS), was assessed in the aorta of CKD and normal rats. Femoral AVFs were created in CKD and normal rats. AVF lumen diameter was measured by ultrasound, and animals were euthanized for histology.

**Results:** In CKD rats, plasma creatinine and BUN increased 3-fold after 10 wk on AD (p=0.013). In addition, BAPN treatment upregulated the elastin and fibronectin genes in the fistula wall. Next, we electro-spin a PLGA/BAPN (15:1.5) scaffold to locally deliver the drug around the juxta-anastomotic area of experimental AVFs for 21 days post-op. In vitro, BAPN release from the scaffold was almost complete within 7 days, while it took 60 days at 37°C for the scaffold to be fully degraded. Local delivery of BAPN to experimental AVFs improved vascular remodeling by decreasing fibrosis, compared to AVFs wrapped with scaffold alone (n=6 per group, p=0.043). Furthermore, local delivery of BAPN increased distensibility and decreased the incremental elastic modulus (E<sub>50</sub>) (4.93 ± 0.85 vs. 2.22 ± 0.39 x 10<sup>6</sup> dynes cm<sup>-2</sup>, p=0.019) as determined by pressure myography.

**Conclusions:** In conclusion, we have demonstrated that inhibition of LOX mediated cross-linking with BAPN significantly improved vascular compliance and the biomechanical properties of experimental AVFs.

*Funding:* NIDDK Support

**TH-PO748**

**Decreased Collagen Cross-Linking Improves the Biomechanical Performance of Experimental Arteriovenous Fistulas**

*Diana R. Hernandez,*2 Yuntai Wei,*2 Fotios M. Andreopoulos,*2 Laisel Martinez,*2 Loay H. Salman,*2 Roberto I. Vazquez-Padron,*2 *Albany Medical College, Albany, NY,*3 *University of Miami Miller School of Medicine, Miami, FL,*4 University of Miami, Miami, FL.

**Background:** The role of lysyl oxidase (LOX) in arteriovenous fistula (AVF) remodeling has never been studied. As the enzyme that catalyzes the cross-linking of collagen and elastin precursors in the vascular wall, a deficiency in LOX activity may impair wall integrity while excessive activity may lead to stiffness and favor occlusive stenosis. This study hypothesizes that local or systemic inhibition of β-aminopropionitrile (BAPN) prevents excessive cross-linking of collagen and other extracellular matrix (ECM) proteins and improves the biomechanical performance of experimental AVFs.

**Methods:** Surrogate indicators of vascular remodeling included fibrosis (% area of collagen) by Masson’s trichrome staining, and gene expression of ECM proteins by RT-PCR. Biomechanical properties were evaluated by pressure myography.

**Results:** We first demonstrated that gene expression of LOX, but not of LOX-like enzymes (LOXL1-4), was significantly upregulated in a rat AVF model created by anastomosing the left epigastric vein to the nearby femoral artery. Systemic administration of BAPN (100 mg/kg, ip) decreased collagen deposition in treated versus control AVFs (p=0.013). In addition, BAPN treatment upregulated the elastin and fibronectin genes in the fistula wall. Next, we electro-spin a PLGA/BAPN (15.1:5.1) scaffold to locally deliver the drug around the juxta-anastomotic area of experimental AVFs for 21 days post-op. In vitro, BAPN release from the scaffold was almost complete within 7 days, while it took 60 days at 37°C for the scaffold to be fully degraded. Local delivery of BAPN to experimental AVFs improved vascular remodeling by decreasing fibrosis, compared to AVFs wrapped with scaffold alone (n=6 per group, p=0.043). Furthermore, local delivery of BAPN increased distensibility and decreased the incremental elastic modulus (E<sub>50</sub>) (4.93 ± 0.85 vs. 2.22 ± 0.39 x 10<sup>6</sup> dynes cm<sup>-2</sup>, p=0.019) as determined by pressure myography.

**Conclusions:** In conclusion, we have demonstrated that inhibition of LOX mediated cross-linking with BAPN significantly improved vascular compliance and the biomechanical properties of experimental AVFs.

*Funding:* NIDDK Support

**TH-PO749**

**Altered Molecular Profiles in Hemodynamically Vulnerable Segments of Arteriovenous Fistulae (AVF) in a Uremic Pig Model**

*Jaroslav Janda,*2 Begoña Campos,*2 Aous Jarrouj,*1 Frank C. Brosius,*1 Lindsay N. Kohler,*1 Prabir Roy-Chaudhury,*1 Diego Celdran-Bonafonte,*1 *Baylor University of Arizona, Tucson, AZ,*2 University of Arizona, Tucson, AZ,*3 University of Arizona / BIO 5 Institute, Tucson, AZ,*4 University of Cincinnati, Cincinnati, OH,*5 Southern Arizona VA Healthcare System, Tucson, AZ.

**Background:** Arteriovenous fistulae (AVF) are the preferred vascular access for hemodialysis patients but are subject to stenosis, disrupted flow and failure. The uremic pig serves as a useful model for studying the pathogenesis of AVF dysfunction in humans. Previously, we reported properties of vascular structure and flow in pig AVF that mimicked changes in human AVF. In the current project, we determine whether hemodynamics in AVF hemodynamics between the inner and outer curves of the venous segment of an AVF and between the anastomotic and more proximal segments, were associated with altered gene expression for 8 candidate genes in adjacent AVF segments.

**Methods:** Renal insufficiency in 4 Yorkshire pigs was surgically induced by 5/6 nephrectomy, and 2 weeks later bilateral AVFs were created between femoral arteries and veins. The inner and outer curves of each AVF were harvested 6 wk later. Four sequential hemodynamic profile segments (4-5 cm) were identified, and between the anastomotic and more proximal segments, were associated with altered gene expression for 8 candidate genes in adjacent AVF segments.
for each AVF. cDNA was generated from total RNA from these individual segments. Quantitative real-time PCR reactions were performed for ICAM, VCAM, NOS3, NOX4, KLF2, CCL2, MMP2, and MMP9.

Results: MMP9 levels (average of all four venous segments) were consistently and significantly higher in the outer curve of the AVF than the inner curve (p < 0.05). ICAM and VCAM mRNA levels also showed similar trends. cNOS levels trended towards being lower at the anastomosis (both inner and outer curves) as compared to the most proximal venous segment.

Conclusions: Our findings suggest that differences in fluid hemodynamics especially wall shear stress (we have previously demonstrated differences in wall shear stress [WSS] between the inner and outer curves of an AVF, and also between the anastomosis and more proximal segment), could be important determinants of the molecular profile (and subsequent stenosis or lack thereof) in AVFs. Future studies will aim to assess whether manipulation of both upstream WSS and downstream molecular biology (as identified in subsequent stenosis or lack thereof) in AVFs. Future studies will aim to assess whether manipulation of both upstream WSS and downstream molecular biology (as identified in this work) could reduce AVF stenosis in our uremic pig model.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO750
MRM Modeling of Arteriovenous Fistula (AVF) Stenosis in a Pig Model: Creating a Test Bed for Mechanistic and Therapeutic Innovation

Diego Celdran-Bonafonte,1 Begoña Campos,2 Aous Jarrouj,1 Keith L. Saum,2 Jaroslav Janda,1 Lindsay N. Kohler,1 Frank C. Brosius,1 Prabir Roy-Chaudhury,1,3 1University of Arizona, Tucson, AZ; 2University of Cincinnati, Cincinnati, OH; 3SAVAHCS, Tucson, AZ.

Background: Arteriovenous fistula (AVF) stenosis (resulting in the use dialysis catheters) is an important cause of morbidity and mortality in hemodialysis patients. We have previously described a pig model of AVF stenosis. We now describe the use of MRI imaging in this model to enhance its capabilities for mechanistic and therapeutic innovation.

Methods: AVFs were created in the groin in 6 male Yorkshire Cross pigs. Black blood contrast-free MRIs were performed at days 28 and 56 (Figure A). MIMICS software was used to quantify vein cross-sectional area and to create a model for average stenosis, using cross-sectional images at 5mm intervals (Figure B). Flow data was collected and is currently being analyzed.

Results: MRI imaging described a peri-anastomotic stenosis very similar to the human lesion (Figure B). The mean maximal stenosis area was 10.042 and 13.037mm² at 28 days to 32.626 mm² at 56 days respectively. Mean minimal stenosis (maximal dilation) was 34.175 and 28.863 mm² at 28 days to 32.626 mm² at 56 days respectively. The average sectional area of the entire venous segment increased from 28.863 mm² at 28 days to 32.626 mm² at 56 days.

Conclusions: The use of sophisticated 3D MRI technology to obtain standardized MR images of standard arterial and venous segments could be important determinants of the molecular profile (and subsequent stenosis or lack thereof) in AVFs. Future studies will aim to assess whether manipulation of both upstream WSS and downstream molecular biology (as identified in this work) could reduce AVF stenosis in our uremic pig model.

Funding: NIDDK Support

TH-PO751
Study of Vascular Intimal Thickness around Different Locations of Catheter Tips in Dog Model

Li H. Wang,1 Lan Jia,2 Hui B. Yu,4 Fang Wei,4 Ai L. Jiang,1 1Department of Kidney Disease and Blood Purification Centre, institute of Urology & Key Laboratory of Tianjin, Tianjin, China; 2Department of Kidney Disease and Blood Purification Centre, 2nd Hospital of Tianjin Medical University, Tianjin, China; 3Department of Kidney Disease and Blood Purification Centre, 2nd Hospital of Tianjin Medical University, Tianjin, China; 4Department of Kidney Disease and Blood Purification Centre, 2nd Hospital of Tianjin Medical University, Tianjin, China.

Background: Many studies have found intimal thickness around catheter tip after catheterization. Meanwhile Caveolin-1 is a shear sensor that may transmit mechanical change into biochemical signals resulting in vascular remodeling.

Methods: TDCs were inserted into the left jugular vein and right femoral vein in eight dogs for 28 days. Histological and immunohistochemistry were performed to confirm specific cell populations after extracorporeal circulation.

Results: The use of catheter dysfunction rates and low blood flow rates in the femoral vein group compared to left jugular vein group. There was intimal hyperplasia around the catheter tip in both group with no significant difference. There were also caveolin-1 expression between the different groups.

Conclusions: After catheter placement, focal areas of intimal thickening were seen in the venous wall adjacent to the catheter tip with a high expression of caveolin-1. These findings indicate that different catheter tip locations may influence catheter function and targeting of specific caveolin-1 could be possible future novel therapies for haemodialysis vascular access stenosis.

Comparison of catheter function of study groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Right Femoral vein catheter group</th>
<th>Right jugular vein catheter group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelium thickness (mm)</td>
<td>0.2 (1.15)</td>
<td>0.3 (0.15)</td>
<td>0.05</td>
</tr>
<tr>
<td>Epithelium surface area (mm²)</td>
<td>0.2 (1.15)</td>
<td>0.3 (0.15)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Funding: NIDDK Support

TH-PO752
AFE System Treatment Rapidly Dilates Ovine Cephalic Veins before AVF Surgery

F. Nicholas Franoa,1 Howard M. Lorcé,1 J. S. Richardson,1 Dale M. Groth,2 Manesh Taneja,3 Lesley A. Szenay,1 Barrett S. Hutto,4 Bradley S. Dixon,3 1Flow Forward Medical, Inc., Olathe, KS; 2Dale Groth Preclinical Consulting, LLC, Forest Lake, MN; 3Surpass, Inc., Osceola, WI; 4CIRTEC Medical Systems LLC, Las Gatos, CA, 1University of Iowa Hospital and Clinics, Iowa City, IA.

Background: Suboptimal wall shear stress (WSS) and cyclic stretching may slow AVF outflow vein dilation and lead to maturation failure. The AFE System® is a medical device that delivers non-pulsatile blood flow to a peripheral vein, stimulating vein dilation prior to AVF surgery. During treatment, blood flow can be adjusted to maintain a mean WSS dose of 4 Pa in the vein. Use of larger veins to make AVFs may result in greater eligibility for AVF surgery, faster maturation, reduced maturation failure, and better primary and secondary patency rates.

Methods: AFE System prototypes were used to treat five sheep (54-68 kg). The devices comprised an extracorporeal centrifugal blood pump, heparin-coated and cuffed inflow and outflow conduits, and a benchtop controller. The inflow conduit was inserted into an external jugular vein and the tip was positioned in the superior vena cava. The outflow conduit was connected to a cephalic vein. Three sheep were treated using a duckbill tip inflow conduit and an outflow conduit with a distal ePTFE segment sutured to the vein. Two sheep were treated using an inflow conduit with a duckbill tip surrounded
by a nitinol cage to prevent vein wall suction and an outflow conduit with an intravascular connector attached to the vein.

**Results:** Mean vein diameter increased significantly from 4.5 to 8.4 mm with 6-11 days of treatment (n=5, p=0.005). Variation in conduit designs had no effect on final vein diameter. The average rate of vein dilation was 0.51 mm/day. The intravascular connector simplified placement of the outflow conduit and the inflow conduit tip-protecting nitinol cage prevented low flow events. AVFs were made with the dilated veins in all animals.

**Conclusions:** This pilot study shows the feasibility of dilating peripheral veins with the AFE System prior to AVF surgery.

**Funding:** NIDDK Support, Commercial Support - Flow Forward Medical, Inc.

---

**TH-PO754**

**Vonapanitase Increases Fistula Use for Hemodialysis Using a Robust and Clinically Relevant Definition**

**Anthony J. Bleyer,**1 Bradley S. Dixon,4 Timmy C. Lee,2 Steven K. Burke,2 Rick E. Mishler,1 Arizona Kidney Disease and Hypertension Center, Ltd., Phoenix, AZ; 2Proteon Therapeutics, Inc., Research Triangle Park, NC; 3Wake Forest University School of Medicine, Winston-Salem, NC; 4University of Alabama at Birmingham, Birmingham, AL

**Background:** Vonapanitase is an investigational recombinant human elastase applied to the external surface of the fistula at the time of surgical creation. A recently reported randomized double-blind trial (NCT02119091) showed vonapanitase increased radiocliphe fistula survival and use for hemodialysis (HD) compared with placebo in 311 pre-HD (56%) and HD (44%) patients over 1 year. In other trials, varying definitions of use have been employed, often requiring shorter durations of use but detailed information of use was limited.

**Methods:** Successful use was defined as (1) a ≥90 days or (2) ≥30 days and in use at ≥90 days. For placebo patients, use was defined as fistula abandonment prior to use or insufficient duration prior to fistula abandonment.

**Results:** More vonapanitase than placebo patients successfully used the fistula for HD (n=230, 64% vs 44%, p<0.006). Use was established by the 90-day use in 92% and the 30-day use in 8%. Only 3 patients abandoned the fistula following successful use (2 placebo, 1 vonapanitase) and the other continued use in a follow-up registry. Non-use was defined as insufficient duration of use or fistula abandonment prior to use. Those not defined as having use or non-use were considered indeterminate (eg, a pre-HD patient who never initiated HD) and excluded from analysis. Of those with use, 82% had at least one Kt/V or URR recorded. Adequate HD was defined as Kt/V ≥1.2 or URR≥0.65.

**Conclusions:** More than 80% of vonapanitase patients successfully used the fistula for HD and >90% of patients reached a Kt/V of >1.2 within 90 days, demonstrating the feasibility and safety of vonapanitase. Further studies are needed to confirm the findings in larger clinical trials.

**Funding:** Commercial Support - Vascular Therapies, Inc.
lumen. The vascular histology in CKD patients may affect the maturation outcomes of arteriovenous fistulas.

**Funding:** NIDDK Support

**TH-PO756**

**Differences in Vascular Fibrosis Explain Sex Disparities in AVF Maturation Outcomes**

Loayy Angela D. Martinez-Garcia,1 Lone M. Christensen,1 Angela Paez,2 Marwan Tabbaraa,3 Diana R. Hernandez,1 Guillermo Selman,1 Loey H. Salaman,1 Omaida C. Velazquez,2 Roberto I. Vazquez-Padron,2 1Albany Medical College, Albany, NY; 2University of Miami, Miller School of Medicine, Miami, FL.

**Background:** Women have a higher risk of arteriovenous fistulas (AVF) maturation failure than men, and the reason for this propensity is still unknown. Several studies have excluded sex-related differences in the diameter of native vessels as the explanation for this disparity, which suggests that the remodeling process in women is inferior. The purpose of this study was to compare two surrogate indicators of venous remodeling in females and males undergoing surgeries for two-stage AVF creation.

**Methods:** We measured intimal hyperplasia (IH) and medial fibrosis in native veins and AVF venous samples obtained during AVF creation (first-stage) and transplantation (second-stage) surgeries, respectively. The analysis of native veins allowed the assessment of pre-existing sex-related differences in IH and medial fibrosis, whereas evaluation of AVFs allowed the comparison of postoperative remodeling between both sexes.

**Results:** Anatomical maturation failure (an AVF that never achieved an internal luminal diameter of 5 mm) occurred in 22/64 (34.4%) females and 18/97 (18.6%) males (p = 0.027). The internal luminal diameter of the native basilic vein was similar between females and males (median 4.0 mm, interquartile range 4.0-4.0 in both, p = 0.7). There were no significant sex-related differences in pre-existing IH and medial fibrosis between AVFs with successful maturation and maturation failure. Postoperative IH was also similar in AVFs with distinct maturation outcomes in both sexes. Interestingly, there was a significant increase in postoperative medial fibrosis in AVFs with maturation failure vs. successful maturation in females (55.0 ± 2.7% vs. 44.0 ± 2.2% [mean ± SEM], p = 0.003), but not in males (51.2 ± 2.9% vs. 48.0 ± 2.6, p = 0.4). Accordingly, logistic regression analyses demonstrated that the degree of medial fibrosis was associated with maturation failure in women (odds ratio [OR] 1.80 per 10% increase in medial fibrosis, p = 0.034) but not in men (OR 1.03, p = 0.4).

**Conclusions:** This study demonstrates for the first time the existence of sex-related differences in vascular remodeling after AVF creation, and that medial fibrosis is a major contributing factor to the increased risk of maturation failure in females.

**Funding:** NIDDK Support

**TH-PO757**

**Extracellular Vesicles as Novel Markers in Hemodialysis Access Complications**

Tushar Chopra,1 Sabrina La salvia,2 Luca Musante,2 Kanbizi Kalantari,3 Nicolaistatalgata,4 Thi H. Le,1 Uta Erbruegger.1 1None, Nashville, TN; 2University of Virginia, Charlottesville, VA; 3University of Virginia Health System, Charlottesville, VA.

**Background:** Failure of hemodialysis vascular access (HVA) is the most common cause of hospitalization and morbidity among end stage renal disease (ESRD) patients. Extracellular vesicles (EVs) are potential candidate biomarkers to identify patients at risk for these HVA complications and failure. We hypothesize that these circulating EVs reflect endothelial damage in patients with vascular access complications, are pro-coagulant and predict VA long-term outcome.

**Methods:** EVs were isolated from platelet free plasma from citrated blood of 19 patients with recurrent HVA complications (mean age 64, HD vintage 2.8 years) and 16 patients without (mean age 61, HD vintage 5.7 years). Enumeration and phenotyping of EVs was performed using imaging flow cytometry. CD42 positive, CD31, S-Endoglin (CD105), E-Selectin (CD62E) and Annexin V (AnV) positive EVs were used as surface markers for circulating EVs. The size and concentration of EVs were measured with tunable laser-based equipment. The EV concentration, EV size profile and endogenous thrombin potential (ETP) were determined by centrifugation (12,000 x g, 5 min, RT), the clear homogenate was extracted with Trizol, transferred to 2-mL RNase-free microcentrifuge tubes, and further homogenized by a nitrogen gun. The homogenate was then disrupted of the tissue by guanidine isothiocyanate-based RNA extraction buffers. The total RNA yield had a median of 44.5 ng/μl (interquartile range [IQR] 32.1 – 68.0) in veins and 124.0 ng/μl (IQR 85.2 – 220.0) in AVFs. High-quality RNA (RNA integrity number [RIN] > 5) was obtained in 79.4% of veins and 86.7% of AVFs as demonstrated using an Agilent 2100 Bioanalyzer.

**Conclusions:** In conclusion, we have developed a new protocol for isolation of high-quality RNA from small vascular biopsies. We have successfully used these RNAs for RT-PCR and highly sensitive techniques for transcriptome analysis (RNA-seq).

**Funding:** NIDDK Support

**TH-PO758**

**Isolation of High-Quality RNA from Human Veins and Arteriovenous Fistulas**

Guillermo Selman,1 Nieves Santos,2 Laisel Martinez,2 Juan C. Duque Ballesteros,2 Marwan Tabbara,3 Loay H. Salaman,1 Roberto I. Vazquez-Padron.2 1Albany Medical College, Albany, NY; 2University of Miami, Miller School of Medicine, Miami, FL.

**Background:** Functional genomics and transcriptome analysis of pre-access veins and arteriovenous fistulas (AVF) require RNA of high quality and integrity. However, the sample size and proportion of intraprocedural vascular biopsies have a small size, are low in cell density, and rich in collagen and other extracellular matrix components that hinder the complete disruption of the tissue by guanidine isothiocyanate-based RNA extraction buffers. The application of current extraction protocols to AVF samples typically results in low RNA yields with poor quality. In this work, we developed a standard operating procedure that combines a pulverizing method that keeps the tissue completely frozen for RNA extraction with commercial reagents for purification.

**Methods:** We optimized this method using RNA-later (Qiagen) preserved veins (n=63) and AVFs (n=30) that were obtained intraoperatively during the creation of two-stage brachiobasilic fistulas in consented patients at the University of Miami. Briefly, 50-60 mg of tissue was cut in small pieces and ground to a fine powder in a Spec/ Mill 6770 (15 min pre-cooling; 30 sec run; 2 min cycle cooling; 15 cycles total, 10 Hz rate) in the presence of 100 μl of Trizol. The homogenate was collected with 700 μl of Trizol, transferred to 2-mL RNAse-free microcentrifuge tubes, and further homogenized using an Ultra-Turrax T8 instrument for 30-45 seconds. After removing cellular debris by centrifugation (12,000 x g, 5 min, RT), the clear homogenate was extracted with Trizol according to the standard Trazol protocol, and 0.55 volumes of ethanol were added prior to loading onto an Omega EZNA column for further purification (Omega Bio-tek). On-column DNAse digestion was applied as desired. Total RNA was eluted with 40 μl of RNAse-free water.

**Results:** The total RNA yield had a median of 44.5 ng/μl (interquartile range [IQR] 32.1 – 68.0) in veins and 124.0 ng/μl (IQR 85.2 – 220.0) in AVFs. High-quality RNA (RIN > 5) was obtained in 79.4% of veins and 86.7% of AVFs as demonstrated using an Agilent 2100 Bioanalyzer.

**Conclusions:** In conclusion, we have developed a new protocol for isolation of high-quality RNA from small vascular biopsies. We have successfully used these RNAs for RT-PCR and highly sensitive techniques for transcriptome analysis (RNA-seq).

**Funding:** NIDDK Support

**TH-PO759**

**Percutaneous AV Fistula Creation for Vascular Access**

Randy I. Cooper,1 Rajeev Narayan,2 Matthew E. Schafer,1 Umair Wahed.3 1San Antonio Kidney Disease Center, San Antonio, TX; 2Southwest Kidney Institute, PCL, Phoenix, AZ.

**Background:** In the era of Fistula First, nephrologists are well versed on the pitfalls of arterio-venous fistula (AVF) failure rates and surgical issues related to AVF creation. USRDS 2016 reports a primary fistula failure rate of 35.9%. Few innovations have evolved in AVF creation but recently several novel devices have been developed that can create AVF percutaneously.

**Methods:** Two nephrology groups with vascular centers were among 5 centers in a U.S. multi-center study using a percutaneous device (Ellipsys, Avena Medical, San Juan Capistrano, CA) to create AVF. Patients were selected based on suitable anatomy as determined by ultrasound mapping. All procedures were performed in the physician’s centers. The primary outcome is maturation rate, defined as percentage of fistula suitable to allow successful cannulation for dialysis within 90 days including vein size and flow. The device is a single catheter that engages the walls of a perforating vein and proximal radial artery in the forearm. The AVF is created using thermal energy to “heat weld” the vessels together and cut the anastomosis.

**Results:** The Interventional Nephrologists (INs) in the study reported an average procedure time of 23 minutes. In addition, available 12 month follow-up data indicate a high patency rate of 96% and no significant clinical sequelae such as mega-fistulas or steal syndrome have been reported. One year data will be provided at the meeting.

**Conclusions:** Despite the advances from Fistula First, 80% of incident patients still initiate dialysis without a functioning AV access and 30% are still dialyzing with a catheter at 1 year. Our study demonstrates that PAVF offers a minimally invasive option for AVF creation that can be safely performed in an office-based setting by INs. The 90 day and 1 year data demonstrate technical and clinical success as well as a reduction in the maturation period in comparison to surgically created AVF. It is estimated, with the process under the control of the nephrologist, that catheter contact time (CCT) can be reduced by 90 days or more.

**Funding:** Commercial Support - Avena Medical

**RESULTS**

<table>
<thead>
<tr>
<th>Fistula Type</th>
<th>Technical Success</th>
<th>Time to Maturation*</th>
<th>Serious Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ellipsys-PF100</td>
<td>90.7%</td>
<td>40 days</td>
<td>0/120 (0%)</td>
</tr>
<tr>
<td>Ellipsys-PF150</td>
<td>86.9%</td>
<td>40 days</td>
<td>2/120 (1.6%)</td>
</tr>
</tbody>
</table>

*Access had flow suitable for dialysis (>4 mm vein) (>500 ml flow)

Ave. Flow @ 90 days/1092 ml/min (cephalic) 1269 ml/min (basilic)

Ave. Vessel diameter @ 90 days - 6.7 mm (cephalic) 6.2 mm (basilic)
TH-PO760

Real-World Experience Utilizing Endovascular Arteriovenous Fistula (endoAVF) to Deliver Hemodialysis Treatment Frank Dellanna, Christoph Radosa, Ralf Hoffmann, Linda Nath, Robert Shalverdyan, Tobias Steinke. MVZ DaVita Rhein-Ruhr GmbH, Duesseldorf, Germany; Universitätsklinikum Carl Gustav Carus, Dresden, Dresden, Germany; Schönh Klinik Düsseldorf, Düsseldorf, Germany.

Background: The arteriovenous fistula (AVF) is the primary option for end stage renal disease patients to receive hemodialysis treatment. However, the surgical trauma of dissecting, mobilizing and suturing the vein to the artery can lead to early AVF failure rates as high as 60% [1-4]. A novel endovascular approach to create AVFs has been developed to avoid this surgical trauma. This report describes the initial real-world experience with the endoAVF at two European vascular centers.

Methods: Consecutive dialysis and pre-dialysis patients who underwent the endoAVF procedure were followed to assess the ability to create a functional vascular access. Eligible patients were traditional surgical candidates for upper arm AVFs. Patients did not receive an endoAVF if they were ideally suited for a radiocephalic fistula (healthy arteries with a >2.5 mm forearm cephalic vein) or had a previously failed upper arm vascular access. Patients were followed to assess the technical success of the procedure, functional usability via two-needle cannulation, interventions necessary to mature and maintain the endoAVF and maturation time.

Results: An endoAVF was attempted in 23 patients between 2017/05 and 05/2018. The median age was 60 (25-84) with 65% male 61% pre-dialysis, 9% having a failed forearm fistula and typical comorbidities of the German dialysis patient population. Technical success was reported at 100%. Dialysis was successfully administered via 2-needle cannulation in 72% (13/18) of the patients; three patients were still pre-dialysis, one patient had less than 2 months follow-up and one was lost to follow-up. Three pre-planned vein elevations as well as three interventions to augment flow were performed. The median maturation time was 56 days (range: 10 – 86 days) at one center and 63 days (range: 26 – 137) at the other with the longest maturation times associated with elevation procedures.

Conclusions: The endoAVF procedure produced usable AVFs with high technical success. These real-world results are consistent with the results demonstrated in previous endoAVF clinical studies, FLEX [5] and NEAT [6].

TH-PO761


Background: For hemodialysis (HD), arteriovenous fistulas (AVF) are the preferred type of vascular access (VA). Most data on VA durability originate from North America. As practice patterns and patient characteristics differ between Europe and the US, we evaluated outcomes of radiocephalic (RCAVF) and upper arm AVFs and arteriovenous grafts (AVG) in a large retrospective cohort of Dutch HD patients.

Methods: This Dutch Vascular Access Study cohort consists of 1,656 VAs in 1,221 patients in 8 hospitals. To obtain independent observations, only the first matured VA per patient was included. Primary patency started at VA creation and ended at the first intervention or abandonment. Functional patency started at the first cannulation and ended at death or transplant. Patency was censored at death or transplant. Patency is presented death/transplant-censored primary and functional patency.

Results: 563 VAs (420 RCAVF, 341 upper arm AVF, 102 AVG) were analysed. The median primary patency for RCAVFs was 13.8 ± 1.8 months, for upper arm AVFs 26.6 ± 4.5 months and for AVGs 11.4 ± 1.8 months. The hazard ratio for loss of primary patency was higher for AVGs than RCAVFs (HR 1.52, 95% confidence interval: 1.18 – 1.96), and lower for upper arm AVFs (HR 0.74, 0.60 – 0.90). The median of functional patency was not met during the follow-up (fig 1). At 48 months 82% of RCAVFs, 79% of upper arm AVFs and 73% of AVGs were still functionally patent (death-censored). The number of procedures was lowest for RCAVFs (0.8 ± 2.1/year) versus upper arm AVFs (1.4 ± 3.7/year) and AVGs (2.5 ± 5.8/year).

Conclusions: In the Dutch Vascular Access Study cohort, long-term functional patency was comparable between the 3 groups of arteriovenous access configurations. However, the number of procedures required to maintain AVG patency is 3-fold higher compared to RCAVFs.

Funding: Commercial Support - Proton Therapeutics

TH-PO762

The Significance of a Maturing Fistula or Graft at HD Initiation Rita L. McGill, Eduardo K. Lacson, Tufts University School of Medicine, Boston, MA; University of Chicago Medicine, Chicago, IL.

Background: Increasing use of fistulas (AVF) and grafts (AVG) is a national priority, especially for incident hemodialysis (HD) patients. One-quarter of patients who initiated HD with catheters (CVC) have an accompanying ‘maturing’ AVF or AVG. We examined the characteristics and one-year outcomes of these patients.

Methods: All patients initiating HD from 7/2010 – 12/2011 were assessed. Medical Evidence forms were used to determine baseline characteristics and vascular access at 1st outpatient HD. HD claims were used to assess changes in vascular access, and treatment history files were used to identify deaths during the first year of HD.

Results: Among 52,573 patients initiating HD with CVCs, 12,201 (23.2%) had a maturing AVF/G. Compared to patients with CVC-only, patients with maturing AV/G were more likely to be black (30.6 vs. 27.3%, P<0.01) and diabetic (61.7 vs 55.6%, P<0.01), but similar in age, sex, and body mass index. Patients with pre-HD nephrology care were twice as likely to have maturing AV/G (31.1 vs. 15.6%, P<0.001). Over the first year, 10.9% of patients with maturing AV/G died, 71.6% converted to AVF/G use, and 14.1% had CVC at one year. Among patients with CVC-alone, 23.0% died, 42.7% converted to AVF/G, and 23.8% had CVC at 1 year. Among patients who transitioned to AVF/G, median catheter-days were 131 (IQR=94-194) for patients with maturing access versus 195 (IQR=95-252) for those with CVC-only. The distributions of maturation times were unimodal for both groups.

Conclusions: HD initiation with a maturing AVF/G is associated with improved first-year outcomes relative to CVC as sole access, suggesting that vigorous efforts to secure access may be beneficial even in advanced CKD. Although a maturing AVF/G was associated with fewer catheter days, CVC use was prolonged in both groups. The reasons for prolonged CVC use merit further investigation.
TH-PO764
Prediction for Maturation of Arteriovenous Fistula by Vascular Ultrasound

Background: Fistula maturation success is strongly dependent on adequate dilatation therapy. However, because most patients with end stage renal disease have poor vascular condition, the rate of success in maturation of arteriovenous fistula (AVF) is lower than expected. We aim to investigate the predictors for successful AVF maturation through the ultrasound examination which was performed at pre and post AVF surgery.

Methods: We collected the data of vascular sonography from the seventy patients undergoing AVF formation surgery at Wonju Severance Christian hospital in South Korea. We performed ultrasound vascular mapping as a pre-evaluation searching appropriate vessels for AVF, and followed it at around one-month after the surgery to evaluate whether the AVF is matured possible to use for hemodialysis. In the ultrasound mapping, we measured the diameter of artery (A1) and vein (V1) before surgery, and feeding artery (A2) and AVF (V2) after AVF formation. Additionally, we evaluated blood flow (BF) of AVF and calculated the change of diameter in artery (A2-A1, delta A) and vein (V2-V1, delta V).

Results: Thirty-seven men and thirty-three women comprised of the subjects. The mean age was fifty-nine years old. We defined the cases with BF≥600 ml/min as a poor maturation group and the other cases with BF<600 ml/min as a good maturation group. The independent T-test showed that there were significant differences in the parameters of delta A (p=0.013) and delta V (p=0.000), delta A in patients with BF≥600 ml/min (7.4±4.7 mm) was significantly smaller than patients with BF<600 ml/min (13.5±8.7 mm). BF of AVF was significantly associated with V2-V1 (p=0.000), BF of AVF and delta V were significantly associated with V1-V2 (p=0.013). In multivariate regression test, the results demonstrated that delta A predict the success in the AVF maturation.

Conclusions: In conclusion, the change of the arterial diameter before and after AVF formation is the most important factor for AVF maturation.

TH-PO765
Influence of Arterial Dilatation on Fistula Maturation with Adequate Blood Flow: Supports Concept That Arterial Elasticity Has Key Role

Background: Fistula maturation success is strongly dependent on adequate dilatation of the inflow artery and outflow vein. The Rule of 6s emphasizes an adequate vein lumenal diameter is needed to allow successful cannulation. However, poor arterial elasticity is associated with maturation failure, probably because of failure of the inflow artery to dilate adequately. In order to elucidate this issue, we conducted a mathematical model of this in vivo scenario.

Methods: Mathematical model was a brachiocephalic fistula that included cephalic vein plus radial artery connected to the cephalic vein by a straight segment of 3.11 mm. We then simulated such a fistula in vivo in rats and expressed the results as the distance from the proximal end of the fistula in which the outflow vein dilates but the artery dilates minimally or not at all.

Results: A fistula with an arterial diameter of 2 mm is predicted to have a blood flow ranging from only 232 to 241 ml/min despite widely accepted adequate venous diameters ranging from 4 to 8 mm. Even arterial dilatation to 3 mm diameter will provide only minimal blood flows ranging from 581 to 665 ml/min. Flows in the range of 1,000 ml/min or more require an arterial diameter of at least approximately 4 mm. Development of stenosis at the arteriovenous anastomosis will significantly impair flow and thereby require even larger arterial diameters if blood flow is to be adequate.

Conclusions: These results support the concept that dilatation of the inflow artery is a key step in fistula maturation. Arterial properties are as important as venous in assessing suitability of vessels for fistula formation. Poor arterial elasticity may result in a high resistance fistula circuit despite adequate dilatation of the outflow vein. An arterial diameter of 2 mm is widely accepted as a minimally acceptable proteroprestriat diameter, but such an artery cannot support a high blood flow unless it is able to dilate.
Results: The laser Doppler vibrometry provided excellent high-resolution measurements of the "skin" movements. The "skin" movements clearly depended on both AVF pressure and stroke volume (Fig.2a, b and Fig.3a-c).

Conclusions: Our in vitro study demonstrates that, first, the laser Doppler vibrometry can determine regional "skin" vibrations above AVF with high accuracy and precision. Second, vibration characteristics ("thrill") of the "skin" above the AVF depend on both flow and pressure. Clinical studies are required to extend these findings to hemodialysis patients with AVF as vascular access.

TH-PO768
Postoperative Vascularization of the Arteriovenous Fistula Is Not Associated with Maturation: A Pilot Study
Juan C. Duque Ballesteros,1 Laisel Martinez,2 Angela Paez,2 Marwan Tabbara,2 Guillermo Selman,1 Looy H. Salaman,1 Roberto I. Vazquez-Padron.1 

1Albany Medical College, Albany, NY; 2University of Miami, Miller School of Medicine, Miami, FL.

Background: The venous vasa vasorum provides oxygen and nutrients to the walls of native veins and arteriovenous fistulas (AVF). Nonetheless, whether expansion or growth of the AVF microvasculature has an effect on clinical outcomes remains undetermined. The purpose of this study was to evaluate the association of AVF vascularization with maturation and with the development of medial fibrosis and intimal hyperplasia (IH).

Methods: We assessed pre-existing and postoperative vascularization in both native veins and AVF using samples (i.e., tissue pairs) from 19 patients undergoing two-stage AVF creation. Patients with successful maturation (N=9) and maturation failure (N=10) were matched with respect to age, demographics, and comorbidities. Vasa vasorum density (VVD; microvessel count/area) was quantified in the vascular layers of CD31-stained cross-sections. Change in vascularization after AVF creation was calculated by subtracting pre-existing VVD and VVA from the postoperative values in tissue pairs.

Results: Total VVD in native veins was 6/mm² (interquartile range [IQR] 2-10), with no significant change in AVFs as determined by pairwise comparisons (p=0.3). Total VVA increased during remodeling, from 956 um² with no significant change in A VFs as determined by pairwise comparisons (p=0.3). Total VVD in native veins was 6/mm² (IQR 5-11) and 2/mm² in AVFs (IQR 766-2578; p=0.046), with the most significant increase in A VFs (IQR 786-2578; p=0.046), with the most significant increase in A VFs (IQR 786-2578; p=0.046), with the most significant increase in A VFs (IQR 766-2578; p=0.046), with the most significant increase in A VFs (IQR 766-2578; p=0.046), with the most significant increase in A VFs (IQR 766-2578; p=0.046).

Conclusions: Our study showed that AVF vascularization is not associated with AVF maturation and does not determine maturation.

Funding: NIDDK Support

TH-PO769
Outcome of Endovascular Salvage of Immature Hemodialysis (HD) Arteriovenous Fistulae (AVF) 
Hyue Eun Yoon, Yaein Kim, Byung ha Chung, Bumsoon Choi, Cheol Whee Park, Chul Woo Yang, Yong-Soo Kim.
The Catholic University of Korea College of Medicine, Seoul, Republic of Korea.

Background: To assess the anatomical causes of immature AVF and the outcome of endovascular salvage.

Methods: Anatomical causes, clinical characteristics, and the success rate of endovascular salvage of 110 immature AVF were analyzed.

Results: A total of 110 patients included 52 females and 64 diabetics. The mean age was 63±13 years old. The access types were radiocephalic (n=62), brachiocephalic (n=45), and transposed brachio basilic (n=3) fistulae at the time of angiography. Seventy-five patients were maintained on HD using catheters. Mean interval between AVF creation and referral to angiography was 94±69 days. Angiography revealed stenoses (n=49; 26 inflow, 9 outflow, and 14 mixed), accessory veins (n=16), and inadequate selection of vessels (n=2) in 62 patients with radiocephalic fistulae. It revealed stenoses (n=41; 14 inflow, 17 outflow, and 10 mixed), accessory veins (n=11), deeply located cephalic veins (n=2), and inadequate selection of vessels (n=4) in 48 patients with upper arm fistulae. Endovascular procedures performed in 107 patients included percutaneous transluminal angioplasty (PTA) (n=95) and accessory vein obliteration (n=27; 1 percutaneous, 12 suture ligatures) and 14 coil insertions (n=12). There were no significant differences in VVD or VVA between A VFs with distinct maturation.

Conclusions: Our study suggests that aggressive and timely intervention can salvage the majority of cases with high success and patent rates. The presence of mixed stenoses is associated with poor outcome.

TH-PO770
Tailored Selection of Elevation Transposition and Lipectomy for Superficialization of Cephalic Arteriovenous Fistula Veins 
Shouwen Wang, Arizona Kidney Disease and Hypertension Center, Phoenix, AZ.

Background: Cephalic vein arteriovenous fistulas are the most commonly used vascular accesses for hemodialysis. However, as high as 34% of these fistulas are situated too deep under the skin and require superficialization before use. Various superficialization techniques have been employed, such as tunnel transposition, elevation, elevation transposition, and lipoectomy. Each of these techniques may have advantages and disadvantages, and there have been few reports comparing their outcomes. This report compares the clinical outcomes of cephalic elevation transposition (CET) vs lipoectomy and discusses tailored selection of these techniques.

Methods: The clinical data of patients who underwent second-stage cephalic vein elevation transposition or lipoectomy at an ambulatory surgery center were collected and analyzed. The patients who underwent basilic elevation transposition (BET) were included for comparison with CET.

Results: A total of 240 patients were included. Comparing the CET group (n=118) vs the BET group (n=28) vs the BE group (n=94); males were 28% vs 32% vs 59%; the mean age was 58.0±14.1 vs 56.3±12.1 vs 60.0±15.0; the mean body mass index was 36.9±7.8 vs 38.1±7.2 vs 26.8±6.9; the percentages of upper arm fistulas were 84% vs 61% vs 100% and of the forearm fistulas were 16% vs 39% vs 0%; and the mean follow-up was 18.8±17.6 vs 37.1±24.4 vs 24.6±20.0 months. For the CET vs the lipoectomy vs the BET groups, the primary patency rates of the whole fistula conduit were 40% vs 49% vs 44% at one year and 17% vs 37% vs 37% at three years; the assisted primary patency rates were 93% vs 96% vs 97% at one year and 78% vs 96% vs 88% at three years; the secondary patency rates were 99% vs 100% vs 100% at one year and 96% vs 100% vs 100% at three years; the primary patency rates of the superficialized fistula segments were 72% vs 67% vs 65% at one year and 57% vs 51% vs 53% at three years; and the mean numbers of percutaneous interventions required for the superficialized fistula segments were 0.5±0.4 vs 0.3±0.7 vs 0.6±0.3 per access year.

Conclusions: CET and lipoectomy are reliable approaches for superficialization of cephalic fistula veins that yield high cumulative fistula survival rates, which are comparable to that of BET for basilic fistula veins. The selection of CET or lipoectomy is mainly based on the location and depth of a fistula vein.

TH-PO771
Changes in Blood Pressures, Adequacy, and Blood and Dialysate Flow Rates before and after Arteriovenous Access Angioplasty 
Hao Han,1 Tommy C. Blanchard,1 Hanjie Zhang,2 Murat Sor,1 Elsie Koh,1 Yue Jiao,3 Solene Nahon-Maghari,1 Maarten P. Usvyat,1 Peter D. Potamkin,1 Franklin W. Maddux,1’Fresenius Medical Care North America, Waltham, MA; 2Fresenius Vascular Care, Malvern, PA; 3Renal Research Institute, New York, NY.

Background: Stenosis is a common complication in arteriovenous fistulas and grafts (AVFs/AVGs), and is a major cause of hospitalizations and dialysis access failure. Clinical predictors for early detection of severe stenosis in AVFs/AVGs are sparse. To determine predictors of stenosis, we investigated trends in levels of predialysis systolic and diastolic blood pressures (SBP, DBP), dialysate flow rate (Qd), and dialysate flow rate (Qd) before and after angioplasties in hemodialysis (HD) patients.

Methods: We analyzed data from 7,910 Fresenius Kidney Care HD patients who had an AVF/AVG angioplasty in 2015 and 2016. The preSBP, preDBP, Kt/V, Qb, and Qd were tracked in HD patients for 90 days before and after an angioplasty, and plotted using a penalized B-spline to fit the mean with 95% confidence limits. To determine predictors of stenosis, we investigated trends in levels of predialysis systolic and diastolic blood pressures (SBP, DBP), dialysate flow rate (Qd) before and after angioplasties in hemodialysis (HD) patients.

Results: The presence of mixed stenosis is associated with poor access outcome. Endovascular procedures can salvage the majority of cases with high success and patency rates. The presence of mixed stenoses is associated with poor outcome.
individually these are small changes in patient parameters, they can be useful for creation of comprehensive AVF/AVG stenosis prediction models. Nonetheless, further analyses are needed to confirm these observations and assess their usefulness.

**Funding:** Commercial Support - Fresenius Medical Care North America

**TH-PO772**

**Arterial Diameter Following AVF Creation May Predict Aneurysmal Formation**

Alexis M. Cahalane, Vivek G. Sahani, Zubin Irani, Jie Cui. Massachusetts General Hospital, Boston, MA.

**Background:** Aneurysmal formation in arteriovenous fistulae (AVF), which is the preferred vascular access for hemodialysis in end-stage renal disease, can lead to insufficient hemodialysis, risk of rupture and access abandonment.

**Methods:** This retrospective chart review study looked at patients with AVF aneurysmal dilatation requiring surgical correction between 01/01/2014 and 07/30/2016. All fistulogram images were reviewed and the diameter of the feeding artery, venous outflow, maximum aneurysmal segment (AnS), and length of AnS were measured. Location of any stenotic lesions were also recorded.

**Results:** 10 female and 12 male patients were identified. 21 patients (77.78%) had brachiocephalic fistula and 6 had radioactive fistula (22.22%). Mean interval between surgical creation of the AVF and access revision was 1411 ± 955 days. On the first fistulogram, there was a significant correlation between diameter of feeding artery and diameter of fistula (r=0.51, p=0.02), the maximum diameter of the aneurysm (r=0.67, p=0.003) and the length of the AnS (r=0.92, p=0.0001). The most common venous outflow was cephalic arch stenosis (64.7%), while 7 patients had no outflow stenosis. Interval between first recorded fistulogram and surgical revision was 818 days. On the presurgical fistulogram the diameter of the artery was strongly correlated with the diameter of the artery in the first fistulogram (Figure 1A, p=0.05). Furthermore, the length of the AnS on the last fistulogram also correlated with the diameter of the artery in the first fistulogram (Figure 1B).

**Conclusions:** Aneurysmal formation is a long-term complication of AVF. In AVF created using the cephalic vein, cephalic arch stenosis was the most common stenosis lesion. The diameter of the feeding artery at time of the first fistulogram can predict the likelihood of aneurysm formation and its calibre. AVF with relative larger arterial diameter should be closely monitored for aneurysm formation and early intervention may avoid loss of the access.

**Funding:** Clinical Revenue Support

**TH-PO773**

**Vein Grafting – A Novel Approach for Forearm Dialysis Arteriovenous Fistula Creation**

Jian Chen, Jie Tang. University Medicine, Brown University, Providence, RI.

**Background:** With the growing need for reliable and durable forearm hemodialysis access, here we describe a novel “autologous vein grafting” technique for the creation of forearm arteriovenous fistula (AVF).

**Methods:** All study participants failed to have native distal cephalic or basilic vein large enough for forearm AVF creation. Therefore, we harvested a segment of contralateral forearm mid-branch vein or leg great saphenous vein from the same patient, and performed an end-to-end anastomosis to the radial artery and an end-to-end anastomosis to the midcephalic or basilic vein to create a forearm AVF. We identified patients who underwent this procedure between January 2014 and January 2016, and report measurements of fistula diameter (at 1 cm from the arterial anastomosis) and doppler flow at 6 weeks and 3 months after surgery, as well as 1-year primary unassisted patency, cumulative patency, and complications.

**Results:** We identified a total of 7 study participants. 6 underwent surgeries for radiobasilar AVF and 1 for radiocephalic AVF. Among the 6 who had radiocephalic AVF, 5 used contralateral forearm basilic vein segments, 1 used great saphenous vein segment. 6 weeks after surgery, the mean diameter of AVF was 5.1 mm (range 4.6-5.3 mm), the mean fistula flow was 756 ml/min (range 627-820 ml/min). The 1-year primary unassisted patency was 86%, and cumulative patency was 100%.

**Conclusions:** Autologous vein grafting appeared to be an effective way to create a forearm AVF.

**Funding:** Clinical Revenue Support

**Vascular Characteristics of Study Participants**

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>AVF</th>
<th>RVF</th>
<th>Grave</th>
<th>Cephalic</th>
<th>4-week Flow</th>
<th>6-week Flow</th>
<th>Yearly Flow</th>
<th>3-year Flow</th>
<th>5-year Flow</th>
<th>Complications</th>
<th>Patency</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>Male</td>
<td>0.01</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>100%</td>
</tr>
<tr>
<td>60</td>
<td>Male</td>
<td>0.01</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>100%</td>
</tr>
<tr>
<td>60</td>
<td>Male</td>
<td>0.01</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>100%</td>
</tr>
<tr>
<td>65</td>
<td>Male</td>
<td>0.01</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>100%</td>
</tr>
<tr>
<td>60</td>
<td>Male</td>
<td>0.01</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>100%</td>
</tr>
<tr>
<td>62</td>
<td>Male</td>
<td>0.01</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>100%</td>
</tr>
</tbody>
</table>

* status post angioplasty

**TH-PO774**

**Racial and Gender Disparities in Initial Hemodialysis Access among Medicare Beneficiaries**

Silvi Shah, Anthony C. Leonard, Charuhas V. Thakar. University of Cincinnati, Cincinnati, OH.

**Background:** Arteriovenous (AV) access confers survival and economic benefits over catheters in incident hemodialysis (HD) patients. However, after considering the influence of pre-dialysis health status (defined as nephrology care and acute care hospitalizations), the effects of race and gender in the utilization of HD access is not known.

**Methods:** We evaluated 47,602 adult incident HD patients (1/1/2008 to 12/31/2008) from the United States Renal Data System (USRDS) with linked Medicare data for 5 years prior to HD initiation. Information on pre-dialysis health status was obtained from form 2728 and linked Medicare claims. Using case-mix adjusted logistic regression models; we examined the effects of race and gender on type of vascular access (arteriovenous [AV] access vs. catheter) at HD initiation.

**Results:** The majority of patients were male (55%) and White (62%). Catheter was the dominant access method used to initiate HD (82% vs. 18% AV access). A higher rate of Blacks (19%) and Asians (19%) initiated HD with AV access than did Whites (17%), Native Americans (16%) or Hispanics (15%) (unadjusted p=0.001). Pre-dialysis nephrology care was received by 58% of patients; and was associated with higher rate of AV access for initial HD than those without pre-dialysis nephrology care (27% vs. 8%, p<0.001). Acute hospitalization during the 2 years prior to HD initiation occurred in 89% of patients; and was associated with lower rate of AV access than those without pre-dialysis acute hospitalization (15% vs. 40%, p=0.001). In adjusted analyses, Blacks were more likely than Whites (odds ratio [OR], 1.10; 95% confidence interval [CI], 1.03-1.17) and Hispanics were less likely than Whites (OR, 0.82; CI, 0.74-0.90) to initiate HD with AV access. Similarly, females were less likely to initiate HD with AV access than were males (OR, 0.83; CI, 0.72-0.97).

**Conclusions:** Among Medicare beneficiaries, Blacks are more likely than Whites to use AV access for first outpatient HD; whereas Hispanics are less likely than Whites and females are less likely than males to initiate HD with AV access. These differences across race and gender are independent of pre-dialysis health status, among other factors. Further investigation of biological and process of care factors is warranted to reduce these disparities.

**TH-PO775**

**Effects of Denosumab in Osteoporotic Hemodialysis (HD) Patients with Secondary Hyperparathyroidism (SHPT)**

Satoshi Funakoshi,2 Naoto Taguchi,2 Jyunichiro Hashiguchi,2 Makiko Yamashita,2 Tayo Kawazu,2 Osamu Sasaki,2 Hiroshi Ichinose,2 Kenji Sawase,2 Yoko Obata,2 Tomoya Nitshino,2 Takashi Harada.2 Nagasaki University School of Medicine, Nagasaki, Japan; 2Nagasaki Kidney Center, Nagasaki, Japan.

**Background:** Denosumab, a human monoclonal antibody which binds to RANKL, inhibits osteoclast differentiation/activation and exerts primarily anti-resorptive action. Denosumab also inhibits bone formation and hence may correct high bone turnover observed in HD patients. Meanwhile serum markers for bone metabolism are reported to correlate with PTH but not with circulating fibroblast growth factor 23 (FGF23), which decreases bone mineralization and is markedly increased in HD patients.

**Methods:** Among HD patients with secondary hyperparathyroidism (SHPT) who received intravenous pulse therapy with vitamin D (VD) analogues, those with bone mineral density < 70% YAM were enrolled in this study after their informed consent was obtained. Serum calcium, phosphate, PTH, bone metabolism markers and FGF23 were measured before and 4 weeks after subcutaneous administration of 60mg of denosumab.

**Conclusions:** A steep decline in serum calcium levels was observed in all 16 subjects (5 males and 11 females; mean age, 66.7±4.7 years old; mean HD duration, 11.4±7.6 years), and calcium-based phosphate binders and KD algorithms were started to adjust their calcium levels. After 4 weeks of denosumab administration, significant decreases were seen in the bone resorption markers TRCP-2B and NTx, and the bone formation markers BAP and PINP as well as in PTH; furthermore, FGF23 was significantly decreased (table).

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

Underline represents presenting author.
Conclusions: Study results suggest that denosumab may potentially correct bone turnover in osteoradionephritic HD patients with SHPT. A possible explanation for decreased FGF 23 could be that the addition of calcium-based phosphate binders lowered the phosphate burden in HD patients and that VD signalling resulting in a negative feedback loop within FGF family.

Funding: Private Foundation Support

Change of Serum Bone Metabolism Markers and FGF 23 after Denosumab Administration

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before HD (mean±SD)</th>
<th>After HD (mean±SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mg/dL)</td>
<td>9.3±0.7</td>
<td>9.1±0.4</td>
<td>0.3001</td>
</tr>
<tr>
<td>Phosphate (mg/dL)</td>
<td>4.6±1.7</td>
<td>4.1±1.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>FGF 23 (ng/mL)</td>
<td>219.4±139.5</td>
<td>175.0±109.0</td>
<td>0.029</td>
</tr>
</tbody>
</table>

TH-PO776

Hemodialysis (HD) Treatment Can Improve Taste Sensitivity to Salt – Assessment by the Filter Paper Disc (FPD) Method

Satoshi Funakoshi,1 Kent Torioge,2 Miki Torioge,3 Asami Nakamura,4 Makiko Yamashita,5 Osamu Sasaki,6 Hiroshi Ichinose,7 Kenji Sawase,7 Takashi Harada,8 Yoko Obata,9 Tomoya Nishino,10 Juichi Hashiguchi,11 Nagasaki Kidney Center, Nagasaki, Japan,1 Nagasaki University Hospital, Nagasaki, Japan.

Background: Several studies in chronic uremic and HD patients indicate decreased taste sensitivity. However, whether a single HD session can improve their sensitivity or not warrants investigation. The aim of this study was to determine if the taste sensitivity to salt is affected by HD treatment in maintenance HD patients by using FPD method, a reliable method to measure taste with a high degree of reproducibility.

Methods: All subjects were assessed for their taste sensitivity to salt by the FPD method before and after HD sessions. Filter paper discs prepared with different concentrations of sodium chloride from 0.6 mg/cm² (level 1) to 1.6 mg/cm² (level 6) for scoring, and the lowest level at which taste was identified was defined as the taste threshold to salt. Relevant clinical parameters were determined in each patient, and the correlation to the taste sensitivity was analyzed.

Results: At our Facility, 122 HD patients (mean age, 66.5±28.2 years old; mean HD duration, 12.0±9.5 years) were assessed for taste sensitivity by FPD method. According to the taste threshold subjects were diagnosed as normal (score <2), moderately impaired (score 3-4) and severely impaired (score >5). As shown in table, a significant decrease in taste sensitivity was observed in the moderately-impaired group, but not in the group with normal taste sensitivity to salt. There was no correlation between altered taste sensitivity and various parameters including age, gender, HD vintage, serum zinc and prescribed medications.

Conclusions: Our findings suggest that HD treatment favorably affects tasting function by improving uremia. It remains to be seen whether taste sensitivity is correlated with various clinical factors in HD patients.

Funding: Private Foundation Support

Average Taste Threshold to Salt Before and After HD (mg/cm²)

<table>
<thead>
<tr>
<th>Group</th>
<th>Before HD</th>
<th>After HD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal group (n=63)</td>
<td>9.4±2.9</td>
<td>5.7±2.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>moderately impaired group (n=111)</td>
<td>11.1±2.7</td>
<td>6.8±2.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>severely impaired group (n=88)</td>
<td>17.0±2.7</td>
<td>10.0±1.8</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

TH-PO777

Factors Associated with Gastrointestinal Bleeding in ESRD Patients


Background: Gastrointestinal (GI) bleeding is a serious problem among patients with End Stage Renal Disease (ESRD), affecting this population at rates almost two orders of magnitude higher than in the general population (Yang et al., 2012). We aimed to characterize the demographic, treatment, and laboratory parameters in dialysis patients with GI bleeds and build prediction models that could identify patients at a higher risk of experiencing a GI bleed.

Methods: We analyzed data on all dialysis patients treated at Fresenius Medical Care North America dialysis clinics as of December 2016. We used a logistic regression with 40 variables including demographics, comorbidities, treatment parameters and laboratories to identify factors highly associated with GI bleeds and measured the effect size. Variables on treatment and laboratory parameters were determined from mean values at 90 to 183 days prior to December 2016.

Results: We studied data from 141,973 dialysis patients, of which 0.7% were diagnosed with a GI bleed. We found that lower hemoglobin, calcium, and transferrin saturation (TSAT) values were associated with GI bleeds. Variability in calcium and hemoglobin (using standard deviation) was also associated with GI bleeds. Further, GI bleeds were more common among those diagnosed with ulcers and with older patients. When tested on a held-out set of 50% of the data, the model was able to accurately predict which patients have a GI bleed with a receiver operating characteristic area under the curve of 0.81.

Conclusions: Our analysis identifies several factors associated with GI bleeds in dialysis patients, which may be useful for predicting patients who are likely to experience a GI bleed. Further research validating the accuracy of the prediction of patients with GI bleed is needed to confirm these findings.

Funding: Commercial Support - Fresenius Medical Care North America
Outcomes in ERSD Patients on Hemodialysis Taking Patiromer for Hyperkalemia Dinesh K. Chatoth,1 Peter M. Wahl,2 Viacheslav Rakov,3 Carly R. Van Zandt,1 Kathryn P. Anastassopoulos,4 Sam Colman,5 Tyler Knight,6 Nina Ostreicher,6,7 Ann Mooney,1 David M. Speigel,1 Matthew R. Weir,1 Fresenius Medical Care North America, Waltham, MA; Covance Market Access Inc., Gaithersburg, MD; Vifor Pharma, Glattbrugg, Switzerland; Frenova Renal Research, Waltham, MA; Relypsa Inc., a Vifor Pharma Company, Redwood City, CA; University of California, San Francisco, San Francisco, CA; University of Maryland Medical Center, Baltimore, MD.

Background: Real-world data on hyperkalemia (HK) treatment with patiromer in dialysis patients in the United States (US) are limited. We sought to examine outcomes of end-stage renal disease (ESRD) patients on hemodialysis (HD) and treated with patiromer for HK at US Fresenius Kidney Care (FKC) centers.

Methods: We identified patients who initiated patiromer between 10/1/2015 and 7/31/2016; were prescribed permanent in-center HD ≥3 times per week; and had ≥1 serum potassium (sK) lab value in the 91 days prior to patiromer initiation (baseline). We examined changes from baseline in sK values and potassium (1K) baths over 6 months.

Results: Among 268 patients included in the analysis, mean age was 57.5 years, 55.2% male, and 77.2% white, with a mean of 4.9 years on dialysis. Median patiromer daily dose was 8.4 g/day. Overall, sK decreased by 0.5 mEq/L (decrease of 0.8 and 1.7 among those with baseline sK >5.5 and sK >6.5, respectively) (Table 1). Unobserved events may have prompted treatment in patients with baseline sK <5.5 mEq/L. The percentage of patients treated with 1K baths decreased by 2.2%.

Conclusions: These results demonstrate that treatment with patiromer lowers sK levels in real-world settings, with the greatest effect among patients with sK >6.5 mEq/L. The predominant use of the recommended starting dose (8.4 g/day) supports the feasibility of this dose for long-term (≥6 months) sK control.

Funding: Commercial Support - Vifor Pharma

Table 1. Change in Serum Potassium Over 6 Months Following Patiromer Initiation

<table>
<thead>
<tr>
<th>Baseline sK (mEq/L)</th>
<th>Baseline</th>
<th>Follow-Up Period After Patiromer Initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 1</td>
<td>Week 2</td>
</tr>
<tr>
<td>n (%)</td>
<td>268 (100)</td>
<td>181 (67.5)</td>
</tr>
<tr>
<td></td>
<td>Week 3</td>
<td>Week 4</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>5.9 (0.8)</td>
<td>5.3 (0.6)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>4.9 (0.7)</td>
<td>4.6 (0.6)</td>
</tr>
<tr>
<td>n (%)</td>
<td>59 (22)</td>
<td>59 (22)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>6.7 (0.6)</td>
<td>5.7 (0.6)</td>
</tr>
</tbody>
</table>

Abbreviations: Δ, change; SD, standard deviation; sK, serum potassium.

Th-PO780

Patient Characteristics and Correlates of Patiromer Initiation for Hyperkalemia in Hemodialysis Hemodialysis: Epidemiology, Outcomes, Clinical Trials - Non-Cardiovascular - I

Poster/Thursday

Patient Characteristics and Correlates of Patiromer Initiation for Hyperkalemia in Hemodialysis Hemodialysis: Epidemiology, Outcomes, Clinical Trials - Non-Cardiovascular - I

Poster/Thursday

TH-PO779

Severe hyperkalemia who failed SPS. Studies are needed to determine the clinical impact of patiromer.

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

Table. Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Parameter</th>
<th>SPS (n=852)</th>
<th>Patiromer (n=959)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Mean (SD)</td>
<td>59 (14)</td>
<td>61 (14)</td>
<td></td>
</tr>
<tr>
<td>Race: Black</td>
<td>67%</td>
<td>49%</td>
<td></td>
</tr>
<tr>
<td>Primary Physician, Mean</td>
<td>78.5%</td>
<td>73.5%</td>
<td></td>
</tr>
<tr>
<td>Dialysis: Varing (Mean, SD)</td>
<td>5.7 (4)</td>
<td>5.4 (4)</td>
<td></td>
</tr>
<tr>
<td># HD sessions ≤90 days/ind</td>
<td>57.8 (34)</td>
<td>37.2 (42)</td>
<td></td>
</tr>
<tr>
<td>Dialysis: Varing (Mean, SD)</td>
<td>5.7 (4)</td>
<td>5.4 (4)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Δ, change; SD, standard deviation; sK, serum potassium.

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

Underline represents presenting author.

301
TH-PO782

The Influence of Frailty and Body Composition on Risk of Mortality in Incident Hemodialysis Patients Jessica Fitzpatrick,1 Stephen M. Sozio,2 Bernard G. Jaar,2 Michelle M. Estrella,2 Jose M. Monroy-Trujillo,2 Dorry L. Segev,2 Rulan S. Parekh,1 Mara McAdams-DeMarco,1 University of Toronto, Toronto, ON, Canada; 2Johns Hopkins University, Baltimore, MD; 3UCSF/San Francisco VA Medical Center, San Francisco, CA.

Background: Increased body mass index (BMI) is associated with lower risk of mortality in end stage renal disease (ESRD). Frailty is a phenotype of decreased physiologic reserve common among hemodialysis (HD) patients and associated with sarcopenia in this population. We sought to understand the role of body composition on mortality among frail and non-frail incident HD patients.

Methods: This study included 370 incident HD patients enrolled in the Predictors of Arrhythmic and Cardiovascular Risk in ESRD (PACE) Study. Frailty was defined as presence of 3 of the following: shrinkage, weakness, reduced gait speed, exhaustion, and low physical activity. General and abdominal adiposity were assessed with BMI and waist-to-hip ratio (WHR), respectively. Proportional hazards regression was used to estimate the association of frailty and WHR with all-cause mortality.

Results: The mean age was 55 years, 42% were female, 73% were African American, 57% had diabetes, the mean comorbidity index was 5.2, and 52% were frail. BMI, but not WHR, was higher (P<0.05) among frail vs. non-frail participants. There were 81 deaths over a mean of 2.5 years of follow-up. Frailty, but not WHR, was associated with higher mortality risk. There was no evidence of an interaction between frailty and BMI (P=0.33) or WHR (P=0.88). There was, however, a trend for stronger association between frailty and mortality among those above the median WHR.[Figure]

Conclusions: Frailty was associated with higher risk of mortality independently of BMI and WHR. These results suggest that general and central adiposity do not mitigate the influence of frailty on mortality among HD patients.

Funding: NIDDK Support

TH-PO783

FRAX-HD: A Two-Year Incident Hip Fracture Risk Assessment Tool for Japanese Hemodialysis Patients Naohiko Fuji, Takayuki Hamano, Ikuto Masakane.1 1Honcho-Yabuki Clinic, Yamagata, Japan; 2Hyogo Prefectural Nishinomiya Hospital, Nishinomiya, Japan; 3Osaka University Graduate School of Medicine, Suita, Japan. Group/Team: Committee of Japanese Renal Data Registry, Japanese Society for Dialysis Therapy.

Background: Dialysis patients are at 5-to-6-fold higher risk of hip fracture than general population. FRAX® is a useful tool for assessing future fracture risk; however, it is not optimized for hemodialysis (HD) patients. Our aim was to create a 2-year risk assessment tool for hip fracture among Japanese HD patients (FRAX-HD).

Methods: We extracted patients on facility-based HD, aged 20-100, with ≥1 yr of vintage at the end of 2007 using the Japanese nation-wide dialysis registry (JDRR-08102). Hip fractures were detected annually up to 2 years by questionnaire. We excluded patients who later received cinacalcet during the follow-up period, and randomly-selected 60%, 20%, and 20% of the eligible subjects to generate TRAIN, VALIDATE, and TEST sets, respectively. Multivariable Poisson regression analyses with interaction terms were performed to create prediction models, and validation was done later.

Results: TRAIN, VALIDATE, and TEST sets included 73999, 24667, and 24665 patients and 1574, 525, and 524 hip fractures, respectively. The subjects, aged 65.2 ± 12.3, included 39% of female and 34% of diabetes, with median vintage of 2.6 yrs. In TRAIN set, there were significant interactions between sex and age, sex and prior PTX/PEIT, and diabetes and vintage. Incidence rate ratio (IRR) elevated with age more prominently in female than in male (IRR 5.62 [95%CI: 3.32, 7.91]; females aged ≥80 vs. males aged <50). Prior history of PTX/PEIT was associated with lower risk only in female (IRR 0.58 [0.36, 0.81]). The model including these interactions demonstrated best performance and was selected as final model, which also achieved similar results in TEST set (AUC 0.739).

Conclusions: We successfully generated a 2-year risk assessment tool for hip fracture among HD patients. Further refinement and sensitivity analyses are required before its clinical application.

TH-PO784

Fracture Rates and Post-Discharge Outcomes Among Patients Undergoing Hemodialysis Across Etiologies of Kidney Diseases Berenice Y. Gittomer,1 Lorien S. Dalrymple,1 Zhiying You,1 Norma J. Osthus,2 Franklin W. Maddux,4 Tamara Isakova,1 Isidro B. Salusky,1 Myles S. Wolf,3 Michel Chonchol.1 1Div. Renal Diseases and Hypertension, Aurora, CO; 2Duke University, Durham, NC; 3Feinberg School of Medicine, Northwestern University, Chicago, IL; 4Fresenius Medical Care, Waltham, MA; 1Fresenius Medical Care North America, Waltham, MA; 3Mittal Children’s Hospital, Los Angeles, CA; 4UC Denver, Aurora, CO; 5University of Colorado, Aurora, CO.

Background: We have previously identified a low bone turnover state in patients with autosomal dominant polycystic kidney disease (ADPKD) and normal kidney function based on histomorphometric measurements. This is indicated by both decreased indices of bone formation and resorption measured in trabecular bone. However, the rates and risk of fracture have not been characterized in ADPKD patients compared to other etiologies of kidney disease among hemodialysis patients.

Methods: The cohort included incident in-center hemodialysis patients aged 18–100 years with kidney disease secondary to diabetes, hypertension, glomerulonephritis (GN) or ADPKD starting hemodialysis at Fresenius Medical Care North America 2000-2013. Cohort was followed through 2014 for the first fracture-related hospitalization and up to one additional year for post-fracture mortality. Fractures were identified using ICD-9-CM diagnosis codes. Fracture rates were calculated within strata of etiology of kidney disease. Among patients with complete data, one year mortality following hospital discharge was examined using Cox regression models.

Results: A total of 10,131 fracture-related hospitalizations were observed during follow-up. Age, gender, and race adjusted fracture rates per 1,000 person-years (PYs) varied across etiology of kidney disease: patients with ADPKD had the lowest rate (8.1, 95% CI 6.6-10.0) and patients with diabetes had the highest rate (12.3, 95% CI 11.4-13.4). Patients with hypertension and GN had fracture rates of 8.8 (95% CI 8.1-9.6) and 8.9 (95% CI 7.9-9.9), respectively. Patients with ADPKD had a significantly lower adjusted incident rate (aIRR) of fractures compared with patients with diabetes [aIRR: 0.66 (0.53, 0.82); p=0.0002]. After adjustment for demographics, vintage, comorbidities, albumin and measures of mineral metabolism, the mortality in the first year post-discharge for a
fracture-related hospitalization was lower in patients with ADPKD compared to patients without ADPKD (HR 0.65% 95% CI 0.46-0.92; p=0.01).

Conclusions: The decrease in bone formation rate observed in patients with early ADPKD does not appear to increase the risk of fracture or portend a worse prognosis among those who survive hospitalization when compared to other etiologies of kidney disease.

Funding: NIDDK Support

TH-PO785

Change in Serum Phosphorus, Pill Burden, and Medication Possession Ratio among Chronic Hemodialysis Patients Who Converted to Sucroferroic Oxysoludrine as Part of Routine Care

Kathryn S. Gray,1 Linda H. Ficocciolo,2 Abigail Hunt,1 Claude Mullon,2 Steven M. Brunelli,1 1DaVita Clinical Research, Minneapolis, MN; 2Fresenius Medical Care - North America, Waltham, MA.

Background: The large pill burden associated with many phosphate binders (PB) may decrease adherence to PB therapy. The current analysis examines the changes in serum phosphorus, PB pills/day, and medication possession ratio (MPR; estimate of adherence) among patients who converted from a baseline PB to sucroferroic oxysoludrine (SO) as part of routine care.

Methods: Patients eligible for analysis were ≥18 years, received chronic hemodialysis at a large dialysis organization (LDO), and received benefits through the LDO’s pharmacy management service. MPR is the proportion of time that a patient had enough medicine to take as prescribed (56.14% ± 7.35% at period 1; 63.07% ± 34.74% at period 2 and 63.29% ± 7.35% at period 3). Each study period was separated by a washout of 2 weeks. Results: There were 490 patients who converted to SO. The majority of patients (66%) were using sevelamer at time of SO initiation, followed by calcium acetate (19%). There was an improvement in serum phosphorus (sP; mean [95% CI] sP was 6.9 mg/dL [4.6-9.1] at SO initiation and 6.8 mg/dL [4.6-9.1] at SO-F (P=0.03). The percent of patients achieving sP ≤5.5 mg/dL increased from 21.7% at BL to 28.8% at SO-F (P=0.001). The mean total pill burden at BL was 10.8 pills/day and this decreased by 49% to 5.5 pills/day at SO-F (P=0.001). Among patients who were not using the LDO refill management service (n=30), mean total pill MPR was 0.68 at BL and 0.65 at SO-F (P=0.07).

Conclusions: A hemodialysis patients prescribed SO through a renal pharmacy service as part of routine care, improvements in sP were observed along with a 49% decrease in prescribed PB pills/day and, as observed among patients not enrolled in the LDO pharmacy automated refill management service.

Funding: Commercial Support - Fresenius Medical Care

TH-PO786

Phosphate Removal in Maintenance Hemodialysis with Different Dialyzer Membrane and Different Dialyzer Diameter Fang Lin,1 Xi Li,1,2 Jing Liu,1 Li Fang,1 Hong Ye,1 Junwei Yang,1 Nanjing Medical University, Nanjing, China; Second Affiliated Hospital, Nanjing Medical University, Nanjing, China.

Background: Hyperphosphatemia is one of the most common complications of maintenance hemodialysis (MHD) patients, and the association with an increased risk of mortality has been demonstrated. The normalization of phosphate plasma levels is therefore an important goal in the treatment of MHD patients. Accordingly, the potential risk of phosphate removal by hemodialysis (HD) is important to improve phosphate control in patients on maintenance HD.

Methods: 48 MHD patients enrolled in this study underwent three period: one week HD with B3-1.6a (Toray, 1.6m², low-flux) (period 1), then one week HD with TS-1.6SL (Toray, 1.6m², high-flux) (period 2) and switched to another week hemodiafiltration (HDF) with TS-1.6SL (period 3). Each study period was separated by a washout of 2 weeks. Blood samples were collected at 0 min, 30 min, 60 min, 120 min, 180 min, 240 min after the start of dialysis and 60 min postdialysis. Effluent dialysate samples were collected every 15 min during the 4-hour HD treatment to measure the phosphate removal. Predictable levels of serum calcium, potassium, hematocrit, intact parathyroid hormone, alkaline phosphatase Echocardiogram, clinical and dialysis characteristics were obtained.

Results: The reduction of phosphate concentration of blood in dialysis process were 34.74%±6.01%, 48.10%±6.62%, 60.76%±9.98%, 63.81%±7.35%, 63.07%±7.93% at 30 min, 60 min, 120 min, 180 min, 240 min respectively and returned to 52.41%±9.18% at 60 min postdialysis. There were statistical differences in the period 1, period 2 and period 3 at 30min point (29.79%±3.79%, 36.79%±8.82% and 36.64%±5.93%, P=0.000), 60min point (43.36%±6.49%, 49.86%±6.87% and 51.07%±5.44%, P=0.002), 120 min point (56.41%±6.30%, 63.80%±2.72% and 63.29%±2.88%, P=0.007), 240min point (76.54%±5.77% and 76.54%±5.77% between period 4 hour treatment. The first hour of treatment removed 39.85%±5.39% of the total mass, and 24.41%±1.67%, 18.34%±1.94%, 17.52%±3.00% at the second, the third and the forth hour respectively. However, no statistical differences were found in the three periods.

Conclusions: The maximum reduction of blood phosphate concentration was about 60% at 120 min point, and risen again postdialysis. The reduction of blood phosphate concentration was higher with HDF or with high-flux dialyzer.

Funding: Government Support - Non-U.S.
Low Parathyroid Hormone Levels Predict Infection-Related Mortality in Incident Dialysis Patients

Yu ah Hong, Su Hyun Kim, Yong-Lim Kim, Yon Su Kim, Shin-Wook Kang, Seong il Jo, Yoon-Kyung Chang, Suk young Kim, Yong Kyun Kim.

The Catholic University of Korea, Daegu, Republic of Korea; College of Medicine, The Catholic University of Korea, Daegu, Republic of Korea; Chong-Ang University Hospital, Seoul, Republic of Korea; Kyungpook National University Hospital, Daegu, Republic of Korea; Seoul National University College of Medicine, Seoul, Republic of Korea; College of Medicine, BK21, Yussei Univ, Seoul, Republic of Korea.

Background: Background/Aims: Dialysis patients have increased susceptibility to infection, and infection related mortality is considerably high in dialysis patients. Parathyroid hormone (PTH) receptors were located in most immunologic cells, and has been known as an immunoregulatory factor. We evaluated the impact of intact PTH (iPTH) levels on infection related outcomes in incident dialysis patients.

Methods: Methods: Incident dialysis patients were selected from the Clinical Research Center registry a prospective Cohort study on dialysis patients in Korea. Serum iPTH levels were divided into three groups (iPTH <150 pg/mL, 150 ≤ iPTH <300 pg/mL, and iPTH ≥300 pg/mL). The primary outcome was all cause and infection-related mortality and the secondary outcome was infection-related hospitalization.

Results: Results: A total of 1,260 hemodialysis and 511 peritoneal dialysis patients were included. The median follow-up period was 24 months. During follow up period, 1751.711 (9.9 %) was died and 351.722 (2.0 %) was died of infection related cause. Kaplan-Meier analysis showed that the all-cause mortality rates (p < 0.001, Log-rank) as well as infection-related mortality rates (p = 0.003, Log-rank) were significantly higher in patients with lower iPTH levels than in patients with higher iPTH levels. There were no significant differences in infection-related hospitalization rates between those with iPTH levels by KDIGO guideline, 150 ≤iPTH< 300 pg/mL, after adjusting for confounding variables (Hazard Ratio = 2.439 [1.027-5.793], P = 0.043). However, there was no significant risk for all-cause mortality after adjusting for confounding variables.

Conclusions: Conclusion: Low iPTH level was an independent predictor marker of infection related mortality after adjustment of multiple confounders in incident dialysis patients.

TH-PO797


Background: Hepatitis C virus (HCV) infection is still common among dialysis patients. The Centers for Disease Control and Prevention (CDC) recommends that chronic hemodialysis (HD) patients should be screened for HCV antibody upon admission to the dialysis clinic and every six months thereafter if susceptible to HCV infection. However, prevalence data are rare in dialysis patients in anti-HCV-negative HD patients.

Methods: Methods: We examined 41 anti-HCV negative HD patients (M:F = 31:10, median age 42 years, range 18-68), median hemodialysis duration: 29 months (range: 2-345), diagnosed with third generation enzyme immunosassay. One patient was HBsAg positive.

HCV viraemia was evaluated using a sensitive (cut-off 12IU/ml) reverse transcriptase polymerase chain reaction (COBAS AmpliPrep/TaqMan system) test for HCV-RNA.

Results: Results: None of the 41 anti-HCV-negative HD patients were shown to be viremic.

Conclusions: Conclusion: Routine HCV RNA testing appears not to be necessary in HD antibody negative HD patients.

TH-PO798

Direct-Acting Antiviral Agents Therapy Reduce Beta2 Microglobulin Levels of Hemodialysis Patients with Hepatitis C Virus Infection Minoru Itou, Yahuki Hospital, Yamagata City, Japan.

Background: Hepatitis C virus (HCV) infection is still major comorbidity in patients receiving hemodialysis. Recently, the direct-acting antiviral agents (DAAs) against HCV has been allowed to use for end-stage renal disease patients in Japan. Moreover, a prior study reported that HCV infection was related to serum beta2 microglobulin (β2MG) elevation. Beta2MG is known as a causative substance of dialysis-related amyloidosis (DRA). In this study, we evaluated the β2MG lowering effect of the DAAs therapy to hemodialysis patients with HCV infection.

Methods: Methods: We treated 41 HCV (serotype 1)-infected hemodialysis patients with DAAs between October 2015 and April 2017. We prescribed daclatasvir and asunaprevir combination for twelve patients, and elbasvir and grazoprevir combination for four patients. We evaluated the sustained virologic response (SVR) and the serum β2MG level before and after DAAs therapy.

Results: Results: 16 patients were enrolled in this study (age: 62.2 years old, dialysis vintage: 20.4 years, male 12, female 4). All the 16 patients completed the DAAs therapy without remarkable side effects. At the end of treatments, all patients had undetectable HCV RNA levels. However, one patient had a virological failure a month before the start. The serum β2MG levels before the treatment were higher than the target level that several clinical guidelines recommend (β2MG levels of 1.9 mg/L vs. 2.48 mg/L, p=0.0016). β2MG levels of 15 patients with satisfactory results remained lower after several weeks (observational periods) of treatment. A patient with virological failure showed β2MG level increased again immediately.

Conclusions: Conclusion: β2MG-reducing therapies have developed dramatically. Online-hemodialfiltration, hemodialfiltration with high-flux membrane and β2MG apheresis column show high β2MG removal performance. However, these treatments were insufficient for the patients with HCV infection. In this study, we found the β2MG lowering effect of DAAs therapy. DAAs therapy is highly likely to prevent DRA for dialysis patients with HCV infection.
were living near a VA center without a surgeon used a CVC, as compared to 27% who lived near a VA center with a surgeon.

Conclusions: Our findings suggest that incident and prevalent HD patients residing in the proximities of an outpatient VA center with a surgeon on site are more likely to have a permanent access, possibly due to better access to care. Additional studies are necessary to confirm this observation and assess longitudinal trends for VA utilization.

Funding: Commercial Support - Fresenius Medical Care North America

TH-PO794

Attitudes of Dialysis Patients to Information Technology: Disinterest or Overload? Anna B. Ilievama,1 Andrew J. Lin,1,2 University of California Davis, Sacramento, CA;1University of California Davis Medical Center, Sacramento, CA.

Background: The utilization of information technology in enhancing the delivery of healthcare is becoming ubiquitous. Dialysis patients tend to have access to a number of technologies (smart phones, computers etc) and utilize these as an essential part of their daily lives. The question is whether these patients would be interested in incorporating their devices in their overall dialysis and medical care.

Methods: This is an English-language, 1 page questionnaire-based study, of prevalent in-center adult HD patients from 5 clinics in an urban Northern California city. The questionnaires were answered by the patients or read to them and filled out by a nurse. All questionnaires were completed within a one-month period. The questionnaire consisted of 7 "yes or no" questions related to: 1) access to text messages; 2) access to "smart phone" and computer technologies; and 3) willingness to use or receive information on these devices.

Results: Out of a population of 355 in-center HD patients, 245 (69%) completed the questionnaire. In total, 194 patients (79%) could potentially receive text messages; 160 patients (65%) had a phone that could receive text messages. An additional 34 patients had a caregiver who could receive texts. When asked if they would like to receive text message about upcoming medical appointments or dietary reminders such as to take oral phosphate binders, only 90 patients who had access to texts (46%) would be willing to participate. When asked about access to a "smart device" or computer for viewing educational materials, 106 patients (43%) had a "smart phone", 38 patients (16%) had a caregiver with a smart phone, and 22 (9%) had access to a computer. Therefore, 166 (68%) had potential to view educational materials related to diet and overall health on HD, if they brought their device into the clinic. However, when asked if willing to view such videos, only 80 (48% of those with access) indicated a desire to do so.

Conclusions: Most of our in-center HD patients (or through their caregivers) were able to receive text messages for appointment, medication or dietary reminders. However, more than half of the patients who had access to these technologies desire not to participate. This attenuates the main goal of integrating technology platform in dialysis patients care and more research is needed in this regard to fully understand their perceptions of such integration.

TH-PO795

Burden of ESKD in Latin America: An Analysis of the Latin American Registry of Dialysis and Transplantation, Montevideo, Uruguay;1 Hospital Italiano de Buenos Aires, Buenos Aires, Argentina.

Group/Team: RLADTR Delegates.

Background: End Stage Renal Disease (ESKD) represents a major challenge for Latin America (LA). The strategic plan from the Panamerican Health Association (PAHO) has proposed goal for ESKD in LA: Renal Replacement Therapy (RRT) prevalence of at least 700 patients per million population (pmp) in 2014, but only 6 countries have a prevalence above of goal of PAHO. HD prevalence continues to be the choice of treatment (90%). The RRT prevalence correlated positively with GNI (r 0.81; p < 0.001) and life expectancy at birth (r 0.56; p < 0.01). A comparison of 259 incident vs 2333 prevalent patients on hemodialysis (mean values) indicates that there is opportunity to improve predialysis management, especially in terms of earlier placement of a permanent vascular access prior to start of hemodialysis.

Methods: Participant countries completed an annual survey to provide data on incident and prevalent cases of patients undergoing RRT by means of all modalities: Hemodialysis (HD), Peritoneal Dialysis (PD), and transplantation as well as other relevant parameters. Analyses of these variables were performed to determine correlations with GNI and life expectancy at birth as well as other socioeconomic indexes. For the statistical analysis, the Pearson (r) coefficient was applied, and a p-value < 0.05 was considered significant. The incidence and prevalence of RRT in LA countries was compared with developed countries in Europe.

Results: 20 countries participated in the survey, more than 90% of the LA countries. The prevalence of RRT in LA increased from 1991 to 709 patients pmp in 2014, but only 6 countries have a prevalence above of goal of PAHO. HD complications to be the choice of treatment (90%). The RRT prevalence correlated positively with GNI (r 0.81; p < 0.001) and life expectancy at birth (r 0.56; p < 0.01). A wide incidence rate variation was observed, from 420.9 pmp in Jalisco to 22.6 in Paraguay. When compared with the United States data from 2014, incidence in LA, was substantially higher (157.6 vs 370 respectively), but when compared to the European ERA/EDTA registry (133 pmp) the rate is higher in most LA countries. Diabetes remained the leading cause of ESRD in the region. The most frequent cause of death was cardiovascular. There is a wide rate variation of nephrologists by country. The heterogeneity or even the absence of registries in some LA countries is congruent with the inequities in access to RRT in such countries, as well as the availability of qualified personnel. The SLANH in cooperation with PAHO, is currently running training programs as well as cooperation programs between LA countries to support less developed ESKD programs. In this spirit, RLADTR is training personnel to carry out dialysis and transplant registries in LA.

TH-PO796

Outcomes of Chronic Dialysis in Infants under Two Years

Nasathra Jawa,1 Claire M. Gallibors,1 Damien G. Noone.1,2 The Hospital for Sick Children, Toronto, ON, Canada;2Paediatrics, University of Toronto, Toronto, ON, Canada.

Background: Infants with end-stage renal disease require renal replacement therapy in the form of dialysis, until of sufficient weight to be transplanted; typically by age two. Infant dialysis is associated with significant morbidity and mortality. Peritoneal dialysis (PD) has historically been the preferred choice for infant dialysis, due to technical complexities and risk for complications associated with hemodialysis (HD). Management of very young patients on HD has improved in recent years, but outcomes have yet to be assessed. This study retrospectively reviewed long-term patient- and dialysis-specific outcomes of chronic PD and HD in a contemporary cohort of infants less than two years of age and weighing <10 kg at The Hospital for Sick Children, Toronto.

Methods: Infants <2 years of age and <10 kg undergoing chronic dialysis from 2005-2015 were included. Demographic, dialysis-related and outcome data were extracted from patient’s electronic medical records. Summary statistics were analyzed using STATA v.14. Median with interquartile range is provided.

Results: A total of 28 infants (64.3% male) were included. 20 (71.4%) were diagnosed antenatally. Time from birth to dialysis initiation was 13.5 (10, 67) days. 14 (50%) were initiated on PD and 14 (50%) on HD. 8 infants switched modalities a median of 3 (2, 11) times. In patients on PD, the rate of peritonitis was 1 episode/22 patient months. In patients on HD, 11 (64.7%) required a central line change and the central line associated blood stream infection (CLABSI) rate was 1.48 per 1000 central line days. Median time in hospital from dialysis initiation until death/transplant was 8.5 (3.6, 16.7) months. 6 (21.4%) infants died, 17 (61%) were transplanted and 5 (17.9%) remain on dialysis at study end. In those receiving a transplant, median time to transplantation was 2.1 (1.8, 2.7) years.

Conclusions: There has been an increase in the use of HD in recent years. Survival and transplantation rates have improved over time as compared to previously reported rates; however this is associated with prolonged hospital stays and multiple switches between dialysis modalities.

TH-PO797

An International Multicenter Analysis of Incident Patients on Hemodialysis – Practice Patterns, Vascular Access, Demographics and Laboratory Profiles

Alejandro Ferreiro,1 Mciej B. Drozdz,1 Andrew I. Chin.2,3 Werner Kleophas,3 Szymon Brzozko,1 Abdalkareem Abuwaida,1,2 DaVita Poland, Dialystok, Poland;3 Nephrology, Davita, Lisbon, Portugal;2King Saud University, Riyadh, Saudi Arabia; DaVita, Washington, DC;3 DaVita Deutschland, Dusseldorf, Germany;3Nephrology, Dandyer Hospital, Stockholm, Sweden.

Background: Mortality rates are particularly high in the first few months following initiation of hemodialysis. The risk is associated with characteristics of predialysis care including delayed nephrology referral, type of vascular access and failure to attain guideline-based targets. In this study we analyzed the clinical characteristics in a large international cohort of incident dialysis patients from 6 countries.

Methods: We analyzed patient demographics, practice patterns, and laboratory data (February 2017) from 2592 patients (median age: 62 years; 46% female) receiving hemodialysis in 25 DaVita centers in Poland (8 centers, 529 patients), Portugal (5 centers, 529 patients), and Saudi Arabia (12 centers, 1306 patients) with the objective of comparing incident and prevalent patients. We considered the 10th percentile of time on hemodialysis (4.7 months) and compared practices and laboratory data between incident patients (<4.7 months on dialysis; mean 2 months) and prevalent patients (>4.7; mean 34 months).

Results: Incident patients (n=259) were younger (p<0.001) than prevalent patients (n=2333), and had lower Charlson comorbidity index (p<0.001) and BMI (p<0.001). There were significant differences in renal anemia, nutrition, and mineral bone disease variables (Table). Incident patients were more often treated using a central dialysis catheter (CDC, p<0.001). The proportion of patients within treatment targets for K/UV (1.3), Hb (10-12 g/dL), phosphate (<5.5 mg/dL) and albumin (>35 g/L) were all lower in incident patients compared to prevalent patients (all p<0.001).

Conclusions: This large, international, multicenter analysis of incident hemodialysis patients indicates that there is opportunity to improve predialysis management, especially in terms of earlier placement of a permanent vascular access prior to start of hemodialysis. Survival is high after initiation of dialysis, such efforts may contribute to improved treatment results.

Comparison of 259 incident vs 2333 prevalent patients on hemodialysis (mean values)
CHRONIC PAIN: A SIGNIFICANT BURDEN ON LIVES OF DIALYSIS PATIENTS

Research, Minneapolis, MN; 2DaVita, Inc, Denver, CO

Background: Chronic pain is common in end-stage renal disease (ESRD) due to multiple comorbidities as well as the dialysis treatment itself. Given differences in dialysis treatment and underlying health status, it is possible that pain perception and burden may differ for in-center hemodialysis (ICHD) and peritoneal dialysis (PD) patients. We characterized the impact of pain on the daily life among patients treated in a large dialysis organization (LDO).

Methods: Pain was assessed monthly by LDO nurses using the Wong-Baker 0-10 scale (May 2016-April 2017). For those patients indicating the presence of pain (rating ≥ 2), a follow-up survey was administered further assessing pain characteristics and burden.

Results: There were a total of 1,094,897 pain assessments performed for ICHD patients (6.5 screenings per patient on average) and 173,739 for PD patients (7.2 screenings per patient on average). Of these, 161,800 (14.8%) ICHD and 23,101 (13.3%) PD assessments had ratings ≥ 2. Back pain was the most common location for both modalities. ICHD patients were more likely to report dialysis-related pain (8.5% responses; 5.7% in PD) and pain of duration ≥ 3 weeks (73.8% vs. 67.0%). Chronic pain had a great impact on lives of both ICHD and PD patients. Use of pain medications was more common in ICHD (74.8%) vs PD (65.1%). For both modalities, acetaminophen (ICHD 15.4%, PD 13.5%) was more common.

Conclusions: Our results indicate that pain poses a great burden on lives of dialysis patients, affecting many everyday activities and likely contributing to depressive symptoms. Interestingly, perception of pain and its impact were largely similar between ICHD and PD patients, suggesting that the dialysis treatment process may only play a marginal role. There is a need to integrate pain management in the care of dialysis patients in order to optimize quality of life.

Funding: Commercial Support - DaVita, Inc

IMPACT OF PAIN ON QUALITY OF LIFE IN ICHD AND PD PATIENTS

Internet-Based Positive Psychological Intervention for Hemodialysis Patients with Comorbid Depression: Design and Feasibility

Brett Burrows,1 Ken Wilund,1 Michael A. Cohn,2 Judith T. Moskowitz,3 Shuo Xu,3 Rosalba Hernandez.1 University of Illinois at Urbana-Champaign, Urbana, IL;2 University of California San Francisco, San Francisco, CA;3 Northwestern University, Chicago, IL

Background: Depression is the most pervasive psychological issue facing hemodialysis (HD) patients and treatment strategies have mainly concentrated on the use of pharmacotherapy. Alternative treatment strategies that circumvent drug-related side effects and poor medication adherence (i.e., psychosocial interventions) have not been the focus for therapy and few published studies exist. The aim of the current trial was to determine the feasibility and acceptability of a 5-week Internet-based positive psychological intervention in HD patients with comorbid depression.

Methods: HD patients (n=14) with elevated symptoms of depression were enrolled in a single-arm pre-post pilot trial with clinical assessments at baseline and immediately post intervention. Chairside during regularly scheduled HD treatment, patients completed online modules promoting skills for increasing positive emotion over a 5-week period using an Apple IPad. Targeted skills included noting of daily positive events, cultivation of gratitude, practicing positive reappraisal, partaking in acts of kindness, and engagement in mindfulness/meditation.

Results: Mean age was 57.4 years; 50% female; 50% non-Hispanic White; mean duration on dialysis was 3.6 years. Twelve of 14 patients completed the program for an 85.7% retention rate. Participants felt satisfied overall with each session and offered feedback for depression symptoms (15.3 vs. 10.9, p=0.04) as measured by the Center for Epidemiological Studies Depression Scale. Statistical trends indicated clinically meaningful improvement in emotional well-being, kidney disease burden, and quality of social interactions as per the Kidney Disease Quality of Life Instrument.

Conclusion: This study indicates that an innovative and low-cost Internet-based positive psychological intervention represents a feasible and useful therapeutic option for HD patients with comorbid depression. This psychosocial strategy can be a valuable self-guided tool that reduces costly face-time with clinical staff.

Impact of Baseline Scores on the Responsiveness of Quality of Life (QOL) Tools to Interventions: An ACTIVE Dialysis Trial Secondary Analysis

Meg J. Jardine,1,2 Brendan Smyth,1,2 Oliver van den Broek-Best,1,3 Nicholas A. G. de Vries,1,4 Christoper T. Chan,5 Janak R. de Vries,5 Kirsten Howard,1 Kris Rogers,1 Vlado Perkovic,1 The George Institute for Global Health, UNSW, Sydney, NSW, Australia; 2Nephrology, Concord Repatriation General Hospital, Sydney, NSW, Australia; 3University of Sydney, Sydney, NSW, Australia; 4Sunshine Coast University Hospital, Birtinya, NSW, Australia; 5Toronto General Hospital, Toronto, ON, Canada; 6Waiitmaru District Health Board, AUCKLAND, New Zealand; 7School of Public Health, University of Sydney, Sydney, NSW, Australia. Group Team: ACTIVE Dialysis Steering Committee.

Background: There is little clarity on the relative validity, reproducibility and generality of available tools for measuring the patient experience in the trial context. The ACTIVE Dialysis trial found no benefit from extended hemodialysis (HD) hours for the utility-based QOL measure, EQ-SD, with small but significant benefits for generic health-related SF-36 QOL. Participants in extended hours trials have better average health than patients overall raising the possibility EQ-SD responsiveness may be limited by a ‘ceiling’ effect. Aim: To explore whether the impact of extended hours HD on QOL scores is dependent on baseline scores.

Methods: The ACTIVE Dialysis trial randomized 200 HD patients to standard (median 12) or extended (median 24) weekly HD hours for 12 months. Dialysis population-validated QOL assessments including the EQ-5D utility instrument and SF-36 Physical (PCS) and Mental (MCS) Composite Scores were administered by blinded interviewers during the trial. After confirming the absence of an interaction of the score with time, the average intervention effect was determined using mixed linear regression and analysed in subgroups defined by tertiles of the relevant baseline score.

Results: Overall extended weekly HD hours had no impact on EQ-SD (mean difference 0.05, CI 0.03-0.09, p=0.60) with small but significant improvements in PCS and MCS (mean difference PCS 2.30, 95%CI 0.32-4.27, MCS 2.54, 95%CI 0.43-4.65). The lack of impact on EQ-SD results were consistent across all tertiles (lowest third 0.01 [CI 0.12-0.14, p=0.89], middle third 0.05 [CI 0.03-0.13, p=0.26], highest third 0.02 [CI 0.07-0.12, p=0.50], p-interaction 0.80). The benefits for PCS and MCS were similarly consistent across tertiles (p-interaction: PCS 0.96; MCS 0.34).

Conclusions: These findings indicate that hemodialysis patients who screen positive for depression are more likely to be hospitalized and be non-adherent to dialysis treatment schedules. Since the PHQ-2 may underestimate actual depression rates, our results represent conservative estimates of the possible impact of depression on clinical outcomes. Clinical initiatives should be designed to specifically target high-risk patients who screen positive for depression.

Funding: Commercial Support - DaVita, Inc

IMPACT OF PAIN ON QUALITY OF LIFE IN ICHD AND PD PATIENTS

Hospitalization and Missed Dialysis Treatments Are More Common in Hemodialysis Patients with Depressive Symptoms

Kathryn M. Aebel-Groesch,2 Duane V. Dunn,3 Angie Major,1 Sean Mayes,2 Deborah A. Benner,2 Francesca Tentori,1 DaVita Clinical Research, Minneapolis, MN; 2DaVita, Inc, Denver, CO.

Background: Depression is common in end-stage renal disease and is likely to have a negative impact on patient engagement in self-care and clinical outcomes. Here we characterized incidence of hospitalization and missed dialysis treatments among in-center hemodialysis patients who screened positive for depressive symptoms.

Methods: We analyzed data from a large dialysis organization electronic health record database. Depression screenings were performed biannually (May 2016-April 2017) with the PHQ-2 scale (range 0-6). Patients with active diagnosis of depression, bipolar disorder, cognitive impairment, language barriers, or who were hospitalized were not screened. Rates of hospitalization and of missed dialysis treatments due to non-adherence in the 3 months after screening were compared in patients with depressive symptoms (PHQ-2 score ≥ 2) and those without.

Results: A total of 54,441 (17.3%) screenings were positive for depression. The hospitalization rate was higher among those with depressive symptoms compared to those without (2.2 vs 1.5 admissions per patient-year). Patients who screened positive for depression were also more likely to miss dialysis treatments (7.7 vs 5.1 missed HD session per patient-year). Overall, patients with higher PHQ-2 scores were more likely to have higher hospitalization and missed treatment rates.

Conclusions: These findings indicate that hemodialysis patients who screen positive for depression are more likely to be hospitalized and be non-adherent to dialysis treatment schedules. Therefore the PHQ-2 may underestimate actual depression rates, our results represent conservative estimates of the possible impact of depression on clinical outcomes. Clinical initiatives should be designed to specifically target high-risk patients who screen positive for depression.

Funding: Commercial Support - DaVita, Inc
Conclusions: The impact of extended dialysis hours on EQ-5D, PCS and MCS QOL was not dependent on baseline scores. The scores appear to be at least internally robust to variation in baseline QOL. NCT00649298

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

TH-PO082
Identifying the Critical Dimensions of Fatigue for a Core Outcome Measure for Trials in Haemodialysis: An International Survey

Angela Ju,1 Mark L. Unrth,2 Jonathan C. Craig,3 Allison Tong,1 The University of Sydney, Sydney, NSW, Australia; 3University of New South Wales, Sydney, Australia; 4Dongguk University, South Korea

Background: Measures of fatigue used for research in patients on haemodialysis have differing dimensions, length, and scales. The extent to which of the dimensions of fatigue are valued by patients and health professionals are unknown.

Methods: An online survey was conducted among patients/caregivers and health professionals in English and Spanish. The survey consisted of 11 content dimensions of fatigue such as ‘life participation’ and ‘muscle weakness’, and 4 modes of assessment such as ‘severity’ and ‘frequency’, identified in existing measures. A 9-point Likert scale was used to assess absolute importance and relative importance obtained from a best-worst scale (BWS) task. Multivariate regression analysis was used to examine the Likert scores and mixed-multinominal regression for the BWS scores.

Results: 1,065 English-speaking and 463 Spanish-speaking respondents completed the survey. 39% of respondents had a primary renal disease, 57% had chronic renal disease, and 80% had diabetes as a co-morbidity. ‘Life participation’ and ‘Muscle weakness’ were the most important dimensions in both English and Spanish surveys.

Conclusions: Impact of fatigue on life participation was identified as a critical dimension of fatigue, and severity the most important metric. Differences in relative importance of fatigue dimensions suggest cultural differences in priorities. The core outcome measure for fatigue should include severity of impact upon life participation with consideration of cultural validity.

Funding: Government Support - Non-U.S.

TH-PO083
The Association of RAAS Blockade and the Progression of Residual Kidney Function Decline: A Nationwide Prospective Cohort Study

Yunmi Kim,1 Kyung Don Yoo,2 Clara T. Kim,3 Yun Kyu Oh,3 Shin-Wook Kang,3 Chul Woo Yang,3 Yong-Lim Kim,3 Yun Soo Kim,3 Chon SooLim,3 Jung Pyo Lee,4 College of Medicine, BK21, Yonsei University, Seul, Republic of Korea; 2Seoul St. Mary’s Hospital, Seoul, Republic of Korea; 3Department of Internal Medicine, Boramae Medical Center, Seoul, Republic of Korea; 4Dongguk University, Gyeongju Hospital, Gyeongsangbuk-do, Republic of Korea

Background: RAAS blockade failed to clarify the protective effect for RRF. Further research is needed to provide optimal treatment for ESRD patients undergoing dialysis and correlated well with physical activity questionnaires used in general population. However, this instrument has not been validated against a more objective measure.

Methods: We performed a cross-sectional study and recruited 55 ambulatory patients receiving HD or PD for at least 3 months from 3 dialysis facilities in San Francisco during 2016-7. Spontaneous walking activity was measured by pedometers over 7 days including a dialysis-free weekend and used as the reference. Patients were instructed to record their activities and step count readings. Study coordinators administered the LoPAQ and recorded patients’ responses during a dialysis session (HD) or clinic visit (PD).

Results: Fifty-two dialysis patients (HD=45, PD=7) completed the LoPAQ. Mean age was 57±12 years with 80% men. Median dialysis vintage was 39 (IQR, 17-70) months. Total daily activity in kcal/wk was 2052±1176 kcal/wk. Patients with high step counts had improved QOL (r=0.88, p=0.001).

Conclusions: The LoPAQ was easier and less time-consuming than previously validated physical activity questionnaires. LoPAQ demonstrated a good correlation, similar to other widely used physical activity instruments, with objective pedometer step counts among dialysis patients.

Funding: NIDDK Support

TH-PO084
Validation of a New Physical Activity Instrument against Pedometers among Dialysis Patients

Piyawan Kittiskulnam,1 Anoop Sheshadri,2 Kirsten L. Johansen,1 Chulalongkorn University, Bangkok, Thailand; 2None, San Francisco, CA; 3University of California, San Francisco, San Francisco, CA

Background: The newly developed Low Physical Activity Questionnaire (LoPAQ) was designed to capture the low activity level among physically inactive patients undergoing dialysis and correlated well with physical activity questionnaires used in general population. However, this instrument has not been validated against a more objective measure.

Methods: We performed a cross-sectional study and recruited 55 ambulatory patients receiving HD or PD for at least 3 months from 3 dialysis facilities in San Francisco during 2016-7. Spontaneous walking activity was measured by pedometers over 7 days including a dialysis-free weekend and used as the reference. Patients were instructed to record their activities and step count readings. Study coordinators administered the LoPAQ and recorded patients’ responses during a dialysis session (HD) or clinic visit (PD).

Results: Fifty-two dialysis patients (HD=45, PD=7) completed the LoPAQ. Mean age was 57±12 years with 80% men. Median dialysis vintage was 39 (IQR, 17-70) months. Total daily activity in kcal/wk was 2052±1176 kcal/wk. Patients with high step counts had improved QOL (r=0.88, p=0.001).

Conclusions: The LoPAQ was easier and less time-consuming than previously validated physical activity questionnaires. LoPAQ demonstrated a good correlation, similar to other widely used physical activity instruments, with objective pedometer step counts among dialysis patients.

Funding: NIDDK Support

TH-PO085
Incidence and Association of Urologic Malignancies with ESRD: A Meta-Analysis

Patricia C. Komaritis,1 Charu Thongprayoon,1 Sandhya Manohar,2 Wisit Cheungpuisophon,2 Sandra Herrmann,3 Bassett Medical Center, Cooperstown, NY; 2Mayo Clinic, Rochester, MN; 3Nephrology, Mayo Clinic, Rochester, MN.

Background: Previous studies have suggested higher incidence of urologic malignancies in patients with end-stage renal disease (ESRD). However, incidence trends of urologic malignancies in ESRD patients remain unclear. The study’s aims were 1) to investigate the pooled incidence/incidence trends 2) to assess the risks of urologic malignancies in ESRD patients.

Methods: A literature search was performed using MEDLINE, EMBASE and Cochrane Database from inception through April 2017. Studies that reported incidence or odd ratios (OR) of urologic malignancies among ESRD patients were included. Pooled OR and 95%CI were calculated using a random-effect model. The protocol for this study is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42017067687).

Results: Eighteen observational studies with 1,872,952 ESRD patients were included. The pooled estimated incidence of kidney cancer and bladder cancer in ESRD patients were 0.4% (95%CI: 0.3%-0.6%) and 0.5% (95%CI: 0.3%-0.7%), respectively. Meta-regression showed significant positive correlation between incidence of urologic malignancies in ESRD patients and year of study (slopes=0.06, p=0.001 for both kidney and bladder cancers). Compared to non-ESRD status, ESRD was significantly associated with both kidney cancer (pooled OR 5.68; 95% CI 4.39-7.35) and bladder cancer (pooled OR 3.82; 95% CI 2.51-5.82).

Conclusions: Our study demonstrates a significant association between ESRD and urologic malignancies. The overall estimated incidence rates of kidney cancer and bladder cancer are 0.4% and 0.5%, respectively. There is also a significant positive correlation between the incidence of urologic malignancies and year of study.

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

Underline represents presenting author.
TH-PO806


Background: Prior studies have defined “early” vs. “late” renal replacement therapy (RRT) initiation based on eGFR at the time of RRT. Few studies have described timing of RRT based on time spent in CKD stage 5. Our goal was to compare time that could be spent in CKD stage 5 if RRT were initiated after a fall in eGFR to below 5mL/min/1.73 m\(^2\) (a conservative threshold for RRT) vs. actual observed time spent in CKD stage 5.

Methods: We used mixed models to estimate the person-specific trajectory of renal function decline (using all eGFRs prior to RRT) among 736 Chronic Renal Insufficiency Cohort (CRIC) participants followed longitudinally for 9.6 years who eventually began RRT. We used these trajectories to estimate the expected amount of time in CKD stage 5 (between eGFR of 15 and 5mL/min/1.73 m\(^2\)), which we compared to the observed time spent in CKD stage 5 (until actual receipt of RRT). We then tested for differences between predicted and actual times in stage 5 according to known risk factors for CKD progression.

Results: Overall, the median difference between the predicted and actual time spent in CKD stage 5 was 9.6 months (i.e., patients started RRT 9.6 months before they were predicted to reach an eGFR of 5mL/min/1.73 m\(^2\)). Variations in the predicted time in CKD stage 5 were observed by race and ethnicity, co-morbidities, and laboratory parameters, but not by age or sex (figure). In general, patients at lower risk of progression were started earlier than those at higher risk (Figure), with the time difference being largest among white patients (10.1 months), those with SBP <140 mmHg (9.7 months) and proteinuria <1 g/g (9.1 months).

Conclusions: We found marked differences in the actual vs. predicted amount of time spent in CKD stage 5 based on various risk factors of interest. RRT initiation occurred 10 months earlier than would be expected based on projected time to eGFR of <5 mL/min/1.73 m\(^2\). Given the lack of mortality benefit to early RRT initiation, we have identified subgroups that may especially benefit from more a concerted effort to delay RRT.

Funding: Other NIH Support- NHLBI

TH-PO807

Association between Low-Molecular-Weight Heparin and Risk of Bleeding among Hemodialysis Patients: A Retrospective Cohort Study

Study Hind H. Luzrak,1 Emilie Rene,1 Naoual Elftouh,1 Annie-Claire Nadeau-Fredette,2 Louis-Philippe Laurin,1,3 Jean-Philippe Lafrance,1,2 Research center, Maisonneuve-Rosemont hospital, Montreal, QC, Canada; 1Division of nephrology, Maisonneuve-Rosemont hospital, Montreal, QC, Canada.

Background: Low molecular weight heparins (LMWH) replaced unfractionated heparin (UFH) in multiple indications. While their efficacy in hemodialysis was proved through multiple studies, their safety remains controversial. The potential bioaccumulation in patients undergoing chronic hemodialysis raised the question of bleeding risk among this population. The aim of this study was to evaluate bleeding risk among patients with chronic hemodialysis receiving LMWH or UFH for the extracorporeal circuit anticoagulation.

Methods: We conducted a retrospective cohort study of patients undergoing chronic hemodialysis in 22 participating centers using data extracted from administrative databases in Quebec, Canada, from January 2007 to March 2017. Minor, major and total bleeding risk for a first event with LMWH compared to UFH was estimated using a proportional Cox model with time-dependent exposure using demographics, comorbidities and drug use as covariates.

Results: We identified 5322 prevalent and incident chronic hemodialysis patients. The incidence rate for minor, major and total bleeding was 9.5 events /1000 patient-year (95%CI: 7.6-11.0), 2.42 events /1000 patient-year (95%CI: 2.15-2.71) and 32.9 events /1000 patient-year (95%CI: 29.8-36.3) respectively. We found similar risks of minor (adjusted hazard ratio (HR)=1.04; 95%CI: 0.67-1.61), major (HR=0.84; 95%CI: 0.64-1.10) and total bleeding (HR=0.91; 95%CI: 0.72-1.15) when comparing LMWH to UFH.

Conclusions: LMWH was not associated with a higher minor, major or total bleeding risk compared to UFH in a large cohort of chronic hemodialysis patients. LMWH is a suitable alternative to UFH in hemodialysis.

TH-PO808

Survival in Patients on Hemodialysis: Effect of Sex According to Body Mass Index and Creatinine

Mas Index and Creatinine Jong-Hak Lee,1 Jeong hoon Lim,1 Min-soo Han,1 Hee-Yeon Jung,2 Ji-Young Choi,3 Sun-Hee Park,1 Chan-Duck Kim,2 Jong-Hee Cho,3 Yong-Lim Kim,3 1Daegu Fatima Hospital, Daegu, Republic of Korea; 2Kyungpook National University Hospital, Daegu, Republic of Korea; 3Kyungpook National University School of Medicine, Daegu, Republic of Korea.

Background: The association of a higher body mass index (BMI) with better survival is a well-known “obesity paradox” in patients on hemodialysis (HD). However, men and women have different body compositions, which could impact the effect of BMI on mortality. We investigated the effect of sex on the obesity-mortality relationship in Korean patients on HD.

Methods: This study included 2,833 maintenance patients on HD from a multicenter prospective cohort study in Korea (NCT00931970). The relationship between categorized BMI and sex-specific all-cause mortality was analyzed by an adjusted Cox proportional hazard model with restricted cubic spline analyses. We also investigated the effect of changes in BMI over 12 months and serum creatinine level on survival in male and female patients on HD.

Results: The mean BMI was 22.6 ± 3.3 kg/m\(^2\) and the mean follow up duration was 24.2 ± 3.4 months. The patients with the highest quintile of BMI (≥25.1 kg/m\(^2\)) showed lower mortality (Hazard ratio [HR]=0.63, 95% confidence interval [CI]=0.42-0.95, P=0.026) compared with those with the reference BMI quintile. When analyzed by sex, male patients with a BMI over 25.1 kg/m\(^2\) had lower mortality risk (HR=0.43, 95% CI=0.25-0.75, P=0.003); however, no significant difference was found in female patients. Increased BMI after 12 months and high serum creatinine were associated with better survival only in male patients on HD.

Conclusions: BMI could be used as a risk factor for mortality in male patients on HD. However, the mortality of female patients on HD was not related with baseline

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

308
and follow-up BMI. This suggests that BMI is a good surrogate marker of lean body composition, especially in male patients on HD.

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

**TH-PO809**

**Pre- and Post-ESRD Trajectories of Serum Albumin among Incident ESRD Patients: A Transition of Care in CKD Study**

**Patricia W. Lee,1 Melissa Soochoo,2 Christina Park,2 Connie Rhuec,2 Csaba P. Kovesdy,3 Kamyar Kalantar-Zadeh,2 Elani Streja.2 UCLA, Los Angeles, CA; 3UC Irvine, Orange, CA; 4University of Tennessee Health Science Center, Memphis, TN.**

**Background:** Hypoalbuminemia is a strong predictor of mortality in chronic kidney disease patients, however the extent of change in serum albumin (Alb) in the year surrounding transition to end-stage renal disease (ESRD) is relatively unknown.

**Methods:** We examined serum Alb trajectories in the 1-year pre- and post-ESRD initiation for patients who transitioned to ESRD from 2007-2010 using a mixed-effects regression model. Trajectories were stratified by baseline Alb levels in the 6-month pre-ESRD (prelude) period. Finally, we examined the association of 1-year pre-ESRD Alb slope with early mortality using Cox models adjusted for demographics and lab variables.

**Results:** The mean±SD age of the cohort was 68±11 years and included 2% females and 30% blacks. The median[IQR] of 1-year prelude Alb slope was -0.22[-0.48, 0.23] g/dL/year. Among baseline Alb 2.8±g/dL, there was a sharp decline at initiation and a slow rise then plateau towards a normal range in the year after initiation. In patients with Alb <2.8 g/dL, there was a steep drop and a sudden increase in Alb in the few months surrounding transition. Moreover, a steep drop in pre-ESRD Alb of greater than -0.5 g/dL/year was associated with the highest risk of early 12-month post-ESRD mortality compared to no change in Alb slope [HR[95%CI]: 1.07[1.01, 1.13].

**Conclusions:** Across baseline albumin levels, pre-ESRD serum albumin tends to drop and then rise in the months around ESRD transition, while distinctions are observed for low baseline Alb. Also, a drop in Alb was associated with a higher risk of early mortality. Screening for rapid drops in Alb in the prelude period may identify those at greatest risk of early ESRD mortality. Further studies are required to determine if dietary and medication intervention to maintain elevated Alb impacts early ESRD outcomes.

**Funding:** NIDDK Support

**TH-PO810**

**Employment among Patients Starting Dialysis in the United States**

**Kevon F. Erickson,2 Bo Zhao,2 Vivian Ho,1 Wolfgang C. Winkelmaier.2 1Baker Institute for Public Policy, Houston, TX; 2Baylor College of Medicine, Bellaire, TX.**

**Background:** Patients with end-stage renal disease (ESRD) face significant challenges to remaining employed, and the rate of employment among the prevalent population of patients receiving dialysis is low. It is unknown when in the course of their kidney disease patients stop working. We examined employment trends among patients in the United States who are initiating dialysis and in the six months prior to ESRD.

**Methods:** We selected patients aged 18-54 who initiated dialysis between 1996 and 2013 from a U.S. registry of patients with ESRD. We compared unadjusted trends in employment at the start of dialysis and six months prior to ESRD, and used linear probability models to estimate changes in employment over time after adjusting for patient health, demographic and socioeconomic characteristics along with local unemployment rates in the general population. We also examined employment among selected vulnerable patient populations.

**Results:** Employment was low among patients starting dialysis throughout the study period at 22%-23%. However, after adjusting for observed characteristics, the probability of employment increased over time; patients starting dialysis between 2008 and 2013 had a 25 percentage points higher chance of being employed six months prior to ESRD, and used linear probability models to estimate changes in employment over time after adjusting for patient health, demographic and socioeconomic characteristics along with local unemployment rates in the general population. We also examined employment among selected vulnerable patient populations.

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

**Underline represents presenting author.**
understand determinants for dialysis clearance and mineral bone disease with patients satisfaction. More is also needed to understand factors behind relationship of for-profit status and dialysis unit size with patients satisfaction.

**TH-PO813**

## Trends in Insurance Coverage among ESRD Medicare Beneficiaries

**Claudia Dahleen, John Wheeler, J. M. Messana, John Stephen, Tempie H. Shearon, Yi Li. University of Michigan, Kidney Epidemiology and Cost Center, Ann Arbor, MI.**

**Background:** The 2010 Patient Protection Affordable Care Act (ACA) reduced the number of uninsured in the U.S. general population. Most ESRD patients are eligible for and covered by Medicare; however, it is unclear how implementation of the ACA impacted insurance status for ESRD Medicare beneficiaries. The ACA increased access to Medicaid for more people and made it possible for more people to purchase private health insurance. This potentially resulted in an increase in patients with Medicare/Medicaid Dual Eligibility (DE) coverage. Our objective is to examine whether there were changes in insurance status of ESRD dialysis patients in the initial period following ACA implementation.

**Methods:** Administrative data (Medicare claims files and Medicare Enrollment Data Base for 2012-2015) were used to classify ESRD dialysis patients by whether they were covered by both Medicare and Medicaid (Medicare/Medicaid DE). Trends were examined for coverage changes.

**Results:** From 2012-2015, there was an increase of 9.7% in the number of patients with ESRD eligible for Medicare. Over this period, the number of DE patients increased by 14.9%. Therefore, the percentage of Medicare ESRD patients with DE rose steadily from 56.8% in 2012 to 61.9% in 2015.

**Conclusions:** The ACA extended Medicaid eligibility to more people in states choosing to participate in the Medicaid expansion. As a result, the trend in growth of persons with Medicare-Medicaid dual eligibility exceeded that of the overall Medicare ESRD population. This aspect of the ACA may therefore have improved access to dialysis care for more relatively low income people, by enabling them to afford the coinsurance and deductibles of the Medicare ESRD Program.

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

Number of ESRD Beneficiaries by Insurance Coverage and Year

<table>
<thead>
<tr>
<th>Insurance Coverage</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicare/Medicaid DE Eligible</td>
<td>185,796</td>
<td>191,770</td>
<td>187,349</td>
<td>192,634</td>
<td>13.2%</td>
</tr>
<tr>
<td>Medicare Only</td>
<td>421,699</td>
<td>436,738</td>
<td>448,611</td>
<td>457,568</td>
<td>2.0%</td>
</tr>
<tr>
<td>All Medicare</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.7%</td>
</tr>
</tbody>
</table>

**TH-PO814**

## Utilization of Benchmarks to Reduce Transportation Costs for Dialysis Patients

**Terri L. Ketcher,1 Michael P. Martin,1 Chris Richmond,1 Greg S. Garza,2 Daniel E. Geary,1 John W. Larkin,1 Marta Reviriego-Mendoza,2 Len A. Usyut,1 Franklin W. Maddux,1 Fresenius Health Partners, Austin, TX;2 Fresenius Medical Care North America, Waltham, MA.**

**Background:** End stage renal disease (ESRD) patients have high costs for transportation services. We examined if using benchmark data to identify outliers was associated with reductions in transportation costs. Through the Comprehensive ESRD Care (CEC) Model, Fresenius Medical Care, North America (FMCNA) has partnered with CMS to identify, test, and evaluate new ways to improve care for Medicare beneficiaries with ESRD. We examined if using benchmark data to identify outliers was associated with reductions in transportation costs.

**Methods:** We analyzed annual transportation costs and monthly treatment rates before and after the implementation of the initiatives.

**Results:** Mean transportation cost was $174 per member per month (PMPM) at the six ESCOs in 2015. ESCO “A” and “B” were identified as outliers with a transportation cost of $681 PMPM, and $263 PMPM, respectively. After implementation of the QI initiatives, ESCO “A” and “B” showed decreased transportation cost PMPM of 25% and 30%, respectively. As % of total PMPM, there was a decrease of 19% in transportation cost PMPM for ESCO “A”, and a 30% decrease for ESCO “B”. Associated with these QI initiatives, ESCO “A” and “B” recognized year-over-year reductions in transportation costs equal to $1,798,940 and $791,185, respectively. We found no differences in dialysis treatment rates before and after the implementation of the initiatives.

**Conclusions:** Our findings suggest that benchmarking transportation costs in ESCOs may help to identify outliers and lead providers to implement QI initiatives to reduce healthcare costs.

**Funding:** Commercial Support - Fresenius Medical Care North America
TH-PO816

Socioeconomic Status and Dialysis Quality of Care

Sreedevi K. Jetha,1 Paul D. Lawton,2 Nicholas A. Gray.3
1Sunshine Coast University Hospital, Birtinya, QLD, Australia; 2University of Queensland School of Medicine, Brisbane, QLD, Australia; 3Menzies School of Health Research, Casuarina, NT, Australia.

Background: Socioeconomic status (SES) has been associated with increased mortality in end stage kidney disease (ESKD) populations across USA, South America, Europe and Australia, less is known about the association between SES and the quality of care (QOC) delivered to dialysis patients.

Methods: This study included all non-Indigenous adults commencing hemodialysis (HD) or peritoneal dialysis (PD) registered between 2002 and 2012 (n=16867). Each patient’s location at dialysis start was classified into SES quartiles of advantaged through to disadvantaged using Australian Bureau of Statistics socio-economic indexes for areas. National and international guidelines were used to set limits for QOC attainment. The association between area-level SES and attainment of QOC indicators at 6-18 months and 18-24 months after dialysis start were assessed using logistic regression models. QOC measures included pre-dialysis phosphate, calcium, hemoglobin, transferrin saturation and ferritin. HD-related parameters included single pool Kt/V and percentage with functioning arteriovenous fistula/graft. PD-related parameters included weekly Kt/V and percentage lost to HD.

Results: The median age was 65 years (interquartile range 53-74), 62.2% were male and 85.1% were Caucasian. There were no significant differences in attainment of biochemical targets, PD or HD adequacy between the SES quartiles at 6-18 months after dialysis commencement. The least advantaged quartile were less likely to achieve hemoglobin target [Odds Ratio (OR) 0.89, 0.79-0.99, p=0.03] or to have a functioning fistula or graft [OR 0.75, 0.61-0.94, p=0.01] compared with the most advantaged group at 18-24 months.

Conclusions: Area-level SES has minimal impact on QOC attainment among non-Indigenous dialysis patients in Australia, where all residents have equal access to government funded healthcare. Increased mortality in lower SES groups is therefore likely due to pre-dialysis, other area-level and individual patient factors such as health-related behaviors, lifestyle and literacy, rather than disparities in QOC.

Funding: Government Support - Non-U.S.

TH-PO817

CAHPS Domains as Predictors of Dialysis Facility Star Ratings and QIP

Abhijit V. Kshirsagar,1 Amir Alishehhatabi,2 Heejung Bang,3 Shou-Yih D. Lee.1 1The University of North Carolina at Chapel Hill, Chapel Hill, NC; 2UC-Davis, Davis, CA.

Background: Recent national initiatives have focused on differing aspects of dialysis care quality in the United States. The Dialysis Facilities Compare (DFC) star rating & the Quality Incentive Program (QIP) generate distinct scores from clinical measures to quantify care quality. The Consumer Assessment of Healthcare Providers and Systems (CAHPS) survey evaluates the patient experience to assess the perceived quality of care (QOC). We analyzed data from 2016. With the CAHPS domains as independent variables, we calculated odds of a 5-star rating or high QIP.

Methods: This study included all non-Indigenous adults commencing hemodialysis (HD) or peritoneal dialysis (PD) registered between 2002 and 2012 (n=16867). Each patient’s location at dialysis start was classified into SES quartiles of advantaged through to disadvantaged using Australian Bureau of Statistics socio-economic indexes for areas. National and international guidelines were used to set limits for QOC attainment. The association between area-level SES and attainment of QOC indicators at 6-18 months and 18-24 months after dialysis start were assessed using logistic regression models. QOC measures included pre-dialysis phosphate, calcium, hemoglobin, transferrin saturation and ferritin. HD-related parameters included single pool Kt/V and percentage with functioning arteriovenous fistula/graft. PD-related parameters included weekly Kt/V and percentage lost to HD.

Results: The median age was 65 years (interquartile range 53-74), 62.2% were male and 85.1% were Caucasian. There were no significant differences in attainment of biochemical targets, PD or HD adequacy between the SES quartiles at 6-18 months after dialysis commencement. The least advantaged quartile were less likely to achieve hemoglobin target [Odds Ratio (OR) 0.89, 0.79-0.99, p=0.03] or to have a functioning fistula or graft [OR 0.75, 0.61-0.94, p=0.01] compared with the most advantaged group at 18-24 months.

Conclusions: Area-level SES has minimal impact on QOC attainment among non-Indigenous dialysis patients in Australia, where all residents have equal access to government funded healthcare. Increased mortality in lower SES groups is therefore likely due to pre-dialysis, other area-level and individual patient factors such as health-related behaviors, lifestyle and literacy, rather than disparities in QOC.

Funding: Government Support - Non-U.S.

TH-PO818

Patient Reported Clinical Symptoms Are Associated with Patient Outcomes

Dugan Maddux,1 Hao Han,2 John W. Larkin,3 Len A. Usuyat,4 Frank van der Sande,2 Jeroen Kooman,3 Franklin W. Maddux.1 1Fresenius Medical Care North America, Waltham, MA; 2Maastricht University Medical Centre, Maastricht, Netherlands.

Background: Traditional outcomes-related research on dialysis patients typically focuses on biomarkers such as blood pressure, body size, albumin (ab) and hemoglobin. During dialysis treatment, however, nurse-reported “chairside” patient information is also collected, and majorly includes patients’ symptoms that may have an effect on patients’ clinical outcomes. The association of chairside data with patient outcomes has not been well described. We aim to understand the relationship of “shortness of breath” (SOB), a nurse-reported patient symptom, to patient outcomes.

Methods: We included all patients who initiated dialysis treatment in the network of Fresenius Medical Care North America clinics between Jan 1, 2013 and June 30, 2015. Only patients who survived the first 365 days on dialysis were included. Patient laboratory and treatment parameters including The Kidney Disease Quality of Life (KDQOL) survey were computed as averages of the first year on dialysis. Patient hospitalization outcomes were assessed in year 2 on dialysis. We computed percent of treatments where patients experienced SOB symptoms as determined by either nursing notes or checkbox-based assessment in the electronic health record. A Poisson model using hospital admissions as an outcome was utilized to calculate the association of SOB to hospital admissions.

Results: We analyzed data on 39,594 dialysis patients. In a univariate analysis, we noted that the strongest correlation with percent of treatments with SOB were hospital admission rate (r=0.14, p<0.001), ab level (r=-0.09, p<0.001), KDQOL physical composite score (r=-0.12, p<0.001), and KDQOL symptom problem score (r=-0.11, p<0.001). We also observed that the percent of treatments with SOB was clearly significantly associated with more hospital admissions.

Conclusions: Chairside observation and clinician documentation of patient-reported symptoms may be an important predictor of outcomes in dialysis patients. Additional analyses are needed to understand the association of SOB and other symptoms to patient outcomes.

Funding: Commercial Support - Fresenius Medical Care North America

TH-PO819

Transplantation as a Competing Risk in Dialysis RCTs

Chiristos Argyropoulos,1 Maria-Eleni Roumeliotis,4 Mark L. Unruh,2 V. Shawn Pankratz,1 Francesco Locatelli,4 Adelheid Gauly1 1Azienda Ospedaliera Della Provincia di Lecco-Ospedale Alessandro Manzoni, Lecco, Italy; 2University of New Mexico, Albuquerque, NM; 3University of New Mexico, Albuquerque, NM; 4University of New Mexico, Albuquerque, NM.

Background: Transplantation is a competing risk and potential confounder in the analysis of outcomes in ESRD RCTs. We examined whether results of RCTs are affected by the method to account for these informative censoring events.

Methods: We analyzed patient level data from the NIDDK sponsored HEMO and the EuroHaemo PO RCTs of high flux (HF) membranes. Together these two studies contribute 96% of the evidence for the use of HF in clinical practice. We compared conventional Cox proportional hazards (CPH) models and methods for competing risk events (cumulative incidence functions, CIF) and relevant regrssions models.

Results: In HEMO there were 194 transplantation out of 1846 patients; 170 out of 647 participants were transplanted during MPO. In unadjusted analyses of CIF,[figure], HF dialysis was not associated with improved survival (p=0.20). In adjusted CPH analyses, treatment effects differed in both studies (HR 0.82 in MPO, but 0.95 in HEMO). Treatment was accounted for the competing risks of transplant, treatment effects were similar in magnitude [table]. Furthermore, when the studies were analyzed together HF was associated with 16% reduction in the incidence of death (p=0.022).

Conclusions: Effect sizes, and perceived congruency of interventions in RCTs in ESRD, may depend on the methods for handling censoring due to transplantation. Our findings mirror recent reports in hemodiafiltration (HDF) RCTs [Nephrol Dial Transplant (2017) 32: i31–i39], raising the question whether many negative (e.g. statins) and/or discrepant results in nephrology (HF or HDF) are due to the statistical methods employed to analyze trials.

Funding: Clinical Revenue Support

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

Underline represents presenting author.

* p < 0.001

Adjusted for age, gender, black race, albumin, diabetic status and country
TH-PO820
Early Mortality Comparison between Hemedialysis and Peritoneal Dialysis Patients Who Transition with an Optimal Outpatient Start

John J. Sim,1 Hui Zhou,1 Juxiao Shi,1 Sally F. Shaw,2 Scott A. Ragsan,3 Csaba P. Kovandy,4 Karinya Kolanlant-Zadeh,5 Steven J. Jacobsen,1 Kaiser Permanente Southern California, Pasadena, CA; 2University of California Irvine, School of Medicine, Orange, CA; 3University of Tennessee Health Science Center, Memphis, TN.

Background: Lower early mortality observed in peritoneal dialysis (PD) compared to hemodialysis (HD) may be due to differential pre- end stage renal disease (ESRD) care and the stable setting of transition to dialysis. Specifically, PD starts occur more frequently in an outpatient setting rather than during a hospitalization. To account for these circumstances, we sought to compare early mortality among PD and HD patients who had optimal ESRD starts and first transitioned to dialysis on an outpatient basis.

Methods: A retrospective cohort study (1/1/2002-12/31/2013) within Kaiser Permanente Southern California (an integrated health system) was performed on chronic kidney disease patients who had optimal start transition to ESRD in an outpatient setting. Optimal start was defined as 1) initiation of HD with an arteriovenous fistula or graft or 2) initiation with PD. Propensity score modeling factoring sex, race, age, co-morbidities, eGFR level, and change in eGFR prior to ESRD was used to create a matched cohort of HD and PD patients. All-cause mortality odds ratio (OR)’s were estimated for 6 months, 1 yr, and 2yr post transition to ESRD.

Results: A total of 2,094 (1398 HD and 696 PD) patients had an optimal outpatient transition to ESRD. The mean age was 62 yrs with 40% females, 39% Hispanics, 26% whites, and 21% blacks. In the 2 year observation period, 20% PD patients switched to HD while only 2% of HD patients switched to PD. 547 HD patients were matched to 547 PD patients on the propensity score with caliper distance <=0.001. All-cause mortality OR in HD compared to PD patients were 1.09 (0.47-2.57), 1.64 (0.92-2.93), and 0.90 (0.61-1.33) for 6 months, 1yr, and 2yrs, respectively. While race and age >/=60 yrs were associated with higher mortality.

Conclusions: There were no differences in early mortality between PD and HD patients who transitioned to ESRD with an optimal start in an outpatient setting. While prior observations have suggested an early survival advantage with PD, our findings suggest that the pre-ESRD care and the stable transition to dialysis likely account for lower early mortality among the ESRD population.

Funding: NIDDK Support

TH-PO821
KDOQI Nutrition Guideline 21 Associates with Overfeeding in Critically Ill ESRD Patients

Eli McKenna-Weiss,1 Daniel L. Landry, Patrick Mailloux, Young hee Kim, Gregory L. Braden. Medicine, U Mass Medical School/ Baystate, Springfield, MA.

Background: KDOQI nutrition guideline 21 states that critically ill ESRD patients(pts) less than 60 yr old receive at least 35 kcal/kg/day of total parenteral nutrition(TPN) & pts over 60 should receive 30-35 kcal/kg/day TPN. U.S. guidelines for ICU nutrition suggest 22-24 kcal/kg/d for critically ill non ESRD pts.

Methods: We studied 11 intubated ESRD pts (4W/7M) in the ICU with the Puritan Bennett indirect calorimeter on 3 different non dialysis days while NPO and during TPN with 25 or 38 kcal/kg/d. 4 pts were under age 60 & 7 pts were over age 60. Only 1 pt had diabetes mellitus. Causes for the ICU: sepsis 4, respiratory failure 5, cva 1. Mean time on hemodialysis was 1.5 years and mean serum albumin pre study was only 2.4+/-. Mean times and mean serum albumin pre study was only 2.4+/-0.2 g/dl. Pts were studied from 5 am to 1 pm & the results of resting energy expenditure (REE), VO2 (ml/min), VCO2 (ml/min) and respiratory quotient(RQ) were calculated by the continuous machine averages for all parameters. Time averaged glucose levels 4 hours were calculated. TPN intake ratios for both the 28 and 38 kcal studies were: 20% protein, 30% fat & 50% carbohydrates.

Results: Baseline REE for age under 60 was 26.0 +/-4 kcal/kg/d and for over 60 was 22.0 +/- 2 kcal/kg/d despite sepsis in 2 pts in each group (p NS). REE for all NPO pts was only 23.5 +/- 4 kcal/kg/d & only 24.5 +/- 4 & 26.0 +/- 3 kcal/kg/d (p NS). The mean +/- SE for indirect calorimetry are shown in the table:

<table>
<thead>
<tr>
<th></th>
<th>VO2 (ml/min)</th>
<th>VCO2 (ml/min)</th>
<th>REE</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPO</td>
<td>200 +/- 30</td>
<td>160 +/- 45</td>
<td>80</td>
<td>100 +/- 15</td>
</tr>
<tr>
<td>28 kcal/kg/d</td>
<td>200 +/- 50</td>
<td>192 +/- 27</td>
<td>100</td>
<td>105 +/- 20</td>
</tr>
<tr>
<td>38 kcal/kg/d</td>
<td>239 +/- 58</td>
<td>214 +/- 26</td>
<td>108</td>
<td>96 +/- 15</td>
</tr>
</tbody>
</table>

# p < 0.05 compared to NPO. The increased VCO2, RQ & glucose levels suggest carbohydrate overfeeding and increased lipogenesis in the TPN groups. No differences found between 28 and 38 kcal groups in any parameter.

TH-PO822
Limitations of the KDQoL for Assessing Quality of Life Among Patients with ESRD

Andrew Leg,1 Dena E. Cohen,1 Scott Bibbel,3 Deborah A. Benner,2 Steven M. Brunelli,1 Francesca Tentori,1 DaVita Clinical Research, Minneapolis, MN; 2DaVita, Inc, Denver, CO.

Background: Achieving the best possible quality of life (QoL) is a key goal for patients with end-stage renal disease (ESRD). The Centers for Medicaid and Medicare Services mandate regular assessment using the Kidney Disease Quality of Life (KDQoL) survey. Given concerns that the KDQoL may not adequately capture QoL among contemporary ESRD patients, we examined its construct validity.

Methods: We considered 282,895 KDQoL surveys completed by 175,826 adult patients receiving in-center hemodialysis at a large US dialysis organization (2014-2016). Correlations between item responses, domain scores, and interdialytic weight gain (IDWG) were calculated using Pearson correlations computed with pairwise complete observations.

Results: Patient perceptions of general health were not correlated (R<0.05) with any other question in the physical composite score (PCS) or the symptoms and problems subscale (SPS). Mean SPS (77.9 ± 16.9) exceeded mean PCS (56.3 ± 12.3); correlation between the two was modest (R=0.42). Many items in the SPS showed ceiling effects: for all 12 items, <10% of patients were “extremely bothered,” while >65% of patients reported being “not at all” or only “somewhat bothered,” for 3 items, >85% of patients gave these two responses. IDWG was not correlated with patient-reported shortness of breath, PCS, or SPS.

Conclusions: We identified possible limitations in the mandated tool that is used for assessment of QoL in ESRD patients. New measures of QoL that focus on factors that affect a considerable proportion of contemporary dialysis patients, particularly those that can be addressed by modifiable clinical practices, are needed.

Funding: Commercial Support - DaVita, Inc

TH-PO823
Adverse Drug Effects in Patients with ESRD Who Present to the Emergency Department

Lili Chan,1 Priti Poojary,1 Aparna Saha,1 Kinsuk Chauhan,1 Steven G. Coca,1 Pranav S. Garimella,2 Girish N. Nakdarni,1 Icahn School of Medicine at Mount Sinai, New York, NY; 2University of California San Diego, San Diego, CA.

Background: Patients on dialysis are at high risk for adverse drug effects (ADEs) due to impaired renal clearance of medications and polypharmacy. We aimed to explore trends and outcomes of ADEs in dialysis patients.

Methods: We utilized a nationally representative database, the Nationwide Emergency Department Sample, to identify dialysis patients who present to the emergency department.
TH-PO824
Impact of Pre-Dialysis Acute Hospitalizations on Post-Dialysis Outcomes in Incident Dialysis Patients
Silvi Shah, Anthony C. Leonard, Charuhas V. Thakar. University of Cincinnati, Cincinnati, OH.

Background: Mortality in end stage renal disease (ESRD) patients is highest during the first year of dialysis. Although survival is similar in hemodialysis (HD) and peritoneal dialysis (PD), overall costs of care are lower in PD. In spite of the increasing burden of cardiovascular (CV) disease and infections with kidney disease progression, the impact of pre-dialysis acute hospitalizations on dialysis modality and on mortality in dialysis patients is not known.

Methods: We evaluated 49,645 adult incident dialysis patients (1/1/2008 to 12/31/2008) from the United States Renal Data System (USRDS) with linked Medicare data for at least 2 years prior to dialysis initiation. Using case-mix adjusted logistic regression models (16 variables), we examined the impact of pre-dialysis acute hospitalizations on type of dialysis modality (PD vs. HD) and one-year all-cause mortality. We evaluated 4 groups of patients by cause of hospitalization: CV related, infection related [INF], both CV and INF [CV+INF], and neither CV nor INF related.

Results: The sample was 55% male, 63% White with a mean age of 72±11 years. Only 4% of patients received PD as initial modality. Among the study cohort, 89% had at least one pre-dialysis hospitalization [CV-34%, INF-11%; CV + INF-12%; and 33%-neither CV nor INF]. In adjusted analyses, as compared with no pre-dialysis hospitalizations, patients with INF, CV, CV+INF and neither CV nor INF hospitalizations were more likely to be started on HD (odds ratio [OR] 2.7, 95% confidence interval [CI] 2.2-3.2; OR 2.7, CI 2.37-3.08; OR 3.3, CI 2.68-4.08; OR 2.6, CI 2.3-2.93 respectively). In adjusted analyses, one-year mortality was higher with pre-dialysis INF hospitalizations (OR, 1.41; CI 1.28-1.54), CV hospitalizations (OR, 1.47; CI 1.35-1.59) and INF+CV hospitalizations (OR, 1.87, CI 1.7-2.05), compared with no pre-dialysis hospitalizations.

Conclusions: Pre-dialysis hospitalizations are frequent; infection or cardiovascular related hospitalization independently increases the odds of HD vs. PD; and is an independent predictor of one-year mortality in incident dialysis patients. Effects of pre-ESRD hospitalization should be considered while comparing mortality as quality of dialysis care. Reducing pre-ESRD hospitalizations may improve survival and costs of care after initiating dialysis.

TH-PO826
Weekend versus Weekday Admission in Dialysis Dependent Patients
Yuemeng Wen,1,2 Di Pan,1,2 David Martiuna,1,2 Michael Gramuglia,3 Ira S. Meiners,1,2 Division of Nephrology, Department of Medicine, Mount Sinai St. Luke’s and Mount Sinai West Hospitals, New York, NY; ‘Icahn School of Medicine at Mount Sinai, New York, NY; ‘Department of Medicine, Montefiore Medical Center, Scarsdale, NY.

Background: End Stage Renal Disease (ESRD) is a major cause of worldwide mortality and morbidity. ESRD requiring chronic dialysis is associated with high mortality and morbidity, requiring frequent hospitalization for complications from dialysis and comorbidities. The aim of this study is to determine the differences in outcomes and resource utilization of dialysis dependent patients hospitalized on weekends compared to weekdays.

Methods: This is a retrospective cohort study using the 2014 National Inpatient Sample, the largest publically available inpatient database in the United States. The inclusion criteria were age above 18 and an ICD-9 CM code for diagnosis of ESRD on chronic dialysis. Patients hospitalized for elective procedures were excluded. The primary outcome was in-hospital mortality. The secondary outcomes were morbidities, as measured
by the development of shock and acute respiratory failure, as well as resource utilization including transfers of hospital stay (LOS) and total hospitalization charges. Analysis is performed by using Stata, version 14.2. Odds ratio (OR) and means were adjusted for the following confounders using multivariate regression models: demographics, Charlson Comorbidity Index, early dialysis in hospital (defined as receiving dialysis within 1 day of admission), payer insurance, hospital bedsize, hospital region and household income.

Results: 934,575 patients with ESRD on chronic dialysis were included in the study. Patients admitted on weekends were associated with significantly higher in-hospital mortality rates (5.45% versus 4.87%, p<0.02) and higher rate of acute respiratory failure (3.99% versus 3.32%, OR 1.11, p=0.001). The development of shock was not significantly different (OR 0.97, p=0.69). Weekend admission was associated with greater length of stay (6.90 versus 6.89, p=0.001), however the total hospital charges were not significantly different (p=0.67). Patients admitted on weekends had lower rate of receiving early dialysis (42.72% versus 52.72%, p=0.001).

Conclusions: Compared to weekday admission, weekend admission in patients with ESRD on chronic dialysis was associated with higher rates of mortality and acute respiratory failure, as well as greater length of stay even after controlling for early dialysis. Patients admitted on weekends were less likely to receive early dialysis.

TH-PO827

Urgent Start Dialysis: Peritoneal Dialysis versus Hemodialysis via a Central Venous Catheter

Neelam M. Bhalla, Neha Arora, Jeanne A. Darbinian, Sijie Zheng, Kaiser Permanente, Oakland, CA; The Permanente Medical Group, Oakland, CA; nephrology, kaiser permanente, Hayward, CA.

Background: Though underutilised in the US, PD is a safe and effective home modality of renal replacement therapy. One reason for under use of PD is the practice of initiating patients on HD via a central venous catheter (CVC) if they do not have a functional AVF/AVG. When compared with AVF/AVG, CVC use is associated with increased mortality. Recently, use of urgent start PD has gained interest since it decreases use of CVCs, while affording a mechanism of increased PD utilization. In this retrospective cohort study, we compared complications and outcomes between the two urgent start dialysis modalities.

Methods: We identified a subgroup of KPNC members who met clinical criteria for being in urgent need of beginning PD or HD between 1/1/2011 and 12/31/2014. Urgent start PD patients were matched 3:1 with PD urgent starts on selected characteristics. Medical records of all cohort members were reviewed by three nephrologists. Complications and outcomes occurring after initiation of dialysis were compared between the modalities using Chi-square or Fisher exact tests.

Results: We compared 335 HD starts with 84 PD starts. There were no modality switches in the PD cohort; in HD start cases one changed to home HD and four to PD. Transferring to hospice accounted for 92% of modality terminations in HD; reasons in PD were psychosocial (43%); medical (28.6%); peritonitis (14.3%) and others (14.3%). Major complications were low in both groups (~5%), though rate of catheter malfunction was higher in HD (12.8% vs. 6.0%, p=0.09). There was a statistically significant difference in overall infectious complications between PD (20%: peritonitis -13%; exit site - 7%) and HD (9%: bacteremia - 7.2%; exit site - 1.8%, p=0.01). There were more deaths in the HD group (19.7% vs 7%, p=0.015). Furthermore a higher proportion of deaths was observed in patients with bacteremia compared with those who had peritonitis (25 vs 16.7%). Pericatheter leaks developed in 7% of PD cases and in no HD patients.

Conclusions: Urgent PD start is a viable alternative to urgent HD start via CVC. Although infectious complications were higher in PD, peritonitis was associated with less mortality than bacteremia. Notably there is a high patient retention rate, leading to increased utilization of PD.

TH-PO828

Urgent-Start Peritoneal Dialysis by the Nephrologist

Javier Soto-Vargas, Heriberto R. López, Martín D. Vargas ezquivel, Carlos Daniel Jiménez Mejía, Ana L. García-Vera, Rodolfo A. Cortina, Alfonso Ramos, Renato Parra, Mario A. García-Chávez, Bexar Mexico, San Jerónimo Chicaualco, Mexico; ISSSTE, MEXICO CITY, Mexico; Regional General Hospital 46, Mexican Institute of Social Security, Guadalajara, Mexico, Guadalajara, Mexico.

Background: Urgent-start peritoneal dialysis is an alternative to initiation of renal support in patients with end-stage renal disease. The objective is to describe our experience with an urgent-start PD program.

Methods: In this prospective observational study, we report on our experience in a single academic center. All patients treated with urgent-start PD, defined as PD therapy initiated within 1 week after catheter insertion, and from September 2016 to April 2017 were included. Peritoneal dialysis catheters were inserted percutaneously by puncture. Dialysis was initiated in an inpatient setting whith a fíx dose of 60 liters in fast cycles. The Gastrointestinal Symptoms in Peritoneal Dialysis Patients

I-kuan Wang, Chin-Chi Kuo, Chi-Cheng Huang. Taiwan; China Medical University Hospital, Taichung, Taiwan.

Background: Gastrointestinal (GI) symptoms such as gastrointestinal reflux, constipation, abdominal pain and diarrhea are common in peritoneal dialysis (PD) patients. Constipation is a risk factor of PD-related peritonitis. The aim of this study is to evaluate the prevalence of GI symptoms in PD patients.

Results: Patients undergoing PD more than one month in China Medical University hospital was enrolled from July 2011 to March 2013. To evaluate the presence of GI symptoms, PD patients were asked to complete the gastrointestinal symptom rating scale (GSRS). The GSRS, a questionnaire, include 15 items, which could be classify into abdominal pain, reflux, diarrhea, indigestion, and constipation. Each item was rated as 0, 1, 2, and 3 according to severity.

Results: A total of 40 patients completed the questionnaire. The mean age was 49.58 ± 11.49 years. The duration of PD was 43.26 ± 31.47 months. 21 (52.5%) patients were female. The etiology of ESRD includes chronic glomerulonephritis (19 patients, 46.3%), diabetes (8 patients, 20%), hypertension (6 patients, 15%), chronic tubulointerstitial nephritis (4 patients, 10%) and polycystic kidney disease (3 patients, 7.5%). Only 3 patients (7.5%) have no GI symptoms. The prevalence of abdominal pain, reflux, diarrhea, indigestion, and constipation was 40% (16 of 40), 35% (14 of 40), 37.5% (15 of 40), 77.5% (31 of 40), and 62.5% (25 of 40). The prevalence of 0, 1, 2, 3, 4, 5 GI symptoms was 7.5% (3 of 40), 15% (6 of 40), 30% (12 of 40), 20% (8 of 40), 20% (8 of 40), and 7.5% (3 of 40), respectively.

Conclusions: GI symptoms are highly prevalent in PD patients. Medical staffs have to pay attention to and take good care of these GI problems.
Allopurinol Does Not Protect Renal Function in Patients on Peritoneal Dialysis

Background: Preservation of renal function in peritoneal dialysis (PD) patients is essential, since it is directly associated with increased survival in this method. Although there is evidence that allopurinol protects residual renal function (RRF) in patients with chronic renal disease not yet on dialysis, whether there is still benefit after these patients started PD is unknown. Therefore, we examined a cross-section of incident patients on PD to test the association between uric acid (UA) and the use of allopurinol with preservation of RRF.

Methods: Patients starting PD between January 2009 and December 2016 in an academic center, with demographic, clinical and laboratory data were included. The outcome of interest was renal Kt/V, obtained in two moments: within the first 6 months of PD and at the end of the follow-up period. The difference between final and initial Kt/V was defined as Kt/V delta.

Results: Sixty-nine patients (age 47±18 years, 47% male, 79% hypertensive and 25% diabetic) were included. The UA was 7.2±1.8, ranging from 3.2 to 12.8 mg/dL. More than half of the patients (53.6%) presented UA higher than 7.0 mg/dL, with no difference in Kt/V delta (r=0.43 (0.55, -0.05) vs. -0.19 (-0.44, -0.01) in patients with UA higher and lower than 7.0 mg/dL, respectively, p = 0.382). Delta Kt/V correlated with UA delta (r= -0.39 (0.51, -0.05) vs. -0.29 (-0.66, 0.93; -0.02, respectively; p = 0.443). Multiple regression analysis showed that neither UA nor UA delta (adjusted for allopurinol use) were independently associated with Kt/V delta.

Conclusions: The use of allopurinol had no impact on the preservation of RRF in patients on PD. In view of possible harm associated with allopurinol, prospective and interventional studies are required prior to recommendation of a regular prescription of such a drug for the PD population, as an attempt for renal preservation.

Uremic Cardiomyopathy in Young Incident Peritoneal Dialysis Patients

Background: Uremic cardiomyopathy is responsible for high morbidity and mortality rates among patients with end-stage renal disease. Our objective was to describe and compare the echocardiography characteristics of young incident peritoneal dialysis (PD) patients with and without access to Public Health Services (PHS).

Methods: Seventy-two incidents PD patients under 35 years old and with no history of cardiovascular disease underwent Doppler echocardiography evaluation. The results were reported according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging.

Results: Thirty-six patients with universal medical care access and 36 without it were evaluated. Fifty-seven (79.2%) of the total cohort had at least one alteration on Doppler echocardiography evaluation. Thirteen (18.1%) had systolic dysfunction, and the median VEF was 60% (IQR: 55, 71-73), in 9 (12.5%) patients diastolic dysfunction was present and 21 (31.1%) had a degree of pulmonary hypertension. The patients without access to PHS were younger (median 20 years, IQR 19-24, p<0.005), had higher left ventricle mass (median 238 grams, IQR 200-270, p<0.000), greater systolic dysfunction, VEF (median 55, IQR 42.25-60, p=0.003), higher pulmonary arterial pressure (median 30 mmHg, IQR 28-40, p<0.000), had more frequency of cardiomyopathy (91.7% vs 66.7%, p=0.018), and severity of the cardiomyopathy (66.7% vs 33.3%; p=0.017).

Conclusions: The uremic cardiomyopathy is highly prevalent in young incident peritoneal dialysis patients. There is a difference according to the social security status, in the frequency of echocardiographic alterations and their severity.
**TH-PO834**

The Effect of Combined Therapy with Peritoneal Dialysis and Hemodialysis on Patient Survival: A Prospective Multicenter Study in Japan

Yukio Maruyama,1,2 Keitaro Yokoyama,1,2 Masaki Nakayama,1,2 Chieko Higuchi,1,2 Tsutomu Sanaka,1,2 Yoshihide Tanaka,1,2 Ken Sakai,1,2 Yoshikiko Kanno,1,2 Munekazu Ryuzaki,1,2 Tsutomu Sakurada,1,2 Tatsuo Haseyama,1,2 Division of Internal Medicine, Tokyo Women’s Medical University Medical Center East, Tokyo, Japan;1 Department of Nephrology, Toho University School of Medicine, Tokyo, Japan;2 Division of Nephrology, Tokyo Saiseikai Central Hospital, Tokyo, Japan;1 Center for Advanced Integrated Renal Science, Tohoku University Graduate School of Medicine, Sendai, Japan;1 EARTH (Evaluation on the Adequacy of Renal Replacement Therapy) Study Group, Tokyo, Japan;1 Department of Nephrology, Tokyo Medical University, Tokyo, Japan;2 Center of CKD and Lifestyle Related Diseases, Edogawa Hospital, Medical Center, Tokyo, Japan;1 Division of Nephrology and Hypertension, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan;1 Department of Pathophysiology and Therapy in Chronic Kidney Disease, The Jikei University School of Medicine, Tokyo, Japan;1 Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan;1 Group/Team: EARTH Study Group.

**Background:** Combined therapy with peritoneal dialysis (PD) and hemodialysis (HD) was widely performed to correct underdialysis and/or overhydration in Japan. However, its clinical result was only reported in retrospective observational studies, and the effect on patient survival is unknown. Hence, we conducted a prospective study to investigate its clinical efficacy in Japan.

**Methods:** In this prospective multicenter study, we recruited 164 patients started PD from January 1, 2011 to December 31, 2016 (59,7,5,10,11,12,13 months after PD initiation, respectively). Median follow-up period was 35 months (range, 0-71 months). During follow-up, 21 patients were switched to the combined therapy with PD and HD, and 15 were switched to HD alone 30±16 and 23±13 months after PD initiation, respectively. The reasons for switching therapy were underdialysis in 8 (22%), overhydration in 12 (33%), both in 1 (3%), and others or unknown in 15 patients (42%). Nineteen patients (11.6%) died of all causes, including 6 (3.7%) died of CVD. Sixteen patients on PD alone, 1 patient on HD alone, and 2 patients on combined therapy were dead. Mortality after switching therapy was no significantly difference between patients on HD alone and those on combined therapy (Log-rank p=0.25, Figure 1).

**Conclusions:** The effect of switching combined therapy with PD and HD from January 1, 2011 to December 31, 2016 (59,7,5,10,11,12,13 months after PD initiation, respectively). Median follow-up period was 35 months (range, 0-71 months). During follow-up, 21 patients were switched to the combined therapy with PD and HD, and 15 were switched to HD alone 30±16 and 23±13 months after PD initiation, respectively. The reasons for switching therapy were underdialysis in 8 (22%), overhydration in 12 (33%), both in 1 (3%), and others or unknown in 15 patients (42%). Nineteen patients (11.6%) died of all causes, including 6 (3.7%) died of CVD. Sixteen patients on PD alone, 1 patient on HD alone, and 2 patients on combined therapy were dead. Mortality after switching therapy was no significantly difference between patients on HD alone and those on combined therapy (Log-rank p=0.25, Figure 1).

**Funding:** Commercial Support - TERUMO, Private Foundation Support

---

**TH-PO835**

Patient-Reported Advantages and Disadvantages of Peritoneal Dialysis: Results from the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS)

Jeffrey Perl,1 Junhui Zhao,2 Douglas S. Fuller,3 Brian Bieber,4 James A. Sloan,5 Laila Subramanian,6 David W. Johnson,7 Matthew J. Oliver,8 Kriang Tungsanga,9 Tadashi Tomo,9 Rachael L. Morton,2 Bruce M. Robinson,7 St. Michael’s Hospital, Toronto, ON, Canada;1 Arbor Research Collaborative for Health, Ann Arbor, MI;1 Baxter Healthcare Corporation, Deer ied, IL;2 Princess Alexandra Hospital, Brisbane, QLD, Australia;3 Sunnybrook Health Sciences Center, Toronto, ON, Canada;4 King Chulalong Memorial Hospital, Bangkok, Thailand;5 Oita University Hospital, Yufu, Japan;6 The University of Sydney, Sydney, NSW, Australia. Group/Team: On behalf of clinical application of PD therapy working group.

**Background:** Compared to facility-based hemodialysis, home-based peritoneal dialysis (PD) may offer patients advantages and disadvantages. We sought to better understand patient-reported perceptions of the advantages and disadvantages of PD treatment.

**Methods:** PDOPPS is a prospective cohort study of PD treatment and outcomes in Australia, Canada, Japan, New Zealand, Thailand, the United Kingdom (UK) and the United States (US). Opinions on how PD treatment impacts 17 aspects of daily life were assessed using the self-reported PDOPPS patient questionnaire (PQ).

**Results:** Between 2014 and 2017, 2641 patients returned a PQ, item-level response rates ranged from 88% to 96%. Among the 11 factors of expected advantages (Figure 1A), “receive treatment at home” was most commonly perceived as an advantage (95%), followed by “do not require accessing of blood” (89%). The most commonly cited disadvantages of PD treatments were “feeling full with PD fluid in abdomen” (43%) and “space taken up by PD supplies” (overall 33%, Figure 1B), which was particularly regarded as a disadvantage by patients in UK (53%), Canada (40%), US (36%), vs. 16-32% elsewhere. Fewer patients in Japan and Thailand (28% and 43%, respectively, compared to over 57-67% elsewhere) perceived “able to travel more easily” as an advantage of PD.

**Conclusions:** Abdominal fullness and space taken up by PD supplies appear to be concerns for a substantial minority of patients receiving PD, while treatment receipt at home obviating the need for accessing blood appear to be the predominant advantages. Better understanding of the patient, treatment and regional variation associated with these concerns may provide insights into improving the patient experience of PD and allow for more informed dialysis modality education.

**Funding:** Commercial Support - Amgen, AstraZeneca, Baxter Healthcare, Kyowa Hakko Kirin, Hexal AG, Janssen, Keryx, Proteon, Relypsa, Roche, Vifor Fresenius Medical Care Renal Pharma, ERA-EDTA, Japanese Society for PD, Association of German Nephrology Centres, Societies for Nephrology in Germany, Italy, & Spain., Private Foundation Support, Government Support - Non-U.S.

---

**TH-PO836**

Transitions from Peritoneal Dialysis (PD) to In-Center Hemodialysis or Death: Trends in the United States Renal Data System from 1996-2011

Nidhi Sukul,1 Purna Mukhopadhyay,1 Jeffrey Pearson,1 Douglas E. Schaubel,2 Marc Turenne,1 Rajiv Saran,2 Bruce M. Robinson,1 Ronald L. Pisoni.1 Arbor Research Collaborative for Health, Ann Arbor, MI;1 University of Michigan, Ann Arbor, MI;2University of Sydney, Sydney, NSW, Australia.

**Background:** Transitioning from PD to in-center hemodialysis (ICHD) is disruptive to care. To understand changes in rates of mortality and transition from PD to ICHD among incident PD patients, we examined trends in the US Renal Data System from 1996-2011.

**Methods:** Annual cohorts of incident PD patients were followed for up to 3 years (Fig.1) for the outcomes of death, transition to ICHD, or the combined outcome of the two. Time at risk (expressed per 100 patient years [PY]) was calculated as days from PD incidence until date of transplant, death, 30 days after switching to ICHD or home hemodialysis, recovery of renal function, loss to follow-up, discontinuation of dialysis, or

---

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

Underline represents presenting author.
end of follow-up. Kaplan-Meier curves for 5-year survival on PD, adjusted for age, sex, race, ethnicity, and primary cause of ESRD, are shown for 5 annual cohorts (Figure 2).

**Results:** Trends in transition rates per 100 PY from 1996-2011 were: 20.2 to 10.7 for death, 24.7 to 20.7 for ICHD, 44.9 to 31.3 for death/ICHD (Fig.1). The Kaplan-Meier curves demonstrate that 50% of patients died or transitioned to ICHD by 1.63, 1.72, 1.83, 2.02, and 2.18 PY for 1996, 2002, 2005, and 2009 (Fig.2).

**Conclusions:** While rates of mortality and transition to ICHD have both declined, this was greater among mortality rates. Overall longer PD survival seen in recent years could potentially be due to better PD education, treatment, and/or patient selection. Further investigation is needed to better understand patient- and center-level predictor of these outcomes to further extend survival time on PD and the experiences of patients selecting this modality.

**Funding:** NIDDK Support

---

**TH-PO837**

**The Superiority of Combination Therapy with Peritoneal Dialysis and Hemodialysis over Conventional Hemodialysis**

**Hironori Nakamura,** Anayama Mariko, Yasushi Makino, Manaki Nagasawa.

**Nephrology, Shinonoi General Hospital, Nagano, Japan.**

**Background:** Combination therapy consisting of peritoneal dialysis (PD) and hemodialysis (HD) is a type of renal replacement therapy that possesses the advantages of both types of dialysis. In Japan, approximately 20% of all PD patients receive this unique combination of PD and HD (PD+HD) therapy, which consists of 6 days of PD and 1 session of HD a week. However, little is known about the differences in clinical characteristics or QOL between PD+HD and HD patients.

**Methods:** The aim of this study was to verify the superiority of PD+HD over HD in the clinical characteristics and Kidney Disease Quality of Life Short Form (KDQOL-SF36) score in dialysis patients. One single-center cross-sectional comparative study was conducted. Seven PD+HD patients and 11 control patients were included, age (±3 years) and dialysis duration (±5 months) matched controls were selected from HD patients who were undergoing HD thrice a week in our dialysis center.

**Results:** The mean age of the patients was 73.1 ± 5.7 years, and dialysis duration was 66.7 ± 42.3 months. Laboratory data showed that the values for blood urea nitrogen (44.0 ± 9.2 vs. 58.6 ± 13.4 mg/dL, p = 0.015), potassium (4.1 ± 0.70 vs. 5.0 ± 0.88 mg/dL, p = 0.028), iron (72.5 ± 17.0 vs. 42.3 ± 15.5 mg/dL, p = 0.005), transferrin saturation (27.0% ± 7.8% vs. 17.9% ± 6.4%, p = 0.039), pH (7.40 ± 0.02 vs. 7.34 ± 0.04, p = 0.005), and HCO₃⁻ (23.6 ± 2.8 vs. 19.7 ± 1.7 mEq/L, p = 0.018) were significantly better in PD+HD than HD patients. Total protein (5.5 ± 0.48 vs. 6.2 ± 0.39 mg/dL, p = 0.01) and albumin (2.7 ± 0.48 vs. 3.3 ± 0.38, p = 0.019) levels were lower in PD+HD than HD patients. Regarding the KDQOL questionnaire results, the score for the item indicating patient satisfaction to dialysis care was significantly higher in PD+HD than HD (9.0 ± 8.9 vs. 66.6 ± 19.2 points, p = 0.004). No significant items were observed for the superiority of HD over PD+HD.

**Conclusions:** Our results suggested that PD+HD may have meaningful advantages in terms of iron metabolism, acid-base balance, and patient satisfaction compared with those in conventional HD in this study population.

**TH-PO838**

**Evaluation of Healthcare Resource Consumption in Simulated Patients on Automated Peritoneal Dialysis (APD) Using a Remote Monitoring System**

**Kiyotaka Kasai,** Kohkichi Morimoto, Shu Wakino, Souzana S. Deenitchina, Hiroshi Itoh. 1Baxter, Tokyo, Japan; 2Baxter Limited Japan, Tokyo, Japan; 3Keio University, Tokyo-to, Japan; 4Keio University School of Medicine, Tokyo, Japan; 5Keio University, School of Medicine, Tokyo, Japan; 6School of Medicine, Keio University, Tokyo, Japan; 7keio university, school of medicine, Tokyo, Japan.

**Background:** Studies are in progress to evaluate the usefulness of remote monitoring (RM) in chronic disease patients. For patients undergoing peritoneal dialysis (PD), who also have chronic disease (e.g., end-stage renal failure) and are basically on home care, RM is highly likely to contribute to better prognosis and improved quality of life (QOL). However, evidence is scarce in this area. Automated peritoneal dialysis (APD) involves the use of a device to enable automated PD while the patient is asleep, and has greatly contributed to the improved QOL of PD patients. However, no APD device with RM function is available in Japan. In this preliminary study, we evaluated the usefulness of RM in APD patients employing a simulated patient approach.

**Methods:** We prepared two clinical scenarios with RM (RM+) and without RM (RM-), consisting of 12 simulated patients with PD-related problems commonly experienced in daily clinical practice, with modifications from the original US Baxter’s scenarios to reflect the actual clinical situation in Japan. Each scenario was evaluated by two teams consisting of one nephrologist and one nurse each, or by two nephrologists for the frequency of healthcare resource consumption, such as “hospitalizations” and “emergency room visits”, for comparison between the RM+ and RM- groups.

**Results:** The RM+ group showed a significantly reduced total healthcare resource consumption (36.8 vs. 107.5 times, p = 0.002), as compared to the RM- group. More specifically, the RM+ group showed significantly lower frequency of the following resource consumption: “unplanned hospital visits” (p = 0.003), “emergency room visits” (p = 0.003), “home visits” (p = 0.020), “exchange over the telephone” (p = 0.002), “change to hemodialysis” (p = 0.003) and “other” (p = 0.004).

**Conclusions:** The present results indirectly demonstrate the usefulness of RM in reducing the frequency of healthcare resource consumption in APD patients. This is the first time this evidence has been found in Japan.

**Funding:** Commercial Support - Baxter Ltd.

---

**TH-PO839**

**Peritoneal Dialysis Annual Drop Out Monitoring Increases Patient and Technique Survival**

**Dan Marron,1 Delia Timofe2, Michael Roesch,3 Janusz Orosz,4 Gustavo L. Moretta,5 Paul Stroumza,6 Elisabeth Fabricius,7 Jorgen Hegbrant.1 1Medical Office, Diaverum, Madrid, Spain; 2Sema Clinic, Diaverum, Bucharest, Romania; 3Schlankmeye Clinic, Diaverum, Hamburg, Germany; 4Wloclawek Clinic, Diaverum, Wloclawek, Poland; 5Keio Clinic, Diaverum Hungary Ltd, Budapest, Hungary; 6Frondani Clinic, Diaverum, Bucharest, Romania; 7Bajcsy Clinic, Diaverum, Budapest, Hungary; 8LATAM Medical Office, Diaverum, Buenos Aires, Argentina; 9Marseille Clinic, Diaverum, Marseille, France; 10Vishy Clinic, Diaverum, Visby, Sweden; 11Medical Office, Diaverum, Lund, Sweden.

**Background:** PD drop out (DO) is often not routinely measured and seldom reported in the literature.

**Methods:** Observational, prospective registry in 9 countries (FR, DE, HU, PL, RO, SE, AR, CL, UR) during 2 years. Only EU countries with ≥100 prevalent PD patients (pts) [RO, DE, PL, HU] are presented here. All PD pts were tracked on a monthly basis for DO due to: TX, RRF recovery, transfer to HD (due to peritonitis, exit site or catheter issues, UFF, low adequacy, burn out or others), transferred to other centers, death or others. Total DO, controllable DO (transfer to HD and to other centers) and underlying causes are provided as percentage of pts at risk.

**Results:** 565 pts (372 prevalent, 193 incident) in 47 clinics, 2015 and 813 (623 prevalent, 190 incident) in clinics, 2016. DO results (2016 vs. 2015) was as follows: total DO (49 vs. 41% p = 0.04), controllable DO (19.1 vs. 18.3% p = 0.04), TX (9.3 vs. 5.9% p = 0.020), “exchanges over the telephone” (p = 0.002), as compared to the RM- group. More specifically, the RM+ group showed significantly lower frequency of the following resource consumption: “unplanned hospital visits” (p = 0.003), “emergency room visits” (p = 0.003), “home visits” (p = 0.020), “exchange over the telephone” (p = 0.002), “change to hemodialysis” (p = 0.003) and “other” (p = 0.004).

**Conclusions:** The present results indirectly demonstrate the usefulness of RM in reducing the frequency of healthcare resource consumption in APD patients. This is the first time this evidence has been found in Japan.

**Funding:** Commercial Support - Baxter Ltd.
TH-PO840

Amyloidosis Mimicking Calciphylaxis in a Peritoneal Dialysis Patient
Mabel H. Aoun,1,2 Christelle Riachi,1 Dania Chelala,1 Saint-Georges Hospital Ajaltoun, Beirut, Lebanon; 2Saint-Joseph University, Beirut, Lebanon; 3Holy Spirit University, Kaslik, Lebanon.

Background: Skin lesions in ESRD patients on dialysis are frequent mostly benign related to itching. More severe necrotic lesions usually point out to calciphylaxis. However the diagnosis is not so easy to establish in some cases and appears to be a real challenge.

Methods: We report the case of a 60-year-old Caucasian male who presented to our clinic in October 2013 for advanced chronic kidney disease. He had hypertension and several episodes of malaria 10 years ago treated with chloroquine. He was known to have focal and segmental glomerulosclerosis confirmed by a kidney biopsy in 2008 and was put on ARB. He was started on peritoneal dialysis in July 2014. Six months later during the pre-transplant work-up he was diagnosed with triple coronary artery disease and he underwent coronary artery bypass graft. Following the surgery, he developed severe oral aphtosis and necrotic lesion of the sternotomy that took 6 months to heal. He was treated with colchicine for his presumed cutaneous Behcet disease. His ANA were negative. After the thoracic healing he presented with ulcerative lesions of the legs that raised the suspicion of calciphylaxis. The PTH level was 88 pg/ml, serum phosphorus 6 mg/dl and serum calcium 10.1 mg/dl. He was put on lanthanum instead of calcium carbonate. He was started on peritoneal dialysis in July 2014. Six months later during a peritoneal equilibration test showed abnormal absorption rate of glucose from dialysate. In this case, we examined the inhibitory effects of SET7/9 on peritoneal fibrosis in mice and human peritoneal mesothelial cells (HPMCs). We also investigated SET7/9 expression in nonadherent cells isolated from peritoneal dialysis (PD) effluent from actual PD patients.

Results: Epimorphin expression was increased at 2 days rather than at 1 day after the last CG injection, and significantly decreased at 3, 7 and 14 days compared to 2 days after the last CG injection. Epimorphin expression was increased at 2 days rather than at 1 day after the last CG injection, and significantly decreased at 3, 7 and 14 days compared to 2 days after the last CG injection. However changes were assessed by Masson’s Trichrome staining. Epimorphin expressions were harvested at 1, 2, 3, 7, and 14 days after the last CG injection.

Methods: Epimorphin was induced by the injection of 0.1% chlorhexidine gluconate in 15% ethanol and 85% normal saline (CG-injected mice) into peritoneal cavity of 10 week-old male C57/B6 mice every other day for three weeks. As the repair phase of peritoneal fibrosis mice model, we used peritoneal tissues of the CG-injected mice which were harvested at 1, 2, 3, 7, and 14 days after the last CG injection. Morphologic peritoneal fibrosis changes were assessed by Masson’s Trichrome staining. Epimorphin expressions were assessed by immunohistochemically and real-time RT-PCR.

Results: In the repair of CG-injected mice, the thickening of the submesothelial compact zone was observed in Masson’s trichrome staining. However epimorphin expression was increased at 2 days rather than at 1 day after the last CG injection, and significantly decreased at 3, 7, and 14 days compared to 2 days after the last CG injection.

Conclusions: These findings suggest that epimorphin may have important role in the repair of peritoneal fibrosis similar to that of UUO release model in mice as reported previously.

TH-PO842

A Way to Woman’s Heart Is through Her Stomach: A Case of a Pericardial-Peritoneal Fistula
Natsaha N. Dave, Jingyin Yan,1 Baylor College of Medicine, Houston, TX; 2None, Houston, TX.

Background: An exceedingly rare and potentially life-threatening complication of peritoneal dialysis (PD) is the development of a pericardial-peritoneal fistula (PPF). Typically this communication can occur in cases of pericardite especially in patients with an embologenous defect in diaphragmatic closure. We report a case of a young female who developed PPF after history of multiple pericardial windows.

Methods: A 26-year-old woman with a history of end stage renal disease (ESRD) on PD presented to cardiology clinic for kidney transplant clearance. She was diagnosed with ESRD secondary to focal segmental glomerulosclerosis (FSGS) 6 months ago. At that time, she had a large pericardial effusion deemed uremic pericarditis warranting a sub-xiphoideal pericardial window. She was initiated on hemodialysis (HD) then transitioned to PD and has since been compliant with a Kt/V above 2.0. In clinic, an echocardiogram showed a large circumferential pericardial effusion and early right ventricular diastolic collapse. She was taken to surgery for drainage of pericardial effusion with pericardial biopsy and creation of pericardial window into the left pleural cavity. The biopsy showed fibrosis and mild chronic inflammation. Immediately after the surgery, she resumed PD. Two weeks later, she developed shortness of breath (SOB) with exertion and orthopnea during dialysis. A chest X-ray revealed an enlarged cardiomedial silhouetted and large left sided pleural effusion; she was taken to surgery. Intra-operatively the previous upper midline incision was dissected down to the subxiphoid matter. The surgeon was able to identify the defect in the pericardium that communicated with the abdominal cavity above the caudate lobe of the liver. A second window was made through the left thoracotomy and the defective area was sutured closed. About 2 L of serous pleural fluid was drained as well. Post-operatively, she tolerated low volumes of CCWP and was discharged with a prescription to advance dialysis as tolerated. One month later, she developed recurrent episode of SOB secondary to a left sided pleural effusion. A CT peritoneography was negative for peritoneal leakage. She transitioned to HD and her symptoms have since resolved.

Results: These findings suggest that epimorphin may have important role in the repair of peritoneal fibrosis patient. This is the first report showing secondary amyloidosis presenting as necrotic skin lesions in a peritoneal dialysis patient. This case highlights the importance of an early skin biopsy to confirm the diagnosis and lead the treatment.

Results: This is the first report showing secondary amyloidosis presenting as necrotic skin lesions in a peritoneal dialysis patient. This case highlights the importance of an early skin biopsy to confirm the diagnosis and lead the treatment.

Conclusions: These findings suggest that epimorphin may have important role in the repair of peritoneal fibrosis similar to that of UUO release model in mice as reported previously.

TH-PO843

Inhibition of H3K4 Methyltransferase SET7/9 Ameliorates Peritoneal Fibrosis
Eyo Tamura, Shigehiro Ooi, Ayumu Nakashima, Kenseki Sasaki, Toshinori Ueno, Takao Masaki. Hiroshima University Hospital, Hiroshima, Japan.

Background: Transforming growth factor-β1 (TGF-β1) is widely recognized as a major mediator of peritoneal fibrosis. TGF-β1 is reportedly responsible for the expression of the H3K4 methyltransferase, SET7/9. SET7/9-induced H3K4 monomethylation (H3K4me1) has a critical function in transcriptional activation of fibrotic genes. In this study, we examined the inhibitory effects of SET7/9 on peritoneal fibrosis in mice and human peritoneal mesothelial cells (HPMCs). We also investigated SET7/9 expression in nonadherent cells isolated from peritoneal dialysis (PD) effluent from actual PD patients.

Methods: Peritoneal fibrosis was induced by intraperitoneal injection of methylglyoxal (MGO) in male C57/B6 mice for 21 days. Sinefungin, a SET7/9 inhibitor, was administered subcutaneously just before MGO injections at 10 mg/kg. In in vitro experiments, HPMCds were pre-incubated with 3 or 10 μL/mL sinefungin 1 hour before stimulation with 5 ng/mL of TGF-β1.

Results: SET7/9 expression increased in both MGO-injected mice and nonadherent cells isolated from effluent of PD patients, and was positively correlated with dialysate-to-plasma ratio of creatinine. Immunohistochemical staining showed that sinefungin suppressed expression of mesenchymal cells and collagen deposition, which was accompanied by decreased H3K4me1 expression. A peritoneal equilibration test showed that sinefungin attenuated the transport rate of blood urea nitrogen from plasma and the absorption rate of glucose from dialysate. In in vitro experiments, sinefungin suppressed TGF-β1-induced expression of fibrotic markers while inhibiting H3K4me1.

Conclusions: These findings suggest that inhibition of H3K4 methyltransferase SET7/9 ameliorates peritoneal fibrosis by inhibiting H3K4me1.
TH-P0844

Abstract Withdrawn

TH-P0845

Mortality after Switching from Peritoneal Dialysis to In-Center Hemodialysis: Trends in the United States Renal Data System from 1996-2013

Nidhi Sukal,1 Purna Mukhopadhyay,1 Jeffrey Pearson,1 Douglas E. Schaubel,1 Marc Turenne,1 Rajiv Saran,2 Bruce M. Robinson,1 Ronald L. Pisoni,1 1Arbor Research Collaborative for Health, Ann Arbor, MI; 2University of Michigan, Ann Arbor, MI

Background: Switching from peritoneal dialysis (PD) to in-center hemodialysis (ICH) is disruptive to patients' care, and transitioning from PD to ICHD has been associated with higher mortality risk when transitions are unplanned. To understand how mortality rates after a switch from PD to ICHD have changed over time, we examined trends in the United States Renal Data System from 1996-2013.

Methods: Five annual cohorts of incident PD patients who initiated PD within 180 days of ESRD designation and switched from PD to ICHD for a day were followed for death events for up to 180 days after switch. This 180-day risk period was divided into six consecutive 30-day segments. Death and time at risk were determined in each time segment, censoring for transplantation, return to PD, recovery of renal function, or loss to follow-up. Death rates are expressed per 100 patient years (PY).

Results: In each cohort, mortality was highest in the first 30 days post-switch, thereafter gradually declining (Figure). Death rates during the first 30 day period following switch to ICHD were 42.4 and 31.2 deaths/100 PY for the 1996 and 2013 cohorts, and decreased to 27.1 and 23.2 deaths/100 PY for the 151-180 days post-switch period. The percentage of patients in the first 30-day risk set who died decreased from 3.4% to 2.2% from 1996 to 2013, and in the 151-180-day risk set decreased from 2.2% to 1.6%. The summary death rate (combining the six time periods) was 33.2 deaths/100 PY for 1996 and 22.6 deaths/100 PY for 2013.

Conclusions: The initial 30 days post-switch from PD to ICHD is a high risk period, though there is an extended period of elevated risk after transition. The lower mortality rate for more recent cohorts may reflect improved per-transplant care in more recent years. Next steps will include adjusted analyses, and defining patient and center-level predictors to help inform means to improve mortality rates during this high-risk period.

Funding: NIDDK Support

TH-P0846

Apoptosis Inhibitor of Macrophage Ameliorates Fungus-Induced Peritoneal Injury Model in Mice

Yusuhiko Inoue,1 Takako Tomita,1 Masashi Mizuno,2 Yasuhiko Suzuki,2 Fumiko Sakata,2 Yoshifumi Takei,1 Shoichi Maruyama,2 1Aichi Medical University, Nagakute, Japan; 2Nagoya University Graduate School of Medicine, Nagoya, Japan; 3Aichi Gakuin University, Nagoya, Japan

Background: Fungal peritonitis is not common, but carries a most serious and poor prognosis due to severe inflammation. In addition, a single episode of fungal peritonitis can reportedly induce encapsulating peritoneal sclerosis. A decrease in the clearance of debris, such as that of apoptotic or necrotic cells, has been reported to prevent resolution of inflammation and tissue remodeling, leading to fibrosis and organ dysfunction. Recently, apoptosis inhibitor of macrophage (AIM/CD5L) was reported to enhance the phagocytic removal of debris by epithelial cells, contributing to kidney tissue repair. In this study, we investigated the roles of AIM in zymosan-induced fungal peritonitis models (zymosan models) that we previously reported (J Immunol 2009).

Methods: We studied zymosan models in wild and AIM deficient mice and evaluated the effects of recombinant AIM (rAIM) in AIM deficient zymosan models. We investigated whether rAIM enhances engulfment of cell debris by cultured macrophages and mesothelial cells.

Results: Inflammation with necrosis was much more severe in the AIM deficient mice at 4 weeks. M1 macrophages and neutrophils were predominant on days 7 and 14. M2 macrophages were higher in wild mice than in AIM deficient mice on days 21 and 28. IL-6, TNF-α, iNOS, and CD86 mRNA expression was significantly higher on day 28 in AIM deficient mice compared with wild mice. AIM levels in serum increased and peaked on day 14, and AIM was strongly detected in the necrotic area in zymosan models of wild mice on day 14. Inflammation with necrosis was suppressed by administration of rAIM in AIM deficient mice on day 28. In vitro, AIM enhanced the engulfment of necrotic debris by macrophages derived from zymosan-induced peritonitis, M1- and M2a-like bone marrow derived macrophages, as well as by mesothelial cells.

Conclusions: AIM was found to play a role in the reduction of inflammation by amelioration of necrotic debris in zymosan-induced peritonitis models. Enhancement of engulfment could be a novel therapeutic strategy for improving fungal peritonitis-induced peritoneal membrane injury and prognosis.

Funding: Government Support - Non-U.S.

TH-P0847

Increasing Staphylococcus Species Resistance in Peritoneal Dialysis-Related Peritonitis over 10 Years in Southern Taiwan

Hoching Chen, E-Da hospital, Kaohsiung City, Taiwan.

Background: Peritonitis remains the major complication of peritoneal dialysis. Staphylococcus species are the most associated gram-positive peritonitis. The increasing antimicrobial resistance rate has become a very important burden when considering the initial choice of antibiotics. The aim of this investigation was to examine the trends of Staphylococcus species, resistance rate and the clinical outcomes from 2006 to 2015 in southern Taiwan.

Methods: We retrospectively investigated all peritoneal dialysis-related peritonitis episodes in southern Taiwan between January 2006 and December 2015. We also evaluated the clinical characteristics, microbiology prevalence, resistance incidence of Staphylococcus species, and outcomes.

Results: Out of 244 episodes of peritonitis, Staphylococcus species accounted for around 50% gram positive bacteria. Methicillin resistance rate among staphylococcus species infection has greatly increased to 64% in 2015 both in Staphylococcus aureus and Coagulase-negative Staphylococci in southern Taiwan. Importantly, Methicillin resistance Staphylococcus species (59.1%) has significant higher hospitalization rate compare to Methicillin-sensitive Staphylococcus species (34.6%) (p<0.01). However, the catheter removal rate and transfer to hemodialysis didn’t have a difference between two groups.

Conclusions: Peritonitis is the most serious complication in peritoneal dialysis patients and microbiological trends have changed during the past 10 years at a single center in southern Taiwan. Methicillin resistance Staphylococcus species has increased significantly. Empirical initial antibiotics therapy should take in consideration according to growing resistance of microbiology.

Methicillin resistance incidence rate in Staphylococcus aureus, CoNS and Staphylococci species

TH-P0848

Astragalus Inhibits Epithelial-to-Mesenchymal Transition of Peritoneal Mesothelial Cells via Suppressing Wnt/β-Catenin Signaling and Promoting Smad7

Jun Shi,1,2 Manshu Yu,1,2 Kun Gao,1 Lu Zhang,1 Meixiao Sheng,1 1First Clinical Medical College, Nanjing University of Chinese Medicine, Nanjing, China; 2Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, China; 3Department of nephrology, the affiliated hospital of Nanjing University of Chinese Medicine, Nanjing, China

Background: Epithelial-to-mesenchymal transition (EMT) is a crucial event inducing peritoneal fibrosis (PF), in which Wnt/β-catenin signaling participates. Smads signaling is reported to interact with Wnt/β-catenin and synergistically regulates EMT. This study was aimed to reveal the effect of Astragalus (a famous Chinese herbal for Wnt/β-catenin signaling in PMCs with EMT, as well as on the crosstalk between β-catenin and Smads.

Methods: Rats with peritoneal fibrosis and the human HMrSV5 peritoneal mesothelial cell line were used to explore the effects of Astragalus on EMT, EMT markers or signaling pathway-related indicators were detected by Western blotting, immunofluorescence, immunohistochemistry, immunoprecipitation and rt-PCR.

Results: β-Catenin knockdown inhibited EMT of PMCs. Astragalus not only relieved EMT and peritoneal fibrosis in rats but also inhibited β-catenin-mediated EMT in the HMrSV5 cell line, resulting from increased E-cadherin and decreased α-SMA.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
The nuclear translocation of β-catenin was suppressed by Astragalus as a result of the stabilization of GSK-3β promoting dissociative β-catenin degradation. Smad7, which was associated with β-catenin, was enhanced by Astragalus during EMT. The knockdown of Smad7 induced an increase in β-catenin and EMT.

**Conclusions:** Astragalus promotes Smad7 expression and effectively inhibits the Wnt/β-catenin signaling pathway during EMT of PMCs, indicating its potential therapeutic effect for PF.

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

### TH-PO849

**Prediction of Peritoneal Membrane Function in Pre-Dialysis ESRD Patients**

**Hui Xu, Nephrology Department, Xiangya Hospital, Central South University, Changsha, Hunan, China, Changsha, China.**

**Background:** Peritoneal membrane function decides the efficiency of peritoneal dialysis (PD). However, an effective method is still lack to value the peritoneal membrane function discrimination for pre-dialysis patient. As a valid classification and prediction tool, random forest using clinical data of 247 patients was used as the prediction tool, random forest using clinical data of 247 patients was used as the validation set. Secondly, random forest-based algorithm was applied in training set for model development and validation set.

**Methods:** Firstly, random forest method was used to build discrimination model for predicting peritoneal membrane function. The clinical data of 247 patients was used as the training set and the other 50 was used as the validation set. Randomly, random forest-based algorithm was applied in training set for model development and validation set.

**Results:** The discrimination model performed well for the primary objective. 10-fold cross validation was considered to be internal validation, the evaluation for this model showed that its accuracy, sensitivity and specificity respectively reached 0.862, 0.877, and 0.795. The coefficients of martensite (MCC) was turned out to be 0.60 and AUC (area under the receiver operating characteristics curve) was 0.840 (Fig 1a).

**Conclusions:** Random forest based model provides a robust tool to predict the peritoneal membrane function in non-dialysis ESRD patients.

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

### TH-PO850

**Percutaneous Re-Positioning of PD Catheter Accidentally Placed in the Subcutaneous Space Leaving the Tunnel and Exit-Site Intact – A Novel Idea**

**Santosh Varughese, Christian Medical College, Vellore, India.**

**Background:** Peritoneal dialysis (PD) catheter insertion by blind bedside percutaneous technique is a simple procedure. Rarely, the intra-abdominal portion of the catheter may accidentally be placed in the subcutaneous space if the introducer needle does not enter the peritoneal cavity during the initial part of the procedure. If this occurs, the catheter insertion has to be redone either percutaneously or surgically. The catheter often has to be replaced as part of it has been externalized and the external portion is unsterile.

**Methods:** A 70 year old man with end stage renal disease underwent PD catheter insertion by blind bedside percutaneous technique. Unfortunately, the catheter was accidentally placed in the subcutaneous space. There was inflow and outflow of PD fluid as the subcutaneous space had expanded with the PD fluid infused during the procedure, but the outflow rate was slow. On CT scan, the intra-abdominal part of the catheter was seen to be lying in the subcutaneous space. A novel technique of repositioning was attempted in which the exit site and tunnel were untouched. The abdomen was scrubbed and cleaned. The skin sutures and subcutaneous sutures at the original insertion site were removed. The deep cuff of the catheter was dissected free of the surrounding tissue. The intra-abdominal part of the catheter was exteriorized. A Veress needle was advanced till it reached the peritoneal space. The track was dilated using a peel-away sheath-dilator assembly. The dilator was removed and the intra-abdominal portion of the catheter (that had just been exteriorized) was slid in and the peel-away sheath was removed. The wound was closed in layers after ensuring good inflow and outflow. Peritoneal dialysis exchanges were begun the same day and was the patient was continued on continuous ambulatory peritoneal dialysis successfully.

**Results:**

**Conclusions:** This novel technique allows for a simple bedside repositioning technique of a PD catheter accidentally placed in the subcutaneous space without change of catheter or disruption of the tunnel or exit-site. Compared to a repeat PD catheter insertion, this procedure has the advantages of saving operating room time, reducing costs, reducing duration of hospital stay and possibly avoiding unnecessary hemodialysis.

### TH-PO851

**Fat Mass Monitoring in the Follow-Up of Peritoneal Dialysis Patients: Prognostic Value of Excessive Fat Gain**

**Jin Kyung Kim, Hyung jik kim, Hyung jik kim,1 Hallym Univ. Sacred Heart Hospital, Anyang, Republic of Korea; 2 Hallym University, Seoul, Republic of Korea.**

**Background:** Visceral obesity caused by fat accumulation is an important change in body composition among patients undergoing peritoneal dialysis (PD). Although a significant portion of patients become obese, its long-term effect is not clear and associated changes in peritoneal characteristics are also unknown.

**Methods:** In this prospective observational study, the prognostic value of excessive fat accumulation on technical failure rate and death was tested. Body composition monitoring was performed twice, 18.0 ± 6.0 months apart, and increment of percentage of body fat (delta_PBF, %) were used to predict long-term outcomes during the following 28.1 ± 8.5 months. Also, accompanying changes of peritoneal characteristics with fat accumulation were evaluated by modified peritoneal equilibration test. Technical failure was defined as a transfer from PD to haemodialysis (HD).

**Results:** Among the 205 patients, 66.8% (N=137) and 59.5% (N=122) experienced BMI increase and PBF gain during the 18 months. The mean PBF was 24.5% and 25.5% at first test, and 25.9% and 37.0% at second test in men and women respectively. Excessive fat gain was defined as a delta_PBF over the gender-specific highest quartile (4.8% for men and 5.7% for women). However, lean mass was not significantly changed. Patients with excessive fat gain was more diabetic and had higher systolic blood pressure. Interestingly, they experienced significantly higher rate of technical failure than those without excessive fat accumulation (90.5 cases vs. 22.4 cases per 1000 patient-year, p<0.002), but mortality was not affected. Even after adjusting the volume status and other comorbidities, excessive fat gain increased the risk of technical failure by 4.86-fold. Furthermore, with excessive fat gain, the peritoneal characteristics showed a tendency to change to a low transporter (p=0.013). However, mortality was not affected by the excessive fat gain.

**Conclusions:** Excessive fat gain during PD have an independent prognostic value for technical failure. Concomitant peritoneal membrane changes, decreased solute clearance in low transporter, may affect the higher rate of technical failure.

**Funding:** Private Foundation Support

### TH-PO852

**Itraconazole Ameliorates Chlorhexidine Gluconate-Induced Peritoneal Fibrosis in Mice through Regulating Hedgehog Signaling Pathway**

**Jin sung Kim,2 Yu ho Lee,1 Eun ji Park,2 Su Woong Jung,2 Chun-Gyoo Ihm,2 Tae won Lee,2 Yang guyn Kim,1 Ju young Moon,1 Sang-Ho Lee,1 Kyung-hwan Jeong,1 Kyung Hee University Hospital at Gangdong, Seoul, Korea, Seoul, Republic of Korea; 2 Kyung Hee University Medical Center, Seoul, Republic of Korea.**

**Background:** Peritoneal fibrosis is a devastating complication of peritoneal dialysis (PD). However, the precise mechanism is unclear and treatment has not yet been established. Recent evidence suggests that Sonic hedgehog (Shh) signaling pathway is...
involved in fibrogenesis, and drugs that inhibit this pathway are emerging in the treatment of fibrous, scarring, an anti-fungal agent, is recently also reported as an inhibitor of Shh signaling pathway. In this study, we investigated whether iraconazole suppressed chlorhexidine gluconate (CG)-induced peritoneal fibrosis in mice.

**Methods:** Peritoneal fibrosis was induced by intraperitoneal (IP) injection of 0.1% CG every other day for 4 weeks, with or without iraconazole treatment (20mg/kg, IP injection on a daily basis). Saline was administered intraperitoneally to the control groups. Male C57BL/6 mice were divided into four groups: saline injection (group 1), saline injection plus iraconazole (group 2), CG injection (group 3), CG injection plus iraconazole (group 4). The effects of iraconazole were evaluated based on peritoneal thickness, immunohistochemical staining, and real-time polymerase chain reaction. The peritoneal thickness was identified by Mason’s trichrome staining.

**Results:** Peritoneal thickening was evident in group 3 (CG injection), and the thickness was significantly decreased in group 4 (CG injection plus iraconazole). (59.9±34.9 µm vs. 16.8±9.0 µm, p<0.001). The mRNA expression of markers for fibrosis, including transforming growth factor-β1 (TGF-β1), fibronectin, and α-smooth muscle actin (α-SMA), were increased in the group 3 and were downregulated in the group 4. Similar results were shown in the markers for Shh signaling pathway. Iraconazole suppressed mRNA expression of Shh, Patched 1 (PTCH1), Smoothed (SMO), and Gli in peritoneal tissues. Immunohistochemistry analysis revealed that the expression of Hedgehog pathway components were increased in group 3, and decreased by using Itraconazole in peritoneal tissues.

**Conclusions:** Our results suggest that iraconazole ameliorates the peritoneal fibrosis by regulating Shh signaling pathway. Iraconazole can be a potential therapeutic strategy for peritoneal fibrosis.

**TH-PO853**

**Hemophagocytic Lymphohistiocytosis Secondary to Tubercular CAPD Peritonitis Manisha Dassi 1, Garima Aggarwal 2.** 1Max Super Specialty Hospital, Vaishali, Ghaziabad, India; 2Amrita Institute Of Medical Sciences, New Delhi, India.

**Background:** Tubercular CAPD peritonitis, though infrequent, has been reported to have a higher incidence in developing countries. HLH, seen in both inherited and secondary forms, is a rare & lethal disorder of the immune system. We report a case of HLH secondary to tubercular CAPD peritonitis.

**Methods:** A 49 years old male ESRD, on CAPD since 01 year presented with CAPD peritonitis. He required CAPD catheter explantation & shift to HD in view of refractory peritonitis. Though fever resolved, he continued to have clear watery discharge from the poorly healed surgical wound. He was lost to follow up & presented again 03 months later with complaints of fever, weight loss, fatigability and copious amount of yellowish discharge from the surgical wound. Clinically, he was hemodynamically stable, febrile, had pallor, multiple cutaneous ecchymotic spots, hepatosplenomegaly, reduced air entry at right lung base and a 5 cm infra-umbilical midline horizontal poorly healed surgical scar mark with surrounding skin inflammation. Relevant clinical & lab parameters are shown in Table 1. NCCT abdomen revealed hepatosplenomegaly, moderate ascites & loculated fluid collection in the right subphrenic space extending & lab parameters are shown in Table 1. NCCT abdomen revealed hepatosplenomegaly, moderate ascites & loculated fluid collection in the right subphrenic space extending.

**Results:** Peritoneal dialysis - I

**Conclusions:** The study reveals a major role of TLR2 and TLR4 in PD solution-associated peritoneal inflammation and fibrosis, identifies Hsp70 and HA as main associated peritoneal inflammation and fibrosis, identifies Hsp70 and HA as main.

**TH-PO854**

**Blunting Toll-Like Receptor Activity with Soluble TLR2 Inhibits PD Solution-Induced Fibrosis**

**Anne-Catherine Raby,1 Guadalupe T. González-Mateo,2 Donald Fraser,1 Manuel López-Cabrera,3 Mario O. Labéta,1 Cardinal University, Cardiff United Kingdom; 2Welsh Kidney Research Unit, University, Cardiff, United Kingdom; 3Consejo Superior de Investigaciones Científicas (CSIC). Spain, Madrid, Spain; 4Molecular Biology Research Centre Severo Ochoa, Spanish Research Council, Madrid, Spain.

**Background:** Membrane failure due to fibrosis limits the use of peritoneal dialysis (PD). Fibrosis results from peritoneal inflammation caused by infections or by ongoing cellular stress induced by PD (sterile inflammation). The immune mechanisms involved in sterile inflammation leading to fibrosis are poorly defined. Toll-like receptors (TLRs) mediate sterile inflammation by recognizing endogenous components released by cellular stress (DAMPs). We hypothesise that TLRs play a crucial role in sterile inflammation and fibrosis by recognising DAMPs released during PD and, thus, are major therapeutic targets for fibrosis prevention.

**Methods:** Results: A range of PD solutions (PDS) underwent comprehensive in vitro characterization of TLR-mediated inflammatory and fibrotic mediator production (genes and proteins) in all PDS elicited proinflammatory and fibrotic responses from primary human uremic peritoneal leukocytes and mesothelial cells. TLR2/4 blockade inhibited these effects. PDS did not induce rapid ERK phosphorylation, suggesting that they do not contain components capable of direct TLR activation. However, PDS increased the mRNA expression of markers for Hemophagocytic Lymphohistiocytosis Secondary to Tubercular CAPD Peritonitis.

**Results:** In this study, we investigated whether iraconazole suppressed fibrosis development by suppressing proinflammatory gene expression, proinflammatory cytokine production and reducing leukocyte recruitment.

**Conclusions:** The study demonstrates that iraconazole can blunts TLR2 activity to prevent PD solution-induced fibrosis by using a TLR modulator, sTLR2.

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

**Underline represents presenting author.**
of different doses of Astragaloside IV (As-IV), which is a cycloartane triterpene saponin with a clear formula(C41H62O14).

Results: The PD solution promotes IL-18 secretion in the condition medium of cultured PMCs as dose- and time-dependent manner. Accordingly, it significantly induced E-cadherin and increased vimentin, α-SMA. 3. Knockdown NLRP3 partially preserves PMCs from MMT by inhibited IL-18 secretion and NLRP3, caspase-1, IL-1β expression in cultured PMC. 4. Therapeutic inhibition of NLRP3 inflammasome with a novel small molecule inhibited NLRP3, caspase-1, pro-IL-1β, IL-1β expression in cultured PMCs. Targeting NLRP3 inflammasome activity by small molecule inhibitor AS-IV abolishes inflammatory factors and blocks mesenchymal conversion of mesothelium.

Conclusions: The activated NLRP3 inflammasome mediates PD solution-induced MMT in PMCs. Targeting NLRP3 inflammasome activity by small molecule inhibitor AS-IV abolishes inflammatory factors and blocks mesenchymal conversion of mesothelium.

TH-P0857

The Effects of Peritoneal Dialysis and Intraperitoneal Amino Acids on Protein Carbamylation Sahir Kalim,1 Jeffrey Perl,2 Megan J. Freeman,1 Caitlin A. Trotter,1 Anders H. Berg,1 Massachusetts General Hospital, Boston, MA; 2St. Michael’s Hospital, Toronto, ON, Canada; 3Beth Israel Deaconess Medical Center, Boston, MA.

Background: Protein carbamylation is a urea-driven post translational protein modification associated with mortality in hemodialysis (HD) patients. Free amino acids (AA) competitively inhibit protein carbamylation and parenteral AA therapy reduces carbamylation in HD patients. Peritoneal dialysis (PD) yields differences in urea clearance and AA balance compared to HD, but its effects on carbamylation are unclear. We assessed carbamylation burden in PD patients and determined the effects of AA enriched PD solutions on carbamylation.

Methods: We measured carbamylation albumin levels (C-Alb; a marker of total body carbamylation load) in 100 diabetic HD subjects, matched by age, sex, and race to 98 PD subjects with MMT. We compared Carbamylation Load (CL) in the IMPENDIA randomized trial (n=180) examined whether low-glucose PD solutions (combination of dextrose, icodextrin, and amino acids) improved metabolic control in diabetic PD patients compared to a control group (dextrose only solutions); 48 treated and 50 control subjects had available samples; C-Alb was compared between HD and PD groups and within IMPENDIA by treatment allocation.

Results: PD patients had a higher baseline C-Alb level compared to HD patients (Table). There were no major differences in basic clinical parameters between the compared IMPENDIA groups. We analyzed two sets of samples available. Among the IMPENDIA participants analyzed, there was no significant difference in C-Alb change from baseline to 6 months in either arm, but treated subjects showed a trend to increased carbamylation (Table). The intervention arm demonstrated a greater change in blood urea nitrogen, possibly explaining the trend for increased carbamylation (Table).

Conclusions: For the first time, we show that carbamylation levels in PD patients run higher than matched HD patients. Incorporating intraperitoneal AA solutions was associated with an increase in urea levels and a marginal increase in C-Alb. PD outcomes may improve if carbamylation burden can be reduced. However, unlike HD where parenteral AA therapy reduces carbamylation, AA-based intraperitoneal solutions as part of the IMPENDIA treatment arm were not effective at reducing carbamylation.

Funding: NIDDK Support, Commercial Support - Baxter Healthcare funded the parent study

Table

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n=180)</th>
<th>Control (n=89)</th>
<th>Intervention (n=91)</th>
<th>p-value (for intervention vs control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamylation albumin</td>
<td>12.9 ± 4.2</td>
<td>12.7 ± 4.2</td>
<td>13.1 ± 4.2</td>
<td>0.19</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>47.3 ± 14.7</td>
<td>46.2 ± 14.7</td>
<td>48.5 ± 14.7</td>
<td>0.03</td>
</tr>
</tbody>
</table>

TH-P0858

Peritoneal Membrane Morphology Following Peritonitis in Low GDP Patients Bruno Ranchin,1 Karel Vondrak,2 Gema Ariceta,1 Ariane Zaloszyc,1 Akos Ujszaszi,1 Franz S. Schaefer,1 Jeffrey Perl,1 Alfonso Ramos,3 Baxter Mexico, San Jerónimo Chichahualco, Mexico; 3Hospital Especialidades Dr Belisario Dominguez SEDESA, Mexico, Mexico.

Background: Peritonitis is a common complication of PD. The impact on peritoneal membrane morphology, however, is not well established. Non-acute post peritonitis peritoneal membrane morphology does not differ with regard to inflammation, EMT, fibrosis and vessel density as compared to children without a history of peritonitis.

TH-P0859

Help of Remote Patient Monitoring in the Assessment of Changes in Ultrafiltration before, during, and after a Peritonitis Episode in Patients on Automated Peritoneal Dialysis Mario R.,1 Alfonso Ramos,1 Baxter Mexico, San Jerónimo Chichahualco, Mexico; 3Hospital Especialidades Dr Belisario Dominguez SEDESA, Mexico, Mexico.

Background: Peritonitis is a common complication in patients on peritoneal dialysis and it has become the single most important cause of failure of the technique. The aim of this study was to compare ultrafiltration (UF) between, during and after a peritonitis episode.

Methods: This report is a retrospective review of a series of cases involving the use of RPM to evaluate UF in Automated Peritoneal Dialysis (APD) patients before, during and after a peritonitis episode. The day of clinical diagnosis of peritonitis was considered day zero. UF volumes from day 7 prior to diagnosis to day 10 after the diagnosis were collected from electronic records of RPM device. For analysis purpose, data were categorized in four groups: Group one: 7 days before the onset of peritonitis; Group 2: One day before the onset of peritonitis; Group 3: 7 days before and after the diagnosis; and Group 4: Days 7-10 after the diagnosis.

Results: Ten patients were studied, 5 female and 5 male, median age of 48 ± 6 years, with a median length of stay in the program of 18 months. The analysis showed a difference in UF between the values measured 1) 7 days before (194 ml) vs the day before the event (-302 ml) (P<0.04); 2) 7 days before (194 ml) vs during the event (-1,062 ml) (p<0.009); and 3) during the peritonitis (-1,062 ml) vs after the peritonitis episode (-319 ml) (p<0.01).

Conclusions: This is the first report documenting the use of RPM for the detection of minor changes in UF in a group of APD patients, which will allow us to suspect the presence of peritonitis and monitor its progress over time before conventional clinical data are available.

TH-P0860

Relation between BCM and Echocardiographic Parameters to Reflect Volume Status in Peritoneal Dialysis Min H. Kim,1 Sunwoo Kang,2 Tae Hee Kim,1 Yeong Hoon Kim,3 Nephrology, Busan Paik Hospital, Busan, Republic of Korea; 1Inje University, Busan, BUSAN, Republic of Korea; 2Inje University Medical School, Busan, Republic of Korea; 3None, Busan, Republic of Korea.

Background: Fluid imbalance is a frequent condition in peritoneal dialysis (PD) patients. Fluid overloading is one of causes to lead to cardiovascular instability. Even though there are no accurate methods to determine volume status in PD, body composition monitoring (BCM) is used as an objective measurement. The aim of this study was to find echocardiographic parameters associated with volume status compared to BCM parameters in PD patients.

Methods: This study was conducted on 74 PD patients in Busan Paik Hospital during 2014 – 2015. We used BCM to assess volume status, echocardiography to evaluate heart function and structure, and collected epidemiologic data. To account for the relation between BCM and echocardiographic parameters, we conducted regression analysis.

Results: Patients were 46±12 years old, 55% female, and 39% diabetic. A total of 6 (8%) all-deaths were reported. 10 (13%) among 74 patients received kidney transplantation, 10 patients transferred from PD to hemodialysis. Median dialysis vintage was 25 months (IQR 1.6, 12.7 months). Relative overhydration had positive correlation with systolic blood pressure (r²=0.12, p=0.003), diastolic blood pressure (r²=0.07, p=0.03), and extracellular water (ECW) (r²=0.27, p=0.001). Conversely relative OH had negative correlation with intracellular water (r²=0.08, p=0.02) and lean tissue index (r²=0.17, p=0.003). Echocardiographic parameters were correlated with left ventricular dimension (LVEDD) (r²=0.27, p=0.001) (Figure 1) and left ventricular diastolic posterior wall thickness (LVPWT) (r²=0.14, p=0.003).

Conclusions: Fluid overload in PD patients was associated with rise in ECW, which increased according as LVEDD enlargement. Echocardiographic parameters of
Left ventricle were good markers of volume status in PD patients. Further studies to understand the change in volume status over time are needed.

**Results:** 121 patients who started PD as their first dialysis modality were included. The mortality rate was 10.7%. LVMI and MACE were occurred in 31 patients. Logistic regression analysis found that LVM and age were independent risk factors of mortality (odds ratio, 1.04 and 1.19; 95% confidence interval (CI), 1.01 to 1.07 and 1.08 to 1.32; p <0.01 and p <0.01; respectively). When patients were divided into two groups according to LVMI, Kaplan-Meier analysis revealed that higher LVMI group had significantly higher mortality, higher incidence of MACE, and lower persistence rate of PD (Log rank: p = 0.003, 0.005 and 0.011, respectively). On ROC analysis, LVM predicted mortality with statistical significance (AUC [95%CI]= 0.87 [0.76-0.98]). The result of Cox proportional hazards model on mortality demonstrated that LVM and age were independent predictor of mortality (hazard ration, 1.02 and 1.08; 95%CI, 1.00 to 1.05 and 1.02 to 1.15; p = 0.02 and <0.01; respectively).

**Conclusions:** LVM at PD initiation may be a predictor of mortality and CVD in patients using BPDs.

**TH-PO863**

Therapeutic Experience of Peritoneal Dialysis Therapy for Patients with Severe Heart Failure and/or Liver Cirrhosis

**Patients**

Matsuura, Kent

Miyamoto, Ai

Nanfang Hospital, Southern Medical University, Guangzhou, China.

**Background:** Left ventricle were good markers of volume status in PD patients. Further studies to understand the change in volume status over time are needed.

**Methods:** This single center study enrolled all prevalent PD from 2014 to 2016. Patients who started PD from 2001 to 2015 at The University of Tokyo Hospital were collected retrospectively. To identify the predictors of death with the mortality or CVD in patients even when they are treated using biocompatible PD solution, alleviate edema and acute left heart failure, which might be an effective potentional of fluid management in severe heart failure and refractory ascites.

**Results:** A total of 47 patients (31 men, mean age 46.8±16.2 yr) were included in this study. The mean duration of CAPD was 26 months (2-195 months). Of the 47 patients, peritoneal dialysis UF was significantly increased when receiving short-time APD than that of CAPD (261.9±32.6 ml vs 706.2±222.3 ml, p< 0.001), and body weights were well controled 3 days after receiving APD (40% vs 70%, p< 0.007). Blood pressure were well controled and body weights were significantly decreased (p<0.001).

**Conclusions:** In conclusion, short-time APD could significantly increase ultrafiltration, alleviate edema and acute left heart failure, which might be an effective method to treat UF and acute left heart failure in PD patients.

**TH-PO864**

Bioimpedance Monitoring and Blood Pressure in Peritoneal Dialysis Patients

Patients Malick Touam,

Marie L. Cottereau,

Didier Birotou,

Dominique A. Joly.

Assistance Publique Hôpitaux de Paris, Paris, France;

Necker Hospital, Paris, France.

**Background:** We used bioelectrical impedance analysis (BIA) to determine body composition parameters in peritoneal dialysis patients (PD), and we compared the relationships of hydration status with home blood pressure (HBP) and office blood pressure (OBP).

**Methods:** This single center study enrolled all prevalent PD from 2014 to 2016. Patients recently started on PD (<3 m) or with recent peritonitis (<2 m) were not included. A bioimpedance monitor (BCM®, Fresenius Medical Care, Germany) was used to assess body composition. Demographic data, blood, 24-h dialysate and urine samples were collected. HBP and OBP measurements were collected the same day. Multivariate analysis was used to determine the relationship between HBP, OBP and extracellular fluid volume (total body water ratio (ECV/TBW)). Potential cofounders included age, diabetes, Charlson comorbidity index, PD method (CAPD, APD), and residual renal function (RFR) were identified.

**Results:** 65 PD were included (59.7 ± 13.4 y; average follow-up 13.6 ± 5.2 m). Systolic Blood Pressure (SBP) and systolic HBP (sHBP) were correlated with ECV/TBW. It was a very strong relationship between sHBP and ECV/TBW (r = 0.92) with sHBP, RRF and residual renal function (RFR) were identified.

**Conclusions:** in conclusion, short-time APD could significantly increase ultrafiltration, alleviate edema and acute left heart failure, which might be an effective method to treat UF and acute left heart failure in PD patients.
Table 1. Predictors of % ECV/TBW

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stage (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>sHRP</td>
<td>0.017</td>
<td>0.017</td>
</tr>
<tr>
<td>RRBP</td>
<td>0.267</td>
<td>0.070</td>
</tr>
<tr>
<td>Secure</td>
<td>0.612</td>
<td>0.010</td>
</tr>
<tr>
<td>C-react</td>
<td>0.006</td>
<td>0.006</td>
</tr>
<tr>
<td>CRP</td>
<td>0.010</td>
<td>0.010</td>
</tr>
<tr>
<td>Age at PD</td>
<td>0.212</td>
<td>0.010</td>
</tr>
<tr>
<td>Mal eude</td>
<td>0.056</td>
<td>0.010</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.495</td>
<td>0.010</td>
</tr>
<tr>
<td>Charlson</td>
<td>0.412</td>
<td>0.010</td>
</tr>
<tr>
<td>sHRP</td>
<td>0.022</td>
<td>0.010</td>
</tr>
<tr>
<td>Omt (eude)</td>
<td>0.010</td>
<td>0.010</td>
</tr>
<tr>
<td>BNP (eude)</td>
<td>0.553</td>
<td>0.010</td>
</tr>
<tr>
<td>CAM vs AP</td>
<td>0.710</td>
<td>0.010</td>
</tr>
<tr>
<td>Atm (eude)</td>
<td>0.212</td>
<td>0.010</td>
</tr>
</tbody>
</table>

Background: Efforts to continue PD when patients undergo CABG may minimize infectious and thoracic complications of temporary HD, alleviate interruptions in therapy, and be more cost effective. To investigate patterns of modality change and post-op complications in PD patients undergoing CABG, we queried the USRDS.

Methods: Incident PD patients from 2004–2011 (n=56,192) who underwent CABG were studied. Groups included: no interruption of PD (PD); planned temporary (PT) HD then back to PD (HD→PD); permanent switch (PS) to HD (HD); urgent temporary (UT) HD then back to PD (HD→HD→PD); or urge (U) HD with PS to HD (HD→PS→HD). Demographics and outcomes were determined. The relative risk (RR) of complications in interruption of PD vs. no interruption of PD up to 90 days post-op were estimated.

Results: 1259 PD patients had CABG, 63% men, 79% White, with mean±SD age 61±2 years, and time on dialysis of 24.1±2.7 months. Readmissions 90 days post-op for complications in PD patients undergoing CABG, were studied. Groups included: no interruption of PD (PD); planned temporary (PT) HD with PS to HD (HD→PD→HD); or urgent (U) HD with PS to HD (HD→PS→HD). Demographics and outcomes were determined. The relative risk (RR) of complications in interruption of PD vs. no interruption of PD up to 90 days post-op were estimated.

Conclusions: Continuing PD during CABG appears safe. A planned permanent switch to HD had the fewest readmissions and a non-significant tendency toward lower complication rates. Restraining PD after planned or urgent HD has a high complication rate. Risk stratification my help identify the best candidates for returning to PD post-CABG.

Funding: Clinical Revenue Support

TH-PO865

PD Patients Undergoing CABG: Modality Change and Complications

John Mufaddal,1 Stephanie L. Baer,2 Rhonda E. Colombo,1 Lu Huber,1 John J. White,1,2 Matt Day,1 Troy J. Plumb,4 N. Stanley Nahman,3 (Augusta University, Augusta, GA; Augusta VA Medical Center, Augusta, GA; Medical College of Georgia at Augusta University, Augusta, GA; University of Nebraska Medical Center, Omaha, NE.

Background: Efforts to continue PD when patients undergo CABG may minimize infectious and thoracic complications of temporary HD, alleviate interruptions in therapy, and be more cost effective. To investigate patterns of modality change and post-op complications in PD patients undergoing CABG, we queried the USRDS.

Methods: Incident PD patients from 2004–2011 (n=56,192) who underwent CABG were studied. Groups included: no interruption of PD (PD); planned temporary (PT) HD then back to PD (HD→PD); permanent switch (PS) to HD (HD); urgent temporary (UT) HD then back to PD (HD→HD→PD); or urge (U) HD with PS to HD (HD→PS→HD). Demographics and outcomes were determined. The relative risk (RR) of complications in interruption of PD vs. no interruption of PD up to 90 days post-op were estimated.

Results: 1259 PD patients had CABG, 63% men, 79% White, with mean±SD age 61±2 years, and time on dialysis of 24.1±2.7 months. Readmissions 90 days post-op for complications in PD patients undergoing CABG, were studied. Groups included: no interruption of PD (PD); planned temporary (PT) HD with PS to HD (HD→PD→HD); or urgent (U) HD with PS to HD (HD→PS→HD). Demographics and outcomes were determined. The relative risk (RR) of complications in interruption of PD vs. no interruption of PD up to 90 days post-op were estimated.

Conclusions: Continuing PD during CABG appears safe. A planned permanent switch to HD had the fewest readmissions and a non-significant tendency toward lower complication rates. Restraining PD after planned or urgent HD has a high complication rate. Risk stratification my help identify the best candidates for returning to PD post-CABG.

Funding: Clinical Revenue Support

TH-PO866

Burkholderia cepacia: An Outbreak in the Peritoneal Dialysis Unit


Background: Introduction Burkholderia cepacia is a gram negative, opportunistic, environmental bacillus which commonly affects cystic fibrosis and immunocompromised patients. Rarely, it can cause peritoneal dialysis exit site infection (ESI). Data on predisposing factors, clinical course and treatment options is limited. Although a common cause of nosocomial infections, no nosocomial outbreaks in peritoneal dialysis (PD) patients have previously been reported. A recent outbreak of B. cepacia ESIs in our PD unit provided a unique opportunity to gain more information on B. cepacia ESIs and to outline an approach to investigating an outbreak in the PD unit. Eight such cases were identified.

Methods: Case description Following the identification of B. cepacia as the causative organism in PD catheter exit site infection in three patients over an eleven week period, we began screening our PD population for B. cepacia exit site colonisation. Over the following sixteen weeks, a further three patients were identified as having asymptomatic colonisation, and a further two patients suffered symptomatic B. cepacia ESI. Of the five symptomatic ESIs, three developed tunnel infections requiring multiple courses of antibiotic treatment and eventual catheter removal. Isolated ESIs were treated with oral and topical antibiotics with full resolution. Five of eight patients were female, three had proud flesh at the exit site, three were diabetic (all of the asymptomatic infections were in non-diabetics; two of the three tunnel infections developed in diabetic patients). A thorough investigation into the likely source of the outbreak implicated the 4% chlorhexidine handwash used by the patients. However, samples from the manufacturer did not contain B. cepacia suggesting mishandling of the product by the patients may have contributed.

Results: This is the first reported outbreak of B. cepacia PD exit site infections. A number of interesting observations were made. Firstly, diabetes may potentially be a risk factor for refractory or more extensive infection. Secondly, treatment should be individualised according to the extent of the infection; our cohort suggests that an isolated ESI can be treated successfully with oral antibiotics whereas tunnel infections generally require catheter removal.

Conclusions: Discussion This is the first reported outbreak of B. cepacia PD exit site infections. A number of interesting observations were made. Firstly, diabetes may potentially be a risk factor for refractory or more extensive infection. Secondly, treatment should be individualised according to the extent of the infection; our cohort suggests that an isolated ESI can be treated successfully with oral antibiotics whereas tunnel infections generally require catheter removal.

Funding: Government Support - Non-U.S.
**TH-PO870**

**Evaluating Bacterial Flush Efficiency and Touch Contamination Across 3 Different Twinbag Systems**  
**Paul Straka, James A. Sloand. Baxter Healthcare Corporation, Deerfield, IL.**

**Background:** Peritonitis is a significant complication of peritoneal dialysis (PD). PD system design to reduce touch contamination by at-home PD patients is critical in reducing peritonitis risk. Impact of connection-design differences on contaminant flux efficiency among three different Twinbag CAPD system was assessed by examining differences in the amount of bacteria entering the fluid path under worst case touch contamination.

**Methods:** 3 studies were performed: A1, A2, and B, with details as follows: A1) Touch contamination at the transfer set connector adapter (TSCA) and the patient connector adapter (PCA) ends, each connector quantified. A2) Touch contamination simulated as in A1, connected and flushed to quantify the bacteria transferred into the fluid path. B) Known levels of bacterial contamination were inoculated into the fluid path, performed CAPD procedure and quantified the patient infusion fluid. Three different commercially available PD delivery systems (System 1, 2, 3) were tested using the above (27 times over a 4 day period) that differed in location of the frangible, the Y-configuration, and the size of the shrouds (short: Canex; long: Hytrel) on the PCA.

**Results:** For touch contamination evaluation (A1), the TSCA had a significant (p-values <0.001) lower mean bacterial level compared to the PCA. For touch contamination evaluation (A2), system 2 had a significantly higher mean count than systems 1 and 3 (p-value <0.001). For the flux efficiency evaluation (B), the three systems were compared within each day. There were no significant differences in the mean log base 10 values among the three systems within days 1, 3 and 4 (p-values >0.05). For day 2, system 3 mean was significantly higher than system 2 mean (p-value = 0.0031).

**Conclusions:** Touch contamination studies show that when contaminated, the smaller surface area of the TSCA when compared to the PCA resulted in lower bacterial counts. Despite what would appear to be a protective design, the deeply recessed Hytrel shroud resulted in significantly higher bacterial transfer into the fluid path than the shallow recessed Canex shroud. These differences are immaterial given no difference between “flush before fill” efficiency of the 3 systems, irrespective of frangible location on the Y connector. This highlights the importance of redundancy in connection design features to reduce PD touch contamination.

---

**TH-PO869**

**Poor Early Exit Site Condition Was Associated with Subsequent Exit Site Infection and Catheter Loss of Peritoneal Dialysis**  
**Masaki Uchida, Takafumi Yamakawa, Takehiko Kawaguchi, Toshiyuki Imasawa, Morotoshi Kadomura. Department of Nephrology, National Hospital Organization Chiba-East Hospital, Chiba, Japan.**

**Background:** Exit site infection (ESI) is a common complication for peritoneal dialysis (PD) patients. A previous study reported that the first ESI before eight months post-implant period was a higher risk of PD related infections. However, it is unclear whether an early condition of exit site after PD initiation is associated with subsequent ESI and PD catheter loss.

**Methods:** We retrospectively examined 46 patients who started PD from 2010 to 2015 at Chiba East Hospital in Japan. The patients were divided into two groups, good or poor exit site condition group (G or P group), according to ISPD exit site scoring system. We defined the poor exit site as the score more than 2 points on the first outpatient visit after PD initiation, or the worse score on the second visit. We compared episodes of ESI more than twice (E), peritonitis (P) and catheter loss (L) between the groups. Cox regression was used to estimate hazard ratios (HRs) adjusting for age and diabetes as primary disease.

**Results:** The patients were mostly male (69.6%), with a mean age of 61.0 years, and 50% of patients had diabetes. There were no statistical differences in baseline characteristics between the two groups. During the median follow-up of 719 days, we observed 13 of Es, 15 of Ps, and 13 of Ls. In unadjusted analyses, we found no statistical difference in P free survival rates, but E and L free survival rates were significantly lower in P group than in G group (Figure). In multivariable analyses, the adjusted HRs (95% CI) for E, P, and L in P group were 29.5 (2.62-331.61), 1.90 (0.61-5.94), and 3.00 (1.01-9.59) respectively.

**Conclusions:** Poor early exit site conditions were associated with subsequent ESIs and PD catheter losses. It may be crucial to keep good exit sites after PD initiation. Further studies are needed to verify that early screening and interventions for poor exit sites can improve the outcomes.

---

**TH-PO871**

**Peritoneal Membrane Transport Characteristics in Uni-Peritoneal Equilibration Test (PET) with Preceding Icodextrin Dwell as Compared to Classic PET with Preceding Glucose Dwell: A Pilot Study**  
**Harbir S. Kohli,1 Gaurav Vohra,2 Vivek Kumar,3 Krishan Lal L. Gupta.1 1Post Graduate Institute of Medical Education and Research (PGIMER), CHANDIGARH, India; 2Postgraduate Institute of Medical Education & Research, Chandigarh, India; 3Postgraduate Institute of Medical Education and Research, Chandigarh, India.**

**Background:** In subjects on CAPD who use icodextrin for long night dwell, it has been recommended that nocturnal icodextrin exchange be replaced by dextrose dwell whenever PET is to be performed. This is because it has been thought that preceding exchange with icodextrin temporarily increases peritoneal membrane permeability and therefore, gives high dialysate/plasma creatinine (D/P cr) and low dialysate glucose at end of PET/dialysate glucose in fresh solution (D/D0) value. Whether this temporary change is an artifact of use of Uni-PET (which involves one hour dwell of 1.5% dextrose followed by 4-hour dwell of 4.25% dextrose) is not known.

**Methods:** In this self, controlled study, subjects on CAPD, who were using icodextrin for long nocturnal dwell for at least 3 months, were screened for enrolment. Pregnancy or lactation, history of any PD related infectious complication in the past one year, oncologic or post malignancy, and poor functional status were exclusion criteria. On day 1 enrolled subjects underwent classic PET with preceding 2.5% dextrose nocturnal dwell and on day 2 Uni-PET was done with preceding 7.5% icodextrin long nocturnal dwell. Difference in D/P cr and D/D0 glucose between the two PETs were primary objectives.

The study was approved by Institute Ethics Committee.

**Results:** Of 26 screened subjects 15 were enrolled over a period of 18 months (July 2015-December 2016). The mean (±SD) age of study population was 60.8±9.1 years. Majority were males and diabetes was the most common cause of CKD. Mean D/P cr were 0.68 ±0.11 and 0.64 ±0.08 in classic PET and Uni-PET, respectively. The difference between the two values was not significant [mean difference between D/P cr (classic PET-Uni-PET): 0.040 ±0.86; 95% CI (-0.007 to 0.888); p=0.09]. Similarly, D/D0 glucose between classic PET and Uni-PET were similar [mean difference between D/D0 glucose (classic PET-Uni-PET): -0.02 ±0.09; 95% CI (-0.06 to 0.03); p=0.448].

**Conclusions:** Peritoneal membrane small solute transport characteristics in Uni-PET with preceding icodextrin dwell are similar to classic PET with preceding glucose dwell. If Uni-PET is used, it is not necessary to replace preceding nocturnal exchange of icodextrin with that of dextrose.
Peritoneal Dialysis - I

TH-PO872
Increasing Peritoneal Inflammation Over Time Drives Increasing Peritoneal Solute Transport: Results from the Global Fluid Study

Background: Local peritoneal inflammation is a feature of peritoneal dialysis (PD) treatment and high concentrations of dialysate IL-6 (dIL6) are a strong determinant of solute transport (PSTR). PSTR is associated with patient survival and increases during long-term PD but it is not known to what extent the rise is driven by dIL-6.

Methods: We conducted a longitudinal analysis of the Global Fluid study, a multinational cohort study from UK, Canada and Korea. All incident patients with 3 or more paired dialysate/plasma samples were assayed for IL-6 by electrochemiluminescence. A linear mixed model with random intercept/slopes assessed associations with PSTR. Covariates included time on PD, centre, glucose exposure, icodextrin use, dIL6, gender, baseline age, comorbidity and urine volume in an adjusted model with backwards selection. pIL6 and dIL6 were log transformed. PSTR was assessed by modified peritoneal equilibration testing to calculate the dialysate to plasma creatinine ratio.

Results: There were 217 patients with 1274 measurements, with a median follow-up time of 2.2 years from 6 centres. PSTR increased from a mean value of 0.735 within the first 6 months to 0.741 after 3.5 years, whilst dIL6 increased from 6.0 pg/ml to 12.0 pg/ml over the same period. When adjusted for centre, icodextrin use, urine volume and dIL6 were significant predictors of PSTR (β = 0.0095% CI 0.056 to 0.083 p<0.001). Time varying dIL6 was a better predictor than baseline dIL6 (AIC = -1377 vs. AIC = -1342). Time became insignificant with both varying and baseline dIL6. The effect of urine volume and icodextrin was reduced over time. Random slopes were significant for time (LRT 19 d.f.=2 p=0.0005).

Conclusions: Both dIL6 and PSTR increase with duration of PD. The increase in PSTR over time is mostly accounted for by changes in dIL6 and urine volume.

Table 1: Hazard ratio for mortality associated with PD compared to HD in patients with low serum albumin, by cause of ESRD

<table>
<thead>
<tr>
<th>Cause of ESRD</th>
<th>HR (PD/HD)</th>
<th>CI (95%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulonephritis</td>
<td>0.71</td>
<td>0.54-0.92</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.79</td>
<td>0.64-0.97</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>0.92</td>
<td>0.53-1.62</td>
<td>0.84</td>
</tr>
<tr>
<td>Others</td>
<td>1.03</td>
<td>0.51-2.12</td>
<td>0.91</td>
</tr>
<tr>
<td>Overall</td>
<td>0.96</td>
<td>0.78-1.17</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Methods: We analyzed USRDS data from 2010-2015 to assess mortality by modality type adjusted for age, sex, race, employment, comorbidities and the year of dialysis initiation.

Results: Low serum albumin (<2.5 gm/dL) was present in 78,625 (19.9%) of 395,656 patients. Those with low serum albumin were less likely to use PD as their first modality than those with higher albumin (3.1% vs. 10.9%; p<0.001). Use of PD was associated with lower mortality compared to HD (hazard ratio [HR]= 0.86, 95% CI 0.80-0.93, p< 0.05) in patients with low serum albumin. This difference was more pronounced in patients who had glomerulonephritis (HR =0.70) or hypertension (HR =0.79) than in those with end-stage renal disease (ESRD) due to diabetes mellitus or other causes [Table 1].

Conclusions: PD is associated with lower mortality than HD in patients with low serum albumin. Therefore, it is of concern that the rate of PD utilization is lower in these patients. We recommend advocating the use of PD in patients with low serum albumin as is associated with a lower mortality rate.

TH-PO873
Transversus Abdominis Plane Block Relieves Perioperative Pain on Peritoneal Dialysis Catheter Insertion

Background: The effectiveness of Transversus Abdominis Plain (TAP) block has been reported in the pain control at abdominal operation. However, its usefulness in pain management remains unclear in peritoneal dialysis (PD) patients undergoing catheter insertion.

Methods: The present study is a single-centred, prospective, randomised study of initiated PD patients between from April 2016 to March 2017. VAS (Visual Analogue Scale), which is often used around anesthesiology and pain management field, was measured as pain assessment. VAS was measured at two points, right after and 24 hours after operation, using t-test with P values.

Results: Overall, 66 PD patients were included (mean age; 67.2 year old, male:female; 42:24, average eGFR 7.63±2.81). Patients were divided into two groups TAP block (n=35) - non-TAP block (n=31). There were significant low VAS in TAP block compared to non-TAP block (p<0.001). Furthermore, even at 24 hours after operation VAS in TAP block was lower (1.55 vs 2.59, p=0.041). There were no cases needed for ventilation and anesthetic drug such as morphine. TAP block-related adverse events were not found.

Conclusions: TAP block technique was significantly associated with relief from post-operative pain in PD catheter insertion. This treatment procedure might be a minimally invasive and effective therapeutic option for perioperative pain management on PD catheter insertion.

TH-PO874
Peritoneal Dialysis Is Associated with Lower Mortality Compared to Hemodialysis in Patients with Low Serum Albumin

Background: Low serum albumin is associated with high mortality in patients on chronic dialysis. Clinicians are reluctant to offer peritoneal dialysis (PD) as an option for dialysis for patients with low serum albumin due to concerns of loss of albumin with PD. We evaluated mortality based on dialysis modality in patients with low serum albumin (<2.5 gm/dL).

Methods: We analyzed USRDS data from 2010-2015 to assess mortality by modality type adjusted for age, sex, race, employment, comorbidities and the year of dialysis initiation.

Results: Low serum albumin (<2.5 gm/dL) was present in 78,625 (19.9%) of 395,656 patients. Those with low serum albumin were less likely to use PD as their first modality than those with higher albumin (3.1% vs. 10.9%; p<0.001). Use of PD was associated with lower mortality compared to HD (hazard ratio [HR]= 0.86, 95% CI 0.80-0.93, p< 0.05) in patients with low serum albumin. This difference was more pronounced in patients who had glomerulonephritis (HR =0.70) or hypertension (HR =0.79) than in those with end-stage renal disease (ESRD) due to diabetes mellitus or other causes [Table 1].

Conclusions: PD is associated with lower mortality than HD in patients with low serum albumin. Therefore, it is of concern that the rate of PD utilization is lower in these patients. We recommend advocating the use of PD in patients with low serum albumin as is associated with a lower mortality rate.

Table 1: Hazard ratio for mortality associated with PD compared to HD in patients with low serum albumin, by cause of ESRD

<table>
<thead>
<tr>
<th>Cause of ESRD</th>
<th>HR (PD/HD)</th>
<th>CI (95%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulonephritis</td>
<td>0.71</td>
<td>0.54-0.92</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.79</td>
<td>0.64-0.97</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>0.92</td>
<td>0.53-1.62</td>
<td>0.84</td>
</tr>
<tr>
<td>Others</td>
<td>1.03</td>
<td>0.51-2.12</td>
<td>0.91</td>
</tr>
<tr>
<td>Overall</td>
<td>0.96</td>
<td>0.78-1.17</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Methods: We analyzed USRDS data from 2010-2015 to assess mortality by modality type adjusted for age, sex, race, employment, comorbidities and the year of dialysis initiation.

Results: Low serum albumin (<2.5 gm/dL) was present in 78,625 (19.9%) of 395,656 patients. Those with low serum albumin were less likely to use PD as their first modality than those with higher albumin (3.1% vs. 10.9%; p<0.001). Use of PD was associated with lower mortality compared to HD (hazard ratio [HR]= 0.86, 95% CI 0.80-0.93, p< 0.05) in patients with low serum albumin. This difference was more pronounced in patients who had glomerulonephritis (HR =0.70) or hypertension (HR =0.79) than in those with end-stage renal disease (ESRD) due to diabetes mellitus or other causes [Table 1].

Conclusions: PD is associated with lower mortality than HD in patients with low serum albumin. Therefore, it is of concern that the rate of PD utilization is lower in these patients. We recommend advocating the use of PD in patients with low serum albumin as is associated with a lower mortality rate.

Table 1: Hazard ratio for mortality associated with PD compared to HD in patients with low serum albumin, by cause of ESRD

<table>
<thead>
<tr>
<th>Cause of ESRD</th>
<th>HR (PD/HD)</th>
<th>CI (95%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulonephritis</td>
<td>0.71</td>
<td>0.54-0.92</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.79</td>
<td>0.64-0.97</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>0.92</td>
<td>0.53-1.62</td>
<td>0.84</td>
</tr>
<tr>
<td>Others</td>
<td>1.03</td>
<td>0.51-2.12</td>
<td>0.91</td>
</tr>
<tr>
<td>Overall</td>
<td>0.96</td>
<td>0.78-1.17</td>
<td>0.53</td>
</tr>
</tbody>
</table>
Barriers to Peritoneal Dialysis in Kenya Ahmed P. Sokwala, Aga Khan University Hospital, Nairobi, Kenya.

Background: Peritoneal dialysis (PD) is not commonly practiced in Kenya. Kenya has approximately 4000 patients on hemodialysis (HD) with less than 20 patients on PD. The perception and attitude of both the patient and the doctor on the modality of chronic renal replacement therapy determines what type of dialysis the patient will be started on. Increase in PD in developing countries with poor infrastructure for HD, will increase the number of patients who can access renal replacement therapy for both acute kidney injury and end stage renal disease.

Methods: A questionnaire was formulated and mailed to the nephrologists to determine their attitude towards PD and to bring out the reasons why they are reluctant to start peritoneal dialysis. A total of 22 questions were formulated and the questionnaires mailed to the 25 nephrologists in the region. Questions were about the nephrologists’ opinions on reasons that limited patients and doctors selection of peritoneal dialysis as initial therapy. After analyzing the reasons, interventions can be put into place to improve the numbers of patients on peritoneal dialysis.

Results: Twenty three out of twenty five (93%) nephrologists responded to the questions. Only 38% of the nephrologists took care of patients on peritoneal dialysis and out of those 55% of the nephrologists had less than 2 patients on PD. Despite that 70% of the nephrologist thought that more than 20% of end stage renal disease patients should be on PD. Most of the doctors said they had adequate training and exposure to peritoneal dialysis in their training. Lack of nursing expertise was one of the main reasons stated by the nephrologist as being the main challenge of starting peritoneal dialysis. Lower physician reimbursement for peritoneal dialysis via a vis haemodialysis was another point brought out, the Government had started paying for hemodialysis rather than peritoneal dialysis. The other major hindrance was insertion and care of the peritoneal dialysis catheter. Most nephrologists thought patients do well on peritoneal dialysis with no mortality difference between PD and HD.

Conclusions: There is positive attitude about PD amongst the nephrologist. Training more nurses on peritoneal dialysis and training doctors on bedside insertion of peritoneal dialysis catheters will probably increase the uptake of peritoneal dialysis in our country. Nephrologists should be equally reimbursed for PD as for HD or even better.


Background: Peritonitis is a devastating complication in peritoneal dialysis (PD) patients. Newer techniques are needed to predict peritonitis development and to characterize potential pathogens.

Methods: In this first-in-kind study, we recruited 4 ESRD PD patients; 2 subjects had peritonitis at the time of enrolment and the remaining 2 did not. We collected 2 serial peritoneal fluid (PF) specimens from these subjects. We performed metagenomic sequencing on PF under single-stranded DNA library preparation using an Illumina NextSeq platform (2x75 bp).

Results: A mean of 3.6 million cDNA fragments was obtained per specimen (N=7 specimens) and these fragments had peaks at 65 bp and 167 bp (Fig A). cDNA profiling confirmed 2 cases of peritonitis (Klebsiella pneumoniae, Staphylococcus epidermidis). Serial profiling showed decreasing adjusted BLAST hits after antibiotic treatment (Fig B). Alignment of cDNA fragments to the reference genome of K. pneumoniae revealed disproportionate coverage over the replication origin, highlighting active growth of K. pneumoniae, and subsequent decrease in growth activity after antibiotic treatment (Fig C). Antibiotic resistance determination revealed the presence of PmrE, PmrF, oxQβ, mlt, F27AMAR, Pat-A-PatB, and mshA, which provide resistance to colistin, novobiocin, ciprofloxacin, and norfloxacin.

Conclusions: Our first-in-kind study demonstrates that cDNA profiling of peritoneal fluid is an all-inclusive approach to comprehensively identify pathogens, bacterial growth dynamics, and antibiotic resistomes, which may be useful in culture-negative peritonitis and recurrent peritonitis.

The Involvement of p38MAPK in Impaired Neutrophil Bacterial Activity of Hemodialysis Patients Yasutaka Kamikawa, Norihiko Sakai, Yasuyuki Shinozaki, Shinji Kitajima, Tadashi Toyama, Akinori Hara, Yasunori Iwata, Miho Shimizu, Kengo Furuchii, Takashi Wada, Division of Nephrology, Kanazawa University Hospital, Kanazawa, Japan; Department of Nephrology and Laboratory Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Japan.

Background: Mortality from infections has been reported to be higher in hemodialysis (HD) patients than in healthy subjects. Previous studies reported that vascular access was the main route of bacterial infection in HD patients and also pointed that the most common micro-organism were staphylococcus aureus (S. aureus). To protect the host from bacterial infection, neutrophils have been thought to play central roles in the pathogenesis of the infection. This far, the dysfunction of neutrophils against bacterial infection in HD patients was reported. However the precise mechanism of neutrophil dysfunction in HD patients against bacteria remains unclear. In this study, we investigated the impacts of neutrophil inflammatory signaling against bacterial infection in HD patients.

Methods: Comprehensive analyses of intracellular signalings were performed in whole blood of HD patients and hypertensive (HT) patients as control using microarray system. None of patients had diabetes, cardiovascular disease and cancer. To confirm the contribution of the signaling to bacterial activity in neutrophils, we examined the

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

Underline represents presenting author.
Dialysis: Infection Rates in Hemodialysis Patients

**TH-PO881**

**Len**

**myeloperoxidase (MPO) release in neutrophils against S. aureus** showed the suppression of p38 mitogen activated protein kinase (MAPK) signaling in HD patients. Neutrophils in HD patients showed the impairment of bactericidal activity against S. aureus compared to healthy subjects. Phosphorylation rate of p38MAPK of neutrophils in response to S. aureus was lower in HD patients than healthy subjects. The levels of ROS produced by neutrophils after co-culture with S. aureus were lower in HD patients, on the other hand, there was no difference of MPO release between HD patients and healthy subjects. A selective pharmacological inhibitor of p38MAPK suppressed bactericidal killing function as well as ROS production in neutrophils of healthy subjects.

**Conclusions:** Impairment of p38MAPK signaling pathway might contribute to the suppression of neutrophil bactericidal activity in HD patients through the less production of ROS.

**TH-PO880**

**Seasonal Variations in Blood Stream Infections in Hemodialysis Patients in the Midwest**

**Marta Revirrego-Mendoza,** Sophie Rosen, Hao Han, Tommy C. Blanchard, Jerry W. Jackson, Julia I. Brennan, John W. Larkin, Len A. Usvyat, Peter Kotanko, Jeffrey L. Hynes, Franklin W. Maddux, Fresenius Medical Care North America, Waltham, MA. **Poster**

**FMC Patient Safety Council, Mountain Brk, AL.** Renal Research Institute, New York, NY. Spectra Laboratories, Rockleigh, NJ.

**Background:** Blood stream infections (BSIs) are the most common cause of morbidity and second leading cause of mortality in hemodialysis patients (HD). Environmental variations, particularly heat and humidity, are known to promote pathogenic growth and be associated with the incidence of BSIs and the worsening of clinical conditions. We aimed to study whether seasonal changes in the Midwest area of the United States are associated with the variations in BSI rates in hemodialysis patients.

**Methods:** We collected data from HD patients treated at Fresenius Kidney Care clinics in the Midwest region from Jan-2014 through Dec-2016. This region was selected due to its more demarcated seasonal changes. Clinics included were those from the following states: Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin. The average monthly BSIs were calculated for HD patients and the association between the mean BSI rate and season was analyzed and plotted using a seasonally varying function that was optimized to the data using a least-squared method (Figure 1).

**Results:** We observed a distinct seasonal variations in BSI rates with a mean fluctuation of 9.25% below and above during July versus December of 2014-2016, respectively. Although BSI rates appeared to increase during warmer months, we observed a 34.3% decrease in BSI rates in the Midwest from 2014 to 2016.

**Conclusions:** Our findings suggest that seasonal variability is associated with alterations in BSI rates. In the Midwest, the highest BSI rates were observed during warmer months. The downward trend in BSI rates may be representative of improvements in infection control in HD facilities. Further analyses are warranted to confirm these results.

**TH-PO883**

**Sex-Specific Differences in Blood Stream Infection and Hospitalization Rates in Hemodialysis Patients**

**Marta Revirrego-Mendoza,** Sophia Rosen, Dugan Maddux, John W. Larkin, Len A. Usvyat, Franklin W. Maddux, Fresenius Medical Care, Waltham, MA.

**Background:** It is known that men and women have physiological, hormonal, and genetic differences that can impact treatment regimens and clinical outcomes. Investigations on sex-specific differences in patients undergoing hemodialysis (HD) are limited. We performed a cross-sectional analysis to investigate if there are sex specific differences in systolic blood pressure (SBP) levels, blood stream infection (BSI) rates and hospitalization rates.

**Methods:** We analyzed data from all Fresenius Medical Care North America HD patients in 2016. Patients were grouped in 17-age categories from 18 years to 95 years based on their age at initiation of dialysis. Yearly average SBP was calculated for each patient and averaged for each age-group. Hospitalization rates per patient year (ppy) and rate of hospitalization were calculated for each age-group. We identified patients who had 1 or more hospitalizations during 2016 and calculated the percent of patients with at least 1 infection in that particular age group.

**Results:** Overall, we studied data from 230,091 patients; 43% were female. We used linear and quadratic regressions with an interaction term for Sex to study the sex-specific differences in hospitalization rates. We observed a significant effect of age on hospitalization rates (p<0.0001). We found that women, in particular those of a younger age, are at a significantly higher risk of BSIs and hospitalization than men. The characterization of these health disparities between the sexes may aid in identifying patients at risk of poorer outcomes.

**Conclusions:** Our analysis shows that women, in particular those of a younger age, are at a significantly higher risk of BSIs and hospitalization than men. The characterization of these health disparities between the sexes may aid in identifying patients at risk of poorer outcomes.

**Funding:** Commercial Support - Fresenius

**TH-PO882**

**Association of Low Molecular Weight Heparin Compared to Unfractionated Heparin and the Risk of Dialysis-Related Infection and Septicemia among Hemodialysis Patients**

**Marta Revirrego-Mendoza,** Sophie Rosen, Hao Han, Tommy C. Blanchard, Jerry W. Jackson, Julia I. Brennan, John W. Larkin, Len A. Usvyat, Peter Kotanko, Jeffrey L. Hynes, Franklin W. Maddux, Fresenius Medical Care North America, Waltham, MA. **Poster**

**FMC Patient Safety Council, Mountain Brk, AL.** Renal Research Institute, New York, NY. Spectra Laboratories, Rockleigh, NJ.

**Background:** Hemodialysis patients have a higher risk of infection compared to the general population. The administration of low molecular weight heparin (LMWH) for the extracorporeal circuit anticoagulation requires less manipulation in comparison with unfractionated heparin (UFH), which may result in a reduced bacterial contamination. The aim of this study is to evaluate the association between the use of LMWH and dialysis-related infection and septicemia compared to UFH among chronic hemodialysis patients.

**Methods:** We conducted a retrospective cohort study of 6012 adult chronic hemodialysis patients (prevalent and incident) using an administrative database in Quebec, Canada. Hospitalizations due to dialysis-related infections or septicemia were identified using ICD-10 codes. Patients’ exposure to LMWH or UFH was determined at the facility level. Infection rates were calculated as person-year and risk of infection was estimated using Cox proportional hazards models, adjusting for demographics, prior hospitalizations, comorbidities and steroids use.

**Results:** The incidence rate of hospitalizations for dialysis-related infections and septicemia was 0.044 patient-year. From the total cohort, 37% of patients were exposed to LMWH. Compared to UFH, LMWH was associated with a statistically significant decrease in infection risk (HR=0.79, 95%CI: 0.64-0.96). Moreover, younger age (HR=0.99, 95%CI: 0.98-1.00), hospitalization in prior year (HR=1.26, 95%CI: 1.00-1.58), chronic pulmonary disease (HR=1.36, 95%CI: 1.09-1.70) and diabetes (HR=1.26, 95%CI: 1.03-1.54) increased the infection risk among chronic hemodialysis patients.

**Conclusions:** Among hemodialysis patients, LMWH use decreased the risk of hospitalization for dialysis-related infection and septicemia compared to UFH.

**TH-PO883**

**An Outbreak of Catheter-Related Bacteremia on Hemodialysis Patients Caused by Serratia marcescens**

**Omar I. Delgado,** Javier Soto-Vargas, Heriberto R. Lopez, Jorge fernando Topete reyes, Ma anabel Salazar lopez, Oscar C. Martinez Garcia, Leonardo Pizarro-Villaseor, Nephrology, Regional General Hospital 46, Mexican Institute of Social Security, Guadalajara, Mexico, Guadalajara, Mexico.

**Background:** Catheter related infections in hemodialysis patients are associated with a great morbidity, hospitalization, and death. Serratia marcescens has been reported to cause nosocomial infection due to their ability to colonize antiseptic soaps. Our objective was to present an outbreak of S. marcescens in HD patients.

**Methods:** In our HD unit there are 27 HD machines, with a total of 945 treatments at week, we have 370 maintenance HD patients with 2 or more sessions per week. During the period of April to May 2015 ninety-five HD patients reported a bacteremia episode during, of which 56 cases were positive to S. marcescens. An epidemiologic search was conducted finding positive cultures on antiseptic soap used by medical personal. During, of which 56 cases were positive to S. marcescens. An epidemiologic search was conducted finding positive cultures on antiseptic soap used by medical personal.

**Results:** There were 95 cases of bacteremia, of which S. marcescens represented the 59% (56) of the cases, 14 (16.1%) we were unable to localize an agent, and other pathogens had a frequency no bigger than 2%. The median age was 35 years (IQR 25-53), 62 (63.3%) were male, 65 (68.4%) patients had HD thrice weekly, and 30 (31.6%) had twice or less HD sessions per week. 46 (48.4%) patients received their treatment on nocturnal hours, 27 (28.4%) on the morning hours and 12 (12.6%) on the evening. There were no association between the time of the HD sessions and the need for hospitalization and catheter removal. Seventy-one percent of the patients had a non-tunneled catheter, 29% had a tunneled catheter, and there were no cases in patients who had FAV as their vascular access. The antibiotic treatment was standardized and in general consisted of antibiotics against the cultures consisting of amikacin in lock therapy and systemic ciprofloxacin. There were no fatal cases, but the infection results in the need of hospitalization and access removal in four cases (4.2%).
Conclusions: The appearance of S. marcescens in blood cultures of HD patients units should alert the possibility of an outbreak, given its ability to colonize antiseptic substances. Early and targeted antibiotic treatment as well as routine microbiology screening is recommended for the prevention of outbreaks.

TH-PO884
Epidemiology and Outcomes of Infective Spondylodiscitis in Hemodialysis Patients
Yuehan Lu, George Kuo, Chao-Yu Chen, Hsiang-Hao Hsu. Kidney Research Center, Department of Nephrology, Linkou Chang Gung Memorial Hospital; College and School of Medicine, Chang Gung University, Taiwan, Taoyuan, Taiwan.

Background: Infective spondylodiscitis, defined as the pathogenic invasion of vertebra and intervertebral disc, is an uncommon but serious disease. As the disease progresses, patients develop neurological deficits, sepsis, and even mortality. Microorganisms reach vertebra and intervertebral discs in different ways, including antegrade bacteremia from the blood stream, retrograde infection from the urinary tract and direct invasion from contiguous tissue or a surgical procedure. Patients on maintenance hemodialysis (HD) have additional risk factors that contribute to blood stream infection because of the repeated vascular puncturing, long-term catheter or Gore-Tex graft indwelling, and contamination of dialysis water purification system. The characteristics and outcomes of infective spondylodiscitis in HD patients may be different from those in the general population.

Methods: The cases of 1,402 patients who were hospitalized for infective spondylodiscitis in a 13 year period in a tertiary hospital were retrospectively reviewed. Of these, 102 patients on maintenance HD were enrolled in this study. Cox’s proportional hazard model was used to evaluate the risk factors of mortality and recurrence.

Results: The 102 enrolled patients had an average age 63.3±11.2 years old and male-to-female ratio of 1:1.04. Back pain was present in 75.5% of patients and the most commonly infected site was the lumbar sacral spine. Infection associated with vascular access was identified in 31.4% of patients and the use of dialysis via central venous catheters was three times higher than in outpatient cohort. Methicillin-resistant S. aureus was the most common pathogen, followed coagulase-negative staphylococci. The patients’ in-hospital survival rate was 82.4%; their vascular access survival was 75.5% their one-year survival was 78.4% and their one-year recurrence rate was 20.2%. Congestive heart failure was associated with an increased one-year mortality. Other variables exhibited no significant relationship with patients’ in-hospital mortality, one-year mortality or recurrence.

Conclusions: The characteristics and outcomes of infective spondylodiscitis in HD patients were elucidated. Most of the demographic and clinical variables, evaluated upon admission, did not predict mortality or recurrence. An algorithm for the diagnosis and treatment of infective spondylodiscitis in an HD cohort is provided.

TH-PO885
Epidemiology and Outcomes of Endophthalmitis in Chronic Dialysis Patients: A 13-Year Experience in a Tertiary Referral Center in Taiwan
George Kuo,1 Hsiang-Hao Hsu,2 Chang-Gung Memorial Hospital, Taiwan, Taoyuan City, Taiwan; 2Kidney Research Center, Department of Nephrology, Linkou Chang Gung Memorial Hospital; College and School of Medicine, Chang Gung University, Taiwan, Taoyuan, Taiwan.

Background: Endophthalmitis is a severe eye infection leading to disabling outcome. We would like to investigate the epidemiology and clinical features of endophthalmitis in chronic dialysis patient in a tertiary referral center.

Methods: We performed chart review and searched discharge diagnosis with ICD9 encoding endophthalmitis during Jan. 2002 to Dec. 2015. Results: In total 32 patients, 25 were endogenous and another 7 were exogenous endophthalmitis. Most patients presented with ophthalmalgia and pericentral swelling, whereas half of the patients suffered blurred vision (n=16, 50%). S. aureus, K. pneumoniae, and P. aeruginosa were the most frequent causative pathogens. Dialysis vascular infection was an important focus. The final visual outcomes in both groups were worse in the chronic dialysis patients compared with previous studies of general population.

Conclusions: This is the first and the largest case series focusing on endophthalmitis in chronic dialysis patients. Our study showed different pathogen spectrum, an unique bacterial origin and worse visual outcome in these group of patients. Prompt referral to ophthalmologists is important.

Funding: Government Support - Non-U.S.

TH-PO886
Reduction in Rates of Blood Stream Infection Associated with Adoption of TeamSTEPPS as a Framework for Improved Hemodialysis Facility Workflows
Jerry W. Jackson,1,2 Norma J. Ofsthun,1 Carol Meredith,2 Marcy E. Goldberg,1 Uddar Onta,1 Franklin W. Maddux,3 JMC Patient Safety Council, Mountain Brk, AL; 2Fresenius Kidney Care, Downers Grove, IL; 3Fresenius Medical Care North America, Waltham, MA.

Background: Blood Stream Infection (BSI) remains one of the most serious adverse events affecting end stage renal disease (ESRD) patients. Multiple barriers and situational factors impede infection control in ambulatory hemodialysis (HD) facilities. We implemented a Quality Improvement Project (QIP) and analyzed its impact on BSI rates in HD facilities.

Methods: We deployed the QIP in 79 Fresenius Kidney Care facilities from January 2016 through March 2017. After performing a Failure Mode and Effects Analysis, we identified 55 HD workflow steps (distributed throughout the HD treatment) with high-risk for infection. The QIP design included training and observational auditing for the high-risk steps, use of TeamSTEPPS training to instill team-oriented care and to reduce barriers to infection control, ongoing coaching and feedback for caregivers in the use of TeamSTEPPS tools, incorporation of an infection control data set for analysis and action-planning during QAPI, and closed-loop communication pathways. The facilities were divided into Low, Mid and Top participatory subgroups based on monthly reported process metrics. Mean BSI rate by subgroup during 2015 was used for baseline. Implementation BSI rates by subgroup were followed Q1 2016 through Q1 2017.

Results: We studied data from a mean census of 10,988 patients. Mean baseline BSI rates (expressed as BSI episodes/1,000 HD treatments) by subgroup were: Low, 0.32; Mid, 0.46; Top, 0.46. Data collected at the end of the QIP showed changes in mean BSI rates of (+) 4.6%, (-) 23.7%, and (+) 32.2% for the Low, Mid and Top subgroups, respectively (Figure 1).

Conclusions: These findings suggest the use of TeamSTEPPS combined with the other interventions of this QIP might be associated with a reduction in dialysis associated blood stream infections.

Funding: Commercial Support - Fresenius Medical Care North America
Dialysis: Infection

TH-PO887

Bloodstream Infection (BSI) Rates in Catheter Patients Are Markedly Higher in Hemodialysis Facilities with Lower Proportions of Catheters Robert S. Brown,1 Kristin M. Brickel,2 Roger B. Davis.3 1 Beth Israel Deaconess Medical Center, Boston, MA; 2DuVita, Naugatuck, CT.

Background: BSI rates of HD patients with catheters (CVC) are greater than with other accesses. Medicare assesses financial penalties and lower Five-Star ratings to high CVC facilities, prompting a study of BSI rates in CVC patients relative to facility CVC percentage.

Methods: CROWNWeb and NHSN data from all 171 Medicare facilities providing outpatient HD patients in the IPRO ESRD Network of Europe throughout 2015 were compared BSI rates of CVC and non-CVC patients based upon facility proportion of CVCs, patient census, batch submitting organization and season. Results: There were an average of 74±20 HD patients with 9.6±13% having CVC accesses per facility. Mean BSI/100 pt-mo was 0.50±1.10 for all accesses, 3.0±8.7 for CVC, and 0.21±0.72 for non-CVC patients (relative risk of BSI for CVC vs non-CVC patient, 10.7, 95%CI 8.7, 13.2, P<0.0001). Surprisingly, annual BSI rates in CVC patients were negatively correlated with the facility’s proportion of CVCs (r=−0.247, P=0.001) but positively correlated in non-CVC patients (r=0.147, P=0.056). Facilities with <5%, 5-10%, 10-15%, 15-20%, >20% CVCs have BSI rates of 11.7, 3.5, 2.5, 1.8, 1.6 per 100 pt-mo, respectively, in CVC patients (P<0.0001). This striking difference was not seen in non-CVC patients (P=0.07, risk ratios in figure). Smaller providers have 1.3-2.6 times the BSI rates of the 4 large dialysis organizations (4.6 vs 1.8-3.6 BSI/100pt-mo, P<0.01) despite similar CVC proportions. There was no effect of facility census or season.

Conclusions: HD facilities with the lowest proportion of CVCs have significantly higher BSI rates (up to 6.9 times) in their CVC patients. This large difference may be explained by “dilution” of CVC patients with those in the lower risk non-CVC pool and by better training and experience in facilities with higher CVC proportions and the larger dialysis organizations. BSI rates in CVC patients may be a better quality parameter than CVC percentage.

TH-PO888

Tunneled Hemodialysis Catheter Care Practices and Blood Stream Infection Rate in Children: Results from the SCOPE Collaborative Oliveria Marsenc,4 Jonathan Rodeman,1 Troy Richardson,1 Bradley A. Warday,2 Alicia Ne,3 1Children’s Hospital Association, Overland Park, KS; 2Johns Hopkins University School of Medicine, Baltimore, MD; 3The Children’s Mercy Hospital, Kansas City, MO; 4Pediatric Nephrology, Yale University, New Haven, CT.

Background: The Standardizing Care to Improve Outcomes in Pediatric End-stage renal disease (SCOPE) collaborative seeks to reduce hemodialysis (HD) catheter associated bloodstream infections (CA-BSI) by increasing implementation of standardized HD catheter care bundles. We report on HD catheter care practices and HD CA-BSI rates from SCOPE.

Methods: Catheter care practices and HD CA-BSI reported between 6/2013 and 3/2017 are included. Catheter bundle compliance is monitored across the reporting period on a sample of patients at each center. Compliance with each element in the care bundle is evaluated as is overall compliance, which is scored as “all or none”, i.e each element must be performed to be compliant. For catheters with multiple observations compliance is reported as a percent compliance across observations. Only observations prior to the CA-BSI are included for catheters with infections. Results are reported as median and interquartile range (IQR) and compared by CA-BSI status with Wilcoxon Rank Sum tests. Associations between CA-BSI status and categorical characteristics are compared with chi-square tests.

Results: 427 catheters in 424 children [median (IQR) age 12.5 years (6,16), M: 54%, F: 46%] at 27 centers were included. 3569 catheter care observations were submitted with median (IQR) 4 (1,12) observations per catheter. 111 CA-BSI from 66 catheters were reported, yielding a rate of 2.0 infections/100 catheter months. Bundle compliance [% median (IQR)] in catheters with and without CA-BSI and their comparisons are presented in the Table.

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

Table 1

<table>
<thead>
<tr>
<th>Category</th>
<th>Compliance</th>
<th>CA-BSI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysis environment</td>
<td>100 (100.00)</td>
<td>100 (100.00)</td>
<td>0.068</td>
</tr>
<tr>
<td>Continuous</td>
<td>100 (100.00)</td>
<td>100 (100.00)</td>
<td>0.221</td>
</tr>
<tr>
<td>Disocation</td>
<td>100 (100.00)</td>
<td>100 (100.00)</td>
<td>0.806</td>
</tr>
<tr>
<td>Cup care</td>
<td>100 (100.00)</td>
<td>100 (100.00)</td>
<td>0.002</td>
</tr>
<tr>
<td>Disosing change and re-use care</td>
<td>67.5 (33.00)</td>
<td>60 (85.00)</td>
<td>0.483</td>
</tr>
<tr>
<td>Overall</td>
<td>87.5 (77.10)</td>
<td>75 (33.30)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

TH-PO889

Infection Rates in ESRD and Renal Transplant Patients Using Real World Claims Data Katherine Belendiuk,1 Richa Rajwanshi,1 Yingjie Ding,2 Kelly Kwon,3 Dominic Borie, Matthew Casciano,1 Jay P. Gurg,1 Thomas Schindler,1 Ha N. Tran,1 Genentech, Inc., South San Francisco, CA; 2Genentech, Inc., South San Francisco, CA; 3Genentech, Inc., Basel, Switzerland.

Background: End stage renal disease (ESRD) patients (pts) are at increased risk of infections due to immune dysregulation, malnutrition, and indwelling dialysis access. After transplant (tx), pts are at further risk due to immunosuppressive therapy. There is a lack of impact of infection on real world outcomes that could better evaluate and understand infection risks in their patients. The objective of this study was to characterize the rates of serious and opportunistic infections in ESRD and renal tx pts.

Methods: We conducted a retrospective cohort study using the Truven Healthcare MarketScan® Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits database between 2000 and 2014. The ESRD cohort index date was the first of either an ESRD or dialysis claim, separated by ≥7 days. The tx cohort index date was the first of ≥2 claims related to kidney tx, separated by ≥7 days.

Results: 23,433 ESRD pts on dialysis and 18,660 renal tx pts were identified. One year following the index date, the rates of serious infections were higher in ESRD patients compared with renal tx pts. Most serious infections required hospitalization in both groups and opportunistic infection rates were comparable (Table 1).

Conclusions: ESRD and post-tx pts experience serious infections with high rates of hospitalization indicating high burden of illness. Physicians should carefully evaluate infection risks when considering pre- and post-tx immunosuppressive regimens.

Funding: Commercial Support - Genentech, Inc./F Hoffmann-La Roche

Table 1

<table>
<thead>
<tr>
<th>Category</th>
<th>No CA-BSI</th>
<th>CA-BSI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death within 30 days</td>
<td>100 (100.00)</td>
<td>100 (100.00)</td>
<td>0.999</td>
</tr>
<tr>
<td>OOP healthcare costs</td>
<td>100 (100.00)</td>
<td>100 (100.00)</td>
<td>0.999</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>100 (100.00)</td>
<td>100 (100.00)</td>
<td>0.999</td>
</tr>
<tr>
<td>Total charges</td>
<td>100 (100.00)</td>
<td>100 (100.00)</td>
<td>0.999</td>
</tr>
</tbody>
</table>

TH-PO890


Background: In ESRD, infections account for 8% of cause-specific mortality. Hospitalizations are frequent, prolonged, and impair quality of life. Inpatient cost is ~$2.7 billion/yr. ICD-10 coding is intended to specifically characterize hospitalization outcomes. We tested whether ICD-10 coding was adequate to capture and distinguishes bloodstream infections (BSI) in ESRD patients with tunneled dialysis catheters from BSI in patients with other implanted devices.

Methods: This is a single-center retrospective chart review in patients with BSI from 10/15-12/31/16. Subjects were grouped: (Gp1) ESRD BSI from tunneled dialysis catheter infection; (Gp2) ESRD BSI with AV fistula (AVF) or graft (AVG); and (Gp3) Non-ESRD BSI from an implanted device (PICC lines, ICD/pacer leads, bioprosthetic/mechanical heart valves, orthopedic hardware, and non-HD grafts/stents (vascular, ureteral). Groupings were based on: (Gp1) Infectious Diseases Society of America Guidelines for Intravascular Catheter-Related Infection (CID 2009:49); (Gp2) Positive blood/wound cultures, Guidelines for Intravascular Catheter-Related Infection (CID 2009:49); (Gp3) Positive blood/wound cultures, physical exam, radiological assessments, and biopsy results. We descriptively compared the use of ICD-10 codes among the clinical groups.

Results: Table shows ICD-10 codes used to classify the BSI events in these 3 groups. For some, >1 ICD-10 code was used. In 12, no code was used. There was substantial overlap in the ICD-10 codes used to describe BSI in patients with ESRD tunneled catheters, AVFs, and AVGs, and non-ESRD BSIs associated with other implanted devices.

Conclusions: In this “Discovery” cohort, the lack of a unique ICD-10 identifier for BSI due to tunneled dialysis catheters makes it difficult or impossible to distinguish these clinical events from other BSIs. “Validation” cohorts at other centers is in progress. A unique code is needed to quantify the burden of this devastating clinical entity.
ICD-10 codes in patients with BSIs

ICD-10 codes

ICD-10 codes

BSI due to central vascular catheter

BSI due to central vascular catheter

[36x616]Dialysis: Infection
[36x580]Public Health, Atlanta, GA; 2Tennessee Department of Health, Nashville, TN; 
Preeti Data—2016

National Healthcare Safety Network Dialysis Bloodstream Infection TH-PO892

Comparison of National Healthcare Safety Network Dialysis Event Validation in Georgia and Tennessee Gianna S. Peralta,1,3 Ashley Fell,2 Elizabeth N. Smith,1 Jeanne Negley,1 Marion Kainer.2 1Georgia Department of Public Health, Atlanta, GA; 4Georgia Department of Department of Health, Nashville, TN; 

CDC/CSTE Applied Epidemiology Fellowship, Atlanta, GA.

Background: 370,000 people in the United States rely on hemodialysis and are at risk for developing serious infections. Outpatient hemodialysis (OHID) facilities are required to report dialysis event (DE) data to the National Healthcare Safety Network (NHSN), including intravenous antimicrobial starts (AMS), positive blood cultures (PBC), and pus, redness, or increased swelling at the vascular access site (PRS). The Georgia Department of Public Health (GDPH) and Tennessee Department of Health (TDH) validated NHSN DE data to assess data quality and identify common reporting errors.

Methods: Sixty OHID facilities were selected for data validation (30 each in TN and GA). Facilities were selected due to having few reported PBCs, or at random. TDH validated data from January-June 2014, while GDPH validated DE data from January-June 2015. Both states followed the CDC DE Data Quality Evaluation Guide. GDPH and TDH validated 30 days of data (2016) for up to 30 patients per facility for medical record review to identify DEs, conduct a concordance check, and survey staff members responsible for NHSN DE data collection and reporting.

Results: Record review TDH reviewed a total of 790 patient records; GDPH reviewed 876. TDH identified 272 (34%) patients with at least one DE for a total of 497 events; GDH identified 201 (23%) patients with least one DE for a total of 332 events. Under-reporting of DEs was common in both states (TN: 28%; GA: 39%). Over-reporting of DEs was lower in TN (5%) vs. GA (12%) than DEs reported in hospitalization, and 10% in GA. A majority of facility administrators in both states did not know how to correctly assign vascular access category (59% in TN; 51%). In TN, 55% of facility administrators could not correctly describe how to count patients for the denominator, compared to 35% in GA. A majority of facility administrators in both states did not know how to correctly assign vascular access category (59% in TN; 78% in GA).

Conclusions: Validation of NHSN DE data provided valuable insight about data quality and common reporting errors that can be addressed through education and training. Reporting deficiencies were identified among all types of DEs. All facilities should have a strong working knowledge of the CDC DE Protocol. Consistent and accurate documentation of DEs can help facilities detect problems, identify trends, evaluate infection prevention activities, and engage staff in quality improvement.

Funding: Other U.S. Government Support

TH-PO893

Bloodstream Infections in Pediatric Hemodialysis Outpatients: National Healthcare Safety Network, 2013-2015 Mark W. Keng,1 Duc B. Nguyen,1 Alicia Neu,2 Birbone W. Apata,3 Bradley A. Warady,4 Priti R. Patel.1 1Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, GA, 2Johns Hopkins University School of Medicine, Baltimore, MD; 3University of Missouri, Kansas City School of Medicine, Children’s Mercy Kansas City, Kansas City, MO.

Background: Compared to adults, children on chronic hemodialysis (HD) are more often dialyzed via a central venous catheter (CVC), which poses a high risk of infection. However, data on bloodstream infections (BSIs) in the outpatient pediatric HD population are sparse. To characterize these infections, we analyzed 2013-2015 BSI data that outpatient HD centers reported to the Centers for Disease Control and Prevention’s (CDC) National Healthcare Safety Network (NHSN), a widely used healthcare-associated infection surveillance system.

Methods: The NHSN dialysis event surveillance protocol defines a BSI as a positive blood culture collected as an outpatient or within one calendar day of a hospitalization. Access-related BSIs are positive blood cultures with a suspected vascular access source or uncertain source. Up to 3 organisms per BSI can be reported. Pediatric BSIs were defined as those occurring in patients < 18 years of age at the time of event, and these BSIs could be reported by any participating HD center (adult or pediatric). Events in patients with a calculated age < 1 year were excluded. We categorized BSI by highest-risk vascular access type present (CVC > graft > fistula).

Results: During 2013 to 2015, 634 BSIs occurred in pediatric patients > 1 year of age. Of the 634 BSIs, 588 (93%) occurred in patients with CVC; 352 (58%) of the BSIs were classified as access-related. A total of 61% (78) BSIs reported in hospitalization, and 10% (21) resulted in death. The most common pathogens identified were Staphylococcus aureus (30%), coagulase-negative Staphylococcus (23%), and Enterococci (8%).

Conclusions: Cathers account for the majority of pediatric HD BSIs reported to NHSN, demonstrating the importance of interventions targeting catheter care and use of permanent vascular access, when possible. Further characterization of the incidence of BSIs in the pediatric outpatient HD population may yield additional opportunities for prevention. A limitation of the analysis is reliance upon calculated age, which may be subject to data entry errors.

Funding: Other U.S. Government Support

TH-PO894

National Healthcare Safety Network Dialysis Bloodstream Infection Data—2016 Duc B. Nguyen,1 Shunte Moon,2 Taylor Guffey,1 Christi Lines,3 Preeti Rvindhara,4 Jonathan Edwards,1 Priti R. Patel.1 1Centers for Disease Control and Prevention, Atlanta, GA; 2Centers for Disease Care and Prevention, Atlanta, GA.

Background: Among hemodialysis (HD) patients, bloodstream infections (BSIs) are often severe adverse events. The Centers for Disease Control and Prevention (CDC) conducts surveillance for these events through the National Healthcare Safety Network (NHSN). We summarized 2016 BSIs data submitted to NHSN Dialysis Event Surveillance and compared to data from previous years.

Methods: A BSI is defined in the NHSN surveillance protocol as a positive blood culture collected in an HD outpatient or within 1 calendar day of a hospitalization. Access-related BSIs (ARBSIs) are positive blood cultures with either a suspected vascular access source or uncertain source as indicated on the event reporting form. Denominator data consist of the number of HD outpatients treated at the facility during the first two working days of each month. BSI rates were stratified by vascular access type (e.g., arteriovenous fistula [AVF], arteriovenous graft [AVG], central venous catheter [CVC]). We compared BSI rates during 2014–2016 controlling for access type using generalized linear models.

Results: In 2016, 6,437 outpatient HD facilities reported 151,943 dialysis events to NHSN, including 27,108 BSIs, of which 20,375 (75.2%) were ARBSIs. Most ARBSIs (62.7%) and BSIs (70.2%) occurred in patients with a CVC. Hospitalization and death associated with events occurred among 52.9% and 2.8% of BSIs, respectively. The rate of BSI per 100 patient-months was 0.56 (0.22 for AVF, 0.37 for AVG and 1.84 for CVC) with 25th and 75th percentile of 0.2 and 0.79, respectively. During 2014–2016, the yearly reduction in rates controlling for access type was 7.1% (95% confidence interval [95% CI]: 5.5% to 8.2%). The BSI rate was 0.56 (95% CI: 0.37 to 0.96) for ARBSIs.

Conclusions: Rates of BSI were highest among patients with CVC. BSI and ARBSI appeared to have decreased during 2014–2016, possibly due to nationwide prevention efforts. Our results suggest that even though progress towards BSI prevention has been achieved, opportunities exist to reduce rates of BSIs and ARBSIs among HD patients.

Funding: Other U.S. Government Support

TH-PO895

Age-Dependent Production of Highly Apoptosis-Resistant CD31 – Memory-Tregs May Cause Chronic Inflammatory Conditions in Dialysis Patients Matthias Schäfer,1 Angèle Leck,2 Florian Käβle,3 Christian Morath,1 Claudia Sommerer,1 Martin von Faber,1 Andrea Steinborn-Kroehl,2 Nephrology, University of Heidelberg, Heidelberg, Germany; 1Gynecology, University of Heidelberg, Heidelberg, Germany.

Background: Dialysis patients have an increased susceptibility for chronic inflammation. In addition, an increased risk for virus-associated cancers and atherosclerotic diseases are documented.

Methods: We analyzed whether age-related differences in the differentiation of both recent-thymic-emigrant (RTE)- regulatory (Tregs) and RTE-responder T cells (Tregs) CD31-memory-Tregs/Tregs led to differences in the suppressive activity of naive and memory Tregs on healthy individuals of different age (n= 89) and dialysis patients (n=80).

Results: Our findings suggest, that the thymic release of RTE-Tregs decreases with age and thereby causes their enhanced differentiation via CD31-memory-Tregs into CD31-memory-Tregs, so that the suppressive activity of both naïve and memory-Tregs is maintained with age in healthy controls. In addition, the decreasing thymic release
of RTE-Tregs may cause their enhanced differentiation via MN-Tregs into CD31-memory Tregs which may enhance the suppressive activity of both naïve CD45RA- and CD45RA-memory-Tregs, especially in young individuals. However, the differentiation of RTE-Tregs via MN-Tregs, seen in healthy volunteers, could not be detected in dialysis patients. Instead, there was an age-dependent increase in the differentiation via CD31-memory Tregs into CD31-memory Tregs in dialysis patients. This effect may strengthen the functionality of Tregs with age and explain why Tregs of elderly dialysis patients show difficulties suppressing autologous Tregs, but preserve the ability to suppress non-autologous Tregs of healthy volunteers.

Conclusions: The aging immune system sustains apoptosis autonomy, but favors the incidence of inflammation. In contrast, the increased age-dependent production of highly apoptotic-resistant CD31-memory T-dysfunction in these patients may cause chronic inflammatory conditions in these patients.

TH-PO895
Serum Sodium and Bacteremia Risk in Dialysis Patients
Connie Rhee,1 Amy S. You,2 Elani Streja,2 Juan Carlos Ayus,3 Hamid Moradi,3 Steven M. Brunelli,1 Csaba P. Kovesdy,2 Danh V. Nguyen,1 Kamyar Kalantar-Zadeh.1 DaVita Clinical Research, Needham, MA; 2Harald Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; 3Renal Care Network, Huntington, TX; 1University of California Irvine, Irvine, Orange, CA; 2University of California Irvine, School of Medicine, Orange, CA; 3University of Tennessee Health Science Center, Memphis, TN.

Background: Hyponatremia is a potential risk factor for infection, which may be due to impairment of IL-17 producing helper T cells that function in host immunity, and concomitant mucosal membrane and cellular edema leading to breakdown of microbial barrier function. While dialysis and infection-related mortality are common in dialysis patients, little is known about the association between serum sodium levels and bacteremia in this population.

Methods: Among 823 dialysis patients from the national Biospecimen Registry Grant Program (BioREG) who underwent serum sodium testing over 1/2008-12/2014, we examined the relationship between sodium level and risk of bacteremia using case-mix adjusted Poisson regression models adjusted for age, sex, and race/ethnicity.

Results: In the overall cohort, the mean±SD and minimum-maximum serum sodium values were 138±2mEq/L and 115-154mEq/L, respectively, approximately 10% of all patients experienced one or more bacteremia events during the follow-up period. Patients with both lower sodium <134mEq/L and higher sodium ≥140mEq/L had higher incident rates of bacteremia in case-mix models (ref. 136–138mEq/L): adjusted IRR [aIRR] 1.99 (1.04-3.81), 0.76 (0.32-1.80), 1.30 (0.73-2.31), 1.83 (1.05-3.18), and 2.07 (1.15-3.72) for sodium levels <134, 134–136, 136–<138, 138–<140, 140–<142, ≥142mEq/L, respectively.

Conclusions: Both lower and higher serum sodium levels were associated with higher incident rates of bacteremia in dialysis patients. Further studies are needed to determine whether correction of dysnatremia ameliorates infection risk in this population.

TH-PO896
Impact of Pre-ESRD Nephrology Care on Early Post-Dialysis Sepsis-Related Hospitalizations
Robert Nee,1,2 Christina M. Yuan,2,3 Lawrence Agodaca,1 Kevin C. Abbott.1 NIDDK, National Institutes of Health, Bethesda, MD; 2Nephrology, Walter Reed National Military Medical Center, Bethesda, MD; 3Medicine, Uniformed Services University, Bethesda, MD.

Background: Pre-ESRD renal disease (ESRD) nephrology care has been reported to improve morbidity and mortality in dialysis patients. However, its impact on infectious complications in dialysis patients has not been studied. Herein we assessed the association between pre-ESRD nephrology care and hospitalizations for sepsis within 12 months after initiation of dialysis.

Methods: Using the US Renal Data System database, we identified 282, 571 Medicare primary patients initiated on maintenance dialysis from 1 January 2009 through 1 June 2013, and followed until 31 December 2013. We abstracted Medicare hospitalization records for “septicemia with total discharge diagnosis” using the International Classification of Diseases, Ninth revision, Clinical Modification (ICD-9-CM) codes 038. xx (x = 0 to 9 inclusive). We conducted Cox regression analyses for sepsis, adjusted for demographic characteristics, cause of ESRD, dialysis modality, comorbidities, vascular access and other clinical variables.

Results: 11,614 (5.4%) patients were hospitalized for sepsis within 12 months after start of dialysis, 33% of whom had more than one hospitalization. Patients with pre-ESRD care had a lower incidence rate of early sepsis compared to those without pre-ESRD care (1.78 vs 1.00 patient-years [PY] vs 1.11 vs 1.00 PY, respectively, p<0.001). Hospital length of stay was shorter in patients with pre-ESRD care compared to those without pre-ESRD care (13.7 days vs 17.6 days, p<0.001). In fully adjusted Cox models, pre-ESRD care was associated with significantly lower likelihood for early sepsis (adjusted hazard ratio [aHR] 0.86, 95% CI 0.80-0.91). Among patients with pre-ESRD care, those who received ≤6 months of pre-ESRD care were less likely to be hospitalized for sepsis (aHR 0.78, 95% CI 0.71-0.86) but the association with those who had 6-12 months of pre-ESRD care was nonsignificant (aHR 0.95, 95% CI 0.86-1.05).

Conclusions: Pre-ESRD nephrology care was associated with lower risk of sepsis-related hospitalizations within 12 months of dialysis initiation. Disclaimer: The views expressed in this abstract are those of the authors and do not reflect the official policy of the Department of the Army/Navy/Air Force, the Department of Defense, National Institutes of Health, or the United States government.

TH-PO897
Erin Weather,1 Jennifer L. Waller,2 N. Stanley Nahman,3 Rhonda E. Colombo,2 Jake E. Turrentine,2 Matthew F. Kheda,2 Sami R. Husain,2,3/1Augusta VA Medical Center, Augusta, GA; 2Augusta University, Augusta, GA.

Background: The incidence of syphilis has increased 67% in 4 years to 7.5 per 100,000 in the US, but is underestimated in the end stage renal disease (ESRD) population. This study examined diagnoses of syphilis and associated risk factors in ESRD patients to identify opportunities for improving screening and risk modification.

Methods: All incident ESRD patients from 2004-2010 in the USRDS were queried. ICD-9 codes were used to determine syphilis diagnoses and related comorbidities. Neurosyphilis (NS) was defined with both an ICD-9 code and an associated lumbar puncture CPT code. The geographical distribution was determined by number of cases per 100,000 ESRD patients in each state. A 5% random sample of patients without syphilis was used for analysis. Statistical analysis was performed using SAS 9.4 and a generalized linear model was used to examine the adjusted relative risk (aRR).

Results: Of 773,600 patients, 585,072 had complete data for analysis. 383 diagnoses of syphilis were identified. The incidence of syphilis diagnosis increased yearly from 2004-2011, with a peak incidence in 2011 of 54 per 100,000. The syphilis diagnoses were: 59% other unspecified, 22% NS and other types 1% or less. Associated risk factors included: hepatitis B (aRR=1.75 95% confidence interval (CI) 1.12-2.71), hepatitis C (aRR=3.60 95% CI 1.99-6.51), herpes simplex virus (aRR=2.05 95% CI 1.46-2.87), and HIV (aRR=7.55 95% CI 5.42-10.52). Demographic risk factors included: male (aRR=4.96 95% CI 3.85-6.40) and other (non-white) race (aRR=1.99 95% CI 1.14-3.47). The highest rates were in the southeast followed by the northeast and west coast.

Conclusions: In the ESRD population, the incidence of syphilis was over 3 fold greater than in the general population in 2011, with the majority of cases in previously diagnosed syphilis followed by NS. The trend of rising incidence from 2004-2011, associated risk factors, and the geographic spread of syphilis in ESRD reflects the general population. These data suggest that routine screening for syphilis in the ESRD population may be beneficial.

TH-PO898
A Case of Leclercia adecarboxylata Hemodialysis Catheter-Related Bacteremia
Yasir Ali,1 Ashit K. Collins. Division of Renal Diseases & Hypertension, George Washington University, Washington, DC.

Background: Leclercia adecarboxylata, formerly known as Escherichia adecarboxylata, was first identified by Leecre in 1962. It is a motile Gram-negative rod that renders an uncommon organism. Here we report a case of L. adecarboxylata bacteremia as part of a polymicrobial infection in a dialysis patient with a tunneled catheter.

Methods: A 50 year-old male with ESRD on HD for 7 months via left internal jugular tunneled catheter, left atrial mass. Antibiotics were started. Blood cultures grew Staphylococcus epidermidis (oxacillin-resistant), methicillin-sensitive Staphylococcus aureus, Pseudomonas floures (resistant to trimethoprim-sulfamethoxazole), Escherichia coli (pan-susceptible), Serratia marcescens (resistant to ampicillin and first generation cephalosporin), and Enterobacter cloacae (pan-sensitive). Antibiotic regimen was changed to vancomycin, gentamicin and levofloxacin. The tunneled catheter was removed and a new right internal jugular tunneled catheter was placed.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
catheter was placed 4 days later, after clearance of blood cultures. He was maintained on the IV antibiotics for another 14 days, and recovered without long-term sequelae.

Results: Conclusions: L. adecarboxylata is a ubiquitous organism and has been isolated from water sources including drinking water in the US. Water exposure is a possible source of infection in the patient presented above. Although there are several case reports of clinically significant infections with L. adecarboxylata in immunocompromised patients, it has been mostly isolated from post-traumatic flora in immunocompetent individuals. ESRD patients may be susceptible to L. adecarboxylata infection as they are relatively immunocompromised. A recent retrospective review on a PubMed search of tunneled hemodialysis catheter-related bacteremia with L. adecarboxylata. This infection can be treated successfully with catheter removal and a course of appropriate IV antibiotics. Most isolates are susceptible to all available antimicrobial agents.

TH-PO989
Mortality Risk and Cause of Death Following Staphylococcus aureus Endocarditis in a Danish Hemodialysis Population

Method: S. aureus IE in hemodialysis patients was identified in The Danish National Registry on Regular Dialysis and Transplantation and The Danish National Patient Registry, and in non-hemodialysis patients in The East Danish Database on Endocarditis which contains data on consecutive patients with S. aureus IE from tertiary centres in the eastern part of Denmark. Independent risk factors of outcome were identified in multivariate Cox regression models.

Results: The cohorts of S. aureus IE included 121 hemodialysis patients and 197 non-hemodialysis patients from the period 1996-2012 and 2002-2012, respectively. The all-cause in-hospital mortality was 22.3% in hemodialysis- and 24.8% in non-hemodialysis patients. At one-year follow-up the all-cause mortality, excluding in-hospital mortality, was higher in hemodialysis patients 26.4% compared to non-hemodialysis patients 15.2% (p = 0.017). In hemodialysis- and non-hemodialysis patients, the cardiovascular in-hospital mortality was 20.7% and 21.7% and one-year mortality, excluding in-hospital mortality, was 21.5% and 12.2% (p = 0.030), respectively. In patients with S. aureus IE, hemodialysis was associated with an increased risk of all-cause mortality at >74 days after admission with a hazard ratio of 2.71 (95% CI 1.78-4.16). Age and diabetes mellitus were identified as independent risk factors of all-cause mortality. Hemodialysis treatment was also associated with an increased risk of cardiovascular death at >56 days after admission with a hazard ratio of 2.76 (95% CI 1.74-4.40).

Conclusions: In hemodialysis patients, the short-term in-hospital mortality rates are similar to the non-hemodialysis population whereas the long-term mortality rates are markedly increased in the hemodialysis population. Further investigations are needed to identify direct IE related reasons for these findings.

TH-PO990
Dialysis Access and Risk of Staphylococcus aureus Bacteremia – A Nationwide Multicenter Study

Method: The end-stage renal disease population was retrieved from The National Registry on Regular Dialysis and Transplantation, in the period from January 1st 1996 to December 31st 2011. Information on SAB was obtained from the national ISDS database. Patients were followed until death, the first episode of SAB, end of study (December 31st 2011), or a maximum of 16 years of follow-up. Independent risk factors were assessed by multivariable Cox regression.

Results: In the study period, 9997 patients commenced renal replacement therapy. The initial dialysis modality in 6626, peritoneal dialysis in 2882 and 289 patients had a pre-emptive kidney transplantation. Changes in renal replacement therapy modality and vascular access was identified and entered time-updated during follow-up, allowing for time-updated exposure. SAB was found in 1278 patients (12.8%). The incidence rate of SAB was highest in uncuffed central venous catheter (CVC) (10.20/100 person-years) (2010-2011), compared to tunneled CVC (9.96/100 person-years) and arteriovenous fistula (4.93/100 person-years). The adjusted hazard ratio for SAB was: in cuffed CVC, 5.77 (95% CI 4.45-7.49), in uncuffed CVC, 7.13 (95% CI 5.39-9.42), in arteriovenous graft, 4.54 (95% CI 2.11-9.77) and in arteriovenous fistula, 3.40 (95% CI 2.78-4.14) compared to peritoneal dialysis. There was no difference in risk of SAB between uncuffed- and cuffed CVC. The first 1.5 months in renal replacement therapy in particular in CVC, diabetes mellitus and male gender were additional risk factors of SAB.

Conclusions: Patients in hemodialysis have a high incidence of SAB, in particular with CVC. In this study, the risk of SAB was similar in cuffed- and uncuffed CVC. The first 1.5 months in renal replacement therapy in particular in CVC, diabetes mellitus and male gender were independent risk factors of SAB.

TH-PO901
Latent Tuberculosis in Dialysis Patients: Prevalence, Risk Factors, and Inflammatory Markers

Method: We reviewed the clinical data of all patients dialyzing at DaVita dialysis units in Jeddah, SA to abstract data about IGRA test, patient demographics, laboratory, radiological and clinical status.

Results: 302 dialysis patients were screened for LTBI using the IGRA, and 92 patients (30.5%) were positive. All positive patients were assessed for presence or absence of suspicious symptoms and a chest X-ray (CXR) was obtained to rule out active disease. A diagnosis was thought to be unlikely in all patients. When patients with positive test were compared to those who tested negative, they were older (54.7±16.05 versus 50.4±16.2 years, p value = 0.033), more likely to have had a previous history of TB (p value = 0.0014), less likely they had received the BCG vaccine in the past (p value = 0.0033), and less likely to be a high ferritin (p value = 0.45). There was no difference between the 2 groups in terms of sex, dialysis vintage, the background rate of DM, HCV, or HBV, lymphocytes count, neuropsilis, platelets, neutrophil to lymphocyte ratio, platelet to lymphocytes ratio, transferrin saturation, or albumin level.

Conclusions: Elderly, those with a past history of TB, and those who have no past history of BCG vaccination are all potentially at risk of LTBI. Although many inflammatory markers are not characteristic high in patients with LTBI, high ferritin level is commonly seen. This is the first study to describe simple inflammatory markers in dialysis patients with LTBI. Screening dialysis patients who have persistent unexplained high ferritin level for LTBI should be considered in appropriate settings.

TH-PO902
First and Recurrent Hospitalized Infections in Home and In-Center Hemodialysis Patients

Method: We analyzed data from the United States Renal Data System. The HHD cohort comprised patients who completed HHD training with the NxStage System One in 2006-2012 and who carried Medicare as primary payer (MPP). The IHD cohort comprised patients who initiated HHD in 2006-2012 and who carried MPP. We followed patients until the first or recurrent infection on HHD, or the first or recurrent infection on IHD, or the first or recurrent IH discharge. We compared incidence rates and trends of infections between HHD and IHD patients with a fistula.

Results: We identified 4304 HHD and 46,988 IHD patients. On both HHD and IHD, the cumulative incidence of IH increased with each additional IH discharge (figure). For HHD versus IHD, the adjusted hazard ratio (AHR) of first IH was 1.24 (95% confidence interval [CI] 1.14-1.34); the AHR of second IH, following discharge from the first IH, was 1.01 (0.86-1.19); and the AHR of each subsequent IH, following discharge from the preceding IH, was 0.92 (0.78-1.09).

Conclusions: Compared to IHD patients with a fistula, HHD patients with a fistula had higher risk of a first IH, but similar or slightly lower risk of recurrent IHs. However, in both dialytic settings, each additional IH discharge increased the risk of another IH. Less time to first IH in HHD patients prematurely sets in motion the cycle of increasing risk, ultimately manifesting as a higher IH rate on HHD versus IHD. Attention should be devoted to prevention of the first infection on HHD.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Circulating Interferon-λ3, HBV Vaccination, and HBV/HCV Infections in Hemodialysis Patients

Alicja E. Grzegorczewska, Monika K. Swiderska, Adrianna Mostowska, Pawel P. Jagodzinski, PUMS, Poznan, Poland; PUMS, Poznan, Poland; Poznan University of Medical Sciences (PUMS), Poznan, Poland.

Background: Interferon (IFN)-λ3 gene (IFNL3) is known from its crucial role in HCV clearance. Our aim was to investigate circulating IFN-λ3 and single nucleotide polymorphisms (SNPs) of IFNL3 in hemodialysis (HD) patients who differed in response to HBV vaccination and status of HBV/HCV infections.

Methods: In 201 HD patients and 28 controls, plasma IFN-λ3 ng/L was determined using ELISA. IFNL3 SNPs (rs12979860, rs8099917) were genotyped using HRM analysis.

Results: HBV vaccine responders among HD patients showed higher IFN-λ3 than healthy responders (120, 36–233 vs 62, 12.3–280, P=0.0004). In HD group, significant differences in circulating IFN-λ3 were shown between responders and non-responders to HBV vaccination (120, 36–233 vs 43, 15.9–77.4, P=0.001) as well as between HBsAg positive patients and those who developed anti-HBs and became HBsAg negative after HBV infection (39.1, 10.8–134 vs 125, 35–215, P=0.010). Responders to HBV vaccination, who resolved HCV infection, did not differ in circulating IFN-λ3 from non-infected responders (133, 14.8–400 vs 120, 36–233, P=0.714), whereas responders to HBV vaccination, who did not show spontaneous HCV resolution, revealed lower IFN-λ3 than non-infected responders (74, 4.9–275 vs 120, 36–233, P=0.013). Patients with both infections, HBsAg positive/HCV RNA positive subjects showed lower IFN-λ3 (13.3, 9.2–16.1) than only HCV RNA positive patients (57.5, 13.7–203, P=0.031) and lower compared with patients who resolved both infections (88.5, 16.0–300, P=0.020).

Circulating IFN-λ3 showed independent positive association with anti-HBs titer (β±SE 8.4±1.1, P=0.01) and negative associations with HCV RNA (β±SE -32.5±11.4, P=0.005) and HBsAg (β±SE -45.3±22.9, P=0.049) positivity. Non-responders to HBV vaccination, patients HBsAg positive, and subjects replicating HCV composed a group with unfavorable outcomes. The remaining patients were analyzed as having favorable outcomes. The latter showed higher IFN-λ3 (120, 14.8–400 vs 50.7, 4.9–275, P=0.001), but did not differ in distribution of IFNL3 SNPs compared with subjects with unfavorable outcomes.

Conclusions: Higher IFN-λ3 concentrations are associated with response to HBV vaccination, self-limited HBV infection, and spontaneous HCV resolution.

Accelerated Vaccination Schedule against HBV with Combined Hepatitis A and B Vaccine among Hemodialysis Patients: Does It Work?

Mahmoud H. Imam, Internal medicine Department, Faculty of Medicine Benha University, Benha, Egypt.

Background: Hemodialysis patient possesses particular attributes which increase susceptibility to HBV infections. HBV vaccination significantly decreased the number of new HBV-infected patients. Using the conventional dosage schedule requires six months of vaccination. The aim of this study is to examine the result of seroprotection using the accelerated vaccination schedule in vaccination of hemodialysis patient through using combined hepatitis A and B vaccine.

Methods: In this study, 114 consecutive hemodialysis patients at New Fiddagh hospital were enrolled. Their age ranged from 18 to 71 years. The inclusion criteria were age above 18 years, [1] A positive serum HBV surface antigen and antibody; [2] participant received a previous course of HBV vaccine, [3] patient positive for HBV surface Ag. Patients were sequentially randomized to receive either Hepatitis B recombinant DNA vaccine or to receive combined hepatitis A and B vaccine injection.

Results: Testing for HBV surface antibodies was done one and three months after completion of the mentioned dosage schedule. The primary outcome was the detection of seroprotection using serum HBV surface antibodies a HBsAb ≥ 10 mIU/mL. Adverse reactions were evaluated regarding both fever and post-injection pain scale.

Results: After one and three months of completion of the vaccination schedule, there were no statistically different proportion of positive seroprotected patients among both groups.

Conclusions: Accelerated vaccination schedule using combined hepatitis A and B vaccine may be equivalent to the conventional dosage of Hepatitis B.
chronic inactivated form of hepatitis infection. A month later her repeat hepatitis panel showed seroconversion back to HBsAg negativity.

**Results:**

- **Conclusions:** HBsAg negative patients with normal serum transaminases and low (<2000 IU/mL) or undetectable HBV DNA are considered to be in an inactive carrier state.
- **Methods:** We conducted a randomized, double-blind, placebo-controlled clinical trial (www.clinicaltrials.gov. NCT02914132) to evaluate the safety and efficacy of Seraph in reducing CVC-related BSI. The Seraph was placed in series, upstream from a FX80 high-flux dialyser (FMC), during a regular hemodialysis session.
- **Results:** Blood cultures were mandated before any antibiotic administration for suspected BSI, and BSI was reported monitored through an internal QC program developed for National Healthcare Safety Network (NHSN) reporting.
- **Background:** CVCs are associated with catheter-related bloodstream infection (BSI) resulting in increased morbidity and mortality. Following our report of significantly reduced infection when 320 mg/mL gentamicin in 4% citrate is used as the CVC locking solution (Morgan AJKD 2012), this has remained the standard of care in patients dialyzing with a CVC, unless physician order requested otherwise. The infection rates were measured through an internal QC program developed for National Healthcare Safety Network (NHSN) reporting.

**Background:** Blood stream infections are the 2nd leading cause of mortality among CKD5D patients. To subvert the host immune response many pathogens bind to heparan sulfate, a key receptor on cell surfaces. The Seraph® 100 Blood Filter (Seraph) uses this affinity to bind and remove pathogens, toxins, and cytokines from flowing blood.

**Methods:** The first patients treated with the Seraph as part of an ongoing first-in-man study (www.clinicaltrials.gov. NCT02914132) are presented. The Seraph was placed in series, upstream from a FX80 high-flux dialyser (FMG), during a regular hemodialysis procedure with a 500SH dialysis machine (FMC) (Qb 300 mL/min; Qd 500 mL/min).

**Results:** Two male hemodialysis patients 57 and 82 years of age presented with S. aureus bacteremia. In adjunction to antibiotic therapy they were treated with Seraph concurrent with hemodialysis. As measured by automated blood culture, post-Seraph-pre-dialyzer blood samples had increased time to positivity (TTP) relative to contemporaneous pre-Seraph samples, indicating reduced concentration of bacteria. As estimated from TTP, with a concentration of 4% sodium citrate as a routine catheter lock 320 mg/mL in 4% sodium citrate as a routine catheter lock 320 mg/mL in 4% sodium citrate as a routine catheter lock I. The Seraph comprised of a heparan sulfate sponge and an integrated blood filter with expressed heparin bound in the sponge.

**Conclusions:** Gentamicin 320 mg/mL in 4% sodium citrate as a routine catheter lock demonstrated sustained low CVC-related BSI rates in HD patients, with approximately half the infection rate compared with the national average. Gentamicin-citrate lock should be considered the standard of care in patients with CVC access.

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

**Table 1. Comparison of Antibiotics Prescribing Patterns Between ESRD Non-ESRD Patients**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Non-ESRD</th>
<th>ESRD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides prescribed per patient</td>
<td>0.89 ± 0.07</td>
<td>1.66 ± 0.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elderly</td>
<td>0.67 ± 0.04</td>
<td>1.70 ± 0.32</td>
<td>0.011</td>
</tr>
<tr>
<td>Any ear-ABX prescribed per patient</td>
<td>0.27 ± 0.02</td>
<td>1.58 ± 0.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any ear-ABX prescribed per patient</td>
<td>0.26 ± 0.01</td>
<td>1.40 ± 0.01</td>
<td>0.011</td>
</tr>
<tr>
<td>Urinary</td>
<td>0.60 ± 0.18</td>
<td>1.26 ± 1.43</td>
<td>0.171</td>
</tr>
</tbody>
</table>

**Figure 1:** Monthly Bloodstream Infection Rates for Patients with Any CVC Access from 01/2014 to 12/2016

**TH-PO909**

**Sustained Low Central Venous Catheter-Related Bloodstream Infection Rates in HD Patients with an Antibiotic Lock over a 3-Year Period**

Sumi J. Sun,1 Norma Gomez,1 Fang Yang,1 Graham E. Abra,1 Brigitte Schiller,1,2 Satellit Healthcare, San Jose, CA; 3Stanford University, Palo Alto, CA.

**Background:** CVCs are associated with catheter-related bloodstream infection (BSI) resulting in increased morbidity and mortality. Following our report of significantly reduced infection when 320 mg/mL gentamicin in 4% citrate is used as the CVC locking solution (Morgan AJKD 2012), this has remained the standard of care in patients dialyzing with a CVC, unless physician order requested otherwise. The infection rates were measured through an internal QC program developed for National Healthcare Safety Network (NHSN) reporting.

**Methods:** This study evaluated NHSN data with self-reported infection rates from January 2014 to December 2016 in a non-profit dialysis provider with a total of 57 free-standing dialysis facilities serving more than 5000 HD patients. BSI was reported according to NHSN criteria. Data were audited through comparison to an internal infection control report and discrepancy reconciled prior to final NHSN submission. Blood cultures were mandated before any antibiotic administration for suspected BSI, and 85% or more are sent to one internal lab (Ascend).

**Results:** The rate of catheter-related bloodstream infection over the three years was 1.00 episodes/100 patient-months, 54% lower than the national average of 2.16 for CVC-related BSI (2014 NHSN BSI Pooled Mean Rate/100 patient-months). Monthly BSI rates showed minor fluctuations, however none exceeded the national average in any given month.

**Conclusions:** Gentamicin 320 mg/mL in 4% sodium citrate as a routine catheter lock demonstrated sustained low CVC-related BSI rates in HD patients, with approximately half the infection rate compared with the national average. Gentamicin-citrate lock should be considered the standard of care in patients with CVC access.

**TH-PO908**

**Comparison of Outpatient Antibiotic Use in Dialysis Units of NY State**

Ilay Rajhman,1 Aaron S. Stern,1 Tina Adjei-Bosompem,1 George N. Coritissid,2 Teresa Lobowski,1 Tri-Kuang Lee,1 Carol Lyden,1 1ESRD Network 2, Lake Success, NY; 2Elmhurst Hospital Center, Elmhurst, NY.

**Background:** Little information is available regarding oral antibiotic use in outpatient clinical dialysis settings. Our study compares different prescribing practices in end-stage renal disease (ESRD) patients and non-ESRD patients in both rural and urban areas.

**Methods:** 2015 IPRO Medicare Part D data from all 62 New York State (NYS) counties were reviewed to obtain oral antibiotic (ABX) prescription information for the ESRD and non-ESRD populations. The average number of prescribed ABX per patient and average number of prescription days were compared between rural and urban areas as well as ESRD and non-ESRD populations.

**Results:** We found that ESRD patients were prescribed significantly more ABXs than non-ESRD patients in NYS regardless of urban or rural setting. The average number of ABX prescription days was greater with ESRD patients compared to non-ESRD patients, primarily in urban areas. Urban patients were prescribed Ampicillin (p=0.0295), Cefaclor (p=0.464), Cefadroxil (p=0.003), Dicloxacillin (p=0.018), and Metronidazole (p=0.0078) more often. Urban patients were prescribed Cepodoxime 3.5 times more often than ESRD patients.

**Conclusions:** ESRD patients are prescribed more antibiotics for a longer duration when compared to the general population. Differences in prescribing patterns could be explained by more judicious prescription practices, less diversity of prescribers, fewer individual prescribers or the clinical status of ESRD patients. We cannot answer yet the question of appropriateness of antibiotic prescriptions, but these data can help establish prescription patterns, which can then be applied more broadly. Ultimately the data can be used to modify prescribing practices using evidence based recommendations to decrease inappropriate antibiotic use and promote antibiotic stewardship.
Heart rate, blood pressure, and cardiac output were stable and reproducible. No clinically significant post-treatment changes in hematology or clinical chemistry occurred.

Conclusions: Seraph appears to be well tolerated by patients, and is capable of quickly removing pathogens from blood. It’s rapid, broad-spectrum binding and inherent lack of interaction with patient’s coagulation system make it well suited for dialysis patients. It did not result in any significant post treatment-changes in hematology or clinical chemistry occurred. Sixty-seven percent of patients received elbasvir/grazoprevir, 20% sofosbuvir/velpatasvir, and 13% ledipasvir/sofosbuvir. The SVR rates did not differ by genotype, cirrhosis, treatment history, ethnicity, gender, age, BMI, diabetes, psychiatric history, or transplant status. The SVR rates also did not differ by adherence; 13% of patients reported missing 1 dose of HCV medication during treatment.

Conclusions: Despite a high proportion of cirrhotic patients, all patients achieved SVR. The SVR rates did not differ by treatment or demographics due to the 100% cure rate, and conclusions across groups are limited due to the small numbers. DAA regimens were well tolerated except for anemia in patients receiving ribavirin.

TH-PO912
Incidence of Dialysis-Related Infections in the Automated Peritoneal Dialysis Population in the United States

Background: Infection increases risks of peritoneal dialysis technique failure and death. However, data about the magnitude of and trends in the incidence of all-setting peritoneal dialysis-related infection (DI) in the US are lacking. We estimated incidence of both hospitalized and non-hospitalized DI in the automated peritoneal dialysis (APD) population.

Methods: We analyzed United States Renal Data System records. From 2006 to 2013, we collected cohorts of end-stage renal disease patients on APD. We identified hospitalized and non-hospitalized cases of DI from Medicare claims with ICD-9-CM diagnosis codes [a] 567.x (peritonitis), [b] 996.68 (infection due to peritoneal dialysis catheter), and [c] 038.x (septicemia). We estimated incidence rates with definitions of diagnosis code [a], codes [a]-[b], and codes [a]-[c], respectively, as a function of only principal diagnosis codes. In contrast, as a function of both principal and secondary diagnosis codes, corresponding rates were 45.7 (3.3%), 55.1 (2.7%), and 66.3 (2.1%) events per 100 patient-years. These rates corresponded to one DI case per 26, 22, and 18 patient-months, respectively. With DI defined by both principal and secondary diagnosis codes, hospitalized cases comprised between 53% and 61% of all cases.

Results: In 2013, the incidence rate was 11.2 (annualized rate of change between 2006 and 2013, -6.3%), 25.1 (-4.7%), and 35.1 (-3.1%) events per 100 patient-years with diagnosis code [a], codes [a]-[b], and codes [a]-[c], respectively, as a function of only principal diagnosis codes. In contrast, as a function of both principal and secondary diagnosis codes, corresponding rates were 45.7 (3.3%), 55.1 (2.7%), and 66.3 (2.1%) events per 100 patient-years. These rates corresponded to one DI case per 26, 22, and 18 patient-months, respectively. With DI defined by both principal and secondary diagnosis codes, hospitalized cases comprised between 53% and 61% of all cases.

Conclusions: Between 2006 and 2013, the incidence of DI decreased among APD patients in the US. However, the absolute magnitude of the incidence of DI was uncertain, as rates defined by an array of diagnosis code sets and diagnosis code positions varied by a factor of nearly 6 in 2013. The incidence rate associated with broader claims-based definitions indicated that DI remains a common complication in 2013; for frame of reference, the incidence of all-setting peritonitis ranged from 35 to 40 events per 100 patient-years in Australia between 2012 and 2015. In addition, more than half of DI cases involved hospitalization, a possible marker of inadequate monitoring in the outpatient setting. With continued growth of PD utilization in the US, novel tools to reduce risk of DI on APD are needed.

TH-PO913
Comparison of CAPD and APD Peritonitis in a Nephrology Reference Center in Mexico City

Background: Peritonitis is a major cause of morbidity, mortality and increase health care cost in patients on peritoneal dialysis (PD). PD infection is associated with peritoneal membrane loss, technique failure and mortality. Following an episode of peritonitis, the risk of more peritonitis episodes, hemodialysis switch and death increased during the first month and during the next 6 months.

Methods: We evaluated retrospectively all patients with peritonitis episode from October 2014 to December 2016 in the “National Institute of Cardiology Ignacio Chavez” in Mexico City on different PD modalities: Continuous Ambulatory Peritoneal Dialysis (CAPD) and automated peritoneal dialysis (APD).

Results: 71 patients were evaluated, 36 (50.7%) of female sex with a median age of 50 years, 54 (76.1%) on CAPD and 17 (23.9%) on APD. The main cause of renal failure were diabetic nephropathy in 34 patients (45.1%). On 28 patients (39.4%)no history of peritonitis and the comorbidities were chronic hypertension (47.9%), ischemic heart disease (16.9%) and chronic heart failure (8.5%). The most frequent organism identified on cultures were S aureus in 23 (32.4%) patients, E coli in 7 (9.9%), S marcessens in 5 (7%), S epidermidis with 5 (7%) cases and Candida in 7 patients (9%).

Conclusions: The CAPD group presented more frequently peritonitis episodes. Most frequent infection was gram positive organisms: S. aureus in 39.4%. Mechanical dysfunction presented only in 1 patient of APD patients, and also only 1 patient died in this group. The level of albumin and BUN demonstrated a statistical significance and are associated with worst outcome in all patients.

Table. Clinical and biochemical outcomes APD and CAPD patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>APD (%)</th>
<th>CAPD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>10.5</td>
<td>11.0</td>
</tr>
<tr>
<td>White blood cells</td>
<td>10.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Creatinine</td>
<td>2.5</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
TH-PO914

Effects of Prospective Improvement Trial to Reduce the Incidence of Peritonitis in a Peritoneal Dialysis Population in Qatar

Mohamed amin Khalil elesnawi,1 Fadwa S. Al-Ali,1 Abdullah Hamad,1 Vimala K. Lonappan,1 Sahar Aly,2 Rania A. Ibrahim,2 Ahlam Ali,3 Tarek A. Fouda,4 Hanaa Ahamed.1 1Hamad Medical Corporation, Doha, Qatar; 2Hamad medical corporation, Doha, Qatar; 3Hamad medical corporation, Doha, Qatar; 4Hamad medical cooperation, Doha, Qatar.

Background: Peritonitis is the major complication in patients on peritoneal dialysis (PD). Peritonitis carries high morbidity and mortality. In addition it carries an economic burden of increasing hospitalization. We have 180 PD patients and over the period of 6 months in 2016 the peritonitis was average 4%. With this high incidence we decided to run a prospective improvement trial to reduce the incidence.

Methods: We conducted a random survey for 60% of patients to determine daily practice. Root cause analysis for each case in the 6 months trial to identify risk factors. Based on the data, procedure check list created during monthly visits and re-training at same time. Regular home visit assessment and questionnaire taking for environmental evaluation and daily practice. All aspects of the trial were planned and drawn by Multidisciplinary team (MDT).

Results: 110 Patients took part in the survey and after analysis of the data using pareto chart, 24% had poor hand hygiene, 22% not using mask, 20% had constipation, 14% had an unsuitable environment at home, 8% had poor personal hygiene, 7% traveled abroad and 5% did not have adequate time to undertake the procedure properly. The incidence of peritonitis in the 6 months of the trial has fallen from average 4% to 1.4% which presents a 65% reduction of peritonitis. Furthermore there was 51.6% reduction in the overall medical cost

Conclusions: In this prospective trial we have demonstrated that peritonitis can be significantly reduced by MDT approach and monthly retraining of patients. Although there is medical and economical benefit, there is some cost implication for the monthly retraining. More work is needed to establish what would be the most effective frequency of training.

Funding: Government Support - Non-U.S.

TH-PO916

Services Associated with Increased Cost of Hospitalization for Peritonitis in Pediatric Patients Receiving Chronic Peritoneal Dialysis

Allison C. Redpath,1 Troy Richardson,2 Alicia Neu,3 Bradley A. Wardy,3 1Children’s Hospital Association, Overland Park, KS; 2Johns Hopkins University School of Medicine, Baltimore, MD; 3The Children’s Mercy Hospital, Kansas City, MO; 4University of Wisconsin School of Medicine & Public Health, Madison, WI. Group/Team: SCOPE Collaborative.

Background: Peritonitis is a leading cause of hospitalization in children on chronic peritoneal dialysis. The Standardizing Care to improve Outcomes in Pediatric ESRD (SCOPE) Collaborative has demonstrated a reduction in peritonitis rates and associated hospitalizations resulting in over $7million in cost-savings. Prior investigation has demonstrated that ICU stay and fungal peritonitis are associated with high-cost hospitalizations. The objective of this analysis is to describe service-line utilization associated with high-cost hospitalizations for peritonitis.

Methods: Peritonitis episodes reported by 24/29 SCOPE centers between 10/2011 and 9/2015 were linked with data in the Pediatric Health Information System (PHIS) database. Linkage was performed on the basis of sex, birth month and year, and date of peritonitis episode and hospitalization. Charges in PHIS were adjusted for cost-of-living differences and converted to costs. Detailed billing information was used to compare service-line utilization among the top 25% of infection episodes by cost with bottom 75% and to compare fungal infection episodes to other types of infections.

Results: During the first 48 months of SCOPE, 266 peritonitis episodes were linked to 278 hospitalizations in PHIS. Detailed billing data was available for 246 hospitalizations and 238 peritonitis episodes. The proportions of hospitalization costs were similar between the top 25% of peritonitis episodes (N=66) and the lower 75% (N=180) for pharmacy (p=0.63), lab (p=0.30), imaging (p=0.85), supply (p=0.98), clinical (0.33) and other (p=0.18) service lines. Cost per case was significantly higher (p<0.001) for all service lines in the top 25% group. Compared with other types of infections (N=215), fungal peritonitis episodes (N=23) had elevated costs per episode (p=0.001) in lab, imaging, supply, room and board costs (including ICU costs) and costs associated with hemodialysis (HD).

Conclusions: The increase costs attributed to the top 25% of peritonitis hospitalizations can be attributed to all service lines. Increased hospitalization cost per case among fungal peritonitis infections is driven by increased room and board costs associated with prolonged length of stay, costs associated with HD, and lab costs.

TH-PO917

Comparison in Mortality in Dialysis Requiring AKI (AKI-D) in Native versus Kidney Transplant Recipients

Tripti Singh,1 Sanam Waseed,2 Arjang Djamali,3 Neeetica Garg,3 Kristen Sigsma.1 1School of Medicine and Public Health, University of Wisconsin, Madison, WI; 2UW Health, Madison, WI.

Background: There is limited information on mortality rates in patients with native versus transplant kidneys requiring renal replacement therapy (RRT) for acute kidney injury (AKI).

Methods: We compared one-year patient outcomes in a retrospective single center analysis of all adult patients with acute kidney injury requiring dialysis (AKI-D) admitted between January 2012- June 2016.

Results: 962 patients with native kidney (AKI-N) and 147 patients with kidney transplant (AKI-T) with AKI-D were admitted during the study period. Mean age was 57.6 years for AKI-N and 52.6 years for AKI-T patients (p=0.0001). 63% were males and 48% were Caucasians (p=0.001). Serum creatinine at admission was significantly higher in AKI-T compared to AKI-N patients (4.4 vs 3.2 mg/dL, p<0.0001). Length of stay was similar for both groups (21.6 vs 21.2 days). Continuous renal replacement therapy (CRRT) was utilized in 65% of AKI-N compared to 36.7% of AKI-T (p<0.0001).

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

Underline represents presenting author.
Mortality at discharge was significantly higher for AKI-N compared to AKI-T (35% vs 19.8%, p = 0.0002). However, 1 year mortality for AKI-D was not different between native and kidney transplant recipients (49% vs 41%, p = 0.009) because of poor late outcomes in transplant recipients (Fig 1). Logistic regression analyses determined CRRT (HR 3.6, 95% CI 2.8-4.7, p<0.0001), serum creatinine (HR 0.87 CI .82-.92, p<0.0001), LOS (HR 0.98 CI .98-99, p=0.0001), and age (HR 1.01 CI 1.00-1.02, p<0.005) as significant predictors of one year mortality.

Conclusions: In patients with AKI requiring RRT early mortality is higher in native kidney disease while late mortality is greater in kidney transplant recipients. Overall, AKI requiring RRT is associated with nearly 50%-50% mortality at one year, regardless of transplant status.

Mortality rate in AKI-D in native vs transplant recipients

TH-PO918

A Multi-Platform Approach for the Noninvasive Differential Diagnosis of Acute Dysfunction of the Kidney Allograft

Thangamani Muthukumar,1 Carol Y. Li,2 Catherine Snopkowski,2 Hua Yang,2 Liana S. Perry,2 Stevenes Salvatore,2 John R. Lee,2 Surya V. Seshan,1 Darshana Dathania,1 Manikkm Suthanthiran,2 Well Cornell Medical Center, New York, NY, 1Well Cornell Medical College, New York, NY, 1Well Cornell Medical, New York, NY, 1Well Medical College of Cornell University, New York, NY, 1Well-Cornell, New York, NY, 1Well Cornell Medicine, New York, NY.

Background: We tested a multi-platform approach for the noninvasive differential diagnosis of acute dysfunction of the kidney allograft.

Methods: We studied 118 kidney transplant recipients with acute kidney allograft dysfunction. All had kidney allograft biopsy done that were studied by light, immuno and electron microscopy and were stained for C4d and SV40 large T antigen. Serum samples were obtained at the time of biopsy for detecting donor-specific anti-HLA antibodies by Luminex single antigen bead assay (DSA). Urine specimen was obtained at the time of biopsy for urinary cell mRNA profiling. Using preamplification enhanced real-time quantitative PCR assays, we quantified CXL10 mRNA, and CD3e mRNA levels as well as 18S rRNA levels and expressed their abundance as copies/μg total RNA. Using these three transcript levels, we derived our 3-gene molecular signature (Suthanthiran et al. N Engl J Med 2013). We also quantified BK virus VP1 mRNA levels (Dong et al. Transplantation 2002) in the biopsy matched urinary cells.

Results: Among the 118 kidney transplant recipients, biopsy revealed acute cell-mediated rejection (ACR) in 22 biopsies, acute antibody-mediated rejection (AMR) in 10 biopsies, acute tubular injury (ATI) in 49 biopsies, or polyomavirus nephropathy (PVAN) in 37 biopsies. All biopsies classified as ACR, AMR, and ATI were negative for SV40. The first step in the differential diagnosis was the identification of the patients based on DSA. This identified the 10 patients with AMR. The next step in the differential diagnosis was the measurement of urinary cell VP1 mRNA. Based on our previously published cutoff value of 6.5 x 10^3 BKV VP1 mRNA copy number, 77 of the 81 patients who did not have PVAN were identified and excluded, with a negative predictive value (NPV) of 95%. In the final step, ACR and ATI were distinguished based on our previously published cutoff value of 1.213 of the 3-gene signature. Based on this cutoff value, the NPV was 83%. In conclusion: A multi-platform approach, which involves testing DSA in the serum, BK virus VP1mRNA in urinary cells and the 3-gene signature in the urinary cells, offers a noninvasive method for the differential diagnosis of acute dysfunction of the kidney allograft with a high degree of accuracy.

Funding: Other NH Support - NIAID

TH-PO919

Delayed Grant Function in Living Donor Kidney Transplantation – Risk Factors and Outcomes

Manohar Reddy Mogulla, Philip A. Clayton. Central, and Northern Adelaide Renal and Transplantation services, Adelaide, SA, Australia.

Background: Delayed graft function (DGF) is associated with poorer outcomes in deceased donor renal transplantation recipients. The association of DGF in living donor kidney transplantation has not been well studied. This study reviews the risk factors for DGF in Australia and New Zealand living donor kidney transplant recipients and its association with short and long term outcomes.

Methods: Data that had been prospectively collected in the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry was reviewed. The inclusion criteria were all adult living donor kidney transplants performed between 2004 and 2015. Data from pediatric recipients (<18 years) and donors with pre-existing renal pathology (n=404), with incomplete data (n=46) and those with early graft loss (graft loss within 1 week of implantation)(n=38) were excluded. The variables studied included multivariable logistic regression to identify the risk factors for DGF and the association between DGF and rejection at 6 months; linear regression model to examine the association with eGFR at 1 year; and Cox proportional hazards models to examine the relationships between DGF and patient and graft survival.

Results: We observed DGF in 77 (23.5%) of 3358 transplants. Risk factors for DGF included right-sided kidney (odds ratio [OR] 2.00 [95% CI 1.18-3.40]; donor BMI (OR 1.06 [95% CI 1.01 - 1.12]); increasing time on dialysis and total ischemia time (OR 1.09 per hour [1.00-1.17]). DGF was associated with increased risk of rejection, worse patient and graft survival, and longer renal function at 1 year (Table).

Conclusions: In living donor kidney transplants DGF is uncommon but associated with significantly worse outcomes. The only modifiable risk factor identified was total ischemia time. Attention towards minimization of ischemia time in high-risk patients is recommended.

TH-PO921

Acute Kidney Dysfunction with No Rejection (ADNR) Is Associated with Poor Outcomes in Kidney Transplant Recipients

François Piquet,1 Hans Potter,2 Catherine Bonvoisin,1 Laurent E. Weeckers,1 François Jouret,1 1University of Liege Hospital (ULg CHU), Liege, Belgium; 2KULeuven, Kortrijk, Belgium.

Background: The entity “acute kidney dysfunction with no rejection (ADNR)” has been proposed for kidney transplant recipients (KTR) presenting with acute elevation of serum creatinine without histological evidence of acute rejection (AR). The prognosis of ADNR has not been studied thus far.

Methods: From 2007 to 2015, we retrospectively categorized all KTRs with a for-cause kidney biopsy within 12 months post-kidney transplantation (KTx) into 2 groups: ADNR and biopsy-proven AR. Control group (C) included KTR with no ADNR or AR within 24 months post-KTx. BK virus nephropathy and primary nonfunction were excluded. Estimated glomerular filtration rate (eGFR) was determined using the Modification of Diet in Renal Disease (MDRD) equation. Linear mixed models established intercepts and slopes of eGFR decline from 6 to 24 months post-KTx. Cubic

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

Underline represents presenting author.

338
spline analysis calculated the percentage of patients with a ≥30% reduction of eGFR from 6 to 24 months post-KTx.

Results: The mean age (years) at KTx was 50.2±14.2, 47.9±17.8 and 53.6±12.4 for ADNR (n=93), AR (n=22) and C (n=135), respectively. The female/male ratio was 39.8% (ADNR), 45.3% (AR) et 34.1% (C). The rate of delayed graft function was not significantly different among groups, and reached 26.9% (ADNR), 22.7% (AR) and 14.1% (C). The median time for for-cause graft biopsy was 22 (010-70) and 13 (7-43) days post-KTx for ADNR and AR, respectively. Of note, ADNR included 21 (22.6%) patients with “borderline” histology. At 6 months post-KTx, eGFR was higher in C (55.2±1.6 mL/min) vs. ADNR (45.5±1.9 mL/min; p<0.05) and vs. AR (48.6±3.9 mL/min; p<0.15). The eGFR slope from 6 to 24 months post-tx was positive in C (0.16±0.06mL/min/month) compared to negative slopes in ADNR (-0.04±0.08mL/min/month, p<0.05) and in AR (-0.04±0.16mL/min/month, p<0.06). The proportion of KTR presenting with a ≥30% reduction of eGFR from 6 to 24 months post-KTx reached 7.4% in C vs. 25.8% in ADNR (p<0.05) and 19.1% in AR (p<0.05).

Conclusions: In the present monocentric cohort, ADNR occurs frequently and early post-KTx, and is associated with a significantly lower eGFR at 6 months and a significantly faster eGFR decline from 6 to 24 months post-KTx, in comparison to controls.

Funding: Clinical Research Support

TH-PO922
Value of Intra-Operative PTH Assay during Parathyroidectomy in Renal Transplant Recipients with Secondary and Tertiary Hyperparathyroidism

Kevin Wang, Adeleye A. Edon, David Saxon, Florence Lima, David Sloan, B. Peter E. Sawaya, Amr E. Mohamed. University of Kentucky, LEXINGTON, KY.

Background: In renal transplant patients with secondary and tertiary hyperparathyroidism (HPT), the association between intra-operative parathyroid hormone (ioPTH) levels during parathyroidectomy (PTX) and long-term PTH is unknown. The present study aims at evaluating the value of ioPTH measurements on long-term outcome of PTX in renal transplant recipients in a single center study.

Methods: The ioPTH was measured in 18 renal transplant recipients (12 males and 6 females) who underwent PTX from 2005 to 2015 because of persistent hyperparathyroidism post-transplant. Near-total PTX was performed in 13 patients and partial PTX in 5 patients. The ioPTH monitoring included 3 samples: pre-intubation (pre-iopTH), 10- and 20-minute post-parathyroid gland excision (10-iopTH and 20-iopTH). Patients were followed for up to 5 years (mean ± SD: 2.5 ± 1.6 years).

Results: The median (25th-75th percentile) pre-, 10- and 20-iopTH levels were: 273 pg/ml (173-411), 42 pg/ml (22-73) and 34 pg/ml (20-50), respectively. All patients had a functional kidney transplant at time of surgery with a median serum creatinine of 1.3 mg/dl (1.2-1.7) and eGFR of 55 ml/min (40-60). The median time between renal transplant and PTX surgeries was 22 months (7-81). The median last follow-up PTH level was 59 pg/ml (17-83). There was no significant difference between 20-iopTH and follow-up PTH measurements (p=0.6). The pre-PTX and follow-up PTH levels are shown in the Figure. Three patients (17%) were readmitted within 90 days because of hypocalcemia. Apart from easily treated hypocalcemia, the PTX surgeries were uneventful. No patient required repeat PTX because of recurrent HPT.

Conclusions: The 20-iopTH is a good indicator of long-term PTH measurements. There were minimal complications associated with the procedure.

TH-PO923
A Prospective and Randomized Trial of Zoledronic Acid to Prevent Bone Loss in the First Year After Kidney Transplantation

Igor Marques, Maria Julia C. Araujo, Fabiana Gracioli, Luciene dos Reis, Rosa M. Pereira, Melani Custudio, Vanda Jorggetti, Rosilene M. Elias, Rosa M. Moyzes, Elias David-Neto, Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil; None, Sao Paulo, Brazil; Universidade Nove de Julho, Sao Paulo, Brazil; Universidade de Sao Paulo, Sao Paulo, Brazil; Universidade de Sao Paulo, Sao Paulo, Brazil; University of Sao Paulo School of Medicine, Sao Paulo, Brazil; Unidade do Sistema Urinario, Hospital Universitario da UFPI, Teresina, Brazil.

Background: Bone and mineral disorders occur frequently in kidney transplant (Ktx) recipients and have been associated with a high risk of fracture, morbidity, and mortality. Bisphosphonates may prevent or treat the bone loss promoted by the immunosuppressive regimens used in Ktx.

Methods: We conducted an open-label, prospective, randomized trial to assess the efficacy and safety of zoledronic acid to prevent the bone loss in the first year after Ktx. Ktx recipients were randomized 1:1 to receive zoledronic acid (5 mg at baseline) or no treatment (control group). Both groups received vitamin D supplementation. We evaluated bone mineral density (BMD) and microarchitecture with dual-energy X-ray absorptiometry (DXA) and with high-resolution peripheral quantitative computed tomography (HR–pQCT). Bone histomorphometric analyses were done at the time of Ktx and after 12 months of therapy.

Results: Differing from previous studies, after Ktx, neither zoledronic acid nor control group presented bone loss. Ktx has promoted an increase of BMD in both lumbar spine and total femur (p<0.0001). The late was more pronounced in the zoledronic group (p<0.05). Out of 34 patients, 29 had baseline and follow-up bone biopsies. On histomorphometry, we found that Ktx, but not zoledronic acid, suppressed bone activity without causing adynamic bone disease. Bone trabecular volume decreased only in zoledronic group (p<0.05). There was an improvement in cortical bone, as depicted by an increase in cortical thickness and a decrease in cortical porosity, in both groups.

Conclusions: In conclusion, we have confirmed that Ktx is not associated with significant bone loss, based on histomorphometric data. Therefore, although zoledronic acid had a beneficial effect in total femur BMD, the inclusion of bisphosphonates to prevent bone loss should be reconsidered in face of a contemporary immunosuppressive therapy.

Funding: Government Support - Non-U.S.

TH-PO924
Efficacy and Safety of Different Bisphosphonates for Bone Loss Prevention in Kidney Transplant Patients: A Systematic Review and Network Meta-Analysis

Yan Yang,1 Shi Qiu,2 Xi Tang,1 Ping Fu,1 1Kidney Research Institute, Division of Nephrology, West China Hospital, Sichuan University, Chengdu, China; 2West China Hospital of Sichuan University, Chengdu, China; 3Department of Urology, West China Hospital, Sichuan University, Chengdu, China; 1West China hospital, sichuan university, Chengdu, China; 2Department of Urology, Instr-ative-urology, West China Hospital, Sichuan University, Chengdu, China; 4Sichuan, PR. China, Chengdu, China.

Background: The preferred bisphosphonate regimen for kidney transplantation (KT) patients is still controversial, we aimed to compare different bisphosphonate treatments.

Methods: We searched PubMed, Embase, CENTRAL and reference lists of relevant articles up to April 1, 2017. We included RCTs comparing bisphosphonates in adult KT patients. The primary outcome was BMD change at the lumbar spine and femoral neck. We performed pairwise meta-analyses by random effect model and network meta-analysis (NMA) by Bayesian model. We used the GRADE framework to assess the quality of evidence.

Results: A total of 21 RCTs involving 1332 patients with 6 bisphosphonate regimens were included in the NMA. At the lumbar spine (Figure 1A), calcium alone showed significantly lower percent change in BMD compared to combination with vitamin D analogs or other bisphosphonates except clodronate. Pamidronate with calcium and vitamin D analogs showed improved BMD in comparison to clodronate with calcium. The combination of calcium and vitamin D analogs had a significantly lower influence than adding pamidronate or alendronate. Considering absolute terms (Figure 1B), zoledronic acid and calcium outperformed calcium alone. In terms of percent change in BMD at femoral neck (Figure 1C), both pamidronate and ibandronate combined with calcium revealed a remarkable gain compared with calcium. In absolute terms (Figure 1D), alendronate with or without vitamin D analogs, displayed a significant increase compared to calcium alone. Ibandronate with calcium demonstrated advantages than any other treatments.

Conclusions: New generation bisphosphonates were more favorable in KT patients to improve BMD. Bisphosphonate therapy was well-tolerated without increasing the frequency of adverse events and graft loss.

Funding: Government Support - Non-U.S.
TH-P0925
Prevalence of Vitamin D Deficiency after Kidney Transplantation and Its Association with Clinical Outcomes
Puneet Bedi,1 Nicole A. Hayde,1 Maria Ajaimy,1 Enver Akalin.2 1Montefiore Medical Center, Bronx, NY; 2Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY.

Background: Kidney transplant recipients usually have low vitamin D levels, especially in the early posttransplantation period. Vitamin D deficiency is recognized as a risk factor for progression of kidney disease in general population. However, its association with graft outcomes in renal transplant patients is not well established.

Methods: We measured 25-hydroxyvitamin (OH) D levels and intact-Parathyroid hormone (i-PTH) levels at 6, 12, 24 and 36 months post-transplant in patients transplanted at our center between Jan 2009 and Dec 2014 and measured the association between 6 month post-transplant 25-OH-vit D and i-PTH levels and clinical outcomes.

Results: Prevalence of 25-OH-vit D levels <15, 15-29.9, 30-49.9, and > 50 ng/mL was (29.2%, 22.4%, 34.7%, 13.3%) at 6 months, (21.4%, 23.7%, 35.0%, 19.7%) at 1 year, (14.9%, 21.9%, 41.3%, 21.8%) at 2 years, and (16.8%, 18.5%, 38.5%, 26.2%) at 3 years, respectively. A total of 383 patients were followed up for 3.8 (2.4-5.3) years. There was no difference between the 4 groups in terms of age, sex, race, type of transplant, donor age, donor final creatinine, KDPI score, PRA levels, pretransplant DSA, and type of induction. A negative correlation between 25-OH-vit D and i-PTH levels at 6 months was found to be statistically significant (r = -0.0001). Lower 25-OH-vit D levels did not increase the risk of graft loss. Patient survival, incidence of acute antibody or T cell mediated rejection, transplant glomerulopathy, development of de novo DSA, incidence of opportunistic viral (CMV and BKV) and fungal infections, malignancy, proteinuria and serum creatinine levels at 1.2 and 3 years post-transplant were found to be similar in the 4 groups.

Conclusions: 25-OH-vit D deficiency is common after kidney transplantation and has a negative correlation with post-transplant i-PTH levels. Low 6 months post renal transplant 25-OH-vit D levels are not associated with decreased allograft survival and function or with increased risk for opportunistic infections/malignancy.

TH-P0926
Summary MD and 95%CI from NMA of BMD change. The results are read from top to bottom and left to right. Significant results are in bold. A. Percent change at lumber spine; B. Absolute change at lumber spine; C. Percent change at femoral neck; D. Absolute change at femoral neck.

Prevalence of Body Composition by Dual-Energy X-Ray Absorptiometry and Bioelectrical Impedance Analysis in Renal Transplant Recipients
Thomas J. Wilkinson,1 Danielle Riehler-Potts,2 Jill Neale,2 Alice C. Smith,1 John Walls Renal Unit, Leicester General Hospital, Leicester, United Kingdom; 2Leicester Kidney Exercise Team, Leicestershire, United Kingdom; 3University of Leicester, Leicester, United Kingdom.

Background: Renal transplant recipients (RTR) experience abnormal body composition (BC) changes including obesity and muscle wasting. Aберant BC is associated with poor physical function and graft recovery, and increased mortality. Measuring BC is vital to understanding health status and comorbidity prognosis. Whilst dual-energy x-ray absorptiometry (DXA) is seen as the gold-standard, bioelectrical impedance analysis (BIA) may be an accessible and cheaper alternative. Formulas using anthropometric data that estimate BC may provide an alternative where DXA or BIA is not available.

Methods: We compared DXA, BIA and the Hume formula to measure body composition in 36 RTR (12 females; 52 ± 21 ml/min/1.73m² 12 years; eGFR 54 ± 34 ml/min/1.73m²). Weight, height, age, sex, BMI, weight and weight, BC was estimated using the Hume (1966) formula.

Results: BIA showed ‘excellent’ agreement against DXA (LM r=0.98, FM 0.95, FM’ 0.92). Bland-Altman bias showed that BIA tended to marginally overestimate LM (2.1kg 95% limits of agreement -3.9-8.1), and underestimate FM (-2.1kg ±6.6-4.3) and FM’ (-3.8% -11.7-4.0). The Hume formula performed exceedingly well against DXA. Regression revealed ‘good’ to ‘excellent’ agreement for LM (r=0.99), FM (r=0.92), and FM’ (r=0.79). Like BIA, the Hume formula overestimated LM (+3.5kg -4.7-11.6) and underestimated LM% (+3.8% -11.7-4.0). Remarkably, FM from the Hume was nearly identical to DXA.

Conclusions: Compared to DXA, BIA is a valid and accurate measure of BC. Interestingly, BIA in particular, FM may be calculated using sex, height and weight. Due to its ease, the Hume formula may provide another method using routinely collected data. As unfavourable BC is associated with adverse outcomes in RTR, it should be routinely measured. In the absence of DXA, BIA or the Hume formula are valuable alternatives to estimate BC. Research should investigate the sensitivity of these methods following interventions.

Funding: Private Foundation Support

TH-P0927
Restless Legs Syndrome (RLS): An Unresolved Uremic Disorder after Successful Renal Transplantation (TXR)
Secundino Cigarran,2 Jesus Calvino,1 Lourdes Gonzalez tabares,1 Monica Guijarro,1 Nicolas Menendez,1 Carmen R. Cobelo casas,1 Beatriz Millan,1 Ana maria Sanjurjo amado,1 Sonia Cillero,2 Juan Latorre,3 maria-jesus Sobrido.1 1IDIS. Sergas, Santiago Compostela, Spain; 2Nephrology, Esoi Cervo-Lugo- Monforte, Barela, Spain; 3Nephrology, Esoi Cervo-Lugo-Monforte, Lugo, Spain; 4Neurology, Esoi Cervo-Lugo-Monforte, Lugo, Spain.

Background: RLS is a common disorder of uremia that may improve after TXR. However, RLS frequency might not be as low as expected as some uremic disturbances related with RLS may continue even after a successful graft. The aim of this study was to assess the prevalence and related conditions for RLS in TXR.

Methods: A validated questionnaire fof RLS study group diagnostic criteria was self-administered by 129 TXR, 82 men and 47 women, aged 57 ± 12.8 years followed in the nephrology clinic for more than one year and with stable renal function (creatinine 1.5 ± 0.54 mg/dL). Patients classified as probable RLS according to the questionnaire underwent a subsequent neurological examination in order to exclude RLS mimics.

Results: The frequency of probable RLS according to the questionnaire results was 29.5% (18 men and 20 women). After thorough neurological examination, the diagnosis of RLS was confirmed in 18 patients providing an overall definitive RLS frequency of 14.5% (above the average prevalence reported for the general population). Therefore, RLS mimics were excluded. RLS was established for six men (7.5%) and 12 women (27.3%). These results rendered a positive predictive value for the self-administered questionnaire remarkably higher for women (60%) than for men (33%) pinpointing a higher rate of RLS mimics among men. Besides gender differences, confirmed RLS cases showed no difference regarding age, diabetes, chronic kidney disease, dialysis, condition, BMI, anticonvulsant therapy, renal function, anemia and time from transplantation. Neither blood pressure nor number of antihypertensive drugs was statistically different though RAAS blockade was significantly less frequent among the confirmed RLS cases (22.2% versus 47.2%).

Conclusions: The frequency of probable RLS according to the questionnaire results was 29.5% (18 men and 20 women). After thorough neurological examination, the diagnosis of RLS was confirmed in 18 patients providing an overall definitive RLS frequency of 14.5% (above the average prevalence reported for the general population). Therefore, RLS mimics were excluded. RLS was established for six men (7.5%) and 12 women (27.3%). These results rendered a positive predictive value for the self-administered questionnaire remarkably higher for women (60%) than for men (33%) pinpointing a higher rate of RLS mimics among men. Besides gender differences, confirmed RLS cases showed no difference regarding age, diabetes, chronic kidney disease, dialysis, condition, BMI, anticonvulsant therapy, renal function, anemia and time from transplantation. Neither blood pressure nor number of antihypertensive drugs was statistically different though RAAS blockade was significantly less frequent among the confirmed RLS cases (22.2% versus 47.2%).

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

TH-P0928
Chymase and Neprilysin: Key Regulators of the Renin-Angiotensin System (RAS) in Kidney Allografts
Johannes J. Kovarik,1,2 Christopher Kaltenecker,1 Chantal M. Kopecky,1 Oliver Domenig,1 Marlies Antlanger,2 Johannes Werzerova,2 Farsad A. Eskandary,2 Renate Kain,2 Marko Poglitsch,2 Georg Bohmig,1 Marcus Saemann.4 1Medical University Vienna, Vienna, Austria; 2Medical University of Vienna, Vienna, Austria; 3University of New South Wales, Sydney, NSW, Australia; 4Wilhelminen Hospital, Vienna, Austria; 5Division of Clinical Pharmacology, Vanderbilt University, Nashville, TN; 6Attoquant Diagnostics, Vienna, Austria.

Background: Angiotensin-converting enzyme inhibitors (ACEIs) are well established to be beneficial in patients with heart failure and chronic kidney disease (CKD). Their role in kidney transplantation (KTs), however, remains ambiguous, and the effects of ACEIs on plasma and intrarenal metabolites of the ‘classical’ and ‘alternative’ renin-angiotensin system (RAS) in KT recipients have not yet been studied.

Methods: This prospective study, which was designed to investigate allograft-specific metabolism, included 48 kidney transplant recipients subjected to allograft biopsy for graft dysfunction, progression of proteinuria, and/or DSA detection early (0-24 months; n=14), intermediate (24-144 months; n=18) or late post-KTx (>144 months; n=16).

Results: Patients on ACEI therapy (n=24) had lower plasma levels of angiotensin (Ang) II (p=0.01), but higher levels of Ang I (p=0.05) and Ang(1-7) (p=0.01) than patients without RAS blockade (n=24). Mass spectrometry-based renal biopsy analysis displayed a 2.8-fold increase in renal Ang II formation, with a stepwise increase from the early to the late biopsy group (p<0.005), paralleled by enhanced chymase activity (early group: 34±29%; late: 54±32%; p=0.005). Renal Ang(1-7) formation via neprilysin (NEP) was dominant (59±13%) over Ang II-mediated Ang(1-7) formation (15±10%).

Conclusions: Our study reveals a profound tissue-specific distortion of the RAS within renal allografts in a time-dependent fashion, with chymase and neprilysin being the predominant regulators of the RAS in kidney allografts. While the clinical significance
of these results remains to be determined, a conspicuous role of chymase and neprilysin determining allograft survival may be hypothesized.

TH-PO929

Cardiovascular Risk Prediction in Renal Transplant: Post-Hoc FAVORIT Trial Analyses
Theresa L. Shreman,1 Basma O. Merhi,1 Jessica A. Ogarek,2 Andrew Bostom,1 Nephrology, Rhode Island Hospital, East Greenwich, RI; 1Center for Gerontology and Health Care Research, Brown University, Providence, RI; 2Memorial Hospital of Rhode Island, Chepachet, RI.

Background: Cardiovascular disease (CVD) is the leading cause of mortality and kidney graft failure in renal transplant recipients (KTR), but predictive risk algorithms consistently underestimate the incidence of arteriosclerotic outcomes.

Methods: We conducted a secondary analysis of data from the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) randomized clinical trial. Measures included traditional CVD risk factors along with an expanded list of variables clinically important for KTRs, such as baseline phosphorus, cholesterol (HDL, LDL, remnant), triglycerides, graft vintage, donor type, glomerular filtration rate (eGFR), albumin-to- creatinine ratio (ACR), and diastolic (DBP) and systolic blood pressure (SBP). The cohort was split into training (75%) and validation (25%) samples after excluding individuals with pre-existing CVD. After deriving the most parsimonious risk calculator for the clinically adjudicated CV endpoint (CVE) in the training sample, we then applied the risk score to the validation sample and assessed model fit with area under the curve (c-statistic).

Results: The endpoint were age, smoking status, diabetes, living donor, eGFR ≥ 45, ln(ACR), DBP <70 and SBP <140. Combined with race and gender, the c-statistics for the training model was 0.754 for CVD endpoint, 0.762 for all-cause mortality, and 0.83 for graft failure. The model results from the validation sample generated c-statistics of 0.666 (CVE), 0.682 (ACM), and 0.643 (graft failure).

Conclusions: Important kidney transplant related risk factors (donor type, eGFR, and ACR) add significantly to cardiovascular risk prediction that include more typical measures. Further testing in other cohorts is needed to validate our findings and strengthen the model.

Funding: NIDDK Support, Private Foundation Support

TH-PO930

Hospital Readmissions in Kidney Transplant Recipients with Peripheral Vascular Disease
Michelle L. Lubetzky,1 Layla Kamal,1 Maria Ajatamy,1 Puneet Bedi,1 Enver Akalin,2 Brookdale University Hospital Medical Center, Brooklyn, NY; 1Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY; 2Medicine, Montefiore Medical Center, New York, NY; 1Montefiore Medical Center, Bronx, NY.

Background: The benefits of kidney transplantation (KTx) in diabetic patients with peripheral vascular disease (PVD) are unclear. While patients may have improved survival compared to dialysis, the burden of care post KTx has not been assessed.

Methods: We performed a review of diabetic patients with and without PVD transplanted from January 2012 to June 30, 2015. Data on readmissions, re-operations and length of stay was collected. Patient and graft survival was assessed.

Results: Of 203 diabetic patients reviewed 56 (27.6%) had PVD and 147 no PVD. There was no difference in age, sex, race, or type of KTx between the two groups. At a median of 3.14 years follow up (range 30, 1947) there was no difference in 30 or 90 day readmissions between the groups, however significantly more PVD patients were admitted at 1 year (p<0.03), Figure 1. Additionally, PVD patients spent significantly more time in hospital at 1 year (p<0.03). More patients with PVD had re-operations at 90 days and 1 year (p<0.01, p<0.01). Overall graft survival was worse in diabetic patients with PVD although this was not significant (93.2% versus 85.7% p=0.1). Patients with PVD who were re-admitted had significantly worse graft survival than patients with PVD who were not readmitted (100% vs 78.9% p=0.04, Figure 2).

Conclusions: Diabetic patients with PVD have worse graft survival than those without PVD and utilize more resources after KTx with significantly longer length of stays and more re-operations. Readmission in KTx patients with PVD portends poor graft survival.

TH-PO931

De Novo Heart Failure after Kidney Transplantation: Trends in Incidence and Outcomes
Colin R. Lenihan,1 Sai Liu,2 Anita Deswal,1 Maria E. Montez-Rath,3 Wolfgang C. Winkelmayer,1 Baylor College of Medicine, Houston, TX; 1Stanford University, Santa Clara, CA; 2Stanford University School of Medicine, Palo Alto, CA.

Background: Older US data indicate that heart failure (HF) occurs in 18% of patients in the 3-years following kidney transplant. Herein, we sought to explore secular trends in the incidence of de novo post-kidney transplant HF and its associated mortality.

Methods: We identified adult patients who underwent their first kidney transplant in the US between 1998 and 2010. We required that patients had ≥6 months of continuous Medicare parts A and B coverage prior to transplant. HF diagnosis was ascertained using ICD-9 diagnosis codes. Patients with a diagnosis of HF prior to transplant were excluded from the cohort. Cox models were employed to examine secular trends in 1) de novo post-kidney transplant HF and 2) mortality following de novo post-transplant HF diagnosis. Calendar year of transplant was the primary exposure of interest.

Results: 48,771 patients met the study inclusion criteria. Age at transplant, BMI, dialysis vintage and the prevalence of several baseline comorbidities increased between 1998 and 2010. 7269 patients developed HF within 3 years of kidney transplantation with a median time to HF of 0.76 years and an incidence rate of 6.2 per 100 person-years. When adjusted for demographic, comorbid, and transplant-related characteristics the incidence of de novo post-transplant HF was 31% lower for patients transplanted in the year 2010 compared to those transplanted in 1998 (HR 0.69; CI 0.60-0.79; Figure 1). However, we observed no temporal trend in adjusted mortality following de novo post-transplant HF diagnosis.

Conclusions: When adjusted for demographic and clinical characteristics, the incidence of de novo post-kidney transplant heart failure has declined significantly during the period from 1998 to 2010, with no apparent change in subsequent mortality.
Early Initiation of ACE Inhibitors in the Post Renal Transplant Period: A Study from a State Run Tertiary Care Centre Umesh L. Nephrology, Institute of Nephrology, bangalore, India.

Background: Angiotensin converting enzyme inhibitors (ACEI) comprise drug class, which inhibit the effects of angiotensin II by blocking the synthesis of same. Angiotensin converting enzyme inhibitors (ACEI) are well documented to be potent anti-hypertensives with renoprotective effects but are grossly underutilized in renal transplant recipients. However, these drugs have been reported to cause elevated potassium and creatinine levels in some renal transplant patients. There have been no reports of prospective studies of ACEI in renal transplant patients in the early posttransplant period. The purpose of this study is to assess the safety of an ACEI class, when started in early post transplant period.

Methods: This study is a Prospective observational study. We reviewed 78 kidney transplant patients during the period of January 2012 to march 2017 at our institution. 64 patients were initiated on ACEI therapy within a month of post-transplant. Patients were considered to be enrolled when they met the following criteria: Declining serum creatinine, improving urinary output and serum potassium ≤ 5.5 mEq/L. Exclusion criteria: anaphylaxis to ACEI, use of ACE or ARB for treatment of posttransplant erythrocytosis and serum potassium > 5.5 mEq/L.

Results: 64 Patients were studied, 53(83%) were male and 11(17%) were females. Mean age was 32±15 years (12-56). Minimum duration of follow up was 6 months. For each patient haemoglobin, serum creatinine and potassium levels were analyzed at the beginning of ACE inhibition and at the end of the first, third, sixth month. Average potassium levels, hemoglobin levels did not differ significantly between groups and were in normal clinical ranges. While incidence of graft failure did not differ, death with functioning graft was lower in the ACEI group.

Conclusions: ACEI can be used successfully in post-rental transplant with beneficial long term impact on renal function. There is need for further randomized controlled studies to see the effect of ACEI on graft function and its survival.

Funding: Government support - non-U.S.

Changes in Renal Function in Patients Bridged to Heart Transplantation with a Continuous-Flow Left Ventricular Assist Device (LVAD): Analysis of 2480 Patients Nissreen Elafadaw,1 Sadeer Al-Kindi,2 Anne M. Huml,3 Guilherme H. Oliveira,2 1Division of Nephrology, Department of Medicine, University Hospitals Cleveland Medical Center, Cleveland, OH; 2Harrington Heart and Vascular Institute, University Hospitals Cleveland Medical Center, Cleveland, OH.

Background: Left ventricular assist devices (LVADs) have become an established option for patients with end-stage heart failure. The impact of LVAD on renal function is not well described and remains controversial. Objectives: The aim of this study was to determine the impact of LVAD implantation on renal function in patients with end-stage heart failure and discover risk factors associated with renal dysfunction in these patients.

Methods: We used the United Network Of Organ Sharing registry (UNOS) to identify adult patients who are bridged to heart transplantation with HeartMate II or Heartware continuous-flow LVADs from 2007-2015. We excluded patient on dialysis, intra-aortic balloon pumps, extra-corporeal membrane oxygenation, or inotropes. Calculated glomerular filtration rate (GFR) using CKD-EPI formula was assessed at listing and prior to heart transplantation. Significant change in GFR at time of transplantation was defined a 10 mL/min/1.73 m2 change from baseline. Predictors for worsening in GFR were examined by multivariable logistic regression model.

Results: A total of 2480 patients were included, mean age 54±12 years, 80% were male and 47% were status 1A, and 45% had ischemic cardiomyopathy. Mean time on wait-list was 192 days. Mean baseline GFR was 76±26, mean GFR at time of HTx was 72±26 (p=0.001). Overall, 31% (n=788) showed significant worsening in GFR. Risk factors for worsening GFR were older age (1.03 [1.02-1.04] per year, P<0.001), longer time on wait-list (1.001 [1.000-1.001] per day, P=0.001), higher PCWP (1.02 [1.01-1.03] per 1 mmHg, P<0.001), and higher baseline GFR (1.04 [1.03-1.04] per 1 mL/min/1.73 m2, P<0.001)

Conclusions: Approximately one third of candidates for heart transplantation experience significant GFR worsening after LVAD implantation. Older age, longer wait time, and higher baseline GFR are significant risk factors.
Methods: We assessed 18F-FDG uptake, quantified as target-to-background ratio (TBR) in patients. TBR of 1.5-cm arterial segments, centered on the slice of EFE was calculated as the maximum of mean TBR values for all arterial segments. 18F-FDG uptake at baseline (WH-TBRmax) was calculated as the mean of maximum TBR values for all arterial segments, and WH-TBRmean was calculated as the mean of averaged TBR values of the MDS segments. TH-PO936

Extracellular Fluid Excess Is Significantly Associated with Coronary Artery Calcification in Kidney Transplant Recipients Seohyun Park,2 Arum Choi,1 Heebyung Koh,1 Jaeecol Kwon,1 Tae-Hyun Yoo.2 1Department of Internal Medicine, College of Medicine, Severance Biomedical Science Institute, Brain Korea 23 PLUS, Yonsei University, Seoul, Republic of Korea; 2Department of Internal Medicine, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, Republic of Korea.

Results: Eight patients showed a reduction in right Whole-TBRmax and WH-TBRmean, and left MDS-TBRmax, and WH-TBRmax. Seven patients showed a reduction in right Whole-TBRmax and MDS-TBRmean, and left MDS-TBRmax. There was a tendency of reduction in right WH-TBRmax MDS-TBRmax, and MDS-TBRmean (% reduction [95% CI]: -5.74% [-15.37, -0.02], P = 0.047).

Conclusions: The 18F-FDG uptake of WH and MDS were reduced after renal transplantation. Renal transplantation may confer an anti-inflammatory effect on corotid atherosclerosis in CKD patients. Funding: Government Support - Non-U.S.

TH-PO937

Hypertension, Renal Function, and Histologic Changes in Living Kidney Transplant Recipients from Hypertensive Donors Thomas Dienemann,1 Janna Schellenberg,2 Kerstin U. Amann,3 Christoph Daniel,3 Katharina M. Heller,11 Friedrich - Alexander University Erlangen - Nürnberg, Erlangen, Germany; Uniklinikum Erlangen, Nürnberg, Germany; University Erlangen-Nürnberg, Erlangen, Germany; Nephrology and Hypertension, University of Erlangen, Erlangen, Germany; Department of Pathology, University of Erlangen, Erlangen, Germany.

Background: Due to the ever-increasing organ shortage, centers increasingly accept living kidney donors with preexisting hypertension despite concerns over donor safety for transplant recipients.

Results: Twenty-five KT patients were treated with dapagliflozin 5mg/d. Three recipients had normotensive donors (dNT), 42 recipients had hypertensive donors (dHT). There were no differences in age, sex, BMI, and eGFR between recipients from dNT and dHT. There were no differences in age, sex, BMI, and eGFR between recipients from dNT and dHT. Average systolic and diastolic blood pressure in dHT was significantly higher (131±17 vs. 119±12 mmHg in dNT, p = 0.001 for both). Adjusted for multiple confounders there was no difference in blood pressure, number of antihypertensive drugs, and eGFR in recipients at 1 year. The TRCS showed no difference at time of transplant and at 1 year after transplantation.

Conclusions: In our cohort, recipients of a living kidney transplant from hypertensive donors showed no differences in blood pressure, renal function or the TRCS after a 1 year follow up. Prudent selection in terms of accepting hypertensive donors remains mandatory. However longer follow up data is needed to assess potential long term effects which might affect the commonly superior results of living kidney transplantation in recipients of such kidneys.

TH-PO938

Allograft Rescued from Pseudo Transplant Renal Artery Stenosis Gunmin Kang, Laura H. Horianni, Milagros D. Samaniego-Picota. University of Michigan, Ann Arbor, MI.

Results: One year follow up was complete in 180 patients including a biopsy at transplant (n=13). Arterial protocol biopsy 12 months after transplant was also available. 138 recipients had normotensive donors (dNT), 42 recipients had hypertensive donors (dHT). There were no differences in age, sex, BMI, and eGFR between recipients from dNT and dHT. Average systolic and diastolic blood pressure in dHT was significantly higher (131±17 vs. 119±12 mmHg in dNT, p = 0.001 for both). Adjusted for multiple confounders there was no difference in blood pressure, number of antihypertensive drugs, and eGFR in recipients at 1 year. The TRCS showed no difference at time of transplant and at 1 year after transplantation.

Conclusions: In our cohort, recipients of a living kidney transplant from hypertensive donors showed no differences in blood pressure, renal function or the TRCS after 1 year follow up. Prudent selection in terms of accepting hypertensive donors remains mandatory. However longer follow up data is needed to assess potential long term effects which might affect the commonly superior results of living kidney transplantation in recipients of such kidneys.

TH-PO939

Sodium/Glucose Cotransporter 2 (SGLT2) Inhibitor for Diabetic Nephropathy

Background: Transplant renal artery stenosis (TRAS) is a common vascular complication typically occurring 3-24mos post-transplant and may be due to surgical technique or size discrepancy between donor and recipient arteries. As the transplant population ages, there is increasing recognition of pseudo-transplant renal artery stenosis, in which vascular disease proximal to the arterial anastomosis results in graft failure. Here we present a case of late arterial pseudo-tras complication.

Results: A 53 yo woman with diabetes, hypertension, smoking, without known peripheral vascular disease, who underwent a living unrelated kidney transplant 5yrs ago for PKD, presented with 4 days of graft tenderness and decreased urine output. Physical exam showed BP of 183/94 and tenderness over the left lower quadrant allograft. UA was negative for blood, protein or leukocytes. Serum Creatinine was 7.1 mg/dl (baseline 1.2 mg/dl). She reported compliance with immunosuppressants. A transplant ultrasound with Doppler showed 11.4cm kidney without hydro nephrosis, although a parvus tardus waveform (Fig) was seen in the transplant renal artery with low resistive indices. A CO2 angiogram showed complete left common iliac (CIA) and proximal external iliac artery (EIA) occlusion with almost no flow to the transplant renal artery. Left CIA was stented with improved flow to the graft without any pressure gradient. Within 72 hrs, creatinine 1.8 mg/dl and 1.2 mg/dl in 2 wks.

Conclusions: TRAS is a potentially reversible cause of graft dysfunction in early post transplant period, but patients with CVD risk factors can develop pseudo-TRAS in the iliac vessels as a late complication. Early detection can prevent complete graft loss. Transplant renal artery Doppler should show parvus tardus waveforms, prolonged systolic acceleration with small amplitudes and blunting of the systolic peak suggesting poor arterial inflow to the kidney. Prompt intervention within 24 hrs of initial presentation, in our case, successfully rescued the allograft.

A.Parvus tardus waveform B.Aortoiliac angiogram showing complete occlusion of left CIA C.Post intervention angiogram

TH-PO940

Nephrology,
Iowa City, IA

Transplantation: AKI, Cardiovascular, and Metabolic Complications

Nuria

TH-PO941

Diabetes Weighted Genetic Risk Scores and Prediction of New Onset Diabetes after Kidney Transplantation

Kelly A. Birdwell,1 M. Lee Sanders,2 Dinga R. Velez edwards,1 Tatlat Alp Ikizler,1 Ayush Giri,1 Vanderbilt University Medical Center, Nashville, TN; 2University of Iowa Hospitals and Clinics, Iowa City, IA.

Background: New onset diabetes after transplantation (NODAT) is associated with increased cardiovascular events and mortality, but the underlying pathogenesis is not well understood. We examined the genetics of NODAT in kidney transplant recipients using genetic risk scores constructed from previously identified single nucleotide polymorphisms (SNPs) for type 1 and type 2 diabetes in the general population to observe if NODAT overlaps with these disorders genetically.

Methods: Our study cohort included 54 cases and 248 controls, all European Americans. Identified through our prior genome-wide association study completed using Illumina OMNI1 or OMNI5 platforms. Genetic risk scores (GRS) for type 1 and type 2 diabetes were created using SNPs published in the literature. GRS are used as a tool to summarize risk-associated SNPs across the genome to improve prediction of polygenic diseases. Three types of GRS were created: 1) Full, with 25 type 1 SNPs and 3 HLA SNPs 2) Non-HLA, with 25 type 1 SNPs and 3) HLA-only, with 3 HLA SNPs. For type 2 diabetes, 65 SNPs were used. All SNPs were from independent loci. Both non-weighted and weighted GRS were created. Logistic regression models were run using NODAT as the dependent variable and GRS as independent variables, with and without adjustment for covariates (sex, BMI, steroid use, and CMV infection).

Conclusions: Kidney transplant recipients with NODAT have genetic variants that are associated with those SNPs that predict type 1 diabetes but not type 2. This suggests the underlying pathogenesis might reflect more of a type 1 mechanism.

Funding: Other NIH Support - NIGMS; UL1TR000445 from the National Center for Advancing Translational Sciences

TH-PO942

The Impact of Hyperuricemia in Transplanted Kidney in Women

Takashi Unagami,2 Masayoshi Okumi,2 Hideki Ishida,3 Takashi Yokoo,4 Kazunari Tanabe,5 1Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan; 2Department of Urology, Tokyo Women’s Medical University, Tokyo, Japan.

Background: The progression of arteriolar hyalinosis (AH) and interstitial fibrosis / tubular atrophy (IF/TA) is closely associated with graft failure in patients with kidney transplantation. Several clinical factors (age, hypertension, diabetes, calcineurin inhibitor) influence this mechanism but the significance of hyperuricemia (HUA) was not fully understood. We here postulated that the HUA could influence AH and IF/TA progression in kidney allograft recipients.

Methods: We evaluated 126 recipients who received kidney transplants from January 2005 to December 2009 at the Department of Urology, Tokyo Women’s Medical University. Patients with diabetes mellitus were excluded. AH and IF/TA progression was defined as 3-fold increases over baseline. 4 GRS were created: 1) Full, with 25 type 1 SNPs and 3 HLA SNPs 2) Non-HLA, with 25 type 1 SNPs and 3 HLA SNPs. For type 2 diabetes, 65 SNPs were used. All SNPs were from independent loci. Both non-weighted and weighted GRS were created. Logistic regression models were run using NODAT as the dependent variable and GRS as independent variables, with and without adjustment for covariates (sex, BMI, steroid use, and CMV infection).

Conclusions: The cohort mean age was 42.4 years and 59.9% female. Weighted type 1 GRS, both Full and HLA-only, were significantly associated with NODAT in unadjusted and weighted adjusted models. The odds of having NODAT was 1.25 times higher (OR = 1.25, 95% CI 1.03-1.53, p = 0.03) in the weighted adjusted Full model, and similarly was 1.25 times higher (OR = 1.25, 95% CI 1.01-1.53 p = 0.04) in the weighted adjusted HLA-only model, for each unit increase in weighted GRS score. Noteworthy associations were not observed using the type 1 Non-HLA GRS or the type 2 GRS.

Funding: Other NIH Support - SERGAS

TH-PO943

Advanced Glycation End Products (AGEs) by Skin Autofluorescence (SAF) in Renal Transplant (TxR): Risk and Influence in Clinical Practice

Secundino Cigarran,1 Lourdes Gonzalez tabares,2 Nicolas Menendez,1 Juan Latorre,1 Carmen R. Cobelo casas,2 Beatriz Millan,2 Nuria C. Lopez,1 Sonia Cillerò,2 Ana maria Sanjurjo amado,1 Jesus Calvino,2 1Nephrology, Eoxi Cervó-Lupo-Monforte, Burela, Spain; 2Nephrology, Eoxi Cervó-Lupo-Monforte, Lugo, Spain.

Background: AGEs accumulation constitute a vascular pathogenic mechanism involved in aging, diabetes and chronic kidney disease (CKD) moreover of being a measure of cumulative metabolic stress. Despite removal of uremic toxinsAGEs after a successful TxR, cardiovascular disease (CVD) remains the leading cause of mortality. Our aim was to evaluate AGEs by SAF in TxR and its relation with markers associated to CV risk.

Methods: 191 stable TxR were analyzed (38.7% women, aged 56±13.1 years). All were on CKD stages 1-4 and > 12 months of transplantation. Variables assessed: diabetes, CVD history, subclinical atheromatosis by arm-ankle-index and allograft resistivity index, 24-h ABPM, anthropometric and nutritional markers (including dynamometry), CVD risk factors, subclinical vascular atheromatosis as well as with REGICOR scale (r=0.400 p<.001). After multivariate analysis significant variables were: age, male, steroid use, P and dynamometry.

Conclusions: SAF is a validated, economic, and non-invasive tool to assess cardiovascular risk in TxR.Besides age and male gender, our results suggest that P overload, steroid use and nutritional status are the main significant determinants that promote AGEs accumulation. Further longitudinal studies are required in order to confirm this hypothesis.

Funding: Other NIH Support - SERGAS

TH-PO944

Physical Frailty and Cognitive Change Among Kidney Transplant Recipients

Nadia M. Chu,1 Alden L. Gross,1 Qianli Xue,2 Karen J. Bandeen-roche,1 Richey Sharrett,2 Michelle C. Carlson,1 Dorry L. Segev,2 Mara McAdams-DeMarco,2 1Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; 2Johns Hopkins University, Baltimore, MD.

Background: With restoration of kidney function, kidney transplant (KT) recipients may experience preserved or improved cognitive function. However, KT recipients have a higher burden of frailty at the time of KT, and frailty recipients may not experience this potential benefit. The goal of this prospective study was to assess post-KT cognitive trajectories by frailty status (12/2008 – 12/2016).

Methods: Participants completed a physical frailty exam (five Fried criteria) and global cognitive testing (3MS) at time of KT-admission, as well as at least one cognitive test during post-KT. We used a mixed effects model adjusting for follow-up time, age, sex, race, donor type, and 3MS score at time of KT with a random slope (time) and intercept (person) to describe multiple 3MS scores post-KT by frailty status.

Results: Of 665 KT recipients (mean age 52 years) followed for a mean of 2.2 years (3.7% of 15.2% were frail), and the mean 3MS score was 92.5±20% of 3MS at time of KT. In the first month post-KT, non-frail recipients experienced a significantly greater rate of cognitive improvement (0.53 points-per-week, 95% CI: 0.33, 0.73), however there was no evidence

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

Underline represents presenting author.
Transplantation: AKI, Cardiovascular, and Metabolic Complications

**TH-PO944**

High Hemoglobin Levels Maintain Graft Function in Japanese Kidney Transplant Recipients

**Makoto Tsuchiya, Nagoya Daini Red Cross Hospital, Nagoya, Japan.**

**Background:** Post transplant anemia is an important factor for graft survival in kidney transplant recipients. But how we should manage hemoglobin (Hb) values for better graft survival in Japanese recipients, remains unknown.

**Methods:** This was an open-label, randomized controlled trial to demonstrate high Hb values on graft function. One hundred twenty six stable recipients were randomized into two groups: Hb normal group (12.5-13.5 g/dL, n=65) and Hb subnormal group (10.5-11.5 g/dL, n=61). Either Darbepoeitin alfa or Epoetin beta were included in the study from January 2012 to March 2014 at Nagoya Daini Red Cross Hospital and Maiko Memorial Hospital. Primary endpoint was the difference between both groups rate of decline in kidney function.

**Results:** During the course of this study, 12 patients dropped out. At baseline, the mean age was 49.7 and 49.6 years, eGFR was 35.4 and 35.9 ml/min/1.73m², and Hb 11.3 and 11.2 g/dL in Hb normal group (n=59) and subnormal groups (n=55), respectively. After 24 months(M), the mean Hb was 12.6 and 11.2 g/dL(p<0.001), the eGFR was 34.8 and 32.7 ml/min/1.73m²(p=0.27). Figure 1 showed a change of eGFR from baseline to 24M, the eGFR decreased by a mean 0.1 and 3.7 ml/min/1.73m²(p=0.02). Patients who doubled their serum creatinine levels and reached end stage renal disease were not found. Also no cardiovascular event and acute rejection occurred in both groups.

**Conclusions:** This study shows that high Hb values might be more impactfull on graft function in Japanese kidney transplant recipients.

**TH-PO945**

Relationship of Magnesium and Insulin Resistance in Living Donor Kidney Transplant Recipients

**Joy V. Nolte, Biruh Workeneh, Linda W. Moore, Marie C. Gabour, Ahmed O. Gaber, William E. Mitchell, Baylor College of Medicine, Houston, TX; Houston Methodist Hospital, Houston, TX; MD Anderson Cancer Center, Houston, TX; UMASS Boston, Lexington, MA.**

**Background:** Magnesium (Mg) is an important cofactor for blood glucose control and energy metabolism. Decreased Mg stores have been correlated with increased insulin resistance (IR) in diabetes and chronic kidney disease. It is difficult to assess total magnesium stores because serum Mg does not necessarily correlate with total body magnesium. Dietary intake of Mg before and after kidney transplant (KT) has been heretofore described.

**Methods:** We sought to determine differences in Mg intake before and after KT. We reviewed 31 subjects who completed the ASA24 24hr dietary recall and oral glucose tolerance tests (OGTT) <1 month prior to transplant and 3 months post-transplant. Subjects were noninsulin dependent at KT, mostly male (84%) and an average age of 48yo. IR was indicated by Matsuda Index (MI). Spearman’s correlation (ρ) and mixed model statistics were used.

**Results:** Dietary recalls revealed most subjects consumed inadequate Mg pre- and post-KT(Table 1); however, serum Mg (Smg) remained within range for 83% pre-KT and 90% post-KT. Smg decreased 0.23mg/dl, despite increased dietary intake. Neither Smg correlated with Smg post-KT. Smg was lower than dietary Mg, correlated with fasting insulin and MI at baseline but did not reach significance (p=0.346, P=0.056 and p=0.332, P=0.068). IR significantly correlated with weight (PE=0.007, P=0.0003), waist circumference (PE=-0.096, P<0.0001), and BMI (PE=-0.119, P<0.002) over time but not serum or dietary Mg intake (p=0.001, P=0.61).

**Conclusions:** We found that pre-KT patients do not consume sufficient dietary Mg and a significant number were insulin resistant. Post-KT insulin resistance worsened despite increased Mg intake, but we speculate that treatment with calcinuerin inhibitors and other unidentified mechanisms could be depleting total Mg stores and potentially contributing to the insulin resistance observed post-KT. More accurate resistance observed post-KT.

**TH-PO946**

Proton Pump Inhibitors versus Histamine 2 Receptor Antagonists in Transplant Patients

**Julio L. Chevarria, Barbara O. Kheece, Eceartera Berzan, Neil L. Thompson, Maura Looney, George S. Mellotte, Catherine A. Wall, Peter J. Lavin, Trinity Health Kidney Centre, Tallaght Hospital, Dublin, Ireland.**

**Background:** Proton pump inhibitors (PPIs) are among the most commonly prescribed drugs. It has been estimated that two-thirds of those on PPIs do not have a verified indication. Recent literature has related their use with acute and chronic renal impairment. Therefore it is important to determine if PPIs are being used appropriately.

**Methods:** We performed a cross-sectional study in prevalent transplant patients from January-December 2016. We reviewed their records during that timeframe. We recorded demographic characteristics, principal comorbidities, creatinine and CKD-EPI, PPIs or H2RAs, indication, time of use, steroid dose. For the statistical analysis we used SPSS19. We carried out descriptive and inferential analysis, accepting a p<0.05 as significant.

**Results:** 282 patients were included. 57(20%) were on steroid free regimens and 210(69.7%) were on Smg or less. The mean dose was 3.9mg(SD 2.1). A total of 120(42.6%) were on PPIs, 87(30.9%) on Ranitidine and 75(26.6%) on neither. The most common was Omeprazole(43.3%) followed by Lansoprazole(25.8%), and 99% for more than 90 days. Only 14(6.7%) had a clearly documented indication for their use. The use of PPIs was greater in hypertensive patients(p=0.02, OR 2.05, CI 95% 1.11-3.77), older patients(56.3 vs 51.8 years, p=0.023). The use of PPIs compared to ranitidine was greater in patients with diabetes(p=0.03, OR 2.30, CI95% 1.08-4.90), older patient(56.3 vs 53.2 years, p=0.04) and longer transplant vintage(11.9 vs 7.3 years, p=0.01) and there was no difference in the creatinine or CKD-EPI (p=0.24) at the time of review. The use of Ranitidine over PPIs was more frequent in heavier patients(79.0 vs 73.1 Kg, p=0.04).

**Conclusions:** A large number of patients are being treated with PPIs or Ranitidine without a documented indication. These findings highlight the importance of evaluating appropriate therapy and recommending discontinuation if a clear indication does not exist. Reducing inappropriate prescribing of PPIs in kidney transplant patients can minimize potential for adverse events, and foster controllable cost expenditure.

**TH-PO947**

Higher Risk of Mortality Among Girls with ESRD Is Mediated by Lower Access to Transplant

**Patrick Ahearn, Neil L. Thompson, Barbara A. Grimes, Elaine K. UCSF, San Francisco, CA.**

**Background:** Although women live longer than men in the general population, survival in the adult ESRD population does not appear to differ by sex. Few studies have focused on differences in survival by sex among children with ESRD.

**Methods:** Using data from the United States Renal Database Service (USRDS) we performed a retrospective cohort study of children between the ages of 2 and 19 years who required their first RRT between January 1, 1995 and December 31, 2011. We examined demographic characteristics, cause of ESRD, socioeconomic status, calendar year of diagnosis, and sex of children. We sought to determine whether girl sex is associated with lower access to transplantation, or higher risk of mortality. We used Cox proportional hazards models adjusted for demographic characteristics, cause of ESRD, socioeconomic status, calendar year of ESRD onset, and BMI.

**Results:** We included 13,087 children, of whom 1694 died during 7.4 years of mean follow-up. In unadjusted analysis, risk of death was 45% higher for girls than boys (95% CI 1.42-1.86, p=0.0001). In fully adjusted analyses, in all models of death risk, girls had a 71% higher risk (95% CI 1.22-1.48). This higher risk of death was present regardless of initial RRT modality but was more marked in older girls (a13 years, p<0.05 for interaction). The risk for death was higher in older children (p<0.001 for interaction).
of death for girls was higher both on dialysis and after transplant (p=0.05 for interaction by treatment modality). Girls were also less likely to receive kidney transplant than boys (adjusted HR 0.93 [95% CI 0.90-0.97]). In mediation analysis, when we further adjusted for transplant as a time-dependent covariate in our models for mortality risk, the risk of death in girls was partially attenuated [HR 1.28, Table].

Conclusion: Is, substantially higher for girls with ESRD than for boys. This risk of death is partially attributable to lower access to transplant among girls. However, even after adjustment for transplant access, risk of death remains higher for girls treated with either dialysis or transplant. Further investigation is needed to determine reasons for these observations.

Funding: NIDDK Support, Other NIH Support - NHLBI

Risk of death comparing girls versus boys in unadjusted and adjusted analyses.

<table>
<thead>
<tr>
<th>Group</th>
<th>Overall odds (N=507)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
<td>N=357</td>
<td>0.01</td>
</tr>
<tr>
<td>Girls</td>
<td>N=150</td>
<td></td>
</tr>
<tr>
<td>Total follow up, person-years</td>
<td>43,323</td>
<td>51,513</td>
</tr>
<tr>
<td>Follow up rate contributed to biopsies</td>
<td>18.17</td>
<td>30.01</td>
</tr>
<tr>
<td>Unadjusted model</td>
<td>1.45 (1.22-1.70)</td>
<td>1.0</td>
</tr>
<tr>
<td>Adjusted model</td>
<td>1.35 (1.23-1.48)</td>
<td>1.0</td>
</tr>
<tr>
<td>Risk of starting follow up time attributable to transplant</td>
<td>1.30 (1.24-1.44)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

TH-PO948
Hospitalisations Following Kidney Transplantation in Children Siah Kim,1,2 Rebecca A. Spicer,1 Hugh J. Mccarthy,1 Fiona Mackie,1 Sean E. Kehoe,1,3 Melodyvonne Valente,1 Sydney Children’s Hospital, Westmead, NSW, Australia; 2Sydney Children’s Hospital Network, Westmead, NSW, NSW, Australia; 3School of Women’s and Children’s Health, University of NSW, Randwick, NSW, Australia.

Background: Although there is extensive published information about graft survival and acute rejection among paediatric kidney transplant recipients, there is a paucity of published data on hospitalisations within the first twelve months post kidney transplant.

Methods: We performed a retrospective review of children who received kidney transplants at Sydney Children’s Hospital from 2009 to 2015. We collected data on length of stay (LOS) in hospital immediate post-transplant, LOS in intensive care, elective and non-elective readmissions over the first twelve months following transplantation.

Results: 35 children received kidney transplants over 2009 to 2015, 20 female (57%) and 15 male (43%). 20 received deceased donor grafts, 15 living related including one ABO incompatible and one paired kidney exchange. Mean age of the kidney transplant recipients was 10 years (sd 5 years). Median length of stay was 15 days (IQR 11 to 22 days), with median intensive care LOS 4 days (IQR 3 to 6 days). There were 136 admissions to hospital within the first twelve months with 80 (59%) elective and 56 (41%) non-elective. 22 (63%) of children had non-elective admissions post transplant. Planned admission was due to biopsy (40 admissions) and stent removal (25 admissions). The most common cause for unplanned admission was AKI (14 admissions), UTI (13 admissions) and infective illness (23 admissions). Median cumulative days of hospital admission over the first twelve months was 5 days (IQR 1 day to 16 days) for patients.

Conclusions: Hospitalisation within the first year post transplant is common, however cumulative inpatient days in hospital in the first year post-transplant is relatively short for most children. Our data shows that kidney transplantation is associated with much lower levels of hospitalisation within the first twelve months and will help counsel children and their families about their post-transplant course.

TH-PO949
Results of a Pediatric Transplant Program in a Low Income Country: 10 years of Guatemalan Experience Angie L. Aguilar,1 Sindy Soveranis,2 Edgar E. Reyes,1 Randall M. Lou-Meda,2 Hospital Roosevelt, Guatemala, Guatemala; 3FUNDANIER, Guatemala, Guatemala.

Background: ESRD rates appear to be increasing for many developing countries, becoming more challenging to get access to Renal Replacement Therapy and transplant in particular. Guatemala, situated in Central America, has an incidence of ESRD in children of 4.6 per million and a transplant rate of 0.99 per million (2015). FUNDANIER (Foundation for Children with Kidney Diseases) has become the only center that provides access free to RRT to Guatemalan Children and during the last decade has performed and published data on hospitalisations within the first twelve months post kidney transplant.

Methods: We retrospectively described the results of all transplanted patients between 2007 and 2017. Data including demographic characteristics of recipients and donors were obtained from FUNDANIER data base. Variables like immunosuppression, reasons for discharge of the program, graft loss causes, No. of rejections, acute complications, patient and graft survival at 1 year were analyzed.

Results: 78 patients were transplanted. The mean age was 12.6ys(SD3.12), 54% were male and the etiology of ESRD was unknown in 65%, followed by CAKUT in 21% of patients. Regarding donors, the mean age was 33ys(SD7.62) and 37% were male. Most of the donations were from living donors (88%). The maintenance immunosuppression used in 91% (n=71) of the patients was Tacrolimus, Mycophenolate and Prednisone. The most common acute complication after transplant was infections (19%). In total 26% of patients (18/70) experience at least lepiside of rejection after 1mo post transplant. Of 43 episodes of rejection reported, 53%(23/43) were after 1yr post transplant. The mean time of follow up was 3.5 years (SD1.97)(2329) patients discharged from the program were transferred to another type of RRT due to graft loss. The patient and graft survival at 1 year was 89% and 88%. When divided by type of donation, the 1year graft survival for living and deceased donor was 89% and 79%

Conclusions: After the first decade of the program this is the 1st analysis. Most of the transplants were from young adult donors. Increasing the number of deceased donor is mandatory in order to improve the transplant rate in a country with a high rate of ESRD with unknown etiology. The overall graft survival is 88% at 1 year. The main cause of graft loss is rejection due to poor compliance and acute vascular complications.

TH-PO950
Time to Second Kidney Transplantation after Failed Pediatric Kidney Transplant: A Retrospective Cohort Analysis Korntip Phopholkop2, Yong W. Cho,1 Suphamai Bunnaphadist,2 Mendez National Institute of Transplantation, Los Angeles, CA; UCLA, Los Angeles, CA.

Background: With the prioritization of age ≤ 18 years old at time of registration on the kidney transplant waiting list, deceased donor rates have increased. Majority of these patients require subsequent transplantation at later time. Waiting periods before re-transplantation may vary in length, depend on donor type, PRA, and HLA mismatch. We hypothesized that candidates of those after failed pediatric DDKT would have greater time to subsequent KT than those after failed first living donor KT (LDDK).

Methods: We used data from the Organ Procurement Transplant Network (OPTN/UNOS) as of December 8, 2016. A retrospective cohort analysis was created to examine time to second KT in 1,935 candidates listed at age 18-30 from January 1, 2000 to September 30, 2015 with previous KT at age ≤ 18. Those with ≥ 2 KT episodes or re-transplant were excluded. Candidates were divided into 2 groups according to donor type of first KT: 1) those with failed first DDKT and 2) those with failed first LDDK.

Results: Median time to second KT were 646.5 days and 412.0 days in those candidates with failed first DDKT and those with failed first LDDK, respectively. (p=0.01) First LDDK recipients were more likely to have subsequent LDDK than those with failed DDKT. Median PRA were 85% and 68% (p=0.01), and high PRA (PRAa≥80%) were found 26.0% and 16.0% (p=0.01) in recipients of second KT after failed first DDKT and those after failed first LDDK, respectively.

Conclusions: Candidates with previously failed pediatric DDKT had significant longer time to subsequent KT than those with failed first LDDK as well as higher PRA value. Pediatric KT recipients prioritize DDKT in the past could face a challenge with greater waiting time and PRA before re-transplantation.

TH-PO951
The Incidence of Chronic Changes in Protocol Biopsies in Asymptomatic Young Pediatric Renal Transplant Recipients Sunee Panomboonlert, Patricia L. Weng, Robert B. Ettinger. Mattel Children’s Hospital at UCLA, Los Angeles, CA.

Background: Previous studies of protocol biopsies (Bx) in stable pediatric kidney transplant (KT) patients have found a high incidence of interstitial fibrosis (ci) and tubular atrophy (ct), but the effect of recipient age as a continuous variable is unclear.

Methods: We examined the relationships between recipient age (1-10 yrs vs 11-20 yrs) at Bx and the results of protocol Bx at 6 months, 1 years and 2 years in stable pediatric KT recipients from 2005-2016. Bxs were evaluated for subclinical rejection and ci/ct by Banfi 2013 criteria.

Results: A total of 506 protocol Bxs were performed. Subclinical rejection was found in 5.5%, 3.8%, and 2.5% at 6 months, 1 years, and 2 years, respectively of all Bxs and did not differ significantly by time post-Tx or by patient age at Bx. ci = 1 was detected in 15.1% and ct ± 1 was found in 16.3% at 6 months. There was no relationship between time after transplant and subclinical rejection or the incidence of ci or ct. However, in the 6 months Bxs, the frequency of ci score was 26.8% in patients 1-10 yrs and only greater than 9.5% those 10-20 yrs (p=0.002). Similarly, ct scores were 28.6% vs 10.3% (p=0.002) at 1 year. ci/ct trend increased in both age groups but continued to be significantly higher in patients 1-10 yrs (Table).

Conclusions: Young age as a continuous variable is significantly associated with a higher incidence of chronic tubulointerstitial damage in early pediatric biopsies, and this is unrelated to subclinical rejection.
Effect of Pregnancy Post-Transplant on Rejection and HLA-DSA

Development Nadene J. Khoury, Andrea G. Kattah, Fernando G. Cosio. Mayo Clinic, Rochester, MN.

Background: Pregnancy is known to be a sensitizing event; however, most studies have suggested that allograft function is not impaired. We looked at our transplant cohort to assess for rejection post-pregnancy and development of de Novo donor specific antibodies (DSA).

Methods: We used our transplant database to identify the female patient population who were 16-46 years old at the time of transplant. We included transplants which occurred between 1996 to 2014. Patients with a functioning graft for at least 2 years post-transplant were included in our data analysis. We then used pregnancy codes to select those who had a pregnancy or pregnancy-related event.

Results: We identified 47 patients with pregnancy-specific codes from an initial cohort of 412 patients. After excluding patients who had pregnancies prior to transplant and multiorgan transplants, we were left with 11 patients with appropriate pathology and DSA data. These patients were all Caucasian and received living kidney transplants.

We then analyzed the patients who had a pregnancy post-transplant and did not have pregnancy-related rejections.

Conclusions: Most pregnancies post-transplant carry a benign course; it does appear however, that multiple pregnancies might trigger de novo DSA and chronic antibody mediated rejection. It would be important to have larger studies to further delineate this phenomenon and help counsel women who desire to conceive after transplant.

Preeclampsia Predicts Chronic Dysfunction in Kidney Transplantation

Javier Soto-Vargas,2 Karla L. Lemos,3 Efrain CHAVARRIA-AVILA,1 Renato Parra.1 1UNIVERSIDAD DE GUADALAJARA, GUADALAJARA, Mexico; 2Nephrology, Regional General Hospital 46, Mexican Institute of Social Security, Guadalajara, Mexico.

Background: The goal was to evaluate the renal and obstetric outcomes in pregnancy after kidney transplantation in a Mexican center.

Methods: Kidney transplant recipients who underwent pregnancy after transplantation at Regional General Hospital of the IMSS between January 1997 and January 2016 were identified. Data on demographics, comorbidities and clinical and graft outcomes were collected with a median follow up of 61.3 months post-partum.

Results: There were 41 pregnancies identified in 34 recipients. The median age of recipient at childbirth was 26.5 years (IQR, 22.7-30.5) and the median interval from transplantation to conception was 84.4 months (IQR, 43-106). There was a difference between the median pre-transplant estimated glomerular filtration rate (eGFR) (91.0 mL/min/1.73 m(2); IQR, 71.0-106.0) and median eGFR at time of last post-partum follow up (66.0 mL/min/1.73 m(2); IQR, 37.0-87.5; P=0.001). 31 (75.6%) pregnancies ended in singleton live births. Pre-eclampsia occurred in 16 pregnancies (39.0%). There were 7 (17.1%) patients with chronic dysfunction during the follow up, 4 (9.8%) lost their graft, and only one death was recorded, attributed to histoplasmosis. Only the occurrence of preeclampsia was associated with the development of chronic dysfunction and loss of graft (p=0.009 and p=0.018 respectively) independent of the presence of rejections.

Conclusions: Post-transplantation pregnancies with preeclampsia are associated with the development of chronic dysfunction and loss of graft.

Creatinine Monitoring by Remote Blood Spot Testing in Pediatric Kidney Transplant Recipients

Marian Sinkey,1 Jane Dickerson,1 Jodi M. Smith.1 1Children's Hospital & Regional Medical Center, Seattle, WA; 2Seattle Children’s, Seattle, WA; 3Seattle Children’s Hospital, Seattle, WA.

Background: Pediatric kidney transplant patients are monitored frequently with laboratory testing to assess kidney transplant function and optimize therapeutic drug doses. Dried blood spots could reduce the number of lab draws, benefiting those who are remote, elderly, working, or unable to travel.

Methods: We collected 35 samples via phlebotomy from 30 participants for simultaneously paired venous and finger-poke (capillary) to assess the correlation of venous plasma creatinine with capillary dried blood spot creatinine (DBS had already been validated for immunosuppression levels (1)). This method uses creatinine-d3 as the calibrators, and creatinine-13C3-d3 as internal standard measured with a SCIEX QTRAP 6500. Limits of detection and quantitation were determined on the equivalent of 3 µL dried blood spot extractions.

Results: We demonstrate a strong correlation between venous and capillary (DBS) creatinine values when the creatinine was less than 1.5 mg/dL. There was a small negative bias of -0.1 mg/dL for samples less than 1.5 mg/dL. When the Cr was greater than 1.5 mg/dL, we observed a larger negative bias of -0.7 mg/dL in capillary specimens compared to venous.

Conclusions: The study established that remote (home) dried blood spot testing (DBS) is a logistically possible method of monitoring both creatinine and immunosuppression levels on the same day when the expected creatinine concentration is less than 1.5 mg/dL. Dried blood spots could reduce the number of lab draws, benefiting those who are remote, elderly, working, or unable to travel.

References:

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

Underline represents presenting author.
Live Donor Outcomes and Kidney Transplantation in Pediatric and Ethnic/Racial Groups

Patient Demographics by PACT Score

<table>
<thead>
<tr>
<th>PACT Score</th>
<th>Low PACT (N=46)</th>
<th>High PACT (N=23)</th>
<th>No PACT (N=11)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>28/18</td>
<td>13/10</td>
<td>3/8</td>
<td>0.001</td>
</tr>
<tr>
<td>Female</td>
<td>18/28</td>
<td>12/13</td>
<td>8/3</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>10/14</td>
<td>6/7</td>
<td>2/4</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>15/12</td>
<td>11/13</td>
<td>6/7</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>4/11</td>
<td>2/12</td>
<td>0/1</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1/2</td>
<td>1/2</td>
<td>0/1</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>20.6 (18.4-23.5)</td>
<td>22.1 (20.0-23.5)</td>
<td>23.0 (15.0-28.0)</td>
<td>0.7</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>11.2 (10.0-12.0)</td>
<td>11.3 (10.0-12.1)</td>
<td>10.9 (8.5-12.5)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Conclusions:
- PACT was associated with less medical non-adherence and fewer incidences of acute rejection. Our study highlights PACT score in risk stratifying candidates, which warrants prospective validation.

Clinical Outcomes by PACT Score

<table>
<thead>
<tr>
<th>PACT Score</th>
<th>Low PACT (N=46)</th>
<th>High PACT (N=23)</th>
<th>No PACT (N=11)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplant Age</td>
<td>15.8 (10.0-15.9)</td>
<td>17.0 (16.5-18.0)</td>
<td>13.5 (11.0-16.9)</td>
<td>0.066</td>
</tr>
</tbody>
</table>

Conclusions:
- PACT score reduced (OR 0.15 95% CI 0.03-0.83) while non-adherence increased (OR 5.72 95% CI 1.35-24.28) the chances of acute allograft rejection.

Impact of Immediate Post-Transplant Parenteral Iron Therapy on Prevalence of Anemia and Short-Term Allograft Function in a Cohort of Pediatric Renal Transplant Recipients Oluwatoyin F. Bamgbala, Diego H. Aviles, Franca M. Iorember. Children's Hospital, Scottsdale, AZ, SUNY Downstate Medical Center, Brooklyn, NY; Dept of Pediatrics, Louisiana State University Health Science Center, New Orleans, LA.

Background:
Anemia is common but under-diagnosed and is often inadequately treated in renal transplant (KTX) recipients. Due to high turn over rate during chronic dialysis and blood loss during KTX surgery, iron deficiency (ID) is the major determinant of early-onset (< 6 mo) post-transplant anemia (PTA). We sought to examine the clinical benefit of routine use of parenteral (IV) iron in patients who had KTX surgery.

Methods:
Subjects aged 2 -18 yrs who had KTX between 2011 & 2015 received 1-2 mg/kg of diluted iron sucrose over 1 hr in the first week of surgery. Historical control was their counterparts between 2005 & 2010. We determined i) prevalence rate (PR) and predictors of early- (6 mo) and late-onset (12 mo) anemia, ii) relationship between IV iron therapy and anemia; and iii) association of IV iron treatment with the rates of acute rejection (ARE), allograft dysfunction, infection, erythropoietin (EPO) use and hospitalization (HOS).

Results:
Prevalence rate of anemia for the cohort (n = 79): 85% at 1 mo, 74% at 3 mo, 55% at 6 mo, 60% at 12 mo & 47% at 24 mo. There was greater PR of anemia at 1 mo, 55% at 6 mo, 60% at 12 mo & 47% at 24 mo. There was greater PR of anemia at 3 mo, 55% at 6 mo, 47% at 12 mo & 38% at 24 mo. The best set of predictors for early-anemia (< 6 mo) were: anemia (p = 0.01), female sex (p = 0.03) and no IV iron treatment (p = 0.001) and predictors for late-anemia (12 mo) were: anemia (p = 0.01), female sex (p = 0.03) and no IV iron treatment (p = 0.001). Although not significant, there was greater frequency of allograft dysfunction, ARE, and hospitalization in the Controls. There was greater number of anemia treated with EPO rescue in the Controls (p = 0.03).

Conclusions:
- Subjects aged 2 -18 yrs who had KTX between 2011 & 2015 received 1-2 mg/kg of diluted iron sucrose over 1 hr in the first week of surgery. Historical control was their counterparts between 2005 & 2010. We determined i) prevalence rate (PR) and predictors of early- (6 mo) and late-onset (12 mo) anemia, ii) relationship between IV iron therapy and anemia; and iii) association of IV iron treatment with the rates of acute rejection (ARE), allograft dysfunction, infection, erythropoietin (EPO) use and hospitalization (HOS).

Funding:
- Private Foundation Support, Clinical Revenue Support

With kidney transplants. This is an important self-management tool for transitioning adolescents to adult HCPs.

Malignancies after Pediatric Kidney Transplantation: A Long Term Single-Center Experience in Japan Tomo Yabuuchi, Ken-ichiro Miura, Shoichiro Kanda, Yohei Taniguchi, Takeshi Nagasawa, Ryutaro Hisatomi, Hideki Ban, Yoko Shira, Yoko Takagi, Naoto Kaneko, Kiyonobu Ishizuka, Hiroko Chikamoto, Yuko Akioka, Motohiro Hattori. Department of Pediatric Nephrology, Tokyo Women’s Medical University, Tokyo, Japan; Department of Pediatrics, University of Tokyo, Tokyo, Japan.

Background:
Kidney transplantation (KTx) is the preferred treatment option for children with end-stage renal disease. Today, approximately 11.2% of all deaths after pediatric KTx are related to cancer. With improved graft survival and overall survival, this proportion is likely to rise. Increased cancer risks are well documented in adult KTx recipients. However, the spectrum of malignancies and risk in the pediatric KTx population, particularly in Asia, are less well described.

Funding:
- Private Foundation Support, Clinical Revenue Support

with kidney transplants. This is an important self-management tool for transitioning adolescents to adult HCPs.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: We retrospectively reviewed medical charts of all consecutive pediatric KT patients aged less than 20 years in our center between April 1983 and December 2016.

Results: During maximum 31 years of follow-up, 13 out of 363 patients (3.6%) developed malignancy, which included 3 EBV-associated posttransplant lymphoproliferative disorder (PTLD), 1 EBV-associated post-transplant smooth muscle tumor (PTSTM), 2 brain tumors, 1 B-cell lymphoma, 1 renal cell carcinoma, 1 thyroid carcinoma, 1 lung cancer, 1 bladder cancer, 1 breast cancer, and 1 Wilms tumor. Patients diagnosed with EBV-associated PTLD, EBV-associated PTSTM, and Wilms tumor were more than 10 years of age and the median age at diagnosis of malignancy was 6.6 years (range 5.5-11.5), with a median time to diagnosis of 1.2 years (range 0.6-1.2). In contrast, the median age at diagnosis of other malignancies was 27.6 years (range 20.4-31.8), and the median time from KTxs to diagnosis of malignancy was 15.2 years (range 10.5-17.1). No EBV-associated PTLD has occurred since 2005, when we started regular screening of EBV-DNA load in children at risk for developing PTLD.

Conclusions: This is the first study which investigated occurrence of malignancies in pediatric KT recipients in Asian populations. EBV-associated PTLD and PTSTM occurred during early periods from KTxs. Regular screening of EBV-DNA load might be helpful to prevent EBV-associated PTLD. Other malignancies were diagnosed during early adulthood, emphasizing the need for long term surveillance of these patients.

TH-P0960

Pubertal and Development of Children and Adolescents Following Renal Transplantation


Background: Children with chronic kidney disease often show a delayed pubertal development and growth restriction, which is an enormous psycho-social stress factor. The improvement of renal function following RTx seems to positively influence some of the involved mechanisms. We analyzed pubertal development and growth in children following RTx in order to identify potential risk factors.

Methods: Data of 90 children (0-18 years, 32 ♂♂) from our center who underwent RTx between 2000-2015 have been retrospectively analyzed. Mean observation time was 6.7 years. We studied the influence of gender, age, underlying disease, mode and duration of dialysis, glucocorticoid and growth hormone therapy prior to RTx, renal function, and immunosuppression on the annual course of weight and growth, bone age, testicle volume, estradiol/testosterone levels, age at onset of menarche and change of pubertal Tanner-stage.

Results: Mean age at RTx was 6.8 years (+4.7 years). Length (-1.6SD) and weight (+0.9SD) were reduced prior to RTx and we found a pronounced dissociation between skeletal and chronological age. While all patients gained weight (p=0.007) following RTx, length and dissociation of bone age showed no improvement (p=0.032). On the contrary, the dissociation was more pronounced in the group of patients between 7-12 years (p=0.05). Patients receiving growth hormone therapy prior to RTx showed a negative dissociation and reduced length at time of RTx and presented an accelerated catch-up-growth with no further significant differences after RTx. Living kidney donation was associated with a significantly enhanced length (+0.9SD vs. -1.7SD, p=0.025). Age at onset of menarche (12.9±1.6 years, normal range 11.2-15.6 years) and change from Tanner-stage P1 to P2 (11.2±1.6, normal range 8-12.6 years) were in the upper normal range. Boys were 12.3±1.5 years old (normal range 9.2-15.2 years) at transition to P2. No dependency of gender, age, duration and mode of dialysis, immunosuppression or prior glucocorticoid therapy could be observed.

Conclusions: The majority of our patients showed a timely pubertal development following RTx. Despite a improved renal function, growth and bone age remained retarded.

TH-P0961

Donor and Recipient Size Mismatch Is Associated with Graft Ablation in Pediatric Living Donor Kidney Transplantation

Heather L. Wasik, Rebecca Riebeiner, Corannel S. Proutee, Dorry L. Segev, Allan Massey. Johns Hopkins University, Baltimore, MD.

Background: Studies in adults and adolescents have shown that a small donor body size in relation to recipient body size is associated with increased risk of graft loss following kidney transplantation. Little is known about this relationship in young children undergoing living donor kidney transplantation (LDKT) in whom greater size mismatch is possible.

Methods: We studied first-time LDKT recipients 1995-2015 aged <11y at transplant using SRTR data. Patients were divided into two groups based on donor/recipient body surface area ratio (D/R BSA ratio): BSA ratio ≤ 2 and BSA ratio > 2. Multivariable Cox models were used to compare time to death-censored graft failure (DCGF) between patients in the two BSA ratio groups, adjusting for recipient, donor, and clinical characteristics including recipient age at transplant, recipient BSA, sex, race, cause of ESRD, years of dialysis prior to transplant, donor age, donor/recipient sex mismatch, number of HLA mismatches, and year of transplant.

Results: Of 1,148 pediatric patients undergoing LDKT, 352 (30.8%) had a D/R BSA ratio ≤ 2. Patients with BSA ratio ≥ 2 had a higher incidence of DCGF compared to those with a BSA ratio > 2 (32.3% at 10 years vs. 15.4%, logrank p<0.001). After adjustment, D/R BSA ratio ≤ 2 remained associated with an increased risk of DCGF (aHR (95% CI) 1.62 (1.10-2.39), p=0.01).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
appropriate identification/documentation of post-transplantation UTI risk, UTI history and risk factors were charted. The intervention included the interactive seminar and the supplementary time used to document was also assessed. As a chart was used for analysis.

Results: A total of 14 renal transplant outpatient clinics (77 patients; 126 medical visits) were reviewed from February to May 2017. The baseline documentation of UTI history and UTI risk factors was 45% (n=69/153). After the interactive seminar, the medical record was reviewed 1 year after intervention and UTI risk factor documentation improved by 25% (n=86/153). Similarly, the medical team educational session, an increase of the documentation of UTI risk factors was observed (47% of documentation following educational session) but no significant change in documentation of UTI history (41%). Following implementation of the checklist, documentation of UTI risk factors improved by 21% and 17% respectively. However, categorization of patient’s post-transplantation UTI risk was almost always missing.

Conclusions: UTI is a major clinically significant complication following pediatric kidney transplantation. Implementation of a checklist significantly improved documentation of UTI history and risk factors in children after renal transplantation.

TH-PO964
CMV Viraemia Is Associated with Decline in Graft Function in Paediatric Renal Transplant Patients
Shashidhar Adalat, Martin Gazzini, Gabriletti, Nabil Z. Melhem, Granine M. Walsh, Helen E. Jones, Jenola Stojanovic, Evelina London Children's Hospital, London, United Kingdom.

Background: Little is documented about impact of post-transplant CMV viraemia on graft function in paediatric transplant recipients.

Methods: A retrospective analysis of CMV viral loads, graft outcomes, amendments in immunosuppression (IS) and rejection episodes in renal allografts in a large paediatric transplant centre. CMV donor/recipient status, timing of CMV viraemia, duration of any antiviral therapy and time to CMV seroconversion were analysed. Rejection episodes were noted with correlation to IS changes and decline in GFR was calculated annually using the Schwartz formula.

Results: Of 101 paediatric renal transplants performed over a 5 year period (2010-15), data was analysed for 76 followed-up patients. Follow up ranged 1.3-7.3 years at time of review (mean 4.2 years). Two thirds of all transplants came from living donors and two thirds followed a standard IS protocol of basiliximab, tacrolimus, azathioprine and tapering prednisolone. In 43% both donor and recipient were CMV naïve; both were CMV seroconvertive in 25% and in 25% the donor was positive while recipient was naïve. In 9% recipient positive only. Of CMV naïve recipients with positive donor (n=19), all received 3 months of prophylactic valganciclovir. Despite prophylaxis, 52% developed viraemia of 2(range-27 to 42) ml/min/1.73m². No primary infection in CMV-/- or CMV-+/-. Of 19% recipient positive only. Of CMV naïve recipients with CMV positive donor(n=19), there was a greater decline in graft function in CMV naive patients who develop viraemia regardless of seroconversion. There is no evidence that this is related to changes in immunosuppression at the time of the CMV viraemia.

Conclusions: There is a greater decline in graft function in CMV naïve patients who develop viraemia regardless of seroconversion. There is no evidence that this is related to changes in immunosuppression at the time of the CMV viraemia.

TH-PO965
Tubular Cell Senescence in the Donated Kidney Predicts Allograft Functions, but Not Donor Remnant Kidney Functions, in Living Donor Kidney Transplantation
Tadashi Soejima, Yoshio Kushida, Taro Ozaki, Masahiro Moritoki, Yoko Nishijima, Akira Nishiyama, Tetsuo Minamino, 1Department of CardioRenal and Cerebrovascular Medicine, Kagawa University, Kagawa, Japan; 2Department of Pathology, Kagawa University, Kagawa, Japan; 3Department of Pharmacology, Kagawa University, Kagawa, Japan.

Background: It is uncertain whether kidneys from marginal donors are suitable for living donor transplantation. In deceased donor kidneys, tubular cell senescence in the donated kidney is reported to affect allograft functions. However, the degree of cell senescence in live donors with marginal kidneys has not been reported. In the current study, we assessed the association of tubular senescence with allograft and remnant kidney functions in living donor kidney transplantation by a prospective observational clinical study.

Methods: Thirty-eight living donor kidney transplantsations were analyzed prospectively. Tissue sections obtained from pre-implantation kidney biopsies were immunostained for p16 (9.6-11.5) to indicate tubular senescence. Various kidney biomarkers were analyzed in urine and blood samples. The protocols and informed consent forms were approved and approved by the Ethics Committee of Kagawa University (#H1224-059) and registered in the UMIN Clinical Trials Registry (UMIN000049050).

Results: Of the 38 donors, 21 had marginal factors. Severe tubular senescence was found in living donors with overlapping marginal criteria. Tubular senescence in living donor kidneys was significantly related to donor age and lower recipient kidney function (p=0.036). In the patient’s medical record was 45% and of UTI risk factors (p=0.050), but did not affect remnant kidney functions after donation. Pre-transplant donor factors, such as pre-GFR, hypertension, systolic blood pressure, and albuminuria, did not show any significant AUC for prediction of high tubular cell senescence. High plasma soluble αKlotho levels were associated with a higher predictive value for low tubular cell senescence with an area under the curve of 0.78 (95% confidence interval 0.62-0.93, P<0.01).

Conclusions: The nuclear p16-staining rate in donated kidney tubules is a predictor for allograft kidney functions, but not donor remnant kidney functions in living donor transplantation. Use of αKlotho as a predictive factor of tubular cell senescence may facilitate selection of appropriate living donor candidates.

Funding: Government Support - Non-U.S.

TH-PO966
Validation of Living Donor Nephrectomy Codes Cegan Lam, Krista L. Lentine, Scott Klarenbach, Manish M. Sood, John Paul Kwurowski, Kyla L. Naylor, Greg A. Knoll, Joseph Kim, Amit X. Garg. 1Institute for Clinical Evaluative Sciences, University of Toronto, London, ON, Canada; 2London Health Sciences Centre, London, ON, Canada; 3Ottawa Hospital, Ottawa, ON, Canada; 4Ottawa Hospital Research Institute, Ottawa, ON, Canada; 5Saint Louis University, St. Louis, MO; 6Toronto General Hospital, University Health Network, Toronto, ON, Canada; 7University of Alberta, Edmonton, AB, Canada; 8Institute for Clinical Evaluative Sciences, London, ON, Canada.

Background: Use of administrative data for outcomes assessment in living kidney donors is increasing given the rarity of post-donation complications and challenges with loss to follow-up.

Methods: Using linked healthcare administrative databases in Ontario, Canada, we conducted a retrospective study to determine the feasibility of using billing and procedural codes for living donor nephrectomies. The reference standard was living kidney donation events identified through the province’s tissue and organ procurement agency, with verification by manual chart review. All living kidney donors from 2003 to 2010 who had donated at one of the main major transplantation centers in Ontario were included. Operating characteristics (sensitivity and positive predictive value, PPV) of various algorithms using diagnostic, procedural, and physician billing codes were calculated.

Results: During the study period, there were a total of 1199 living donor nephrectomies performed. Overall, the best algorithm for identifying living kidney donors was the presence of one diagnostic code for kidney donor (ICD-10 Z52.4) and one procedural code for kidney procurement or excision during a hospital admission (ICPS8, ICPS9, ICPS1). Compared to the reference standard, this algorithm had a sensitivity of 97.4% and a PPV of 90.1%. The diagnostic and procedural codes performed better than the physician billing codes (sensitivity 60.1%, PPV 78.3%).

Conclusions: An algorithm consisting of one diagnostic and one procedural code accurately identified living kidney donors. This algorithm can be used to identify and follow living kidney donors for post-donation outcomes.

TH-PO967
Nephrosclerosis beyond That Expected for Age is Predictive of Early New-Onset Hypertension in Living Kidney Donors
Naim S. Issa, Lisa E. Vaughan, Aleksandar Denic, Venkata vamsi Nagineeni, Harini A. Chakkerka, John C. Lieske, Lilach O. Lerman, Sandra J. Talor, Mark D. Stegall, Emilio D. Poggio, Andrew D. Rule. 1Cleveland Clinic, Cleveland, OH; 2Mayo Clinic, Rochester, MN; 3Mayo Clinic Arizona, Scottsdale, AZ.

Background: Nephrosclerosis on kidney biopsy of living donors is known to associate with older age and hypertension (HTN). Whether nephrosclerosis is also predictive of adverse kidney changes early after donation is unclear.

Methods: We retrospectively studied living kidney donors who had an implantation renal biopsy as part of the Aging Kidney Anatomy study. Age-based thresholds (95th percentile for 18-75 yo) were defined for glomerulosclerosis percentage (8-30%), cortical fibrosis (1-10%), number of fibrosis foci (1-6) and arteriosclerosis (60-76%). A Nephrosclerosis Index was defined assigning a value of 1 for each parameter that was abnormal. The Nephrosclerosis Index was assessed as a predictor of residual eGFR, eGFR<60 ml/min/1.73 m², elevated 24-hour albumin excretion, and new onset HTN (<130/80 mmHg) as well as elevated diastolic BP>90 mmHg or use of anti-hypertensive medications) after donation.

Results: There were 1409 donors available to define age-based thresholds of which 741 returned for a follow-up visit 2-24 months after donation (mean and median 9 months). The Nephrosclerosis Index was 0 in 65.3%, 1 in 26.2%, 2 in 6.3%, and 3 or none in 3.3%. Among donors who were 65 to 74 years old, the Nephrosclerosis Index was 0 in 59.3%, 1 in 26.2%, 2 in 6.3%, and 3 or none in 8.2%. After adjusting for clinical predictors, baseline characteristics that associated with Nephrosclerosis Index were age (p=0.001) and HTN (p=0.003). After adjusting for age at donation, pre-donation HTN, and follow up time, the Nephrosclerosis Index was not predictive of change in eGFR (p=0.89) at follow-up, a follow-up eGFR<60 ml/min/1.73 m² (p=0.56), or change in urine albumin (p=0.70). After excluding baseline HTN and adjusting for age and follow up time, the Nephrosclerosis Index per level increase associated with new-onset HTN at follow up (OR=1.9, p=0.021). A Nephrosclerosis Index of 2 or higher was also associated with new-onset HTN at follow up (OR=7.2, p=0.017). An alternative analysis using single-thresholds rather than age-based thresholds for Nephrosclerosis Index found no association with new-onset HTN at follow up.

Conclusions: Although uncommon, nephrosclerosis beyond that expected for age in a living kidney donor is associated with both prevalent HTN at donation and new-onset HTN at follow-up.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Mortality in Living Kidney Donors with ESRD: A Propensity Score Analysis Using the United States Renal Data System

Robert Nac1,2,4
Amarpal Brar1, Dimitre Stefanov1, Rahul M. Jindal1, Madhu R. Joshi1, Bair Cadet1, Moro O. Salifu1
1 SONY Downstate Medical Center, Brooklyn, NY; 2 LSU-Walter Reed Department of Surgery, Uniformed Services University, Bethesda, MD; 3 Medicine, Uniformed Services University, Bethesda, MD.

Background: Living kidney donation has been performed with the premise of acceptable safety of kidney donors. Although a very small percentage of living donors progress to end-stage renal disease (ESRD) after donor nephrectomy, evidence suggest that the rate of ESRD is comparable to that in the general population. However, for those donors who develop ESRD, their survival on dialysis has not been systematically assessed.

Methods: We used the United States Renal Data System (USRDS), and abstracted 274 prior living kidney donors (cases) between 1995 to 2009. There were 690,398 on dialysis without kidney donation (controls). Univariate analysis was used to test differences between the unmatched groups. We used propensity score matching to identify 258 cases and 258 controls. Time-dependent Cox proportional hazards model, adjusted for demographic factors and comorbidities, was used to compare survival between the two matched cohorts.

Results: In the propensity score-matched cohort, mortality was lower in cases compared with controls (19% vs 49%, p<0.0001). Cox model results demonstrated that cases had significantly lower mortality compared with controls (adjusted hazard ratio [AHR] 0.20; 95% CI 0.14-0.28, p<0.0001). Time-segmented analyses showed cases with significantly lower mortality 0–5 years (AHR 0.15; 95% CI 0.10-0.24, p<0.0001), and 5–10 years since start of dialysis (AHR 0.26; 95% CI 0.14-0.48; p<0.0001). After 10 years, the difference in survival was nonsignificant (AHR 0.48; 95% CI 0.17-1.32; p=0.15), likely due to the small sample size of patients in this time interval.

Conclusions: We observed a lower mortality rate in living donors with ESRD compared to matched non-donors. This data will guide clinicians in the informed consent process with prospective donors.

Table 1. The results of 5 renal transplant donors

<table>
<thead>
<tr>
<th>Gender</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>60</td>
<td>62</td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>180</td>
<td>175</td>
</tr>
<tr>
<td>CT based GFR (ml/min)</td>
<td>120</td>
<td>115</td>
</tr>
<tr>
<td>Inulin clearance (ml/min)</td>
<td>150</td>
<td>145</td>
</tr>
</tbody>
</table>

Survival curves of donors vs. matched non-donors with ESRD

A Multivariate Model to Predict Post-Donation Kidney Function and Outcomes in Living Kidney Donors

Sophie Limou,1 Edouard Gardan,1 Simon Nusinovici,1 Matthieu Hanf,1 Maryvonne Hourmant,1 CHU de Nantes, Nantes, France; Inserm UMR1064, Center for Research in Transplantation and Immunology, Nantes, France; Ecole Centrale de Nantes, Nantes, France.

Background: Predicting kidney function after donation is a major challenge in living kidney donors. The aim of this study was to assess a wide range of demographics and clinical variables as non-invasive preoperative markers of post-donation kidney function.

Methods: 110 French living kidney donors who had a 51Cr-EDTA scintigraphy and a measured glomerular filtration rate (mGFR) pre- (D0) and one-year post-donation (Y1) were included. Over 15 characteristics were collected for each subject before and after nephrectomy (e.g., sex, age, hypertension, creatinine and lipids levels). Kidney volume was quantified using three methods: total parenchymal three-dimensional renal volume (3DRV), total parenchymal renal volume contouring (RVC), and renal cortical volume (RCoV). We tested each variable for association with Y1 mGFR using univariate and multivariate regression models. Finally, we produced receiver operating characteristic (ROC) curves to assess the performance of our model in discriminating chronic kidney disease (mGFR<60mL/min) at Y1.

Results: The mean mGFR was 105.2±17.7 mL/min at D0 and 68.1±12.8 mL/min at Y1. Total parenchymal volume measurements exhibited a high correlation with RCoV (R2=0.92 for 3DRV and 0.84 for RVC). In univariate models, the correlation between kidney volume and mGFR was the highest for the RCoV measures with R2=0.44 (P=2x10^-13) at D0 and R2=0.59 (P=3x10^-12) at Y1. Y1 mGFR was also strongly associated with age (R2=0.62, P=7x10^-14) and D0 mGFR (R2=0.68, P=4x10^-14). Using stepwise regressions, we developed a model integrating 5 non-invasive preoperative markers (D0 mGFR, age, RCoV, triglycerides level and birth weight) predicting Y1 mGFR with a R2=0.68. Finally, the ROC curve analysis showed that this multivariate model could reliably predict chronic kidney disease at 1-year post donation (area under the curve [AUC]=0.92).

Conclusions: The integration of non-invasive preoperative characteristics in one statistical model can accurately predict post-donation kidney function and outcomes in French living kidney donors. These results warrant validation in an independent population. Our report therefore opens the way for developing a predictive risk score that would be easily implemented in clinics.

Dynamic Contrast Computed Tomography as a Separate Renal Function Test for Living Renal Transplantation Donors

Midori Hasegawa, Jin Iwasaki, Kazuo Takahashi, Hiroki Hayashi, Shigehisa Koide, Daijo Inaguma, Yukio Yuzawa. Fujita Health University School of Medicine, Toyoake, Japan.

Background: Non-ionic contrast agent is stable in vivo and is eliminated without being metabolized, exclusively by glomerular filtration. The purpose of this study is to establish the method of measurement of glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) by dynamic computed tomography (CT), for use in accurate separate renal function evaluation.

Methods: We performed preoperative abdominal contrast-enhanced CT of renal transplant donor candidates was performed, low level radiation (8 mSv) dynamic CT images were added every 2 for 30 seconds. The region of interest (ROI) was set at the right and left renal artery just before branching, and the CT value in the ROI was obtained. A time-density curve was derived from the CT value and photographing time. ERPF was calculated using the Patlak plot method. GFR was calculated using a 3-compartment model (intra-arterial, extracellular space, glomerulus) analytic method. CT based GFR was compared with inulin clearance results.

Results: Table 1 shows the results in 5 renal transplant donors. CT-based GFR closely coincided with inulin clearance. The filtration fraction (GFR/ERPF) was 0.22±0.03. Figure 1 shows the images of ERPF and GFR.

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

Underline represents presenting author.

Figure 1. The images of ERPF and GFR
Background: To meet the increasing demand for donor organs, selection criteria for living kidney donors have been liberalized. The impact of this liberalization is largely unknown. We compared long-term outcomes of living kidney donors over different time periods.

Methods: In this single-center prospective cohort study, we divided 323 living kidney donors into two groups according to the year of donation (1987-2004, n=81 vs. 2005-2012, n=242). We analyzed differences in age, sex, measured GFR (mGFR, computed glomerular filtration rate), blood pressure, proteinuria, BMI, and number of antihypertensives among the two groups (1987-2004 vs. 2005-2012) at baseline and at 5 years post-donation, using Student’s t-test and Pearson’s Chi-square test.

Results: At donation, sex (41% vs. 50%, p=0.13) and mGFR (105±14 vs. 103±16 ml/min/1.73m², p=0.23) were similar among both groups. However, donors who donated after 2004 were older (46±10 vs. 53±10, p<0.001), had a higher systolic blood pressure (122±11 vs. 129±14 mmHg, p<0.001), and BMI (25±4 vs. 27±4 kg/m², p<0.002), and more often used antihypertensives (5% vs. 15%, p=0.04). At 5 years post-donation, individuals who donated after 2004 had a lower mGFR (72±11 vs. 68±12 ml/min/1.73m², p=0.01) and a more pronounced mGFR reduction compared with pre-donation (−35±12 vs. −39±15 ml/min, p<0.01). There were no differences in systolic blood pressure (126±13 vs. 128±14 mmHg, p=0.44), proteinuria (1.1±0.2 vs. 0.8±0.2 g/24 h, p=0.34), BMI (27±4 vs. 27±4 kg/m², p=0.19) or number of antihypertensives at 5 years post-donation.

Conclusions: Our study confirms a trend in the liberalization of living kidney donors, at least regarding age and blood pressure at donation. Moreover, we observed a small but significant reduction in long-term renal functional life in living kidney donors who donated more recently. Future studies with longer follow-up should address the impact of donor liberalization on outcomes.

Funding: Government Support - Non-U.S.

TH-P0972

Long-Term Renal and Non-Renal Morbidities in Living Kidney Donor Yaerim Kim, Hyunjin Ryu, Young Lee Jae, Jung Shin Choi, Cheolgu Hwang, Mi-yeon Yu, Yun So Kim, Hajeong Lee. Seoul National University Hospital, Seoul, Republic of Korea.

Background: Kidney transplantation (KT) is the best treatment option for end-stage renal disease (ESRD). Safety of kidney donor has become an overarching theme according to increase of KT from living donor. However, risk factors for renal and non-renal morbidities were not clearly identified.

Methods: We observed 1,238 living kidney donors who underwent nephrectomy from January 1986 to February 2016 in a single tertiary hospital retrospectively. We estimated overall incidences of renal morbidities including ESRD and non-renal morbidities: hypertension (HTN), proteinuria, diabetes and malignancy. In addition, we analyzed significant risk factors for renal and non-renal morbidities.

Results: A total of 901 donors who were followed up more than 1 month were finally included. Median age was 42 (IQR, 18-65) years and 67.2% was women. Preexisting HTN was found in 47.4% of donors. Only three donors had impaired glomerular filtration rate at the time of donation. After 27 months of follow-up, final estimated glomerular filtration rate (eGFR) was 71.3 ± 14.3 ml/min/1.73m². One donor progressed to ESRD. Total 20.3% of donors failed to recover up to eGFR of a 60 ml/min/1.73m². Seventy eight (8.7%) of donors progressed to new onset HTN, 448 (44.8%) prediabetes or diabetes, and 17 (1.9%) malignancy after donation. Interestingly, donors with preexisting HTN or diabetes did not show increased inadequate renal recovery. In the multivariate analysis, women, higher BMI and lower initial eGFR contributed to new onset hypertension independently. In addition, older age, higher BMI and inadequate renal recovery elevated new onset diabetes. Malignancy after donation was affected by older age, lower serum uric acid and albumin levels. Finally, inadequate renal recovery was associated with older age, higher BMI and lower initial eGFR.

Conclusions: Post-donation renal and non-renal morbidities are not rare. In our study, donors with older age, higher BMI and lower initial GFR should be monitored meticulously for developing renal and non-renal complications after donation. It is important to control adjustable risk factors strictly such as BMI and uric acid before and after donation to maintain their residual kidney function well.

Funding: NIDDK Support

TH-P0973

Hemodialysis Patient Social Networks Promote Living Donor Transplant Discussions Avrum Gillespie,1 Swati Rao,2 Sarah E. Dawson,2 Heather M. Traino,3 Peter F. Reece,2 Zoran Obradovic,4 Crystal A. Gadebeck, Edward F. Kendrick,2 Jonathan A. Fink,4 Eric F. Fink,4 1Temple University, Levittown, PA; 2Temple University School of Medicine, Philadelphia, PA; 4University of Pennsylvania, Philadelphia, PA.

Background: Social contagion theory posits that ideas, attitudes, and behaviors spread within social networks. However, little is known about the structure and influence of social networks within the unique setting of hemodialysis (HD) clinics. We examine the role of patient HD social networks and discussing living donor kidney transplantation (LDKT), a well-known barrier to renal patients’ access to transplantation.

Methods: Survey and observational data collected between 8/2012 and 2/2015 were used to characterize the social network of 46 hemodialysis patients in a newly opened clinic.

Results: The mean age of participants was 54yrs, 58% were male, 39% Hispanic and 30% African Americans and 65% had discussed transplant with clinic nephrologists. Thirty-seven (76.7%) patients interacted with others to form a social network of friends or developing affiliations with local hospitals.

Conclusions: This study found that patients who discuss transplant with other patients and staff in the hemodialysis clinic are more likely to request consideration of living donation from member of their extra-clinic networks. These findings suggest HD patient social networks are potential target for social network interventions. This research also challenges the current ecological approach to barriers to transplantation which attributes only a small role to the HD clinic and often neglects the role of patient interactions.

Funding: Private Foundation Support
Table 1

<table>
<thead>
<tr>
<th>Gender</th>
<th>23 M, 1 F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>6.2 ± 8.7 yrs</td>
</tr>
<tr>
<td>Patients on maintenance dialysis</td>
<td>39</td>
</tr>
<tr>
<td>Patients on calcimimetic inhibitor</td>
<td>30 recipients and 21 control group</td>
</tr>
<tr>
<td>Time of transplant</td>
<td>2000-2016</td>
</tr>
</tbody>
</table>

TH-PO976
Han Ro,1 Muyeon Han,2 Jong Cheol Jeong,3 Ji Yong Jung,3 Wooyoung Chung,4 Curie Ahn.1

1 Aoy University Hospital, Sapporo, Republic of Korea; 2 Gachon University Gil Medical Center, Incheon, Republic of Korea; 3 Seoul National University Hospital, Seoul, Republic of Korea; 4 Seoul National University Hospital, Seoul, Republic of Korea.

Background: Kidney donor risk index (KDRI) is used in the United States to estimate the deceased donor kidney. However, KDRI is not yet used in Asian population.

We tried to validate KDRI in assessment of deceased donor kidney in a large number of Korean population group.

Methods: The data of Korean Organ Transplantation Registry (KOTRY) between 2009 to 2012 was used in the analysis. Among 1924 deceased donor kidney transplantation, 1582 cases in which KDRI score could be calculated were included in this study. We investigate the impact of KDRI on the graft function and graft survival.

Results: We divided the donors by KDRI tertile (T1: range, 0.6432-1.1792, T2: range, 1.1707-1.48565, T3: range, 1.48630-3.80629). The recipients of T1 were younger and had less diabetes. Mean estimated glomerular filtration rate at post transplant 1 year of each group was 76.1 ± 21.0, 64.7 ± 20.3, 55.5 ± 21.0 m/l/min/1.73 m² respectively. In the Cox regression analysis, KDRI showed good association with death censored graft survival, of which median follow up duration was 24.6 months (hazard ratio 1.778, 95% confidence interval 1.087-2.906, p=0.022).

Conclusions: KDRI is a good tool for estimation of early posttransplant outcomes in Korean population.

Funding: Government Support - Non-U.S.

TH-PO977
Defining the Delays to Kidney Transplant among American Indian Patients with Kidney Disease
Mira T. Koddis,1 Munecb Ilyas,2 Nan Zhang,3 Raymond L. Heilman,1 Amit Sharma.1

1 Mayo Clinic, Phoenix, AZ; 2 Mayo Clinic Arizona, Scottsdale, AZ; 3 None, Phoenix, AZ.

Background: The purpose of this study is to examine differences in the time from kidney transplant (KTx) evaluation to wait-listing and KTx rates in a cohort of American Indian (AI) patients compared to whites from 2012 to 2016 at a single center.

Methods: All AI patients presenting for KTx evaluation at Mayo Clinic Arizona from 2012 to 2016 were included (n=300). A random sample of non-Hispanic white controls matched for year of KTx evaluation was included (n=300).

Results: Compared to white controls, AI patients were younger (mean age 53±12.2 vs 57.2±13.4 years, p<0.0001), more likely to have diabetes (79 vs 41%, p<0.0001) and diabetic kidney disease (66.3 vs 35.7%, p<0.0001) and require dialysis at the time of evaluation (88 vs 58.3%, p<0.0001). They were more likely to have limited functional capacity at the time of KTx evaluation compared to white controls (55.3 ± 26.6%, p<0.0001). Several socioeconomic variables differed between the two groups with AI patients more likely to have the following associations: less than high school education (24.9 vs 7.3%, p<0.0001), single or widowed (32.6 vs 17.8, p<0.008), and unemployed (81.7 vs 68.7%, p<0.001). There was no difference in the rate of prior history of cardiovascular disease between the two groups. AI patients had significantly lower rates of cancer prior to kidney transplant with a PSA because of the concern that it might delay transplant causing more harm than benefit.

Conclusions: Our data confirm that RTx is able to influence MM from the beginning, and that early elevated iPTH levels at 1st month of RTx may play a role in long-term graft outcome.

TH-PO1000
Impact of Elevated PSA on Time to Kidney Transplant and Mortality in ESRD Patients
Nagaraju Sarabu,1 Nicholas K. Schlitz,2 Donald E. Hricik.1

1 Case Western Reserve University, Cleveland, OH; 2 University Hospitals Case Medical Center, Rocky River, OH.

Background: Conflicting opinions and practices exist about screening for prostate cancer prior to kidney transplant with a PSA because of the concern that it might delay transplant causing more harm than benefit.

Methods: This study included incident male ESRD patients over 45 years from the 1999-2012 United States Renal Data System, linked with Medicare claims data. Our main study variable of interest was elevated prostate specific antigen (PSA) as indicated through an ICD-9-CM diagnosis code. Primary outcomes of interest were time to kidney transplant and mortality. We used propensity score matching to control for selection bias, and Cox proportional hazards models and Kaplan Meier curves to compare the risk between men with elevated and non-elevated PSA.

Results: 2789 of 64307 (4.3%) of the patients had elevated PSA. Figure 1 shows the baseline characteristics of 2789 patients with elevated PSA and 2789 propensity based matched controls. Elevated PSA was associated with lesser mortality (HR:0.66; CI: 0.62-0.70), and did not significantly increase time to transplant (HR: 0.80; CI: 0.80-1.06). Kidney transplant significantly improved survival regardless of the PSA status prior to transplant.

Conclusions: Elevated PSA is not a contraindication for kidney transplant, and therefore should not be delayed.
Baseline characteristics of propensity matched groups

**Methods:** Among the 3029 kidney transplant recipients (KTRs) who were enrolled in a multicenter cohort, we examined the association of pre- and post-transplant serum AlkPhos levels and long-term outcomes in KTRs.

**Results:** Pre-transplant serum AlkPhos ≥ 80 IU/L was associated with a hazard ratio (HR) for graft failure of 1.571 (95% CI 1.146-2.152, P = 0.005) in a fully adjusted model. Death-censored graft failure (DCGF) rate in kidney recipients gradually increased along the increments of AlkPhos. Also, a rise in serum AlkPhos by 40 IU/L during the first 3 months after kidney transplantation was associated with higher rates of DCGF (HR 2.353, 95% CI 1.506-3.676) and higher rates of mortality (HR: 2.733, 95% CI 1.479-5.050). Cox regression models using time-varying AlkPhos for initial 3 months after transplantation demonstrated significant relationships between AlkPhos and DCGF (HR 1.39, 95% CI 1.04-1.84) or mortality (HR 2.14, 95% CI 1.39-3.27).

**Conclusions:** Increased pre- and post-transplant serum AlkPhos and a rise of serum AlkPhos during early period after kidney transplantation is associated with graft failure and mortality in kidney transplant recipients.

**TH-PO1003**

**High-Resolution Digital Analysis of Leukocyte Densities in Early Surveillance Biopsies Significantly Improves Prediction of Kidney Transplant Function after Four Years of Follow-Up**

**Background:** Minor histopathological changes are difficult to quantify by eye. The impact of inflammation on renal allograft survival has been demonstrated in grafts with rejection, and, on a molecular level, also in early surveillance biopsies. We assessed leukocyte abundance in early surveillance biopsies by digital image analysis and analyzed impact on outcome.

**Methods:** In 67 surveillance biopsies six weeks after transplantation a full Banff classification was performed. T cell (CD3), B cell (CD20), macrophage (CD68) and dendritic cell (CD209) densities and CD206 and HLA-DR markers were assessed by digital image analysis (Definiens system).

**Results:** Among the 3029 kidney transplant recipients (KTRs) who were enrolled in a multicenter cohort, we examined the association of pre- and post-transplant serum AlkPhos levels and long-term outcomes in KTRs.

**Conclusion:** Minor histopathological changes are difficult to quantify by eye. The impact of inflammation on renal allograft survival has been demonstrated in grafts with rejection, and, on a molecular level, also in early surveillance biopsies. We assessed leukocyte abundance in early surveillance biopsies by digital image analysis and analyzed impact on outcome.

**Funding:** Government Support - Non-U.S.
Renal Parenchymal Calculcations in a Cohort of Renal Transplanted Patients and Their Correlations with Long Term Graft Outcome

Transplant Recipient Education, Adherence, and Novel Risk Factors for Graft Loss

TH-PO1004

Renal Parenchymal Calculcations in a Cohort of Renal Transplanted Patients and Their Correlations with Long Term Graft Outcome

Carlo M. Allieri, Gabriella Moroni, Donata Cresseri, Anna Regalia, Francesca Zanoni, Valentina Binda, Maria Teresa Gandolfo, Mariarosaria Campise, Paolo Simonini, Masami Ikekata, Maria Meneghini, Piergiorgio Mezzapelle, Fondazione IRCCS Ca’ Granda Ospedale Poliambulante, Milan, Milan, Italy.

Background: Renal calculcations(RC) have been described in kidney transplantation(KTx), but the aetiology and significance of this finding are still unclear. Our aim is to evaluate the prevalence an the clinical impact on long term graft prognosis of RC.

Methods: 95 KTxs pts, submitted to renal biopsy(RBxs) on clinical indication from 2009 to 2012 were followed up until 2016(FU time:5-46yrs). Clinical and biochemical data were collected at the time of RBx(TBX),12mth before(T-12) and after(T+12) the RBx. Exposition to Ca, P and PTH during the year before RBx was calculated by averages of the observed values. In yrs after T+12(Tu), creatinine, Ca, P, PTH, ALP, Prot-U were recorded annually and analyzed as averages of observed values. RBxs were studied for general histology and for RC by Von Kossa(VK) staining. In pts with more than 1 RBx, only the 1st one was considered. Pts in which VK was negative or slight positive were defined as group1(VK-1:68,46 slightly positive), while pts with moderate or severe VK positivity were included in group2(VK-2:27,8 high VK positive).

Results: The pts were 51 males and 44 females, age 50±12 yrs. VK groups did not differ for gender, age, type of KTxs, VK-2 had longer time of KTxp(p=0.03). At T-12, TBx and T+12, renal function was similar between the groups. No differences were found in minerals metabolism(MM) at TBx, while VK-2 had a lower exposition to PTH during the year before RBx(p=0.001). VK-2 had higher glomerulosclerosis(GS;p=0.04). During Tu, VK-2 pts had worst st(Crp=0.04) higher PTH and ALP(p=0.03±0.02). 33 pts have lost their graft during the F-U time, with a higher prevalence in VK-2(p=0.0006). By means of Cox regression and Kaplan Meier analysis belonging to VK-2 was the strongest independent parameter related to graft loss (HR=3.49–p=0.001; K-M p<0.0001).

Conclusions: The prevalence of RC in RBxs is quite high. RC correlated with PTH exposition during the year before RBx, but not with Ca and P levels. Time of KTx and GS were also related to RC, assigning to RC a significance of chronic damage rather than a simply result of MM imbalance, at least in the RBx performed on clinical indication. A relation between VK positivity at TBx and long term graft loss was also found.

TH-PO1005

Dynamics of DNA Methylation in Renal Allograft: From Early Ischemia/Reperfusion Injury to Late Fibrosis Response

Sai Vinella Bondha, Valeria Mas. University of Virginia, Charlottesville, VA.

Background: The mechanisms of development of fibrosis post-transplantation are not completely understood. Early graft insults like ischemia/reperfusion injury followed by course of its response/repair may involve changes in molecular determinants including DNA methylation (DNAm) which influence long term allograft function. In the current study we assessed the dynamics of DNAm across 1) pre-implant biopsies post-ischemic injury (PI) 2) post-reperfusion (PR) and 3) >24 months post kidney transplantation (KT).

Methods: Infinium 450K methylation (n = 96) and gene expression (n = 182) arrays were performed in PI, PR and KT renal allograft biopsies and analyzed. Genome runner was used to assess distribution and enrichment of Dme CpGs along regulatory features. Integrative analyses of differentially methylated (Dme) CpGs and corresponding differential gene expression were performed at each matched time points.

Results: PI allografts classified based on progression to allograft dysfunction showed 1,185 Dme CpGs mapped to genes involved in inflammation and metabolism. When paired PI and PR allografts were compared there was apparent change in DNAm of genes involved in pathways like Nrf2 mediated oxidative stress response and functions like cellular assembly and organization, cell death and survival. Integration analysis showed Dme expression of genes involved in energy metabolism, transporters and transcription factors important in regulation of immune response. Further, comparison of post-KT allografts with different outcomes revealed 21,351 Dme CpG sites. The Dme CpGs observed at early time points were mostly hypomethylated and promoter associated. Heat map and box plot were used to represent the pattern was observed in later stages. Dme CpGs were interestingly dysregulated at different molecular levels.

Funding: NIDDK Support

TH-PO1006

Investigating Angiotensin II-Regulated Proteins as Biomarkers of Fibrosis in Kidney Transplant Recipients

Zahra Mohammed-Ali,1 Shelby Reid,2 Tomas Tokar,3 Paul M. Yip,4 Alexandre Tavares-Brum,1 Heloise Cardinal,1 Joseph Kim,2 Ana Konvalinka.3 Centre Hospitalier de l’Université de Montréal, Montréal, QC, Canada; 1Institute of Medical Science, University of Toronto, Toronto, ON, Canada; 2Toronto General Hospital, University Health Network, Toronto, ON, Canada; 3University Health Network, Toronto, ON, Canada; 4University Health Network, University of Toronto, Toronto, ON, Canada.

Background: Angiotensin II, the main effector of the renin-angiotensin system (RAS), causes kidney interstitial fibrosis/tubular atrophy (IFTA). However, specific markers of kidney AngII activity remain unknown. Here we report on the urine excretion of 6 AngII-regulated proteins (BST1, GLNA, LAMB2, LYPLA1, RHOB and TSP1), and show that 1) they reflect IFTA in kidney transplant recipients; 2) they are modified by RAS inhibition.

Methods: A previously developed mass spectrometry-based assay was used to quantify 6 AngII-regulated proteins in urine of 2 cohorts of kidney transplant recipients from a single Canadian centre: 1) 19 patients with IFTA and 19 stable controls with concomitant urine and biopsy samples; and 2) 20 patients with urine and biopsy samples before and after RAS inhibition. Differences in creatinine-adjusted urine levels of AngII-regulated proteins between IFTA and control patients were assessed using two-tailed t-test. Correlations between AngII-regulated proteins and traditional markers of kidney graft function were evaluated using Spearman’s rank correlation. Fixed-effects model was used to assess changes in AngII-regulated proteins following RAS therapy.

Results: Urine excretion of all AngII-regulated proteins was significantly higher in IFTA compared to control (In fmol/mg of creatinine ± SD, BST1: 17.4±6.5 vs 9.7±6.0, p=0.01; GLNA: 9.7±3.0±1 vs 1.6±2.7, p=0.001; LAMB2: 90.2±22.9 vs 54.0±15.5, p=0.03; LYPLA1: 6.6±1.7 vs 2.1±3.0, p=0.002; RHOB: 9.02±3.4 vs 1.10±3.3, p=0.004; TSP1: 8.05±6.81 vs 3.47±0.16, p=0.002). These proteins correctly separated IFTA and control patients in unsupervised hierarchical clustering analysis. Urine excretion of all AngII-regulated proteins correlated with each other, but not with serum creatinine and total urine protein. All AngII-regulated proteins negatively correlated with IFTA receiver operator curve (area under curve = 0.92, fixed effects coefficient=0); however, GLNA and TSP-1 were most significantly decreased (p<0.05).

Conclusions: Urine excretion of AngII-regulated proteins was significantly increased in patients with IFTA and was modified by RAS inhibition. These proteins may represent novel markers of kidney fibrosis, and may be valuable in guidance therapy with RAS inhibitors.

Funding: Government Support - Non-U.S.

TH-PO1007

Clinical and Histologic Review of Transplant Nephrectomy Cases in a Single Center

Soo Ya Baek,1 Chung Hee Baek,2 Su-Kil Park.2 1Asan Medical Center, Seoul, Republic of Korea; 2Asan Medical Center, Songpa-gu, Seoul, Republic of Korea.

Background: Despite advancement in the management of kidney allograft, several indications for transplant nephrectomy still exists. Chronic allograft intolerance syndrome is the most common reason of transplant nephrectomy (TN). Recent studies reported antibody mediated rejection (ABMR) plays an important role in chronic allograft injury and subsequent graft failure. There is few studies about histopathology of TN, resulting lack of knowledge about predominant type of rejection resulting chronic allograft intolerance syndrome. We investigated clinical indications and histologic diagnosis of TN cases, especially the type of rejection.

Methods: From January 1995 to March 2016, 96 cases of TN were done in Asan Medical Center. We reviewed 88 cases of TN for baseline clinical characteristics, clinical indication of TN and histologic diagnosis after TN.

Results: Most common cause of end stage renal disease (ESRD) were primary glomerular nephritis (23.9 %) and hypertension (23.9 %). Most common clinical indication of TN was chronic allograft intolerance syndrome (43.3%). Rejection was the most common histologic diagnosis of TN (73.1%), of chronic allograft intolerance syndrome cases either (92.1%). Among 24 rejection cases diagnosed by Banff 2007, 13 cases were T cell mediated rejection (TCMR), and 10 cases were mixed rejection. Among 10 rejection cases by Banff 2013, 2 cases were TCMR, and 8 cases were mixed rejection. Among 14 cases of chronic allograft intolerance syndrome by Banff 2007 and 2013 classifications, 6 cases were TCMR, and 8 cases were mixed rejection. 9 cases showed discrepancies between clinical indication and histologic diagnosis (10.2 %), 7 cases showed discrepancies in the type of rejection (8.0 %).

Conclusions: Chronic allograft intolerance syndrome was the leading clinical indication for TN, and rejection was the most common histologic diagnosis. By Banff 2007 and 2013 classifications, pure TCMR and mixed rejection cases were predominant. These discrepancies between clinical indication and histologic diagnosis existed, with discrepancies in the type of rejection as well.
**TH-PO1008**

Uncovering the Association between Early Histological Features of Diabetic Kidney Disease and Renal Allograft Outcomes

**Background:** Diabetes Mellitus is a risk factor for worse renal allograft survival, but patients typically do not lose their allograft due to diabetic kidney disease (DKD). However, it remains unclear whether early diabetic changes in the transplanted kidney are associated with worse outcomes. The objective of this pilot study is to determine whether histological features consistent with early DKD are predictive of subsequent graft loss.

**Methods:** We reviewed consecutive, clinically indicated, renal allograft biopsies performed at Stony Brook University Hospital from 2010 to 2015. Biopsies with either mesangial matrix expansion (MME) or thickened basement membrane (TBM) were classified as early DKD (eDKD). Patients with a final diagnosis of transplant glomerulopathy (TG) or overt DKD were excluded. Graft failure, creatinine, and eGFR were also collected at 6 months, 1 year, and 2 years post-biopsy. All data was assessed for normality, and then parametric or non-parametric tests were employed for data analysis.

**Results:** In total, 247 renal transplant biopsies were reviewed. Biopsies were performed at a mean of 3.98 ± 0.93 years post-transplantation. In total, 83 were excluded for either overt DKD or TG. Of the remaining 164 biopsies, 89 (54.2%) were classified as eDKD and the rest (45.7%) as non-diabetic kidney disease (N DKD). Baseline demographics for the two groups are in Table 1. Mean HbA1C was 6.0 ± 0.1% in the eDKD group and 6.2 ± 0.2% in the NDKD group. In all, 25/89 (28.1%) patients in the eDKD had graft failure at a mean of 0.9 years post biopsy, as compared with 16/75 (21.3%) patients in the N DKD group (p= 0.368).

**Conclusions:** In this small cohort, these data suggest there is a trend towards worse renal allograft outcomes in patients with early histological features of DKD. Further analysis of eGFR trends and a larger sample size are required to determine the significance of early DKD changes on allograft outcomes.

**Table 1**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>N</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>at time of transplant</td>
<td>45.8 ± 1.8</td>
<td>0.687</td>
</tr>
<tr>
<td>at time of biopsy</td>
<td>49.4 ± 1.7</td>
<td>0.297</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>48.5%</td>
<td>41.6%</td>
</tr>
<tr>
<td>Female</td>
<td>51.5%</td>
<td>48.4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Race</th>
<th>Caucasian</th>
<th>Black</th>
<th>Hispanic</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>57.3%</td>
<td>19.1%</td>
<td>11.2%</td>
<td>12.2%</td>
</tr>
<tr>
<td>Black</td>
<td>46.7%</td>
<td>22.7%</td>
<td>8.0%</td>
<td>22.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Average HbA1c</th>
<th>6.0 ± 0.1%</th>
<th>6.2 ± 0.2%</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allograft Failure</td>
<td>28.1%</td>
<td>21.3%</td>
<td>0.369</td>
</tr>
</tbody>
</table>

**TH-PO1009**

The Association of Calcium Oxalate Deposition in Kidney Allografts with Graft and Patient Survival

**Background:** Oxalate is a dicarboxylic anion that can precipitate with calcium and cause kidney injury. Patients with end-stage renal disease (ESRD) have elevated plasma levels of oxalate. After kidney transplantation (Tx), hyperuricemia ensues, increasing risk of calcium oxalate deposition (CaOxD) in the allograft. Few studies have examined risk factors for CaOxD in this setting and its association with patient outcomes.

**Methods:** We performed a retrospective cohort study of patients who had allograft biopsies at our hospital within 3 months of Tx, from 10/1999–2/2015. The presence or absence of CaOxD was extracted from biopsy reports. We determined risk factors for CaOxD and evaluated its association with the composite outcome of graft failure or death at 2 years.

**Results:** Of 346 patients, 68 had CaOxD in allograft biopsies. Factors associated with CaOxD in multivariable models adjusting for serum calcium, black race and donor type (living vs. deceased) were: dialysis vintage (odds ratio (OR) 1.15, 95% CI 1.01-1.30 per additional year), diabetes (OR 2.67, 95% CI 1.26-5.63) and elevated serum creatinine at the time of biopsy (OR 1.31, 95% CI 1.16-1.48 per additional mg/dL). After further adjusting for delayed graft function (DGF), these associations became non-significant with only DGF remaining a significant predictor of CaOxD. CaOxD was associated with 2.56-fold (OR 2.56) increased odds of graft failure or death at 2 years in a multivariable model adjusted for black race, donor type, dialysis vintage and acute rejection. After adjusting for DGF, the association between CaOxD and graft failure or mortality became non-significant (OR 1.56, 95% CI 0.68-3.57).

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

Underline represents presenting author.

356

**TH-PO1101**

Dynamic Creatinine Clearance Calculation Enables Early Assessment of Kidney Function and Advances Detection of Functional Decline After Renal Transplantation

**Background:** Immediately after renal transplantation (RTx), graft function can be compromised for which early intervention can be crucial. However, the rapid fall
in plasma creatinine concentration immediately after RTX can conceal graft function decline. We present a strategy to estimate creatinine clearance ($C_Cr$) immediately after RTX and advance detection of functional decline.

**Methods:** $C_Cr$ was derived from 2 subsequent plasma creatinine levels over time using a newly developed method for Dynamic Creatinine Clearance Calculation (D3C) (Fig1A). We estimated $C_Cr$ one day (T1) after RTX by D3C and correlated this to the estimated $C_Cr$, using CG at T12 in 154 uncoupled RTX patients. We also investigated whether monitoring of D3C could advance detection of functional decline in patients with early rejection.

**Results:** Average plasma creatinine at T1 was 350±204µM and 155±75µM at T12. D3C at T1 was 50±22m/min whereas CG estimated $C_Cr$ was 59±21m/min at T12. D3C at T1 correlated to GC estimated $C_Cr$ at T12 (R=0.741, R²=54.9%, p<0.000) (Fig1B), improving upon plasma creatinine correlation at T1 and T12 (R=0.661, R²=43.7%, p=0.000). Detection of functional decline was advanced by identifying a decrease in $C_Cr$ over time as compared to an increase in plasma creatinine concentration over time. This is illustrated by 2 patients with biopsy proven rejection (Fig1C,D) and 2 uncomplicated transplantations (Fig1E,F).

**Conclusions:** One day after RTX D3C significantly correlates to CG estimated $C_Cr$ at T12 in uncoupled RTX patients. Moreover, monitoring of renal function using D3C after RTX advances detection of functional decline on average by 2 days, expediting therapeutic intervention and conceivably improving clinical outcome.

Figure 1A-F

**TH-PO1012**

Proposal of a Score to Predict Outcome of Deceased Donor Renal Transplantation

Carlos Rafael A. Felipe,1 Andre S. Alvarenga,1 Silvana Maria C. Miranda,1 Gerson M. Pereira Jr,2 Pedro Augusto M. Souza,2 Izabela L. Piana,2 Ana elisa S. Jorge,1 Hospital Santa Casa de Belo Horizonte, Belo Horizonte, Brazil; 3Santa Casa de Belo Horizonte, Belo Horizonte, Brazil; 4Faculdade de Minas Faminas BH, Belo Horizonte, Brazil.

**Background:** Kidney Donor Profile Index (KPDI) correlated with graft loss and death. However, patients with kidneys and the same KPDI may have different outcomes.

**Methods:** We developed a score system based on data of 113 deceased donor renal transplants (DDRT) from 01/2013 to 02/2016: mean age 50.7 years; mean cold ischemia time was 13.4 ± 9.3 hours; 62% presented delayed graft function. The mean of the KDPI was 53.5%. The score was calculated assigning one point for KDPI ≥ 70, 0% serum creatinine ≥ 2.0mg/dL and donor age ≥ 50 years (table 1). Patients were divided in 4 groups according to the sum of points (0, 1, 2, 3 points) and graft survival was evaluated for each group.

**Results:** Distribution of patients by points categories: 0 points - 47.8%; 1 point - 27.4%; 2 points - 19.5%; 3 points - 5.3%. One year graft survival was 88.4% for 0 points, 73.6% for 1 point (p = 0.0735 vs 0 pts), 61.5% for 2 points (p = 0.0076 vs 0 pts) and 0% for 3 points (p <0.0001 vs 0 pts). Combining kidneys with a score of 0 and 1 point, 1-year graft survival was 82.9%, significantly higher than kidneys with 2 points (p = 0.0068) and 3 points (p <0.0011) (figure 1).

**Conclusions:** Kidneys with 0 or 1 point had better survival, being acceptable for most transplant candidates. Kidneys with 2 points presented intermediate survival, and may be more suitable for candidates with a low expectation of obtaining a better graft in a timely manner. None of the 6 recipients who received 3-point kidneys had a functioning graft after 1 year, raising serious concerns about the acceptability of these organs.
Transplant Recipient Education, Adherence, and Novel Risk Factors for Graft Loss

Transplantation in later years had lower hazards of death (for various causes) compared to patients who underwent transplant prior to 1996 (Figure 2).

Conclusions: In this national registry of kidney transplant population, cause of death is unknown for substantial proportion of patients dying with functioning allografts. Risk for deaths due to cardiovascular disease and other causes have decreased over time.

TH-PO979

Correlation of Pre Kidney Transplant Psychosocial Factors with Post-Transplant Kidney Graft Survival

Background: Pretransplant psychosocial and nutritional factors are important aspects of kidney transplant evaluation as they may be associated with post-transplant outcomes; however there is scant data on this topic. The aim of the study was to determine the correlations between pretransplant, nonclinical and psychosocial factors to post-transplant kidney allograft survival.

Methods: We selected the following pre-transplant factors: race, gender, food stamp, marital relationship, family support, income status, insurance, education, Karnofsky score, history of depression, active clinical follow up, dialysis compliance, serum albumin level, history of substance abuse, distance from transplant center etc. One year kidney allograft survival was selected as an outcome. The study involved retrospective analysis of 131 kidney transplant patients. There were 56 female patients and 75 male patients. There were 72 Hispanics (53%), 33 African Americans (24%), 22 Whites (16%), 9 Asians (7%). Patients age ranged from 25 years to 77 years. Nominal logistic regression analysis and multinomical logistic regression analysis were used to identify the significant relationship between one dependent nominal variable and one or more continuous-level independent variables. A p-value of ≤0.05 was considered significant.

Results: Female gender (p = 0.02), active pre listing clinic follow up (p = 0.04), stronger immediate family support (p = 0.06), proximity to primary transplant center (p = 0.0012), pre transplant national status as evidenced by serum albumin >3.5 gm/dl, was associated with a better one year graft survival, however food stamps status (p = 0.004), repeat transplant status (p = 0.05) was associated with poor allograft survival. Remaining variable’s did not show a significant relationship.

Conclusions: Pretransplant psychosocial assessment is an important component of kidney transplant work up as it is associated with one year kidney allograft survival. More studies are needed to confirm our findings.

TH-PO980

Health Literacy and Inequity in Access to Transplantation: Results from the ATTOM Study

Background: Access to kidney transplantation is reduced among people with low socioeconomic status, a component of which is low educational level. Transplant preparation requires patients to understand complex concepts, demanding adequate health literacy (HL). In the Access to Transplant and Transplant Outcome Measures (ATTOM) study, low HL was associated with low educational level and was more common in incident dialysis patients compared to wait-listed or transplanted patients. We hypothesised that HL mediates the association between low educational level and reduced access to transplantation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Methods: ATTOM recruited UK incident dialysis patients, 2011-13. Data collected included: exposure (no educational qualifications vs any), outcomes (time to transplant wait listing/time to live donor transplant censored at 2 years), the mediator (HL, defined by ‘Single Item Literacy Screener’ on a five-point scale, 5 indicating lowest HL), and covariates (age, ethnicity, comorbidity by Charlson index). Structural Equation Modelling was used to calculate effect sizes for the exposure on the mediator, the mediator on the outcome and the exposure on the outcome, adjusted for the covariates. From these, the total effect of education on access to transplant and the indirect effect mediated by HL were calculated. Weibull AFT models were used and effect size expressed as time-to-event ratio (TR). p<0.05 was deemed significant. 

Results: 2463 of 2621 recruited patients responded to the SILS, and were included. A 1-point increase in HL score was independently associated with 15% increased time to wait listing (TR 1.15;95% CI 1.07-1.25) and 25% increased time to live donor transplant (TR 1.47;95% CI 1.06-1.47). In the mediation model, the total effect of low educational level was to increase time to wait listing by 22% (TR 1.22;95% CI 1.02-1.48) and time to live donor transplant by 47% (TR 1.47;95% CI 1.04-2.08). The indirect effect mediated by HL accounted for 35% of the increase in time to wait listing and 30% of the increase in time to live donor transplant.

Conclusions: In this large UK cohort study, HL mediated a substantial proportion of the effect of low educational level on reduced access to deceased-donor transplant wait listing and live donor transplantation. Interventions to improve patients’ understanding of the transplantation process have potential to reduce socioeconomic inequity in access to transplantation.


TH-PO981

Effectiveness of iChoose Kidney Decision Aid on Kidney Transplant Knowledge
Rachel E. Patzer, Laura J. McPherson, Mohua Basu, Sumit Mohan, Stephen O. Pastan. 1 Columbia University, New York, NY; 2Emory University, Atlanta, GA; 3None, Peachtree City, GA.

Background: We developed a shared mobile decision aid (iChoose Kidney) that displays individualized risk estimates of survival and mortality for dialysis vs. kidney transplant for patients with end-stage renal disease (ESRD). We examined whether use of iChoose Kidney was associated with improved gains in transplant knowledge.

Methods: In a randomized controlled trial, 470 patients at 3 centers were randomized to receive education with (intervention) or without (standard of care) iChoose Kidney during their transplant evaluation. Patients completed surveys immediately before and after evaluation and gain in transplant knowledge (9 item scale) from pre- to post-education was calculated by subtracting mean pre-survey from post-survey scores. Knowledge gains were assessed by study group and by race, health literacy and numeracy levels.

Results: Among 443 patients completing both surveys, mean age was 51 years, with 63% male, and 48% black. The mean pre- and post-education transplant knowledge scores were 5.1 ± 2.1 and 5.8 ± 1.9, respectively, with a median difference of 0.7 ± 1.7 points. Change in knowledge during the visit was significantly greater among iChoose (1.0 ± 1.8) vs. control (0.3 ± 1.4) for all patients (p<0.0001) (Figure 1) as well as for black (1.1 ± 1.7 vs. 0.4 ± 1.4; p=0.04) and white (1.5 ± 1.8 vs. 0.2 ± 1.9; p=0.003) patients. Intervention (vs. control) patients with moderate (1.2 ± 1.7 vs. 0.4 ± 1.1; p=0.02) and high (1.0 ± 1.8 vs. 0.2 ± 1.5; p=0.001) literacy and moderate (1.3 ± 1.9 vs. 0.2 ± 1.4; p<0.0001) and high numeracy (0.8 ± 1.4 vs. 0.2 ± 1.1; p=0.02) benefited most from the tool; while patients with low literacy (1.0 ± 1.9 vs. 0.7 ± 1.4; p=0.41) and low numeracy (1.0 ± 1.9 vs. 0.7 ± 1.6; p=0.39) had non-significant improvements.

Conclusions: The iChoose Kidney decision aid was effective in improving ESRD patient transplant knowledge among patients undergoing transplant evaluation. Similar, shared decision aids could help clinicians better inform patients about transplant.

Funding: Private Foundation Support

TH-PO982

Impacts of Options Education on Modality Choice in Incident ESRD Patients
Yue Jiao, Marta Reviriego-Mendoza, John W. Larkin, Rob Lynch, Len A. Usvyat, Jeffrey L. Hymes, Franklin W. Maddux. Fresenius Medical Care North America, Waltham, MA.

Background: Dialysis education programs that teach chronic kidney disease (CKD) patients about their renal replacement therapy (RRT) options may help patients to make informed decisions. The impact of educational programs on kidney modality choice remains unclear.

Methods: We analyzed the impacts of an options educational program on incident modality choice for hemodialysis (HD), peritoneal dialysis (PD), or transplant in patients who progressed to ESRD.

Results: For this analysis, we collected data from Fresenius Kidney Care (FKC) patients who progressed to ESRD between 2009 and 2016. Patients were categorized into groups depending on whether they received options education and if they started dialysis as outpatient or inpatient. We determined the annual percentage of ESRD patients that initiated RRT by modality choice (HD, PD, or transplant) in the first 170 days of RRT.

Results: A total of 300,818 patients who progressed to ESRD and initiated a RRT were included in the study; 68,721 patients received options education. In 2016, education prior starting RRT was associated with more patients (1 percentage point) receiving transplant in the first 120 days of RRT, as compared to those without options education. Concurrently, in patients who received options education and started with outpatient dialysis for RRT, there were 16 percentage points more who utilized PD and 17 percentage points less treated by HD when compared to patients without options education. In patients who received options education and started dialysis as an inpatient in 2016, there were 3 percentage points more who were treated with PD and 2 percentage points less treated by HD when compared to patients without options education. Similar findings were observed in during every year in the study period.

Conclusions: These findings suggest that options education prior starting RRT may lead to a higher proportion of patients choosing a transplant or home dialysis when progressing to ESRD. Further analysis is needed to confirm these findings.

Funding: Commercial Support - Fresenius Medical Care North America

TH-PO983

Experiences of Kidney Transplant Recipients as Patient Navigators
Anne M. Huml, Catherine M. Sullivan, Adam T. Perzynski, Kitty V. Barnswell, Kate A. Greenway, Cindy Kamps, Marquisha Marbury, Julie A. Pencak, Derrick L. Wilson, Jacqueline Dolata, Ashwini Sehgal, Comprehensive Transplant Center; The Ohio State University Wexner Medical Center, Columbus, OH; 2Lutheran Hospital Kidney Transplant Center, Fort Wayne, IN; 3MetroHealth Medical Center, Cleveland, OH; 4University Of Louisville, Louisville, KY; 5University of Kentucky, Richmond, KY; 6Center for Reducing Health Disparities, Division of Nephrology, Case Western Reserve University, Cleveland, OH.

Background: The use of trained kidney transplant recipients as patient navigators resulted in increased completion in steps in the transplant process by dialysis patients (1). We sought to understand the experiences of these patient navigators.

Methods: Six kidney transplant recipients were hired and engaged by transplant centers in Cleveland, OH, Columbus, OH, Fort Wayne, IN, Lexington, KY, and Louisville, KY. The transplant navigators received formal training as peer educators, met with dialysis patients on a regular basis, and provided tailored education and assistance about transplantation to each patient. In addition, they worked closely with the pre-transplant coordinators and social workers to learn the details of each patient’s transplant work-up. We queried navigators using open-ended questions delivered by email to learn about their experiences. We used qualitative analyses to compile and code navigator responses and categorize common themes. A thematic auditor reviewed and refined the coding.

Results: Two primary categories of themes emerged from the data about the navigator experience: 1) practical comments that supported programmatic or implementation outcomes of the navigator role, and 2) affective comments that reflected a shared experience among the navigators and the patients. The navigators were able to fill voids in the transplantation and dialysis care process that were not fulfilled by other dialysis caregivers. This was accomplished by a natural bond based upon a shared experience of dialysis (and kidney failure) between the navigator and the patient. The patient and navigator effectively were experiential partners.


TH-PO984

Patient and Provider Perceptions of Medication Safety Issues in Adult Kidney Transplant Recipients
Basbir Hamid, David J. Taber. Medical University of South Carolina, Charleston, SC.

Background: Medication safety adverse events (AEs), which include non-adherence to drug regimens and adverse drug events, are associated with graft loss following transplantation. Although kidney transplant recipients are considered high-risk for developing these issues, there are limited studies analyzing long-term patient and provider perceptions of medication safety issues in this population.

Methods: This was a prospective, cross-sectional study of 176 stable kidney transplant recipients which assessed patient self-reported medication adherence and adverse drug events through surveys and compared these to blinded provider assessments occurring during a coinciding routine clinic visit.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: In the 176 patients, self-reported medication adherence was 38%, 45%, and 73% in low, medium, and high categories, as measured by a validated survey. AEIs were common, with 96% of patients reporting at least one and a mean of 5.9 AEIs per patient-visit across the entire study population. Self-reported AE burden was significantly correlated with medication non-adherence with a one unit increase in self-reported AE burden (measured by the validated Memphis score) increasing the odds of patients being in a lower adherence category by a factor of 1.35 (CI 1.13 to 1.62, P=0.001). The analysis of clinical assessments revealed that providers only assessed 49% of patients to have at least one AE, with a mean count of 0.8 per patient-visit. Patient self-reported AE burden had a weak positive correlation (Kendall tau= 0.15, P=0.008) with providers’ assessment of patient AEIs during routine visits.

Conclusions: These results indicate a significant relationship between AE burden and medication adherence in kidney transplantation. Further, providers tended to under-assess medication AEIs during routine clinic visits, when compared to patient assessments. Improving recognition and management of AEIs in kidney transplant recipients may impact medication adherence.

Funding: NIDDK Support

TH-PO987
Cannabis Dependence or Abuse before and after Kidney Transplantation: Implications for Post-Transplant Outcomes

Krista L. Lentz,1
Tarek Alhamad,2 Nga Lam,3 Ahbiijit S. Naik,4 Farrukh M. Koraishty,5 David A. Axelrod,2 Dorry L. Segev,3 Vikas R. Dharidurkar,6 Daniel C. Brennan,7 Mark Schnitzler,8 Johns Hopkins University, Baltimore, MD; 9Lahey Hospital and Clinic, Burlington, MA; 10None, Ann Arbor, MI; 11Saint Louis Univ, St Louis, MO; 12Saint Louis University, Saint Louis, MO; 13Saint Louis University, St. Louis, MO; 14University of Alberta, Edmonton, AB, Canada; 15Washington University School of Medicine, St Louis, MO; 16Washington University School in St. Louis, MO.

Background: Currently, transplant centers vary in screening practices for marijuana use and requirements for abstinence in kidney transplant (KTx) recipients.

Methods: We examined billing claims for 52,689 Medicare-insured KTx recipients to identify diagnoses of cannabis dependence or abuse (CDOA, International Classification of Diseases-9 diagnosis codes 304.3, 305.2) in the year before and after KTx. Associations of CDOA with post-KTx death and graft failure (adjusted hazard ratio, 95% CI, aHR 95% CI) were quantified by multivariate Cox regression including adjustment for recipient, donor and transplant factors, and propensity for CDOA.

Results: CDOA diagnoses were uncommon, found in 0.5% and 0.3% in the year before and after KTx, respectively. The likelihood of CDOA diagnosis before and after KTx declined with older recipient age, and was increased in men, African Americans, those with less than a college education and unemployed patients. After multivariate and propensity adjustment, CDOA in the year before KTx was not associated with increased risk of death or graft survival in the year after KTx (Fig 1A). However, CDOA in the first year post-KTx was associated with three-times the risk of death-censored graft failure (aHR, 1.72, 95% CI 1.29-2.29) and 2.5-times the risk of all-cause graft loss (aHR, 1.59, 95% CI 1.25-2.02) in the subsequent year (Fig 1B).

Conclusions: Diagnoses of CDOA are uncommon among KTx recipients, and likely reflect in part associated characteristics or conditions, clinical diagnosis of CDOA in the year after transplant appears to have prognostic importance for subsequent allograft survival.

Funding: NIDDK Support
**TH-PO988**

**Prescription Opioid before and after Kidney Transplant**

Ngan Lam, Krista L. Lentine, Zidong Zhang, Dorry L. Segev, Vikas R. Dharnidharka, Gregory P. Hess, Radhika Devraj, Bertram L. Kasiski, Daniel C. Brennan, Mark Schnitzler, Hennepin County Medical Center, Minneapolis, MN; Johns Hopkins University, Baltimore, MD; LDI University of Pennsylvania/IMS, Plymouth Meeting, PA; Saint Louis Univ, St Louis, MO; Saint Louis University, St. Louis, MO; Southern Illinois University Edwardsville, Edwardsville, IL; University of Alberta, Edmonton, AB, Canada; Washington University School of Medicine, St Louis, MO; Washington University in St. Louis, St. Louis, MO.

**Background:** An evolving body of literature suggests the epidemic of prescription opioid use has impacted transplant population.

**Methods:** We examined a novel database wherein national U.S. transplant registry identifiers were linked to records from a large pharmaceutical claims warehouse (2008 to 2015) to characterize antidepressant use before and after kidney transplantation, and associations (adjusted hazard ratios, 95% CIs) with death and graft failure.

**Results:** Among 75,430 eligible patients, 43.1% filled opioids in the year before kidney transplantation, and use was more common among recipients who were women, white, unemployed, publicly insured, and those with longer pre-transplant dialysis. The majority of recipients (60%) with the highest level of pre-transplant opioid use continued opioid use, with the highest level use predicting 45% increased risk of death (aHR 1.28) and 28% increased risk of all-cause graft failure (aHR 1.61), compared to no use. Level 1 opioid use associated with 1.2% increased risk of death (aHR 1.00) and 1.45% increased risk of all-cause graft failure (aHR 1.01) over the subsequent year.

**Conclusions:** While associations may, in part, reflect underlying conditions or behaviors, opioid use history appears relevant in assessing and providing care to transplant candidates and recipients.

**Funding:** NIDDK Support

---

**TH-PO989**

**Provision of Highly Specialized Aftercare by the Transplant Center Strongly Improves Patient and Allograft Survival in Long-Term Follow-Up After Kidney Transplantation**

Thomas Schachtner, Natalie M. Otto, Petra Reinke, Charité Campus Virchow Clinic, Berlin, Germany; Charité Berlin, Berlin, Germany; Charité, Campus Virchow Klinikum, Berlin, Germany.

**Background:** Despite rapid medical advancements in the field of transplantation, mean kidney allograft survival remained at a standstill. If and to what extent a highly specialized and experienced aftercare of kidney transplant recipients (KTRs) impacts patient and allograft outcomes in long-term follow-up, however, remains mostly unknown.

**Methods:** We retrospectively analyzed 1328 KTRs between 1998 and 2015 with respect to patient and allograft survival. KTRs treated regularly in our transplant center in long-term follow-up were compared with KTRs followed by local nephrologists and general practitioners. KTRs that make no use of the transplant center provided aftercare, were assessed by a questionnaire-based survey with respect to allograft survival and their reasons not to make use of it.

**Results:** In total 824 KTRs (62.0%) were followed in our transplant center and 504 KTRs (38.0%) were followed by local nephrologists. Multivariate analysis identified shorter distance to the transplant center (p<0.001), living donation (p<0.001), early registration to the waiting list (p=0.009), and shorter initial hospital stay (p=0.004) as independent factors for strong adherence to the transplant center. KTRs followed in our transplant center showed significantly better patient (72.7% vs. 50.4% after 15 years; p=0.001) and death-censored allograft survival (85.0% vs. 64.4% after 15 years; p=0.001) compared to KTRs followed by local nephrologists. These differences were equally observed in deceased and living donation. Reasons not to make use of the transplant center provided aftercare included distance (47%), prohibitive expensive costs (37%), no identifiable advantages (34%), and negative experiences (7%).

**Conclusions:** Our data strongly indicate that provision of aftercare by the transplant center is highly associated with superior patient and allograft survival. The observed wide differences may be attributed to highly specialized screening protocols, careful and critical guidance of immunosuppression, and more comprehensive medical care. Despite long distances, transplant centers, local nephrologists, and health insurances must encourage patients to make use of transplant center provided aftercare.

---

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

Underline represents presenting author.
TH-PO990

The Impact of Donor BMI on Outcomes after Deceased Kidney Transplantation
Adam Ashraf, Imogen Chappelow, James Hodson, Andrew Ready, Jay Nath, Adnan Shafii; Queen Elizabeth Hospital, Birmingham, Birmingham, United Kingdom; University Hospital Birmingham, Birmingham, United Kingdom; University Hospital Birmingham, Birmingham, United Kingdom; University of Birmingham, Stoke on Trent, United Kingdom; University Hospital Birmingham NHS Trust, Biostatistics, Birmingham, United Kingdom.

Background: The shortfalls of available donor organs means we must reconsider our current policies on donor selection. There is variation in practice between centres as to the acceptable limit to donor BMI in deceased kidney transplantation, with no recommendations in American or UK guidelines.

Methods: Data from the UK National Health Service Blood and Transplantation register was analysed for all patients receiving deceased donor kidney transplants (Jan 2003 - Jan 2015). Transplants were separated into 5 categories depending on the donor’s body mass index (BMI) (kg/m²): 18.50 – 25.00 (normal), 25.01 – 30.00 (obese), > 30.00 kg/m² in 2503 and > 35.00 kg/m² in 1148. On multivariable analyses, increasing donor BMI was found to be an independent risk factor for delayed graft function (p < 0.001), with rates of 27.8%, 31.4% and 32.8% for normal, obese and morbidly obese patients, respectively. However, no evidence of significant differences in longer term outcomes such as patient survival (p = 0.109), graft survival (p = 0.093) or 12-month creatinine values (p = 0.550) were detected between donor BMI groups. A subgroup analysis of DCD recipients was performed (n = 353). Whilst increasing donor BMI was found to be associated with an increase the functional warm ischaemia time (WIT) and standardized WIT by an average 1.80 (p = 0.030) and 2.19 minutes (p = 0.015) respectively, this was not found to have a significant impact on the incidence of delayed graft function (p = 0.464, p = 0.520) or graft survival (p = 0.760, p = 0.423) on multivariable analysis.

Conclusions: In this large national cohort study, we found that there was no evidence of significant differences in long-term outcomes between deceased donors kidney from different BMI groups. Rejection of kidneys based upon donor BMI alone does not appear to be justified.

TH-PO999

The Impact of Recipient BMI on Outcomes after Kidney Transplantation
Adam Ashraf, Imogen Chappelow, James Hodson, Jay Nath, Adnan Shafii; Queen Elizabeth Hospital, Birmingham, Birmingham, United Kingdom; University Hospital Birmingham, Birmingham, United Kingdom; University of Birmingham, Stoke on Trent, United Kingdom; University Hospital Birmingham NHS Trust, Biostatistics, Birmingham, United Kingdom.

Background: A high recipient BMI is still considered a contraindication for transplantation across many centres. However, there is inconsistent evidence as to the influence of recipient BMI on post-transplant outcomes.

Methods: Data from National Health Service Blood and transplantation was analysed for all patients receiving deceased donor kidney transplantations between January 2003 and January 2015. Donor BMI was separated into 5 categories depending on the recipient’s body mass index (BMI) (kg/m²): 18.50 – 25.00 (normal), 25.01 – 30.00 kg/m² (obese), > 30.00 kg/m² in 1546, 30.01 kg/m² – 35.00 kg/m² in 2503 and > 35.00 kg/m² in 1148. On multivariable analyses, increasing recipient BMI was found to be an independent risk factor for delayed graft function (p = 0.001), with rates of 27.8%, 31.4% and 32.8% for normal, obese and morbidly obese patients, respectively. However, no evidence of significant differences in longer term outcomes such as patient survival (p = 0.109), graft survival (p = 0.093) or 12-month creatinine values (p = 0.550) were detected between donor BMI groups. A subgroup analysis of DCD recipients was performed (n = 353). Whilst increasing donor BMI was found to be associated with an increase the functional warm ischaemia time (WIT) and standardized WIT by an average 1.80 (p = 0.030) and 2.19 minutes (p = 0.015) respectively, this was not found to have a significant impact on the incidence of delayed graft function (p = 0.464, p = 0.520) or graft survival (p = 0.760, p = 0.423) on multivariable analysis.

Conclusions: In this large national cohort study, we found that there was no evidence of significant differences in long-term outcomes between deceased donors kidney from different BMI groups. Rejection of kidneys based upon donor BMI alone does not appear to be justified.

TH-PO990

Alteration in Body Mass Index and Estimated Glomerular Filtration Rate after Kidney Transplantation
Ekamol Tantisattamo,1 Possawat Vuthikraivit,2 Multi-Organ Transplant Center, Division of Nephrology, Department of Internal Medicine, Oakland University William Beaumont School of Medicine, Royal Oak, MI; 1PRHANGUK/TLAO COLLEGE OF MEDICINE, BANGKOK, Thailand.

Background: The pattern of post-transplant weight change and renal allograft function is unclear. We aim to determine this association.

Methods: A retrospective cohort study of 70 renal transplant recipients was divided into 3 groups (BMI <25, 25 to <30, and ≥30 kg/m2). Changes in the mean BMI compared to pre-transplant BMI (ABHIM) every 3-month follow-up periods up to 96 weeks post-transplant were correlated with pre-transplant eGFR and changes in mean eGFR (ΔeGFR) during the corresponding 3-month follow-up period.

Results: Compared to pre-transplant BMI, ABHIM at the time of discharge from the transplant admission increased in 3 groups (p = 0.003, 0.000, and 0.514). In normal and overweight groups, BMI was lower during the first 4- and 12-week post-transplant compared to BMI at the time of transplant, respectively (p = 0.236 and p = 0.012-0.069) and then became persistently higher through 96 weeks post-transplant (p = 0.001-0.122 and p = 0.004-0.299). Mean eGFR continued trending up post-transplant until 24-week post-transplant and appeared to be plateau among all 3 BMI groups (Figure). By comparing mean eGFR every 12-week interval during post-transplant, there was no difference among 3 groups. In addition, BMI between consecutive 3-month follow-up period did not associate with ΔeGFR at the corresponding 3-month follow-up period (p = 0.104-0.922).

Conclusions: eGFR appears to increase with weight loss during the first 24-month post-transplantation in all BMI strata; however, it does not significantly change and not associated with BMI alteration thereafter. Pre-transplant obesity may not be the main determinant for post-transplant renal allograft function during early and late post-transplant periods.

TH-PO993

Is Body Mass Index a Significant Independent Risk Factor for Graft Failure and Patient Death in the Modern Immunosuppressive Era? Ho Sik Shin,1 Anil K. Chandraker,1 Kosin University College of Medicine, Gospel Hospital, Busan, Republic of Korea; 2Harvard Medical School, BWH, Transplantation Research Center, Boston, MA.

Background: In previous studies, kidney transplant recipients with high body mass index (BMI) had inferior or superior outcomes compared to patients with lower BMI, and it remains unclear whether BMI is a significant independent risk factor for graft failure and patient death in the modern immunosuppressive era. We used United Network for Organ Sharing (UNOS) data to determine whether obesity affects patient and graft outcome following kidney transplantation.

Methods: From the UNOS database, we identified patients who underwent primary kidney-only transplantation between 1987 and 2016. The study sample consisted of 69,749 from 1987-1999 and 197,986 from 2000-2016. We correlated BMI with graft and patient survival, and created multivariate models to evaluate the independent effect of BMI on graft and patient outcomes, adjusting for factors known to affect graft success and patient survival.

Results: Mean BMI shifted from 25 kg/m² in 1987-1999 to 27 kg/m² in 2000-2016. Higher BMI was associated with significantly worse graft, patient and patient with functioning graft survival from 1987-1999. Lower and higher BMI were also associated with significantly worse graft, patient and patient with functioning graft survival from 2000-2016. In the same BMI group, graft and patient survival rates from 2000-2016 were higher than in 1987-1999. Cox regression modeling hazard ratios showed that obesity also associated with BMI alteration thereafter. Pre-transplant obesity may not be the main determinant for post-transplant renal allograft function during early and late post-transplant periods.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
TH-PO994

Obesity: A Risk Factor for Hypertension after Kidney Transplantation
Ekamon Tantisattamo,1 Possawat Vuthikraivit.2
1Multi-Organ Transplant Center, Division of Nephrology, Department of Internal Medicine, Oakland University William Beaumont School of Medicine, Royal Oak, MI; 2PHRAMONGKUTKLAO COLLEGE OF MEDICINE, BANGKOK, Thailand.

Background: Hypertension (HTN) after kidney transplantation is common. Underweight leads to unfavorable outcomes in ESRD. The magnitude of risk factors including obesity after kidney transplantation is unclear.

Methods: Seventy kidney transplant recipients were enrolled in a retrospective closed cohort study. Post-transplant HTN is defined as SBP ≥ 140 mmHg first detected after 1-month post-transplantation. The incidence of HTN and the association between potential risk factors and post-transplant HTN were determined.

Results: Mean age was 52.66±1.43 years old and 41 patients (58.6%) was male. There were 49 patients (70%) diagnosed with post-transplant HTN, which was an account of the incidence of post-transplant HTN was 48.67 person-year. Mean SBP and DBP at the time of diagnosis were 151 mmHg; whereas, SBP and DBP of the remaining 21 patients (30%) without post-transplant HTN were 119 mmHg, respectively (p= 0.0167, mean difference 31.79, CI 5.9367 to 57.6433). Several traditional risk factors for HTN were significantly associated with post-transplant HTN (RR 1.382 (CI 1.050 to 1.819), p=0.005). The higher the NT-proBNP value, the higher the percentage associated with a reduction in the androidal obesity risk by 4.5% (OR= 0.955 95% CI: 0.923–0.984; p=0.005). The higher the NT-proBNP value, the higher the percentage content of adipose tissue (Spearman rank correlation coefficient: 0.473; p<0.001) in KTx recipients.

Conclusions: Although the reverse epidemiology of non-obesity leading to potential harmful effect in ESRD patients, pre-transplant obesity can lead to poor post-transplant cardiovascular outcomes. Since obesity continues carrying and remains one of the traditional risk factors of HTN after successful kidney transplantation, pre-transplant weight control is still warranted.

Association between systolic hypertension beyond 1-month post-kidney transplantation and its potential risk factors

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (ml/min/1.73m2); RR, relative risk

TH-PO995

Metabolic Responses to Kidney Transplantation: Is Early Weight Gain Benign? Birush Workeneh,1 Joy V. Nolte,2 Linda W. Moore,2 Roman Shypailo,1 Ahmed O. Gaber,2 William E. Mitchell.1 1Baylor College of Medicine, Houston, TX; 2Houston Methodist Hospital, Houston, TX; 3MD Anderson Cancer Center, Houston, TX.

Background: It is widely assumed that modest weight gain following kidney transplantation (KT) is advantageous to patients. However, there is no consensus about what constitutes appropriate degree of weight gain nor has there been rigorous explorations about the nature and metabolic implications of changes in body composition.

Methods: We analyzed 31 living kidney transplant (KT) recipients. Subjects were 18-65yrs old, noninsulin dependent, and received tacrolimus-based immunosuppression. All measurements were obtained <1mo prior to and 3mo post-KT. DXA and BodPod were used to measure body mass and define body compartments. Resting energy expenditure (REE) was obtained by indirect calorimetry and physical activity was assessed by accelerometry. Insulin resistance (IR) was determined by HOMA-IR and dietary intake determined ASA24 dietary recall.

Results: We observed significant increases in body weight and fat (Table1). DXA revealed fat accumulation primarily in the truncal region. Visceral and subcutaneous fat volumes increased significantly, and visceral fat volume positively correlated with IR (r=0.452, p=0.012). REE did not change significantly and there was no relationship with fat or muscle mass. Accelerometry showed subjects were more ambulatory post-KT, 5201 vs 6515 average daily step-gains=0.034). Vector magnitude (total axis activity) also increased. Food recalls showed more calories comprised of fat and protein are consumed post-KT(42% and 17% of total kcals).

Conclusions: We conclude that only 3 months after KT there are small but significant increases in adipose deposition and have reported adverse responses including insulin resistance. Even at this early stage, patients accumulate total body fat and importantly, visceral fat. The changes we observed could not be attributed to changes in other body compartments, decreased metabolic rate, or physical activity but dietary factors may influence orexigenic factors and adipose tissue accumulation.

Funding: Private Foundation Support

TH-PO996

Android Obesity and NT-ProBNP in Kidney Transplant Patients
Magdalena B. Kazink. Chair and Department of Nephrology, Jagiellonian University Medical College, Kraków, Poland.

Background: Adipose tissue is a typical location for storage of water-insoluble toxins in a body. An excess of adipose tissue may be either systemic or local. According to a pattern of fat distribution in the body, we distinguish two types of obesity: android (visceral, abdominal) and gynoid (around bottom and tights, peripheral). The obesity increases a risk of the kidney failure and cardiovascular complications in a group of kidney transplant patients (KTx). An attempt was made to evaluate a relationship between the amount of adipose tissue, obesity type, and NT-proBNP level in KTx patients.

Methods: The study covered 128 patients (60 women and 68 men, average age 49.5 ± 10.8 years) with a functioning renal transplant more than 3 months after the transplant. The amount of adipose tissue was determined using the bioelectrical impedance analysis (BIA) and anthropometric measurements, nutrition status and the obesity type were established by Waist to Height Ratio (WHR) and Waist to Hip Ratio (WHR), the function of the transplanted kidney was evaluated by calculation of the estimated glomerular filtration rate (eGFR) using the MDRD formula, and their relation with the N-terminal pro-brain natriuretic peptide (NT-proBNP) was studied.

Results: In the study group, 22.7% of patients were classified as having a correct body weight, while 56.7% and 20.6% of participants had an android and gynoid type, respectively. In the logistic regression analysis, an increase by 0.2% in a risk of abdominal obesity in KTx patients (OR=1.002 95% CI: 1.001–1.003; p= 0.001) was associated with an increase in NT-proBNP by 100 pg/ml with a functioning renal transplant more than 3 months after the transplant. The amounts of adipose tissue (Table 1) and NT-proBNP value, the higher the percentage content of adipose tissue (Spearman rank correlation coefficient: 0.473; p=0.001) in KTx patients.

Conclusions: A large amount of adipose tissue, particularly in a case of androidal obesity, may be a predictor of kidney or cardiovascular system. Furthermore, high NT-proBNP levels may be associated with an increased risk of obesity in KTx patients; therefore, correct diet and pharmacological management, and physical activity adapted to the physical fitness level of a patient are necessary.
TH-PO997

Waist to Hip Ratio (WHR) as a Predictor of Increased Length of Stay Post Kidney Transplantation

Flore Espinosa, Rohan Patankar, Ramon Norigeia, Brittany L. Schreiber, Vishy Chaudhary, Muhammad A. Mutjaba. University of Texas Medical Branch, Galveston, TX.

Background: Objective: To determine if WHR vs body mass index (BMI) could be used as a reliable predictor of increased length of stay from transplant to first discharge, defined as 7 days or more, in a group of first time kidney transplant recipients.

Methods: Prolonged hospitalizations in renal transplant patients continues to be a concern due to its potential effect on health care costs and patient satisfaction scores. Various factors including BMI are considered while establishing suitability for kidney transplantation. However, BMI has its limitations as it does not take into account body fat distribution. WHR may provide an alternative tool for pre-transplant candidate selection.

We aimed to assess if WHR could be used to predict increased length of stay (LOS) post kidney transplantation.

Methods: This is a single center retrospective analysis of deceased and living donor kidney transplants performed through the period of May 2015 to March 2017. Increased LOS was defined as 7 days or more. A multivariate linear regression analysis was performed comparing BMI and WHR, and results were reviewed. A p-value of ≤ 0.05 was considered significant.

Results: A total of 69 patients were included, 60 of which received deceased donor kidney transplants and 9 received living donor kidneys. All patients were first time kidney transplant recipients. Patients WHR ranged from 0.78 – 1.07. The LOS ranged from 5 to 22 days. Increased WHR was significantly associated with LOS (P-value = 0.04), whereas BMI was not (P-value = 0.84).

Conclusions: Our results suggest that WHR can be used as an accurate tool to predict increased length of stay in first time kidney transplant recipients. Further collaborative efforts and research are needed to fully elucidate the relationships between WHR and increased length of stay with respect to cost, patient satisfaction and graft outcomes.

TH-PO998

Genome Wide Non HLA Alloimmunity Contributes to Graft Loss after Kidney Transplantation

Rainer Oberbauer,1 Roman Rendi-Schwarzinger, Albert Beer, Michael Heinzel, Petra Hrupec,1 Ondrej Vilkicky,1 Georg Bohmig,2 Gottfried Fischer,3 Brendan Keating.1

1Department of Nephrology, Vienna, Austria; 2Medical University Vienna, Vienna, Austria; 3Medical University of Vienna, Vienna, Austria; 4Medical University of Vienna, Vienna, Austria; 5Institute for Clinical and Experimental Medicine, Prague, Czech Republic.

Background: HLA alloimmunity is the main cause of renal transplant loss but the non-HLA alloimmunity has contributed less elucidated thoroughly yet.

Methods: We made use of the iGeneTrain consortium and genotyped 753 donors and 863 corresponding recipients using the Affymetrix Axiom Tx GWAS Array (Affymetrix). Raw genotypes were after an initial quality control phased and imputed with impute2 using GvoN and 1Kg data as reference panels. The ensemble Variant Effect Predictor and ANNOV AR were used for SNP annotation. The number of recipients with a median follow up of 6.5 years were obtained from the Vienna and Prague transplant cohort study. The main available outcomes are death censored graft loss and eGFR slope after follow up of 6.5 years (RR=1.28, 95%CI:1.08–1.52), 5 years (RR=1.21,95%CI:1.04–1.41), and 10 years (RR=1.30, 95%CI:1.12–1.47). For HLA-A+B, the 5-year graft failure rate was higher for 2–4 compared with 0–1 mm (RR=3.17,95%CI:1.20–8.36), but not for 3–4 compared with 0–2 mm (RR=1.49,95%CI:1.70–2.80).

Conclusions: For adults, HLA mismatching is an independent factor affecting graft failure and mortality. HLA-DR mismatching was associated with significantly inferior graft survival (HR=1.08, 95%CI:1.05–1.11), but not HLA-A (HR=1.06,95%CI:1.02–1.14) or HLA-B (HR=1.01,95%CI:1.08–1.14). For children, compared with 0–1 HLA-DR mm, 2 mm significantly increased the risk of graft failure at 1 year (RR=1.41,95%CI:1.11–1.80), 3 years (RR=2.85,95%CI:1.08–7.46), and 10 years (RR=1.35, 95%CI:1.12–1.67). For HLA-A+B, the 5-year graft failure rate was higher for 2–4 compared with 0–1 mm (RR=3.17,95%CI:1.20–8.36), but not for 3–4 compared with 0–2 mm (RR=1.49,95%CI:1.70–2.80).

Funding: Government Support - Non-U.S.

TH-PO1016

Effect of Hyperkalemia on Renal Ammonia Metabolism

Autumn N. Harris,1 P. R. Grimm,2 Hyun-Wook Lee,1 Eric J. Delpire,3 Paul A. Wellin,2 Jill W. Verlander,1 I. D. Weiner,1,4 Nephrology, University of Florida, Gainesville, FL; 1University of Maryland School of Medicine, Baltimore, MD; 1Vanderbilt University Medical Center, Nashville, TN; 1Nephrology, NF/SVHS, Gainesville, FL

Background: Type IV Renal Tubular Acidosis (RTA) is characterized by metabolic acidosis and hyperkalemia, but the mechanism(s) through which the metabolic acidosis

Methods: We systematically searched PubMed, EMBASE, and the Cochrane Library for relevant studies.

Results: For adults, every HLA mismatch(mm) increase was associated with increased risk of overall graft failure (HR=1.06,95%CI:1.05–1.07), death-censored graft failure (HR=1.09,95%CI:1.06–1.11) and mortality (HR=1.05,95%CI:1.02–1.07).

Moreover, HLA-DR mismatching was associated with significantly inferior graft survival(HR=1.08, 95%CI:1.05–1.11), but not HLA-A (HR=1.06,95%CI:1.02–1.14) or HLA-B (HR=1.01,95%CI:1.08–1.14). For children, compared with 0–1 HLA-DR mm, 2 mm significantly increased the risk of graft failure at 1 year (RR=1.41,95%CI:1.11–1.80), 3 years (RR=2.85,95%CI:1.08–7.46), and 10 years (RR=1.35, 95%CI:1.12–1.67). For HLA-A+B, the 5-year graft failure rate was higher for 2–4 compared with 0–1 mm (RR=3.17,95%CI:1.20–8.36), but not for 3–4 compared with 0–2 mm (RR=1.49,95%CI:1.70–2.80).

Conclusions: For adults, HLA mismatching is an independent factor affecting graft failure and mortality. HLA-DR appears to be more essential than HLA-A or -B. For children, HLA-DR and HLA-A+B are important factors affecting graft failure.

Funding: Government Support - Non-U.S.
develops remains in question. In particular, hyperkalemia’s role in the pathogenesis of the metabolic acidosis has been unclear. This discrepancy in vitro models testing the effects of hyperkalemia are difficult to perform because of robust renal K+ excretory mechanisms that limit development of chronic hyperkalemia. To obviate this limitation, we used a genetic model of hyperkalemia that does not target the proximal tubules (PT) or collecting ducts (CD). The presence of not directly target proteins involved in ammonia metabolism and does not alter K intake to determine hyperkalemia’s effect on acid-base homeostasis and ammonia metabolism.

Methods: We used a recently reported DCT-specific constitutively active SPAR (DCT-CA-SPAR) mice to examine the role of hyperkalemia on ammonia excretion. We used thiourea administration to block the NCC over-activity and correct the hyperkalemia.

Results: Under basal conditions DCT-CA-SPAR mice exhibited hyperkalemia and metabolic acidosis. Despite the metabolic acidosis, they had decreased urine ammonia excretion compared to WT mice. Titratable acid excretion was not altered. Thiouamide administration, to reverse the effect of DCT-CA-SPAR on NCC, corrected the hyperkalemia and increased ammonia excretion, but had neither effect in WT mice. Phosphonoformic acid and phosphate-dependent glutaminase, key ammonia generating proteins, expression was significantly less in DCT-CA-SPAR PT. Glutaminase synthetase, which recycles ammonia, was significantly greater in the cortical DCT-CA-SPAR cortical PT. NKCC2 and Rbg expression were unchanged. Thus, hyperkalemia in a genetic model that does not alter K intake, does not directly involve the PT and does not directly alter proteins involved in ammonia metabolism, alters expression of multiple proximal tubule proteins involved in ammonia generation, leading to decreased ammonia excretion, which is reversible with correction of the hyperkalemia.

Conclusions: Hyperkalemia can directly inhibit proximal tubule ammonia metabolism, decreasing ammonia and net acid excretion, and leading to metabolic acidosis. Moreover, the effects of hyperkalemia on ammonia metabolism suppress ammonia excretion are greater than those of metabolic acidosis to stimulate it.

Funding: NIDDK Support, Private Foundation Support

TH-PO1017 Diabetes-Induced Ammoniagenesis and Kidney Growth Are Independent of Acidosis and Increased Filtered Load of Glutamine

Acid Base: Basic

Gunars D.,

Background: Studies have shown that total ammonia (NH₃ + NH₄⁺) causes renal cell hypertrophy. We have previously demonstrated that diabetes-induced kidney growth occurs early during the onset of hyperglycemia and is associated with the stimulation of ammoniagenesis in the proximal tubule (J Am Soc Nephrol 27: 652A, 2016). However, whether the stimulation of ammoniagenesis is secondary to the development of acidosis and/or increased filtered load of glutamine remain unknown.

Methods: The inhibition of carbonic anhydrases by acetazolamide (ACTZ) in the proximal tubule activates the tubulo-glomerular feedback and induces metabolic acidosis by increasing NaCl delivery to macula densa and by increasing bicarbonate wasting in the proximal tubule activates the tubulo-glomerular feedback and induces metabolic acidosis. We used a recently reported DCT-specific constitutively active SPAK (DCT-CA-SPAR) mice to examine the role of hyperkalemia on ammonia excretion. We used thiourea administration to block the NCC over-activity and correct the hyperkalemia.

Results: Under basal conditions DCT-CA-SPAR mice exhibited hyperkalemia and metabolic acidosis. Despite the metabolic acidosis, they had decreased urine ammonia excretion compared to WT mice. Titratable acid excretion was not altered. Thiouamide administration, to reverse the effect of DCT-CA-SPAR on NCC, corrected the hyperkalemia and increased ammonia excretion, but had neither effect in WT mice. Phosphonoformic acid and phosphate-dependent glutaminase, key ammonia generating proteins, expression was significantly less in DCT-CA-SPAR PT. Glutaminase synthetase, which recycles ammonia, was significantly greater in the cortical DCT-CA-SPAR cortical PT. NKCC2 and Rbg expression were unchanged. Thus, hyperkalemia in a genetic model that does not alter K intake does not directly involve the PT and does not directly alter proteins involved in ammonia metabolism, alters expression of multiple proximal tubule proteins involved in ammonia generation, leading to decreased ammonia excretion, which is reversible with correction of the hyperkalemia.

Conclusions: Hyperkalemia can directly inhibit proximal tubule ammonia metabolism, decreasing ammonia and net acid excretion, and leading to metabolic acidosis. Moreover, the effects of hyperkalemia on ammonia metabolism suppress ammonia excretion are greater than those of metabolic acidosis to stimulate it.

Funding: NIDDK Support, Private Foundation Support

TH-PO1019 Hypercapnia Increases Urinary Ammonium Excretion and Upregulates Expression of the NH3/NH4⁺ Transporters Rh Glycoproteins

Acid Base: Basic

Naizir L. Nakhoul 1, L. Lee Ham, 1, Kathleen S. Herings-Smith, 2 Mohammed T. Islam, 1 Solange Abdulnoor-Nakhoul, 1 Tulane Medical School, New Orleans, LA; 2SLVHCS, New Orleans, LA

Background: Hypercapnia and subsequent respiratory acidosis is a serious complication observed in patients with respiratory disorders such as chronic obstructive pulmonary disorder (COPD) and acute respiratory distress syndrome. A recent study shows that the presence of COPD in patients with CKD greatly increases the risk of death. The acute response to hypercapnia is buffering of H⁺ by hemoglobin and other cellular proteins but this effect is limited. The chronic response (usually complete in 3-5 days) is renal compensation that increases HCO₃⁻ reabsorption, mostly in the proximal tubule, and stimulates urinary excretion of titratable acids (TA) and NH₄⁺. However, the main effective pathway is the excretion of NH₄⁺ in the collecting duct. Our hypothesis is that the renal excretion of NH₄⁺ is increased in chronic hypercapnia, and that this is due to an increased expression of the NH₄⁺ transporters Rhb in the collecting duct mediate this response. The effect of hypercapnia on these transporters is unknown.

Methods: We conducted in-vivo experiments on mice subjected to induced respiratory acidosis. We placed two groups of mice in special chambers where breathing gas mixtures can be controlled. One group breathed 8% CO₂ (21% O₂ & 71% N2) to induce respiratory acidosis and the other breathed normal air as control. After 5 days, the mice were euthanized and kidneys, blood and urine samples were collected. We used immuno-histochemistry, Western analysis and qRT-PCR to determine how high CO₂ levels affects localization, abundance and gene expression of the Rh proteins.

Results: Western analysis showed a significant increase in expression of Rhbg (by 43% ± 3.3) and Rhcg by (12.6% ± 3.0) in animals that breathed 8% CO₂ (P<0.01, n=10). In addition, carbonic anhydrase (CA-IV) expression was increased significantly (by 86% ± 9.1) as compared to Controls. ACTZ did not alter food intake but significantly reduced body weight loss in KO mice (F, 14.9, P<0.001). In hypercapnic animals, there was a significant increase in urinary NH₄⁺ excretion (by 50% ± 3.2, P<0.01) but the change in TA was not statistically significant.

Conclusions: These data suggest that hypercapnia (for 5 days) leads to compensatory upregulation of Rhbg and Rhcg proteins that contributes to excretion of NH₄⁺ and NH₃ in the kidney. These studies are the first to show a link between hypercapnia, NH₄⁺ excretion and Rh expression.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO1020 The A-Splice Variant of NBCe1 Is Necessary for Basal and Acidosis-Stimulated Renal Ammonia Metabolism

Acid Base: Basic

Hyun-Wook Lee 1, Gunars Osis, 1 Autumn N. Harris, 1 Lijuan Fang, 1 Heather L. Holmes, 2 Adam J. Rossano, 2 Michael F. Romero, 3 Jill W. Verlander, 4 I. D. Weiner, 5, 6 Nephrology, University of Florida, Gainesville, FL; 7Mayo Clinic, Rochester, MN; 8Nephrology, NF/ SVHIS, Gainesville, FL

Background: Renal ammonia excretion is the largest component of net acid excretion during both basal conditions and metabolic acidosis. Proximal tubule (PT) ammonia metabolism is critical for normal renal ammonia excretion, but the mechanisms through which external stimuli alter PT ammonia metabolism are incompletely understood. This study’s purpose was to determine the role of the predominant proximal tubule NBCe1 splice variant, NBCe1-A, in ammonia metabolism under basal conditions and in response to metabolic acidosis.

Methods: We used mice with specific deletion of the NBCe1-A splice variant generated using TALEN gene editing. Mice were fed normal diet or were acid-loaded by adding HCl to their water to show. All studies compared homogygous deletion (KO) mice with wild-type (WT) littermates.

Results: Under basal conditions, KO mice had spontaneous metabolic acidosis, consistent with proximal RTA from impaired proximal tubule bicarbonate reabsorption. Despite this acidosis, ammonia urinary excretion was not altered in the KO mice. Urine pH was lower in KO than WT mice, indicating that the failure of basal acidification was not

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

Underline represents presenting author.
ammonia excretion was not due to impaired urine acidification. Immunoblots and immunohistochemistry revealed moderate to strong nuclear and cytoplasmic expression of their acidosis-expressing cells, encoding the human chloride-dependent glutaminase (PDG) and phosphoenolpyruvate carboxykinase (PEPKC), key enzymes generating enzymes, throughout the entire PT, and expressed more glutamine synthetase (GS) in cortical PT segments than did WT. After acid-loading, the basal and paracellular increase ammonia excretion was impaired significantly, by ~70%, in KO mice. Immunoblots and IHC showed less change in PEPCK, PDG and GS in the proximal convoluted tubule (PCT) of KO than WT mice. However, in the proximal straight tubule (PST) in the outer medulla, where in the normal mouse NBCe1-A expression is less than in the PCT, PDG and PEPCK upregulation and GS downregulation were greater in KO than in WT mice.

Conclusions: (1) NBCe1-A is a key protein in the signaling pathway through which PCT ammonium metabolism is regulated during basolateral and metabolic acidosis; and, (2) In the PST, one or more additional mechanisms enable responsiveness to exogenous acid-loading, but not to the spontaneous metabolic acidosis, in KO mice.

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

TH-PO1021
The A-Splice Variant of NBCe1 (NBCe1-A) Regulates Citrate Excretion and NaDC1 Expression. Gunas Osis,1,3 Kim K. Lee,2,3 Walter F. Boron.1

1Nephrology, University of Florida, Gainesville, FL; 2Mayo Clinic College of Medicine, Rochester, MN; 3Nephrology, NF/SGVHS, Gainesville, FL.

Background: Urinary citrate affects several critical kidney functions, including acid-base homeostasis and prevention of calcium nephrolithiasis. Proximal tubule (PT) NaDC1 is believed to be the major regulator of urinary citrate excretion. These studies examined the role of the A splice variant of NBCe1 (NBCe1-A) in basal and acidosis-stimulated citrate excretion and NaDC1 expression.

Methods: We used recently developed NBCe1-A-specific deletion (KO) mice and their wild-type (WT) littermates. We performed exogenous acid-loading with dietary HCl for 7 days. We used quantitative immunohistochemistry (qIHC) to examine NaDC1 expression in proximal convoluted tubule in the cortical labyrinth (PCT), proximal straight tubule (PST) in the medullary ray (PST-MR) and PST in the outer medulla (PST-OM). Urinary citrate was measured using H-NMR.

Results: In WT mice under basal conditions, NaDC1 immunolabel intensity exhibited significant axial heterogeneity, PCT < PST-MR < PST-OM. Under basal conditions, NBCe1-A deletion induces spontaneous metabolic acidosis. Although the acidosis, which in normal conditions decreases citrate excretion, citrate excretion was significantly greater in KO than WT mice (~3x-fold). Quantitative IHC showed NaDC1 expression was significantly less in KO than WT mice in all PT sites. Exogenous acid-loading decreased urinary citrate excretion ~98% in both genotypes such that final urinary citrate did not differ significantly between WT and KO mice. Exogenous acid-loading increased NaDC1 expression in WT mice in the PCT and PST-MR, but not the PST-OM. In KO mice, in contrast, exogenous acid-loading did not alter PT NaDC1 expression significantly, but did increase expression significantly in both PST-MR and PST-OM.

Conclusions: (1) Under basal conditions NBCe1-A expression is critical to the normal regulation of citrate excretion and NaDC1 expression; (2) In WT mice, there is significant axial heterogeneity of both basal NaDC1 expression and its response to acid-loading; and, (3) during exogenous acid-loading alternative signaling pathways in NBCe1-A KO mice increase NaDC1 expression with a different axial pattern than in WT mice. We conclude that NBCe1-A is critical to the maintenance of NaDC1 expression and NaDC1uria.

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

TH-PO1024
Expression of Phosphate-Dependent Glutaminase (PDG) in Normal and Neoplastic Human Kidney. Hyun-Wook Lee,1 William L. Clapp,2 Dara N. Wakefield,3 Jill W. Verlander,1,4 I. D. Weiner.1

1Nephrology, University of Florida, Gainesville, FL; 2Mayo Clinic College of Medicine, Rochester, MN; 3Nephrology, NF/SGVHS, Gainesville, FL.

Background: Phosphate-dependent glutaminase (PDG) is a mitochondrial enzyme that has a critical role in renal ammonia metabolism, catalyzing the initial step in renal ammonia metabolism, and may have a role in glomerular-derived ATP generation. The cellular distribution of PDG in the human kidney is currently unknown. This study’s purpose was to determine normal and neoplastic human kidney expression.

Methods: We used human kidney tissues from unused portions of nephrectomy specimens removed during routine treatment of renal cell carcinoma for immunohistochemistry studies. Three separate PDG antibodies were used; all gave similar results. Normal human kidney protein lysates were obtained from commercial sources.

Results: Immunoblot analysis of both human whole kidney and cortical protein samples revealed an ~63 kDa protein. Immunohistochemistry showed PDG immunolabel throughout the nephron and in arterial walls in a granular pattern consistent with mitochondrial expression. Glomerular label was punctate and weak compared to tubules. Tubule distribution of PDG was verified using H-ATPase and NKCC2 as markers. Strong PDG expression was present in proximal tubule, descending and ascending limb, thick ascending limb, distal convoluted tubule, connecting segment (CNT), and throughout the collecting duct (CD). Cellular heterogeneity in label intensity was evident in CNT and CD profiles. PDG expression in kidney neoplasms varied among tumor types. In tumors of presumed proximal tubule origin, clear cell and papillary renal cell carcinoma (RCC), weak, 1+, PDG immunolabel was present. In tumors of presumed intercalated cell carcinoma, oncocytoma and chromophobe RCC, PDG immunolabel was substantially more intense, 2+, and immunolabel intensity was greater in oncocytoma than in chromophobe RCC.

Conclusions: 1) PDG is widely expressed in epithelial and non-epithelial cells in the human kidney. 2) PDG expression in RCC varies with tumor type; it is weakly expressed in clear cell and papillary RCC, whereas in oncocytoma and chromophobe RCC it is expressed more strongly. 3) This wide-spread expression suggests PDG may have critical roles both in ammoniagenesis and glutamine-derived ATP generation.

Funding: NIDDK Support, Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author. 366
Axial Heterogeneity of Phosphate-Dependent Glutaminase Expression and Response to Metabolic Acidosis

Hyon-Wook Lee, Gunars Osis, Autumn N. Harris, Lijuan Fang, Jill W. Verlander, I. D. Weiner.

TH-PO105

Background: Phosphate-dependent glutaminase (PDG) is critically important in renal ammoniagenesis and may also contribute to 2-oxoglutarate generation used for TCA cycle and ATP generation. Although increased proximal tubule (PT) PDG expression during metabolic acidosis is well-recognized, its expression and regulation in other renal tubule cells is not well-characterized. This study’s purpose was to determine PDG’s cellular expression in the kidney and the cell-specific response to metabolic acidosis.

Methods: 57B16 mice were fed normal diet or were acid-loaded by adding HCl to Chow for 7 days. Three separate PDG antibodies were used; all gave similar results.

Results: Under basal conditions, immunohistochemistry (IHC) showed PDG immunolabel throughout the renal nephron, collecting duct and papillary surface epithelium. Immunostaining with antibodies to medullary chondrocyte localization; gold label density was generally greater in mitochondria in distal tubule and collecting duct cells than in PT cells. The cellular distribution of PDG expression was verified using double-immunolabel IHC with NHE3, AQP1, NKCC2, and H+ATPase. Cells with strong PDG expression were present in the proximal convoluted tubule, proximal straight tubule, descending and ascending thin limbs, thick ascending limb, distal convoluted tubule, connecting segment, and throughout the collecting duct. In the PT, label intensity was heterogeneous, with interspersed intensely- and weakly-labeled cells. In medullary collecting tubules, intercalated cells had greater expression than principal cells. In addition, intercalated cell expression was heterogeneous in CCD and CNT. Acid-loading increased the number of strongly PDG-positive PT cells, did not alter expression in cortical and medullary thick ascending limb (mTAL) in the OSOM or the entire collecting duct and decreased expression in the ISOM.

Conclusions: (1) The finding of cellular heterogeneity in PT PDG expression, with acid-loading increasing the number of PT cells with intense PDG expression, identifies a new ammoniagenic regulatory mechanism. (2) The wide-spread expression of PDG in non-PT cells, which was not altered by acidosis, suggests PDG may contribute to glutamine-derived ATP generation via the TCA cycle.

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

Metabolic Acidosis Inhibits AMPK Function in Kidney Cells

Nuria M. Pastor-Soler, Hui Li, Kazuhiro Omi, Kenneth R. Hallows.

TH-PO107

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

Underline represents presenting author.

Acid Base: Basic

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

Underline represents presenting author.
Results: (1) Mice having been fed a low-Na\(^+\) diet showed a significant upregulation of ENaC. (2) After the administration of HCT urine output was increased in both groups. (3) HCT caused an increase in Na\(^+\) excretion that did not reach significance. (4) K\(^+\) excretion rates increased markedly after HCT administration from 18.55±3.83 to 31.67±7.62 in the control diet group and from 22.95±3.68 to 48.71±8.36 µmol/h in the low-Na\(^+\) diet group. (5) Importantly, no changes in urine pH were observed after the administration of HCT in both groups.

Conclusions: Despite the induction of acute kaliuresis by HCT, indicating an increased electrogenic transport of Na\(^+\) via ENaC, an acute increased H\(^+\) secretion was not observed, neither under control conditions nor under conditions of marked ENaC upregulation. Thus, this study supports our previous finding that H\(^+\) secretion by furosemide takes place in the TAL.

Funding: Government Support - Non-U.S.

TH-PO1030 Two Year Follow Up on Chronic Hemodialysis (HD) Patients Prescribed Sucroferric Oxyhydroxide as Part of Routine Care Stuart M. Sprague,1 Vidhya Parameswaran,1 Linda H. Ficociello,1 Norma J. Ofsthun,1 Claudey Mullon,1 Robert J. Kossmann,2 Daniel W. Coyne,1 1NorthShore University HealthSystem University of Chicago Pritzker School of Medicine, Chicago, IL; 2Washington University School of Medicine, St. Louis, MO; 1NorthShore University Health System University of Chicago Pritzker School of Medicine, Chicago, IL.

Background: Controlling serum phosphorus (sP) in HD patients is challenging, in part, due to lack of compliance with the high pill burden typically associated with phosphate binder (PB) therapy. Sucroferric oxyhydroxide (SO) is a PB with a starting dose of 3 pills per day. The current analysis aimed to assess the long-term effectiveness of SO in lowering sP and PB pill burden.

Methods: Adult Fresenius Kidney Care HD patients switched during 1/1/14 -3/31/15 from PB monotherapy to SO monotherapy and continued on SO for two years were included (n=241). Baseline was defined as the 3 months before SO, when prior PB was used. Mean prescribed PB pills/day and sP levels were calculated using mixed effects linear regression. In-range sP was defined as sP ≤ 5.5 mg/dl.

Results: Patients had a mean age of 54 years and dialysis vintage of 57 months at baseline. The majority of patients (67%) were on sevelamer before switching to SO. Mean pill burden decreased by 48-53% from baseline (9.4 pills/day) to SO follow-up (4.4-4.9 pills/day). Prior to switching to SO, 15.8% of patients had a sP ≤ 5.5 mg/dl, after switch this increased to 30.8% at Q1 (a 95% increase or 1.9x from baseline) to 44.1% at 2 years (a 179% increase or 2.7x from baseline) [Figure].

Conclusions: During two year follow-up after switching PB to sucroferric oxyhydroxide, patients were 1.9x to 2.7x more likely to have sP ≤ 5.5 mg/dl (95%-179% increase from baseline) while being prescribed 50% less PB pills/day compared to baseline.  

Funding: Commercial Support - Fresenius Medical Care North America

Effectiveness of Sucroferric Oxyhydroxide (SO) in Lowering Serum Phosphorus (sP) in 4,925 Chronic Hemodialysis (HD) Patients Prescribed SO as Part of Routine Care Daniel W. Coyne,1 Linda H. Ficociello,1 Vidhya Parameswaran,2 Norma J. Ofsthun,2 Claudey Mullon,2 Robert J. Kossmann,2 Stuart M. Sprague,1 1NorthShore University HealthSystem University of Chicago Pritzker School of Medicine, Chicago, IL; 2Washington University School of Medicine, St. Louis, MO; 1NorthShore Medical Care North America, Waltham, MA; 2NorthShore University HealthSystem University of Chicago Pritzker School of Medicine, Chicago, IL.

Background: Although the majority of HD patients are prescribed phosphate binders (PB), hyperphosphatemia is highly prevalent. A barrier to phosphorus control can be the high pill burden of most PB. The current analysis aimed to assess the effectiveness of SO in lowering sP and PB pill burden in a large patient population.

Methods: Patients included in the analysis were all Fresenius Kidney Care (FKC) patients switched during 1/1/14 -12/31/16 from PB monotherapy to SO monotherapy for at least three months. Baseline was defined as the 3 months before SO, when prior PB was used. Patients were followed until end of analysis period, end of monotherapy SO, or discharge from FKC. Mean prescribed PB pills/day and sP levels were calculated using mixed effects linear regression. In-range sP was defined as sP ≤ 5.5 mg/dl.

Results: Patients (n=4925) had a mean age of 55 years and dialysis vintage of 53 months. During baseline the majority of patients were hyperphosphatemic (only 18.9% had sP ≤ 5.5 mg/dl). Achievement of sP ≤ 5.5 mg/dl improved over SO from 28.5% at Q1 to 41% at Q8. Patients were prescribed, on average, 9.5 pills/day and this was reduced by >50% (4.2 to 4.7 pills/day) during SO follow-up. At baseline, patients were treated with sevelamer (Sev), calcium acetate (CaAc), ferric citrate (FC), or lanthanum carbonate (LC). Figures demonstrate the increases in patients achieving sP ≤ 5.5 mg/dl by the 4 baseline PB.

Conclusions: In a large cohort of patients switching to SO, improvements in achieving sP ≤ 5.5 mg/dl were observed across all baseline PB.

Funding: Commercial Support - Fresenius Medical Care North America
TH-PO1032

Changes in Mineral Bone Disease (MBD) Markers in Hemodialysis (HD) Patients Switched to Sucroferric Oxyhydroxide (SO) Sandeep Shori,1 Vidhya Parameswaran,2 Linda H. Ficociello,2 Clausy Mullon,2 Robert J. Kossmann.1,2 1None, Westlake, TX; 2Fresenius Medical Care North America, Waltham, MA.

Background: Elevated levels of MBD markers (sP, PTH, Ca) increase patient’s risk of morbidity and mortality. This current analysis assesses the changes in MBD markers in patients who lower sP to ≤ 5.5 mg/dl when switching to SO.

Methods: Adult, baseline (BL) hyperphosphatemic (sP> 5.5 mg/dl) Fresenius Kidney Care HD patients switched to SO as part of routine clinical care during 1/1/14 -12/31/16 and maintaining sP ≤ 5.5 mg/dl for 2 quarters (Q1, Q2) after the switch were eligible. BL was defined as the 3 months before SO, when prior phosphate binders (PB) was used. Mean prescribed PB pills/day, sP, Ca, and PTH levels were calculated using mixed effects linear regression.

Results: At baseline the majority of patients were treated with sevelamer (66%), followed by calcium acetate (28%), lanthanum carbonate (5%) and ferric citrate (1%). MBD markers and number of phosphate binder pills/day at BL, Q1 and Q2 for 394 patients who achieved sP ≤ 5.5 mg/dl during Q1 and Q2 are presented in the table.

Conclusions: In a cohort of hyperphosphatemic HD patients switching to SO, improvements in achieving sP ≤ 5.5 mg/dl were accompanied by improvements in Ca and PTH and a 46% reduction in number of phosphate binder pills/day.

Funding: Commercial Support - Fresenius Medical Care North America

TH-PO1033

Serum Albumin and Serum Phosphorus among Hemodialysis Patients after Initiating Sucroferric Oxyhydroxide (SO) Kamyar Kalantar-Zadeh,1 Linda H. Ficociello,2 Vidhya Parameswaran,2 Hasit Mondal,2 Nikolaos V. Athienites,1 Clausy Mullon,2 Robert J. Kossmann,2 1University of California Irvine, School of Medicine, Orange, CA; 2Fresenius Medical Care North America, Waltham, MA; 3Renal Medical Care PC, Abington, MA.

Background: Dietary protein intake may result in higher phosphorus burden and increases in serum phosphorus (sP) in hemodialysis (HD) patient, whereas restricting high-protein diet to control phosphorus may lead to hypoalbuminemia. This presents a challenge as both low serum albumin (sAlb) and high sP increase mortality risk. We hypothesized that under routine clinical care scenario, SO can lead to increase in sAlb, while lowering sP and pill burden.

Methods: All adult patients who completed 1 year of uninterrupted SO treatment (Q1-Q4) with sP and sAlb measurements were eligible for the analysis. Hypoalbuminemic patients (Low-Alb) had sAlb ≤ 3.5g/dl during at least one 3 month baseline interval and were matched on gender, race, diabetes status, and age (+/-5 years) to patients with normal sAlb during baseline (Match). 79 matched pairs were created.

Results: The two groups did not differ on matched baseline factors or BMI (31.1 vs 31.2 kg/m 2) but Low-Alb patients had a shorter dialysis vintage (32 vs 60 months) at baseline. Comparing baseline to Q4 of SO follow-up, PB pills/day decreased by 44.9 and 45.1% (both p<0.0001) and sP decreased by 0.7 and 0.5 mg/dl (both p<0.0001), for Low-Alb and Match, respectively. Mean sAlb stayed stable in Match, but increased significantly (p<0.0001) in the low sAlb group from 3.49 mg/dl at baseline to 3.71, 3.73, 3.74, and 3.69 mg/dl during Q1-Q4, respectively. Figure 1 shows monthly changes for sP and sAlb.

Conclusions: Lowering of sP and PB pills/day was observed in Low-Alb and Match patients after switch to SO. Low-Alb patients who received SO also experienced significant increases in sAlb.

Funding: Commercial Support - Fresenius Medical Care North America
TH-PO1034
Diet Induced Iron Deficiency Inhibits Intestinal Phosphate Absorption by a NaPi-IIb-Independent Mechanism
Evans O. Asowata,1 Suriji K. Srai,1 Robert J. Unwin,1 Joanne Marks,2* Centre for Nephrology, University College London, London, United Kingdom; 1Department of Neuroscience Physiology & Pharmacology, University College London, London, United Kingdom; 1Department of Structural and Molecular Biology, University College London, London, United Kingdom.

Background: Recent evidence suggests that iron-deficiency influences phosphate (Pi) homeostasis through altered transcription and processing of FGFR23 in osteocytes. In addition, older studies have provided conflicting data as to whether diet induced iron-deficiency impacts intestinal Pi absorption. We aimed to confirm if iron-deficiency alters intestinal Pi absorption, and if so, to investigate the underlying mechanisms.

Methods: Six-week old male Sprague-Dawley rats and C57Bl/6 mice were fed an iron-deficient (ID) diet (2-6 ppm iron) or control (C) diet (48 ppm iron) for 2-weeks, with both diets including 0.6% Pi. In vivo and in vitro Pi uptake experiments using a physiological Pi concentration (10mM) were used to examine changes in intestinal Pi absorption in these models. Western blotting, qPCR, and ELISAs were employed to understand the underlying mechanisms.

Results: Diet induced iron-deficiency inhibited Pi absorption in the rat duodenum in vivo (C: 6.0±0.6 vs. ID: 2.5±0.6 nmol Pi in 1ml plasma/5cm, n=7, P<0.01), while FGFR23 and 1,25(OH)2D3 levels were unaffected. In contrast, in vitro Pi absorption in the mouse ileum, which is known to be mediated predominantly by NaPi-IIb, was unaffected by iron-deficiency (C: 92.2±9.9 vs. ID: 93.8±3.5 nmol Pi in 1ml plasma/5cm, n=6). In addition, the NaPi-IIb inhibitor, PFA (10mM), did not inhibit in vitro Pi absorption in the duodenum of control rats (C: 32.8±0.25 vs. C + PFA: 32.0±1.32 nmol Pi/100mg, n=6), while iron-deficiency caused a significant reduction (ID: 10.0±0.21, P<0.0001, n=6), suggesting that this response is not dependent on NaPi-IIb. Interestingly, Western blotting showed that iron-deficiency significantly increased the expression of claudin 3 (C: 0.18±0.01 vs. ID: 0.37±0.07, P<0.05, n=6), as well as the apical membrane ion transporter, DMT1 (C: 0.10±0.02 vs. ID: 0.51±0.01, P<0.05, n=3).

Conclusions: We hypothesise that increased DMT1 expression may locally impact intestinal Pi absorption by a mechanism involving DMT1-induced accumulation of intracellular H+ in the enterocyte resulting in increased claudin 3 levels, and subsequent sealing of the tight junction to reduce paracellular Pi absorption. Understanding how diet induced iron-deficiency affects intestinal Pi absorption may identify a novel target for the management of hyperphosphataemia in CKD patients.

TH-PO1035
Incidence, Predictors, and Therapeutic Consequences of Hypocalcemia in Patients Treated with Cinacalcet: The EVOLVE Trial
Jürgen Fleige,2 Kate Tirsitsonis,2 Jan Iles,1 Tilman B. Drueke,1 Glenn M. Chertow,4 Patrick S. Parfrey,1,4 Amgen Inc, Thousand Oaks, CA; 2Amgen Ltd, Uxbridge, United Kingdom; 3Inserm UMR 1018, CESP; Université Paris-Sud, France; 4Memorial University, St. John’s, NL, Canada; 5RWTH University of Aachen, Aachen, Germany; 6Stanford University School of Medicine, Palo Alto, CA.

Background: The calcimimetic cinacalcet is used to treat secondary hyperparathyroidism in patients receiving dialysis. Asymptomatic hypocalcemia is often observed following its initiation. Here we investigated the incidence, predictors and therapeutic consequences of hypocalcemia.

Methods: This was a post-hoc analysis of the randomized, double-blind, placebo-controlled Evaluation Of Cinacalcet Hydrochloride Therapy to Lower CardioVascular Events (EVOLVE) trial. Hypocalcemia was classified as mild (total serum calcium 8.0 – 8.39 mg/dL), moderate (7.5 – 7.99 mg/dL) or severe (<7.5 mg/dL).

Results: At least one episode of hypocalcemia developed within 16 weeks after the first administered dose among 58.3% (1130/1938) patients randomized to cinacalcet versus 14.9% (286/1923) with placebo. Hypocalcemia in the cinacalcet group was severe in 18.4% of the patients versus 4.4% in the placebo group. Severe hypocalcemia following administration of cinacalcet was associated with geographic region (patients with Latin America and Russia had a higher risk relative to USA), higher body mass index, higher baseline plasma PTH, lower corrected total serum calcium and higher serum alkaline phosphatase. Median cinacalcet dose immediately prior to the first hypocalcemia episode was 54.8±28 mg/day and similar in the three hypocalcemia categories. In the majority of patients, hypocalcemia resolved spontaneously within 14 days without modification of background therapy. Among patients who received an intervention, the most common was an increase in active vitamin D sterol dose.

Conclusions: The occurrence of hypocalcemia is a frequent effect following initiation of cinacalcet. The likelihood of developing hypocalcemia was related to the severity of secondary hyperparathyroidism. Hypocalcemia was generally asymptomatic and self-limited.

Funding: Commercial Support - Amgen

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Effect of an Individualized Therapy for Hyperphosphatemia in Hemodialysis Patients – A Single-Center, Open-Label Randomized Clinical Trial

Xinyu Dong, Mengjia Wang, Qian Zhang, Jiayi Zhang, Minmin Zhang, Li Ni, Jing Chen. Huashan Hosipital, Fudan University, Shanghai, China.

Background: We hypothesized that estimation of phosphorus balance would improve the efficiency of treatment of hyperphosphatemia. Thus we compared individualized therapy with traditional therapy of hyperphosphatemia in maintenance hemodialysis (MHD) patients.

Methods: 67 eligible MHD patients with serum phosphate >1.45mmol/L were randomized into Control Group (n=20) and Individualized group (Dietary Group, n=47) for 6 weeks. Phosphorus balance was achieved in Individualized group by the following equation: Diet Pi = 60% × Pi removed by hemodialysis and phosphate binders. Patients in Dietary Group were assigned diet education and individualized diet for 6 weeks, while patients in Combined Group were assigned individualized diet and dietary phosphate restriction in addition to increased hemodialysis sessions. No estimation of phosphorus balance was assessed in Control Group and patients were assigned conventional HD regimen and phosphate binders according to serum calcium and phosphate. Analysis was done among patients with good compliance.

Results: Mean age of the participants was 57.7±9.0 years old. Baseline serum phosphate was 1.96±0.38 mmol/L, 2.08±0.41 mmol/L and 2.13±0.47 mmol/L in Control, Dietary and Combined Group, respectively. Serum phosphate decreased significantly at Week 3 and Week 6 compared to Baseline in Dietary Group (Week 3: 0.18±0.39, P=0.113; Week 6: -0.41±0.42, P=0.004), and in Combined Group (Week 3: 0.35±0.68, P=0.045; Week 6: -0.26±0.54, P=0.056), but not in Control Group (Week 6: 0.09±0.50, P=0.556). No significant change was found in albumin, creatinine, calcium, iPTH, AKP, and sPCR during the follow-up period.

Conclusions: Individualized therapy was effective and safe in correcting hyperphosphatemia without inducing malnutrition. Current study provided a new and applicable approach in treating hyperphosphatemia in MHD patients.

Funding: Government Support - Non-U.S.

TH-PO1039

Can CKD Patients Estimate Phosphate Content (PC) in the Food Correctly? Petr Taborsky, Fresenius Medical Care, Praha, Czech Republic.

Background: Hyperphosphatemia has been identified as a risk factor for survival of CKD patients. Food is the main source of increased serum phosphate in CKD. Patients are advised to control the amount of absorbed phosphate by phosphate binders. Reasonable PC estimation is a prerequisite for successful treatment with phosphate binders and for their adequate dosing.

Methods: Phosphate and protein content of 53 popular food items available on the market in Czech Republic were measured using standard chemical methods. Five typical Czech meals were prepared by nutritional specialist using recipes recommended for dialysis patients. The identical meals were purchased fresh in restaurant or frozen in supermarket and phosphate and protein content of all meals were measured. Virtual menu consisting of meal photos and short descriptions including information on the meal origin was compiled, nutrition facts were blinded. 23 predialysis patients CKD stage 3-5 were asked during their regular visit in nephrology clinic to go over the menu and put together the three days diet corresponding to their kidney function. Importance of low PC in the diet was repeatedly stressed. All patients were previously instructed in renal diet by nutrition specialist using the standard protocol. The optimal diet and the “worst” choice (the lowest and the highest possible content of phosphate) were calculated for comparison.

Results: Calculated PC in dietary regimens ranged from 730 to 1780 mg per day, all diets contained at least 60 g of protein per day. Phosphate to protein ratio in food varies much widely: from 9 mg/g in non-processed beef to 85 mg/g in some brands of spread cheese. PC in home-made meals was 1.2 to 2 times lower than in ready-to-eat meals. Food products labeled as “for children” contained less phosphate. Mean PC in diet chosen by patients was 1420 mg per day ranging from 920 to 1690 mg of phosphate per day. Difference in PC was done mainly by individual preferences of some sorts of dairy products and manufactured pastries.

Conclusions: PC is extremely variable, even within the same sort of food. For ordinary patient without special training the correct estimation of PC in food is very difficult even impossible. Traditional education based on close correlation between protein and PC in food should be changed because of widespread use of phosphate-containing additives.
TH-PO1042

Coordination of Pharmaceutical Care in Dialysis Patients Is Associated with Lower Mortality and Hospital Admission Rates

Methods: We included data from hemodialysis patients in the network of Fresenius Medical Care North America clinics who were first enrolled into FreseniusRx pharmacy in January-February of 2016. This analysis utilized data on patients before and up to 9 months after pharmacy enrollment. We identified control patients not enrolled in the pharmacy by nearest neighbor matching on the logit of the propensity score for demographics, comorbidities, state, insurance type, as well as, baseline lab values, vintage, access, hospitalization rates and other parameters. We compared hospital admission rates and mortality rates in 3, 6, and 9 months after enrollment.

Results: We analyzed data on 7116 patients (3558 in Rx and 3558 matched patients not in Rx). Rx patients had lower hospital admission rates per patient year (Rx vs non-Rx at 3, 6, and 9 months was 1.4, 1.4, 1.4 vs 1.5, 1.6, 1.6; p<0.05, p<0.04 and p<0.03 based on Poisson model). Mortality rates were also lower (HR for Rx vs non-Rx at 3, 6, and 9 months was 1.4, 1.4, and 1.3; p<0.04 and p<0.03 based on Cox model).

Conclusions: Coordinated pharmaceutical care is associated with lower hospital admission and mortality rates in the hemodialysis patient population. Further analyses are needed to understand what elements of this coordinated care are associated with improvements.

Funding: Commercial Support - Fresenius

TH-PO1043

Four Times Daily versus Three Times Daily Dosing of Phosphorus Binders Does Not Improve Serum Phosphorus in Dialysis Patients

Methods: Twenty-nine (29) dialysis patients with hyperphosphatemia received their daily phosphorus binding dose either 3 times a day with meals or 4 times a day with meals and at bedtime for 3 months, crossing over to the alternate dosing schedule for an additional 3 months. The type and total daily dose of binder was not changed and patients continued their usual phosphorus restricted diet.

Results: Standard of care data over the project period was available on 23 patients (3 withdrew, 1 transfer). Serum phosphorus did not change over the 3 month course of treatment, regardless of a 3 times daily with meals (5.63 ± 1.4 to 5.72 ± 1.49) or 4 times daily with meals and at bedtime (5.71 ± 1.01 to 5.95 ± 1.47) dosing schedule. The results were not influenced by baseline serum phosphorus (greater than or less than 6.0 mg/dL) or the type of phosphorus binder.

Conclusions: For enterorehepatic recirculation of dietary phosphorus affects serum phosphorus in dialysis patients, it does not appear to respond to increasing the frequency of dosing.

Funding: Commercial Support - Fresenius

TH-PO1044

Association between Use of Phosphate-Binders and the Risk of Infection-Related Mortality in Hemodialysis Patients: The Q-Cohort Study

Background: Use of phosphate (P)-binders enables hemodialysis patients to continue their usual phosphorus restricted diet. It has been estimated that ~50% of dialysis patients do not take their phosphate binders as prescribed (Ghimire et al. 2015). We aimed to characterize the outcomes of dialysis patients based on their MBD medication adherence levels.

Methods: In this retrospective cohort analysis, we included all patients dialyzed at Fresenius Kidney Care clinics between 2006 and 2016. Patients were characterized based on their MBD medication adherence levels per dietician assessment and categorized as: 1) “taking the medication as prescribed”, and 2) “taking the medication inconsistent or not at all.” The most recent MBD medication adherence assessment per patient was utilized for categorization. Rates of hospital admissions and mortality were calculated during the entire study period per patient basis.

Results: We analyzed data on 135,340 dialysis patients and identified that 9,929 (8%) took MBD medications inconsistently or not at all. Overall, we found lower rates of hospitalizations and mortality in patients who were determined to be adherent to their MBD medications versus those who were non-adherent. The hospitalization rate was 2.1 admissions per patient year (ppy) for the non-adherent group and 1.7 ppy for the patients taking MBD medication as prescribed (p<0.001 using Poisson regression). There were 9.3 deaths per 100 patient years (p100py) in the non-adherent group, and 8.8 p100py in the adherent group (p<0.0013 using a Kaplan Meier analysis).

Conclusions: In dialysis patients with bone disorders, MBD medication adherence appears to be associated with hospitalization and mortality outcomes. Importantly, these results are only reflective of patients with bone disorders and not the overall dialysis population. Further analyses are needed to understand root causes for dialysis patient medication non-adherence.

Funding: Commercial Support - Fresenius Medical Care North America

Clinical implications. Our aim is to associate the magnitude of changes in phosphate concentration with survival taking into account its initial value.

Methods: At quarterly intervals data on phosphate are available in a subset (N=5,487) of the Dutch renal replacement registry. Patients were followed from the date of the first available measurement until death or censoring (transplantation, recovery of renal function, lost to follow-up, end of study period). Time-updated Cox regression analysis was performed with phosphate as well as changes in phosphate between subsequent measurements as continuous exposure variables. To allow for non-linear associations penalized splines smoothing was used. The analyses with changes were also performed stratified for categories of initial phosphate level. Adjustments were performed for age, sex, primary kidney disease, vintage, year of baseline, dialysis modality, previous transplantation.

Results: Both phosphate levels and phosphate changes showed a non-linear, U-shaped association with mortality. Lowest mortality was found for phosphate levels around 1.25 mmol/L. A gradually increase in benefit of phosphate decrease was observed across strata of initial phosphate level (from < 1.5 mmol/L to > 2.00 mmol/L), suggesting a U-shaped association with mortality. Lowest mortality was found for phosphate levels in the range of 1.50 mmol/L to 2.00 mmol/L.

Conclusions: Patients with higher baseline phosphate concentrations appear to benefit from a greater absolute decline. Our data reinforce current clinical practice aiming at a target range for dialysis patients with hyperphosphatemia, instead of a fixed absolute decline.

Funding: Commercial Support - Fresenius

TH-PO1041

Effects of Mineral Bone Disorder Medication Non-Adherence on Dialysis Patient Outcomes

Methods: In this retrospective cohort analysis, we included all patients dialyzed at Fresenius Kidney Care clinics between 2006 and 2016. Patients were characterized based on their MBD medication adherence levels per dietician assessment and categorized as: 1) “taking the medication as prescribed”, and 2) “taking the medication inconsistently or not at all.” The most recent MBD medication adherence assessment per patient was utilized for categorization. Rates of hospital admissions and mortality were calculated during the entire study period per patient basis.

Results: We analyzed data on 135,340 dialysis patients and identified that 9,929 (8%) took MBD medications inconsistently or not at all. Overall, we found lower rates of hospitalizations and mortality in patients who were determined to be adherent to their MBD medications versus those who were non-adherent. The hospitalization rate was 2.1 admissions per patient year (ppy) for the non-adherent group and 1.7 ppy for the patients taking MBD medication as prescribed (p<0.001 using Poisson regression). There were 9.3 deaths per 100 patient years (p100py) in the non-adherent group, and 8.8 p100py in the adherent group (p<0.0013 using a Kaplan Meier analysis).

Conclusions: In dialysis patients with bone disorders, MBD medication adherence appears to be associated with hospitalization and mortality outcomes. Importantly, these results are only reflective of patients with bone disorders and not the overall dialysis population. Further analyses are needed to understand root causes for dialysis patient medication non-adherence.

Funding: Commercial Support - Fresenius Medical Care North America
A Novel, Selective, and Non-Systemic Na+/H+ Exchanger 3 Inhibitor, THP0469711, Potently Enhances Phosphate Excretion with a Favorable Gastrointestinal Tolerability in Rats


Background: Na+/H+ Exchanger 3 inhibitor is known to enhance the excretion of phosphate and expected as a new candidate for anti-hyperphosphatemia drug. However, Na+/H+ inhibitor also causes diarrhea frequently because of the excessive enhancement of Na excretion.

Methods: NHE1, NHE2 and NHE3 activities of THP0469711 (TP) were evaluated by measuring intracellular pH recovery in each NHE over-expressing cells. Na-dependent phosphate transporter 2b (NaPi2b) activity was evaluated by uptake of 32P phosphate in NaPi2b over-expressing cells. To examine the effect of TP on the phosphate absorption and excretion, the radioactivity of 32P phosphate in the blood and feces were measured using [32P]-orthophosphate. The effects of NHE3 by TP were evaluated by measuring pH and luminal Na content in the intestinal tract. Na excretion and water content in feces up to 24 hours were evaluated after oral dosing of TP in rats.

Results: TP inhibited human and rat NHE3 activities with IC50 values of 2.2 and 2.1 nM, respectively. However, TP (3 μM) had no effects on human NHE1, NHE2 and NHE2 activities. Oral administration of TP increased pH of luminal content in the upper intestine in a dose-dependent manner in rats. TP (0.1 mg/kg, p.o.) significantly decreased the area under the curve of plasma 32P phosphate radioactivity by 40.7 ± 4.7 % (n=5, P < 0.001). TP (0.1 mg/kg, p.o.) increased the fecal excretion of phosphate by 62.5% (n=6, P < 0.005), without affecting Na excretion and water content in feces. TP significantly enhanced the excretion of Na and increased water content at a higher dose of 1 mg/kg (n=7, P < 0.001). Over dose of TP (30 mg/kg, p.o.) did not raise plasma concentration (<1 mg/ml), which means TP is a non-systemic NHE3 inhibitor.

Conclusions: We discovered a novel, selective and non-systemic Na+/H+ Exchanger 3 inhibitor, TP0469711, which potently excreted phosphate into feces with a favorable gastrointestinal tolerability in rats. TP is suitable for a new therapeutic agent for the treatment of hyperphosphatemia in patients with end-stage renal disease.

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

TH-PO1047

Efficacy of Tenapanor to Treat Hyperphosphatemia in Patients on Hemodialysis


Background: Tenapanor (TEN) is a small molecule NHE3 inhibitor that reduces Gi sodium and phosphate absorption. This is the first study in haemodialysis patients to test safety, efficacy and tolerability.

Methods: This single arm, open label, dose escalation study used VS-505 in haemodialysis patients, stable on treatment for over 12 weeks. Plasma phosphate (Pi) level had to be between 6 - 10 mg/dl after a 2 weeks wash out from current PB. Other treatment, and dialysis modality remained unchanged. Treatment with VS-505 was 8 weeks with 2-weekly dose escalations, guided by Pi levels, from 1.5 g/dy to 9 g/dy. From screening to treatment day 22, lab parameters were followed weekly, then fortnightly. Primary Efficacy Endpoint was the Pi change during treatment. Secondary Efficacy Parameters were Time to next dose, Area under the curve to end of treatment and Plasma Calcium (Ca) change. Other criteria were trajectory of Iron Parameters, standard dialysis bloodlosses, and Electro-Cardiograms. Tolerability was evaluated with questionnaires. Endpoints analysis is intended to Treat to Full Analysis Set and a Per Protocol Set. A last Observation Forward was applied for patients not completing the study.

Results: Sixteen patients were enrolled. 11 withdrew consent: 3 for diarrhea after dose escalation, 8 for medication-related AE’s. 30% of all patients reported black stools (iron). Only one subject received full dose escalation to 9 g/dy, 4 reported abdnominal pain after the escalation to 4.5 g/dy. No changes of iron parameters were found. Routine parameters remained unchanged. Plasma Pi was significantly reduced in the treatment group, median Pi change -2.40 mg/dl (-30.9%, p<0.0001). Significant lowering of Pi levels were already observed at the lowest given dose of VS-505. There was no change Ca levels, but a significant reduction in iPTH over the treatment period. Conclusions: VS-505 is a promising, effective, safe and well-tolerated PB for the treatment of hyperphosphatemia with advantages over current drugs. Further studies in larger numbers of patients are warranted to find its exact place in routine treatment.

Funding: Commercial Support - KDL Inc, Japan

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Impact of Admission Serum Phosphate Levels on Mortality in Hospitalized Patients

Methods: All adult hospitalized patients who had admission serum phosphate available between years 2009 and 2013 were enrolled. Admission serum phosphate was categorized based on its distribution into six groups (<2.5, 2.5-3.0, 3.1-3.6, 3.7-4.2, 4.3-4.8 and >4.9 mg/dL). The odds ratio (OR) of in-hospital mortality by admission serum phosphate, using the phosphate category of 3.1-3.6 mg/dL as the reference group, was obtained by logistic regression analysis. Pre-specified subgroup analysis stratified by chronic kidney disease (CKD) and cardiovascular disease (CVD) status was performed.

Results: 42,336 patients were studied. The lowest incidence of in-hospital mortality was associated with a serum phosphate within 3.1-4.2 mg/dL. A U-shaped curve emerged demonstrating higher in-hospital mortality associated with both serum phosphate <3.1 and >4.2 mg/dL. After adjusting for potential confounders, both serum phosphate <2.5 and >4.2 mg/dL were associated with an increased risk of in-hospital mortality with ORs of 1.60 (95% CI 1.25-2.05), 1.60 (95% CI 1.29-1.97) and 3.89 (95% CI 3.20-4.74) when serum phosphate were within <2.5, 4.3-4.8 and >4.9 mg/dL, respectively. Among subgroups of patients with CKD and CVD, the highest mortality was associated with a serum phosphate <4.9 mg/dL. ORs of 4.11 (95% CI 3.16-5.39) in patients with CKD and 5.11 (95% CI 3.33-7.95) in patients with CVD while serum phosphate <2.5 mg/dL was associated with increased in-hospital mortality in patients with CVD (OR 3.24, 95% CI 1.82-5.58), the risk was not significantly increased among CKD patients with serum phosphate <2.5 mg/dL.

Conclusions: Hospitalized patients with admission serum phosphate <2.5 and >4.2 mg/dL are associated with an increased risk of in-hospital mortality. In addition, CKD and CVD patients with hyperphosphatemia at admission (>4.9 mg/dL) carry the highest mortality risk.

Mineral Bone Disease after Kidney Transplantation

Background: Mineral bone disorder (MBD), such as hypercalcemia and hypophosphatemia, frequently occurs after kidney transplantation (KT), and its evidence has accumulated. However, the relationship between pre-KT dialysis vintage and post-KT MBD has not been evaluated in detail.

Methods: Ninety-six patients who underwent KT were included. Patients with parathyroidectomy during pre-KT and the 12 months post-KT were excluded. We compared the natural history of post-KT MBD between pre-emptive KT (PKT) and non-PKT. Furthermore, non-PKT group was divided into 3 groups according to the dialysis vintage; <3 years, 3-6 years, >6 years. Parameters of MBDs and kidney function were followed at pre-KT, 1 and 2 weeks, and 1, 2, 3, 6 and 12 months post-KT. We also checked pre-KT parathyroid enlargement by ultrasound evaluation.

Results: Serum calcium levels increased and reached a plateau at the 2 months post-KT in all the groups. Patients with longer dialysis vintage had higher serum calcium levels from the 1 week post-KT, and particularly the group with dialysis vintage > 6 years had persistent hypercalcemia, which was significantly higher serum calcium levels from the 1 month to 12 months post-KT compared to the other groups. Serum phosphate levels substantially decreased until the 1 week post-KT, after which it gradually increased in all the groups. The non-PKT group had significantly lower serum phosphate levels compared to the PKT group from the 1 week to 3 months post-KT, but there was no significant difference depending on dialysis vintage. PTH levels were significantly higher in the PKT group compared to the non-PKT group at pre-KT, but substantially decreased in the PKT group to almost the same levels as the other groups until the 1 month post-KT. The group with dialysis vintage > 6 years had higher prevalence of pre-KT parathyroid enlargement and persistent higher PTH levels during the 12 months post-KT, and its levels were significantly higher at the 12 months post-KT compared to the other groups. Kidney function was comparable among all the groups during the 12 months post-KT.

Conclusions: Our findings suggest that patients with longer dialysis vintage have persistent higher serum calcium levels just after KT, and its levels are significantly higher especially in dialysis vintage > 6 years probably due to persistent parathyroid hyperplasia.

Serum Lithium (Li) Values within Recommended Range May Induce Changes in Renal Tubular Function and Calcium Homeostasis in Patients with Bipolar Disorder (BD)

Background: Li is the first choice for maintenance treatment of patients with BD. However, Li can induce nephrogenic insipidus diabetes and some patients may develop asymptomatic hypercalcemia because Li may cause primary hyperparathyroidism.

Methods: Thus, we studied 76 patients with BD treated with or without Li by a cross-sectional analysis. We collected blood (B) and 24-hour urine (U) samples to evaluate renal function, electrolyte homeostasis and serum (S) hormone levels.

Results: As shown in the Table, we studied more women than men, but they had similar age, eGFR, and S Li values were within recommended range. Both women and men treated with Li had higher U pH and lower U density than Non-Li-treated patients. Li-treated women had also higher levels of 5 PTH, S ionized Ca (S iCa) than that of other

Table 1: Evolution of mineral parameters after kidney transplant

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-transplant (mg/dL)</th>
<th>Post-transplant (mg/dL)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH (pg/mL)</td>
<td>male</td>
<td>30.4</td>
<td>91.6</td>
</tr>
<tr>
<td>P (mg/dL)</td>
<td>none</td>
<td>5.77</td>
<td>3.00</td>
</tr>
<tr>
<td>Ca (mg/dL)</td>
<td>none</td>
<td>8.90</td>
<td>9.72</td>
</tr>
</tbody>
</table>
groups. Moreover, Li-treated women showed a positive correlation between high levels of S iCa and increases of S PTH, diuresis and U pH and low U density when we plotted levels of S iCa and low levels of S PTH, diuresis and U pH and high U density when we plotted levels of S iCa. 

Conclusions: induced changes in both parathyroid and renal tubular function without clinical manifestations justifying a periodically monitored surveillance especially in women patients.

Funding: Government Support - Non-U.S.

TH-PO1053
Association between Mineral Metabolism Parameters and Carotid Intima Media Thickness in a Cardiovascular Risk Population (CORDIOPREV Study) Maria Encarnacion Rodriguez Ortiz,1 Francisco Gomez-Delgado,2 Antonio Arenas-Larivia,3 Antonio Canalejo,4 Purification Gomez-Luna,5 Carmen Maria Herencia,6 Javier Lopez-Moreno,7 Mariano Rodriguez,2 Yolanda Almada peña,2 1Instituto Maimonides de Investigacion Biomedica de CORDIOPREV. Reina Sofia University Hospital/University of Cordoba, Cordoba, Spain; 2Lipid and Atherosclerosis Unit. IMIBIC/Reina Sofia University Hospital/University of Cordoba, and CIBER Fisiopatologia Obesidad y Nutricion (CIBEROBEN), Instituto de Salud Carlos III, Cordoba, Spain; 3Department of Integrated Sciences, University of Huelva. Hospital Universitario Reina Sofia, Instituto Maimonides de Investigacion Biomedica de CORDIOPREV. Reina Sofia University Hospital/University of Cordoba, Cordoba, Spain.

Background: Cardiovascular diseases (CVD) are the main cause of mortality in patients with Mineral Metabolism (MM) alterations, as those with CKD. Thus, factors related to MM may play a key role in the onset and development of CVD. Carotid intima media thickness (IMT-CC) has shown strong associations with well-recognized risk factors of CVD and it is a predictor of coronary artery disease. The aim of this study was to assess whether there is an association between some key parameters of MM and the IMT-CC in a cardiovascular risk population.

Methods: This work was carried out in the setting of the CORDIOPREV study (Clinical Trial Registration NCT000493741), a prospecitive, randomized, controlled trial including 1,002 patients aged 20-75 years with coronary heart disease. Carotid arteries were examined bilaterally using a Doppler ultrasound high-resolution B-mode. IMT-CC was calculated as the mean of three measurements. Basal plasma levels of FGF23, CaSR, P, creatinine (Cr), Mg, 25-OH and calcium (Ca) were measured.

Results: As shown in the table (mean±SE), a significant inverse relationship was observed between IMT-CC and eGFR and Mg, while Cr and FGF23 were directly associated with IMT-CC.

Conclusions: Even within the normal range, there was an association between some MM parameters and the IMT-CC in a cardiovascular risk population. Thus, these factors might be useful for the monitoring of CVD. Grant ISCIII (PI14/00872)

<table>
<thead>
<tr>
<th>WOMEN</th>
<th>MEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>S iCa (mg/dL)</td>
<td>9.54±0.11</td>
</tr>
<tr>
<td>Ca (mg/dL)</td>
<td>9.70±0.13</td>
</tr>
<tr>
<td>P (mg/dL)</td>
<td>3.57±0.19</td>
</tr>
<tr>
<td>Mg (mg/dL)</td>
<td>1.89±0.03</td>
</tr>
<tr>
<td>FGF23 (pg/ml)</td>
<td>5.92±0.25</td>
</tr>
</tbody>
</table>

TH-PO1055
Functional Analysis of Gcm2 in Adult Gcm2 Conditional Knockout Mice Yamada Taku,1 Norifumi Tatsumi,2 Sahoko Kamejima,2 Taketo Uchiyama,2 Ichiho Ohkido,2 Masataka Okabe,2 Takashi Yokoo,4 1Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan; 2Division of Nephrology and Hypertension, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan; 3Jikei University School of Medicine, Tokyo, Japan; 4The Jikei University School of Medicine, Tokyo, Japan.

Background: Gcm2 is exclusively expressed in the parathyroid gland (PTG). The specific role of mice Gcm2 in the development of PTG from the third pharyngeal pouch has been further investigated, although its function in adult mice remains largely unknown. Gcm2 directly regulates calcium-sensing receptor (CaSR) and transactivates it through Gcm2 response elements in the CaSR promoter, which has important implications for the exacerbation of CKD-MBD. Accordingly, it is possible that Gcm2 plays a crucial role in CKD-MBD and particularly, in secondary hyperparathyroidism (SHPT).

Methods: We generated Gcm2 conditional knockout mice in which loxp sites flanked exons 2 and 3 in the Gcm2 allele. We then crossed these mice with tamoxifen-inducible Cre strain. Next, we intraperitoneally injected 40 mg/kg of tamoxifen into 8-week-old mice for five days. The mice were sacrificed one (1KO mice) and seven (7KO mice) months after tamoxifen administration. We then investigated their serum biochemistry and performed histological analysis.

Results: Serum biochemical parameters of 1KO mice were not significantly different when compared with those of control mice. However, compared with control mice, a significant increase in the serum phosphate level and significant decrease in Gcm2 and parathyroid hormone levels were confirmed in the 1KO mice. Staining of PTG with HE showed that normal structure was generally conserved in 1KO mice, except for the presence of a few follicles, whereas normal structure was not conserved in 7KO mice and their PTGs showed many follicles.

Conclusions: 7KO mice showed hypocalcemia, hyperphosphatemia, low parathyroid hormone level, and many follicles in PTG. In addition, normal PTG structure was not observed in these mice. These results suggest that the loss of function of Gcm2 at an adult age leads to hyperparathyroidism, as observed in congenital Gcm2 knockout mice. This animal model is useful to study distinct roles of Gcm2 at different ages and the relationship between Gcm2 and CKD-MBD, particularly SHPT.

Funding: Private Foundation Support

TH-PO1056
3’UTR Regulates the Baseline Protein Abundance and Activity of Mouse NaPi-IIa Hassan Amal, Sulaiman Sheriff, Perwez Alam University of Cincinnati, Cincinnati, OH.

Background: The apical sodium-phosphate cotransporter NaPi-IIa plays an important role in the control of phosphate balance by regulating the rate of inorganic phosphate reabsorption in the kidney proximal tubule. We have previously shown that the 3’-untranslated region (3’UTR) of NaPi-IIa mRNA transcript plays an important role in the post-transcriptional regulation of NaPi-IIa in response to estrogen. However, whether 3’UTR regulates the baseline expression of NaPi-IIa has not been studied.

Methods: We have studied the role of 3’UTR in mNaPi-IIa expression and activity using OK cells transfected with mammalian expression plasmids containing the open-reading frame (ORF) 3’-UTR or 5’-UTR ORF or the full-length (FL) mouse NaPi-IIa transcript. Immunoblotting, Real-time PCR and 32P uptake studies were performed. Further, the role of microRNAs (miRNA) in the function of mNaPi-IIa 3’UTR was examined by luciferase assay using the miRNA target expression vector. Full-length mNaPi-IIa 3’UTR or 4 overlapping (~250bp) fragments (F1-F4 from stop codon) were generated by PCR and individually sub-cloned into the miRNA target expression vector. Subsequently, chimeras of 5’UTR-ORF (F1 to F4) were generated in mammalian expression vector and used to examine the expression of mNaPi-IIa protein in OK cells by immunoblotting.

Results: The protein abundance of mNaPi-IIa is increased by 3-fold in OK cells transfected with 3’UTR-free plasmid (i.e., 5’-ORF), as compared to FL or ORF-3’UTR. The protein abundance of mNaPi-IIa is increased by 3-fold in OK cells transfected with 5’-UTR or 3’-UTR ORF, as compared to FL or ORF-3’UTR. Real-time PCR data showed no difference in the mRNA expression levels between the 3 plasmid constructs. Normalized luciferase activity was increased by 36%, 74%, 54% and 27% for F1 to F4 fragments, respectively, compared to 3’UTR. Interestingly, the protein abundance of NaPi-IIa was significantly reduced in cell transfected with all F1 to F4 chimeras, with a more profound reduction in chimeras 5’UTR-ORF-F4, as compared to 5’UTR-ORF construct.

Conclusions: 3’UTR regulates the baseline expression of mouse NaPi-IIa protein abundance and activity in OK cells. This phenomenon is mediated through a sequence specific post-transcriptional mechanism involving microRNAs, which interact with cis-acting elements distributed throughout the 3’UTR.

Funding: NIDDK Support, Clinical Revenue Support
**TH-PO1056**

**Transition from Low to High Dietary Phosphate Reduces Serum Calcium but Increases Vascular Calcification in Experimental CKD**

**Cynthia M. Pruss, Kimberly J. Laverty, Emilie C. Ward, Bruno A. Svaiger, Paul S. Jeronimo, Mandy E. Turner, Martin P. Petkovich, Rachel M. Holden, Michael A. Adams. Queen’s University, Kingston, ON, Canada.**

**Background:** Chronic kidney disease (CKD) impairs phosphate (PO₄) homeostasis resulting in hyperphosphatemia, which is associated with cardiovascular events and vascular calcification (VC). Animal models of CKD demonstrate pathologies and outcomes similar to those of CKD patients. We examined the impact of dietary phosphate loading on markers of mineral metabolism in controlled adenine-induced CKD.

**Methods:** Sprague Dawley rats were fed a 0.25% adenine, 0.5% PO₄ diet for 4.5 weeks to induce stable CKD (creatinine>250 μM), then fed 0.5% PO₄ diet without adenine. At 5.5 weeks, rats were fed either 0.5%, 1% or 1.5% PO₄ diet, N=9, 10, 6, while another group (N=21) was fed increasing dietary PO₄ every 4 days (0.5%→0.75%→1%→1.5%). Controls were fed 0.5% PO₄ diet (N=8). Serum calcium (Ca), PO₄, FGF-23, PTH, and tissue Ca and PO₄ were determined.

**Results:** At 5 weeks, CKD rats vs control had 3.2±0.6 vs 2.5±0.3 mM PO₄ and 2.8±0.2 vs 2.4±0.1 mM Ca. Off adenine, the 0.5% group was at control PO₄ levels but had elevated Ca at 6.5 weeks. At 7 weeks, the 1.0 and 1.5% groups had marked increases in PO₄, PTH and FGF-23, while Ca dropped. VC was observed in 80% of high PO₄ rats (1 or 1.5%). In the increasing dietary PO₄ group, serum group (N=21) was fed increasing dietary PO₄ every 4 days (0.5%→0.75%→1%→1.5%). Controls were fed 0.5% PO₄ diet (N=8). Serum calcium (Ca), PO₄, FGF-23, PTH, and tissue Ca and PO₄ were determined.

**Conclusions:** In our CKD model, 0.5% PO₄ diet increased serum Ca but did not induce VC. A marked increase in PO₄ of 1% or more led to significant decreases in serum Ca, but generated high serum PO₄, FGF-23, PTH and VC. These findings uncover a new link between dietary PO₄ and Ca and serum Ca.

**Funding:** Commercial Support - OPKO Health, Inc. Renal Division, Government Support - Non-U.S.

---

**TH-PO1057**

**Regulation of Intestinal Phosphate Transport in a Rat Model of CKD**

**Komuraiah E., Eileen M. Sutherland, 1University of Colorado, Denver, CO; 2University of Colorado, Aurora, CO; 3University of Colorado, Denver, CO; 4University of Colorado Denver, Aurora, CO; 5University of Colorado Denver, Aurora, CO; 6University of Colorado, Denver, Aurora, CO.**

**Background:** In chronic kidney disease (CKD) hyperphosphatemia is a common occurrence and plays important roles in cardiovascular and bone disease. The mechanisms however still remain unknown and the role of intestinal phosphate (Pi) transport is subject of ongoing debate.

**Methods:** We studied regulation of intestinal phosphate transport in a model of 5/6 nephrectomy (Nx) induced CKD in the rat fed a relatively high Pi diet (1.5%, 0.6% Ca). Male rats with 5/6 Nx had a marked increase in serum BUN (37.7±2.0 vs. 150.5±29.8 mg/dl in sham control; p<0.02), serum creatinine (0.5±0.06 vs. 1.65±0.23 mg/dl in sham control; p<0.008), and serum Pi (7.48±0.85 vs. 18.19±1.84 mg/dl in sham control; p<0.001). We isolated apical brush border membrane vesicles (BBMV) from the duodenum and the jejunum and studied sodium gradient dependent Pi (Na+/Pi) cotransport as a function of pH. Across every single pH studied, including 5.5, 6.0, 6.5, 7.0, and 7.5 Na+/Pi transport activity was increased in BLM. VC was observed in 80% of high PO₄ rats (1 or 1.5%). In the increasing dietary PO₄ group, serum group (N=21) was fed increasing dietary PO₄ every 4 days (0.5%→0.75%→1%→1.5%). Controls were fed 0.5% PO₄ diet (N=8). Serum calcium (Ca), PO₄, FGF-23, PTH, and tissue Ca and PO₄ were determined.

**Results:** At 5 weeks, CKD rats vs control had 3.2±0.6 vs 2.5±0.3 mM PO₄ and 2.8±0.2 vs 2.4±0.1 mM Ca. Off adenine, the 0.5% group was at control PO₄ levels but had elevated Ca at 6.5 weeks. At 7 weeks, the 1.0 and 1.5% groups had marked increases in PO₄, PTH and FGF-23, while Ca dropped. VC was observed in 80% of high PO₄ rats (1 or 1.5%). In the increasing dietary PO₄ group, serum group (N=21) was fed increasing dietary PO₄ every 4 days (0.5%→0.75%→1%→1.5%). Controls were fed 0.5% PO₄ diet (N=8). Serum calcium (Ca), PO₄, FGF-23, PTH, and tissue Ca and PO₄ were determined.

**Conclusions:** In our CKD model, 0.5% PO₄ diet increased serum Ca but did not induce VC. A marked increase in PO₄ of 1% or more led to significant decreases in serum Ca, but generated high serum PO₄, FGF-23, PTH and VC. These findings uncover a new link between dietary PO₄ and Ca and serum Ca.

**Funding:** Commercial Support - OPKO Health, Inc. Renal Division, Government Support - Non-U.S.

---

**TH-PO1058**

**The Role of Gut Microbiota in Phosphorus Metabolism in Maintenance Hemodialysis Patients Yuanvi Miao,1 Min Xia,2 Yuqing Chen.2 Peking University First Hospital, Beijing, China; 2Renal Division, Peking University First Hospital, Beijing, China.**

**Background:** Disturbance of phosphorus metabolism is a risk factor associated with mortality in hemodialysis patients. Gut absorption is the major source of phosphorus. Recent studies indicated that the intestinal flora of uremic patients changed a lot. And phosphorus is an essential element of bacterial survival and reproduction. The purpose of the study was to explore the role of intestinal microbiota in the control of serum phosphorus.

**Methods:** Microbial DNA was isolated from the stools of 20 healthy controls and 21 maintenance hemodialysis patients from one hemodialysis center. 14 out of the 21 patients were treated with Lanthanum carbonate for 12 weeks, while stools were also collected before and after the treatment. The bacterial composition was analyzed by 16S ribosomal RNA pyrosequencing. Bioinformatics tools, including abundance profiling, taxonomic diversity and correlation analyses were used in microbiome data analyses.

**Results:** Clinical biochemical traits were compared before and after the use of Lanthanum carbonate in MHD patients. The serum phosphorus decreased after using Lanthanum carbonate for 12 weeks (P<0.001). There was no difference in other traits. 13 genera were closely correlated with serum phosphorus and the correlation coefficient was above 0.6 (P<0.05). And 11 genera were positively related to serum phosphorus, suggesting that survival of the 11 genera were related to phosphorus. We also found that 2 genera were negatively related to serum phosphorus, indicating that the 2 bacteria may be involved in the absorption process of phosphorus. 58 bacterial operational taxonomic units (OTUs) were different before and after the use of phosphorus binder. More decreased OTUs were identified after using phosphorus binder. 7 genera were obviously reduced, including Centipedia, Chryseobacterium, Gemella, unclassified, Rhodocyclaceae, Pelomonas, Carvibacter and Parvimonas. Furthermore, the microbial richness and diversity decreased in hemodialysis patients and declined further after phosphorus reduction.

**Conclusions:** Gut flora is related to phosphorus metabolism in hemodialysis patients, and improving intestinal microbiota may regulate the absorption of phosphorus in the intestine. The use of phosphorus reduction drugs lead to decreased microbial richness and diversity.

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

---

**TH-PO1059**

**Vessels Are an Important Depot for Phosphate in Response to an Oral Load in an Experimental Model of CKD Mandy E. Turner, Paul S. Jeronimo, Emilie C. Ward, Kimberly J. Laverty, Rachel M. Holden, Michael A. Adams. Queen’s University, Kingston, ON, Canada.**

**Background:** Disregulated phosphate (PO₄) homeostasis contributes to increased cardiovascular risk in CKD patients, in part due to vascular calcification. We sought to determine if tissue deposition of PO₄ following an oral PO₄ load was altered by level of kidney function and changes in dietary PO₄.

**Methods:** CKD was induced in rats using dietary adenine (0.25%, 0.5% PO₄). At 6 weeks, adenine was stopped and animals were fed either low phosphate (LP) (0.5%, N=48) or high phosphate (HP) (1.0%, N=24) diet for 2 weeks. Non-CKD animals followed a parallel protocol (0.5%, N=12 and 1.0%, N=12). Prior to sacrifice, 6 hr fasted animals consumed 0.1g of PO₄ spiked with ~5mil CPM of ³¹PO₄ for measurement of ³¹PO₄ in blood vessels.

**Results:** The pattern of tissue disposition of PO₄ was altered by kidney function and changes in dietary PO₄. Vessels were an important depot for phosphate in response to an oral load in a model of CKD.

**Funding:** Government Support - Non-U.S.
Conclusions: Changing from an LP to a HP diet in experimental CKD produces maladaptive responses in vascular tissue resulting in preferential and sustained vascular deposition of phosphate that likely associates with the vascular calcification phenotype.

Funding: Government Support - Non-U.S.

TH-PO1060

Phosphate Stimulates Myotube Atrophy through Autophagy Activation – Evidence That Hyperphosphatemia Contributes to Skeletal Muscle Wasting in CKD  

Yue Yue Zhang, Wei Jie Yuan. Shanghai General Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China.

Background: Although evidence indicates that autophagy is involved in the maintenance of muscle homeostasis, it is unidentified if high phosphate could stimulate the activation of autophagy leading to muscle protein loss.

Methods: Immortalized rat L6 myotubes were exposed to a high concentration of phosphate with or without autophagy inhibition. Myotube atrophy was examined by the expression of microtubule associated protein 1 light chain 3 (LC3) and p62 using quantitative real-time PCR and western blot.

Results: Phosphate induced cell atrophy in L6 myotubes with a dose- and time-dependent fashion and these response were not associate with the development of calcification or osteogenesis. Phosphate also dose- and time-dependently increased the abundance of claudin-4 (85 ± 11% vs. 100 ± 23% and mRNA (49 ± 33% vs. 100 ± 17%) expression significantly decreased by phosphate, though serum phosphate and insulin-like growth factor-1 (IGF-1) levels were measured.

Conclusions: High concentration of phosphate induces muscle cell atrophy through the activation of autophagy. Targeting autophagy could be a therapeutic strategy for muscle wasting caused by hyperphosphatemia.

TH-PO1061

Phosphate Retention Induces Growth Retardation in Adolescent Mice  

Makoto Kubo,1 Kazuhiro Shiizzaki,2 Yosithaka Iwazu,3 Yutaika Miura,4 Kenichi Akiyama,1 Yoshihiro Nakano,5 Ruri Kameda,1 Hiroshi Kurosu,1 Makoto Kuro-o,1,2 Jichi Medical University, Shizua, Japan; 3Tokyo Women’s Medical University, Tokyo, Japan.

Background: Growth retardation is a major problem of chronic kidney disease (CKD) in adolescence. It is well known that the effect of supplementation of growth hormone (GH) is not sufficient, so more effective treatments have been requiring. CKD causes the phosphate retention and this control is very difficult due to the nutritional concern. We hypothesized that phosphate retention might be one of pathogenesis of growth retardation in adolescence with CKD.

Methods: Female C57BL/6J mice were fed the regulated diets consists of various amount of phosphate from four to eight weeks old. Body weight, femur length and serum phosphate and insulin-like growth factor-1 (IGF-1) levels were measured. The target genes of GH including IGF-1, acid-labile subunit (ALS), major urinary proteins (MUP) 1 and 3, solute carrier organic anion transporter family member 1a1 (SLCO1A1), and hydroxysteroid dehydrogenase 3f5 (HSD3B5) mRNA, IGF-1 binding protein-1 (IGFBP-1) mRNA as an inhibitor marker of IGF-1 signaling and signal transducers and activators of transcription (STAT) 5 protein levels were evaluated in liver.

Results: The remarkable growth retardation with significantly high phosphate and low IGF-1 levels in serum were confirmed in mice fed the highest phosphate diet. The significantly lower expression levels in all of target genes of GH and STATA5 protein, and higher expression level in IGFBP-1 mRNA were also observed. The mice fed the middle phosphate diets showed the significantly lower levels in serum IGF-1 and in target gene expressions of GH compared with those fed the normal phosphate diet but not growth retardation.

Conclusions: The phosphate retention induces the growth retardation resulting from the inhibitions of both GH and IGF-1 signaling. Its moderate restriction might improve the growth retardation resulting from the improvement of the resistance to IGF-1 even though serum IGF-1 level was low. These findings suggest that the controlling phosphate retention using the phosphate binders and dietary restriction should be considered in adolescent CKD patients who require the supplementation of GH.

TH-PO1062

Alteration of Renal Claudins in Rats with Hypercalcemia  

Gheun-Ho Kim. II Iuhan Oh. Hanyang University College of Medicine, Seoul, Republic of Korea.

Background: Ninety-eight to 99% of the filtered load of calcium is reabsorbed by the renal tubules. Whereas most of the calcium reabsorption passively occurs in the proximal tubule through tight junctions, the distal nephron has been known as the major site for regulation of calcium excretion. Claudins form the conductive and selective part of the paracellular calcium transport, which is regulated by high calcium or salt intake. We hypothesized that the calcium transport in the distal nephron is regulated by high calcium or salt intake, thereby calcium transport might be disturbed during hypercalcemia.

Methods: Male Sprague-Dawley rats were used for three different animal protocols: CaCO3, NaCl, and NH4Cl loading. The rats were randomly divided into control (n=6) and treated (n=6) group in each experiment, and a daily fixed amount of food flurry was given to each rat. The control diet contained 0.8% calcium and 0.3% NaCl, and the treated diet had additional CaCO3 (6%), NaCl (7%), or NH4Cl (7.2 mmol/220 g BW) for 7 days. Plasma and urine data were followed, and kidneys were harvested for immunoblotting and qPCR analysis at the end of our animal experiment.

Results: Hypercalcemia was successfully induced by CaCO3, NaCl, and NH4Cl loading, and fractional excretion of calcium was significantly increased by the loading of CaCO3 (5.00 ± 0.92 vs. 0.27 ± 0.08%, P < 0.05), NaCl (2.07 ± 0.57 vs. 0.25 ± 0.27%, P < 0.05), and NH4Cl (0.90 ± 0.36 vs. 0.27 ± 0.12%, P < 0.05). The abundance of claudin-2 protein was not significantly altered by CaCO3 or NaCl loading, but both claudin-2 protein (85 ± 9 vs. 100 ± 11%, P < 0.05) and mRNA (49 ± 33 vs. 100 ± 17%, P < 0.05) expression were significantly decreased by NH4Cl loading. Expression of claudin-3 protein was significantly increased by CaCO3 loading (29 ± 14 vs. 100% ± 34%, P < 0.05).

Conclusions: We confirmed that hypercalcemia in metabolic acidosis is associated with claudin-2 down-regulation in the proximal tubule. However, hypercalcemia induced by high calcium or salt intake was not accompanied by claudin-2 dysregulation. Further studies are required to investigate the regulatory role of paracellular calcium transport in the distal nephron.

TH-PO1063

Green Tea (GT) Increases Urinary Excretion of Calcium and Phosphorus, but These Effects Were Not Due to Caffeine (CAF)  

Claudia Helou,1 Igor O. Da silva,1 Talita R. Sanches,2 Mirela Santininho,1 Lucia Andrade,2 1Lab Pesquisa Basica LIM12 Fac Medicina Univ Sao Paulo, SP, Brazil; Sao Paulo, Brazil; 2University of Sao Paulo School of Medicine, Sao Paulo, Brazil.

Background: The consumption of industrialized (i) or natural (n) GT increases worldwide because this beverage is rich in antioxidant. However, there is a lack of studies about GT effect on the renal tubular function and a possible role exerted by the presence of CAF.

Results: Changes in renal output of calcium and phosphorus were assessed in rats fed with iGT, nGT, CAF, or CAF with GT (GT+CAF). The consumption of GT significantly increased calcium excretion in both groups (61 ± 15 vs. 20 ± 7 mg/kg/day, P < 0.05). The consumption of GT increased phosphorus excretion in a dose-response manner (2 ± 1 vs. 11 ± 3, 23 ± 11 mg/kg/day, P < 0.05). The consumption of GT+CAF significantly increased phosphorus excretion compared to CAF alone (3 ± 1 vs. 11 ± 3 mg/kg/day, P < 0.05).

Conclusions: The increase in urinary calcium and phosphorus excretion was not due to CAF.
Methods: Thus, we housed Male Wistar rats in individual cages and randomly assigned them to have ad libitum access to tap water (W), G7T (Feel Goods), nGT or 8 mg/kg CAF dissolved in tap water. On day 8, we moved them to metabolic cages and collected 24-h urine samples. The rats were then anesthetized, and we placed a catheter in abdominal aorta to measure blood pressure (BP) and collect blood samples. We quantified creatinine and electrolytes in urine and plasma samples. We removed the kidneys to quantify protein expression (PE) of ion transporters in the cortex (C) and outer medulla (OM), by Western blot. We used ANOVA followed by Newman-Keuls test for statistical analysis.

Results: All groups showed all plasma concentration values within normal range. As shown in the Table, nGT decreased BP and increased intact liquid urine and kidney output. However, both i and n GT increased urinary excretion (UV) of calcium (Ca), phosphorus (P) and magnesium (Mg) and CAF increased only UVMg. With regard to PE of ion transporters, we only evaluated PE of TRPM6 in OM, and PE of NKCC2 and Na-Pi type Ia in OM, and we only found decrease in PE of TRPM6 in GT when compared with nGT, p<0.05, until now.

Conclusions: Even though we have not yet identified the mechanism for which GT induced Ca and P urinary losses we suggest to add GT in the list of risks for lithiasis.

Funding: Government Support - Non-U.S.

Table 1. Multivariable linear regression model on UCE(log)

<table>
<thead>
<tr>
<th>B</th>
<th>95% CI B</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.003</td>
<td>0.006</td>
</tr>
<tr>
<td>eGFR(COEXP)</td>
<td>0.005</td>
<td>0.007</td>
</tr>
<tr>
<td>FGF23</td>
<td>0.07</td>
<td>0.09</td>
</tr>
<tr>
<td>Tm cal/Tm Ca</td>
<td>0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>1.25-ViD</td>
<td>0.004</td>
<td>0.005</td>
</tr>
</tbody>
</table>

**p<0.01 vs other groups;#p<0.05 and ##p<0.01 vs W


Mineral Disease: Ca/Mg/PO4

**TH-PO1065**

The Plant 3,4,5-Tri-O-galloyl Quinic Acid Methyl Ester Inhibits Calcium Oxalate Crystals Growth in a Drosophila Model and Decreases Renal Cell Annexin A1 Surface Expression and Crystal Adhesion

Mohamed A. Abd El-Salah,1 Jairo Bastos,2 Jing Jin Han,2 Daniel Previdi,3 Paulo Donate,2 Michael F. Romero,2 John C. Lieske,1 Mayo Clinic College of Medicine, Rochester, MN;1 Department of Internal Medicine, Division of Nephrology and Hypertension, Mayo Clinic College of Medicine, Rochester, MN;2 Department of Pharmaceutical Sciences, School of Pharmaceutical Sciences of São Paulo, Ribeirão Preto, University of São Paulo, Sao Paulo, Brazil; 3 Department of Chemistry, Faculty of Philosophy, Arts and Sciences, University of São Paulo, Ribeirão Preto, Brazil;

Background: The design of more effective therapies for urinary stone prevention depends on identifying critical pathogenic steps. Adherence and retention of crystals is one potential early event. Many studies have identified crystal-binding proteins (e.g. annexin A1, heat shock protein 90 (HSP90) and α-ensolase) on the apical membranes of renal tubular epithelial cells. Agents that affect expression of these molecules could ameliorate crystal retention.

Methods: The plant metabolite 3,4,5-tri-O-galloyl quinic acid methyl ester (QAME) was prepared by total synthesis and its potential effect on calcium oxalate monohydrate (COM) crystal binding to the surface of Madin-Darby Canine Kidney Cells type I (MDCK I) and crystal growth in a Drosophila melanogaster (fruit fly) Malpighian tubule model were studied. Membrane, cytotic, and total α-ensolase, Annexin A1 and HSP90 levels were evaluated by subcellular fractionation followed by Western blot. Immunofluorescence staining and confocal microscopy were also performed on cultured cells.

Results: Pretreatment of MDCK I cells with QAME for up to 6 h significantly diminished crystal-binding in a concentration-dependent manner. QAME significantly reduced surface expression of Annexin A1 by immunofluorescence microscopy, whereas the intracellular level increased. Western blot analysis confirmed these findings in membrane and cytosolic fractions of QAME-treated cells, whereas total cell QAME remained unchanged. The compound also significantly decreased the size and growth of COM crystals induced ex vivo in the Drosophila melanogaster Malpighian tubule model. Conclusions: These data indicate that QAME decreased binding of COM crystals to cells by decreasing the surface expression of Annexin A1 via changing localization of Annexin A1 from the plasma membrane to the cytosol. Thus, QAME may be useful for the prevention and modulation of stone formation. Further pre-clinical and clinical studies should be done for the use of this compound in urolithiasis.

TH-PO1066

Establishing a Drosophila Model System to Study the Molecular Function of Human Genes Identified from Patients with Nephrolithiasis/Nephrocalcinosis

Fujian Zhang, Qiuxia Fan, Xizhen Hong, Xiaoming Feng, Fan Fan Hou, Division of Nephrology, Nanfang Hospital, Southern Medical University, Guangzhou, China.

Background: Nephrolithiasis/nephrocalcinosis is a frequent condition that affects 15% of adults, causing a huge burden on health care systems globally. Calcium oxalate stones account for more than 75% of renal stone diseases. In recent years, more than 30 genes have been identified as novel monogenic causes of kidney stone disease by using whole exome sequencing. However, the pathological function of the majority of these novel genes have not been validated in vivo.

Methods: First, we established the principal cell-specific gene knock-down method using UAS-RNAi/Gal4 system and examined its effect on calcium oxalate stone formation. Then, we investigated the effect of fly homology of 30 human genes identified from patients with kidney stone disease on calcium oxalate stone formation. We also observed that the formation of large kidney stones significantly shortened the lifespan in adult flies. Furthermore, we found that RNAi knockdown of these nephrolithiasis genes led to the accumulation of calcium oxalate stone formation. We also examined the effect of calcium oxalate stone formation on lifespan. Furthermore, we examined the effect of these genes on the metabolism of oxalate in malpighian tubule cells.

Results: In this study, we found that knockdown of genes encoding v-ATPase protein complex in malpighian tubule principal cells led to the formation of large calcium oxalate stones. We also found that defects in 80% (24 of 30) fly homology of 30 known nephrolithiasis/nephrocalcinosis genes led to the accumulation of calcium oxalate stone in malpighian tubule. We also observed that the formation of large kidney stones significantly shortened the lifespan in adult flies. Furthermore, we found that RNAi knockdown of these nephrolithiasis genes led to the accumulation of oxalate in malpighian tubules, suggesting that these nephrolithiasis genes in principal cells may affect the secretion of oxalate from malpighian tubule.

Conclusions: In this study, we present the first Drosophila model system to study the molecular function of human genes identified from patients with nephrolithiasis/nephrocalcinosis. These results suggest that Drosophila malpighian tubules could be a very powerful system to screen genes involved in the formation of human kidney stones in vivo, and small molecules that could be used to dissolve calcium oxalate stones in patients with nephrolithiasis/nephrocalcinosis.

Funding: Government Support - Non-U.S.
Development of a Humanized Murine Model for Study of O. formigenes Intestinal Colonization Amanda Pebenito, Lama Nazzal, Menghan Liu, Martin J. Blaser 1,2 1 New York University School of Medicine, New York, NY; 2 New York Harbor V.A. Medical Center, New York, NY.

Background: Oxalobacter formigenes (O.f.) are symbiotic bacteria in the human gut that degrade oxalate, a component of most kidney stones. Observational studies suggest that O.f. colonization reduces the risk for kidney stones. Given the importance of oxalate homeostasis, and calcium levels, studies in mice are more practical than in humans; however, O.f. do not naturally colonize laboratory rodents. Our objective was to develop a humanized murine model to investigate the therapeutic potential of O. formigenes in its native microbiome.

Methods: To humanize mice, we transplanted feces from a pool of healthy human donors who were O.f.-negative (confirmed by PCR, qPCR, and oxalate degradation assay), supplemented with a human O.f. strain: OXCC13 (10^6 CFU/mL). The inoculum was introduced to C57BL/6J mice via esophageal gavage three times over six days. We compared two methods of humanization, transplanting inocula into mice that were (i) germ free; or (ii) treated with high-dose, broad-spectrum antibiotics (0.5g/L vancomycin, 1g/L ampicillin, 1g/L neomycin, 1g/L metronidazole in drinking water for 6 days) to suppress their native microbiome. As controls, one group received humanization with no pre-treatment and another received a sham gavage.

Results: Based on qPCR and 16S rRNA sequencing, all humanized groups were stably colonized with O.f. through 8 weeks post-gavage, whereas mice that received sham gavage remained uncolonized (p<0.001). Humanization significantly changed microbial community structure as measured by unweighted UniFrac distances (p<0.001) and humanized germ-free and antibiotic-treated groups were highly similar in β-diversity. We also assessed humanization by the number of shared OTUs between treatment groups and donor inoculum over time. Both germ-free and antibiotic-treated mice had a significant increase in shared OTUs compared to sham (p<0.024, p<0.036). The number of shared OTUs was stable in each group through 8 weeks post-gavage without significant difference between germ-free and antibiotic-treated mice.

Conclusions: Our method of transplanting human feces and O.f. conferred a new microbial phenotype in mice that resembled a human microbiome and was stable over time. Antibiotic pre-treatment, a simpler alternative to germ-free mice, provided comparable results. This model may allow insights to O.f.’s role in preventing calcium oxalate stones.

Funding: Other NIH Support - U01 AI22285

Activation of the PKA Signaling Pathway Stimulates Oxalate Transport by Human Intestinal Caco2-BBE Cells Hatim A. Hassan, Donna L. Arvans, Altayeb Alishaikh, Mohamed Bashir. University of Chicago, Chicago, IL.

Background: Most kidney stones are composed of calcium oxalate, and small increases in urine oxalate affect the stone risk. The mammalian intestine plays a crucial role in oxalate homeostasis and we had recently reported that oxalobacter-derived factors stimulate oxalate transport by human intestinal Caco2-BBE (C2) cells through mechanisms including PKA activation. We therefore evaluated whether intestinal oxalate transport is directly regulated by activation of the PKA signaling pathway. To this end, PKA is activated with forskolin and H89 (10μM). F3, F1 significantly stimulated (4-fold) 14C-oxalate transport by C2 cells (a 49% of which is mediated by the oxalate transporters SLC26A6 [A6]), an effect completely blocked by the PKA inhibitor H89, indicating that it is PKA-dependent. Utilizing selective pharmacological inhibitors in preliminary studies, we found that the PKC, ERK1/2, P38, and Src kinases are not involved in the observed stimulation. Evaluating A6 total and surface (using brush border membrane vesicles) protein expression revealed that the observed stimulation is not due to changes in A6 total and surface protein expression. Assessing 14C-oxalate transport as a function of increasing 14C-oxalate concentration in the flux medium showed that the observed stimulation is due to F1-induced (1.8-fold) in Km (the maximal velocity) and reduction (2-fold) to Kc (the apparent affinity for oxalate) in preliminary studies. siRNA knockdown studies showed that significant components of the observed stimulation are mediated by the A6 and SLC26A2 (A2) oxalate transporters. Since F3 did not affect A6 total and surface protein expression, and in view of the reduced Kc (reflecting greater A6 affinity for oxalate upon PKA activation), it is likely possible that the observed stimulation is due to mechanisms including F1-induced enhanced A6 transport activity resulting from an increased Ca2+ influx and/or increased expression of the plasma membrane transporters. We conclude that activation of the PKA signaling pathway significantly stimulates intestinal oxalate transport by C2 cells through mechanisms including increased intrinsic activity of preexisting A6 membrane transporters, as well as enhanced A2 transport activity (resulting from more A2 membrane transporters and/or increased intrinsic activity).

Methods:

Results: Conclusions:

Funding: NIH DKK Support, Other NIH Support - ARRA

P2X7 Receptor Stimulation Is Not Required for Oxalate Crystal-Induced Kidney Injury Hannah L. Luz, Martin Reichel, Kai-Uwe Eckardt, Robert J. Unwin, Frederick W. Tam, Felix Knaut. 1 Dept of Nephrology and Medical Intensive Care, University Hospital Charite Berlin, Berlin, Germany; 2 Renal and Vascular Inflammation Section, Hammersmith Hospital, Imperial College London and University College London; 3 Dept of Nephrology and Hypertension, University of Erlangen-Nuremberg, Erlangen, Germany; 4 Centre for Nephrology, Royal Free Hospital, University College London Medical School, London, United Kingdom.

Background: Oxalate crystal-induced renal inflammation is associated with progressive kidney failure due to activation of the NLRP3/CASP-1 inflammasome. It has been suggested previously that purinergic P2X7 receptor signaling is critical for crystal-induced inflammasome activation and kidney injury. Therefore, we investigated the role of the P2X7 receptor in response to crystal-induced cytokine release, inflammation, and kidney failure using in vitro and in vivo models.

Methods: Bone marrow-derived dendritic cells (BMDMC) from C57BL/6 (wild-type), Casp1-/- and P2X7-/- mice were stimulated with calcium-oxalate crystals, monosodium urate crystals or ATP. Interleukin-1beta (IL-1β) release was measured using ELISA and western blot analysis. For studies in vivo, age- and gender-matched wild-type, Casp1-/- and P2X7-/- mice were placed on a high oxalate diet to induce oxalate nephropathy. Kidney sections were analyzed for crystal deposition, tubular damage, and macrophage infiltration using F4/80 staining. Renal function was monitored by changes in plasma creatinine sampled retro-orbitally.

Results: Stimulation of BMDMC from wild-type mice with oxalate crystals, urate crystals or ATP induced a robust release of IL-1β. Treatment with the P2X7 inhibitor A74003 selectively abrogated ATP-induced, but not oxalate and urate crystal-induced IL-1β release. In line with this finding, BMDMC from P2X7-/- mice released reduced amounts of IL-1β following stimulation with ATP, while oxalate and urate crystal-induced IL-1β release was unaffected. In sharp contrast, BMDMC from Casp1-/- mice exhibited reduced IL-1β release following stimulation with the three stimulants. In addition, while Casp1-/- mice were protected from crystal-induced renal failure, P2X7-/- mice demonstrated similar degrees of crystal deposition, tubular damage and inflammation when compared with WT mice. In line with these findings, increases in plasma creatinine were no different between WT and P2X7-/- mice.

Conclusions: In contrast to previous findings, our results indicate that P2X7 receptor is not required for crystal-induced CKD and it is unlikely to be a suitable therapeutic target for crystal-induced progressive kidney disease.

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

Structural Alteration of Urinary Tamm Horsfall Protein under Hyperoxaluric Conditions in Rats: Role of Calnexin, a Glycoprotein Chaperone Devinder K. Dhawan, I. Taneez Kaur. 1 Department of Biophysics, Punjab University, Chandigarh, India; 2 Amity Institute of Biotechnology, Amity University, Noida, India.

Background: Tamm Horsfall Protein (THP), a urinary glycoprotein has been studied extensively for its involvement in the progression or regression of renal stone formation. Also, some studies have pointed out the abnormality in structural conformation and glycosylation as the root cause for the altered nature of THP. Calnexin, an ER resident chaperone, deals with the proper folding of glycoproteins in order to ensure their glycosylation as the root cause for the altered nature of THP. Therefore, study was carried out to decipher the role of calnexin and THP under hyperoxaluric environment in rat model mimicking renal stone condition, if any.

Methods: Rats were randomly divided into four groups: control, hyperoxaluric groups i.e. ethylene glycol alone, ethylene glycol with ammonium chloride and hydroxy-l-proline, respectively. After hyperoxaluric induction, urine from the rats was collected for THP isolation. Rats were then sacrificed and kidneys were removed for further investigations. Methods employed to carry out the investigations included protein expression analysis by Western Blot and Immunohistochemistry and gene expression analysis by mRNA studies. Fourier Transform Infrared Spectroscopy and hydrophobicity analysis of isolated THP were carried out in order to demonstrate any structural changes. Sialic acid content was estimated both in renal tissues and isolated THP. In sharp contrast, BMDMC from Casp1-/- mice were placed on a hyperoxalate diet to induce oxalate nephropathy. Kidney sections were analyzed for crystal deposition, tubular damage and inflammation when compared with WT mice. In line with these findings, increases in plasma creatinine were no different between WT and P2X7-/- mice.

Conclusions: In contrast to previous findings, our results indicate that P2X7 receptor is not required for crystal-induced CKD and it is unlikely to be a suitable therapeutic target for crystal-induced progressive kidney disease.

Funding: Private Foundation Support, Government Support - Non-U.S.
TH-PO1071
ALLN-177, a Novel Oral Enzyme Therapy, Reduces Urinary Oxalate Excretion and Plasma Oxalate in Porcine Dietary Model of Severe Hyperoxaluria

Danicia Grujic,1 Paulina Szczerbiak,2 Nadia Mosichuk,2 Liudmila Lozinska,2 Stefan Pierzynowski,2,3 Allenetta, New York, MA;4 Lund University, Lund, Sweden.

Background: Hyperoxaluria (HO) is a chronic metabolic disorder and a major risk factor for nephrolithiasis and oxalate nephropathy. Secondary HO is caused by increased intestinal oxalate absorption from the diet due to enteric disorders or unexplained causes. There are no pharmacologic therapies approved for HO. ALLN-177 is an oral oxalate-specific enzyme therapy (Rx) that degrades oxalate in the gastrointestinal (GI) tract, decreasing oxalate absorption and thereby reducing urinary oxalate. ALLN-177’s ability to decrease urinary crystals assessed by uric and plasma oxalate was tested in a porcine model of HO induced with high oxalate diet (HOD). Pigs were chosen due to physiological similarities to humans in GI and renal function.

Methods: To induce severe HO, 12 pigs were fed HOD for 7 days, followed by a 7-day washout period during which they received their regular dietary oxalate. The remaining dietary oxalate was stopped and urinary oxalate was assessed during the 7-day washout period to determine the baseline urinary oxalate. After the washout period, pigs were randomized to receive daily oral doses of 25, 50, or 100 mg ALLN-177 or HO diet alone. Parameters measured included: body weight, metabolism, plasma oxalate, and renal function (measured by the 24-hour urinary oxalate and calcium excretion). Urinary crystals were observed following the load and determined to be approximately 180 nm in diameter via the Nanosight nanoparticle counter. The effect of the high dietary oxalate load was significant, and a oxalobacter colonization was assessed using PCR for oxalate on fecal samples collected the last day of study treatment with primers designed to detect Oxalobacter formigenes, an anaerobic intestinal bacterium that produces oxalate.

Results: Daily oral ALLN-177 with meals significantly reduced UOx by mean of 38.7 g/g Cr/d (39%) when compared to pre-treatment UOx on HOD (100 ± 21 mg/d, vs. 61.5 ± 14.3 mg/g Cr/d on HOD+ALLN-177; p < 0.001), returning UOx to the range recorded prior to HOD (61 ± 14.5 mg/g Cr/d). In addition, mild hyperoxalemia was induced on HOD plasma oxalate 13.9 ± 2.2 mg/L, which was significantly reduced with Rx to 9.9 ± 2.3 mg/L, p < 0.001. PCR of fecal samples was negative for Oxalobacter indicating absence of colonization. Therapy was well tolerated without adverse effects observed.

Conclusions: Oral administration of ALLN-177 with meals was well tolerated and normalized UOx and plasma oxalate in a pig model of secondary HO.

Funding: Commercial Support - Allena Pharmaceuticals

TH-PO1072
Crystalluria and Monocyte Responses in Healthy Subjects Following a Single Dietary Oxalate Load

Taniae Mitchell,3 Mikhail Pote,2 Vidhush Yarlagadda, Adam D. Ambrosettii, John Knight, Dean G. Assimos, Ross P. Holmes. University of Alabama at Birmingham, Birmingham, AL.

Background: Dietary oxalate has been suggested to play an important role in the risk and progression of stone formation in patients with calcium oxalate (CaOx) kidney stone disease. Oxalate has also been associated with crystal formation and inflammation in renal cells. We have previously determined that monocyte mitochondrial function is decreased in renal cells. We have previously determined that monocyte mitochondrial function of healthy subjects.

Methods: Twenty healthy subjects (29.1 ± 1.7 years old) with an average BMI of 25.0 ± 0.8 kg/m² were enrolled in the study. Participants consumed a low oxalate diet for 3 days prior to consuming a single high dietary oxalate load (spinach smoothie; 8 mols). Urine and peripheral blood was collected prior to the load and 5 hours later. Crystalluria was quantified by measuring oxalate levels using ion-chromatography mass spectrometry (ICMS) and a Nanosight nanoparticle counter. Monocyte mitochondrial responses were assessed using the Seahorse XF36 Analyzer.

Results: A single high dietary oxalate load in healthy subjects significantly increased total urinary oxalate levels (pre-oxalate 2.36 ± 0.6 vs. post-oxalate 35.35 ± 4.8 mg; p < 0.0001). In addition, urinary crystals were observed following the load and determined to be approximately 180 nm in diameter via the Nanosight nanoparticle counter. The effect of the high dietary oxalate load on monocyte mitochondrial responses was variable among participants. Eleven of the healthy subjects (55%) had decreased monocyte mitochondrial function, whereas, 3 (15%) were not affected by the load and 6 (30%) had increased mitochondrial function following the load compared to pre-oxalate samples.

Conclusions: These findings suggest that a single high dietary oxalate load causes crystal formation and changes in monocyte mitochondrial responses in healthy subjects. Understanding these mechanisms further may aid in designing dietary recommendations to reduce crystal formation in patients with CaOx kidney stone disease.

Funding: NIDDK Support

TH-PO1073
Results of a Phase 2 RCT of ALLN-177 in Patients with Secondary Hyperoxaluria

Sagar U. Nigewark,1 James E. Lingeman,1 James A. Bolognese,2 Annamaria T. Kausz,4 IU Health Physicals University, Indianapolis, IN; 3Massachusetts General Hospital, Boston, MA; 4Cylecy, Cambridge, MA; 5Allena Pharmaceuticals, Newton, MA.

Background: Hyperoxaluria (HOx) is a metabolic disorder associated with increased risk of nephrolithiasis and other sequelae including oxalate nephropathy. Secondary HOx is caused by excess oxalate absorption from diet due to enteric disorders (enteric HOx, EH) or long-term period following the load compared to pre-oxalate samples. There are no approved pharmacotherapies for HOx. To address this unmet need, ALLN-177 was developed as a novel oral formulation of crystalline oxalate decarboxylase, an oxalate-specific enzyme that degrades oxalate in the gastrointestinal (GI) tract, thereby reducing urinary oxalate (UOx).

Methods: This double-blind, placebo-controlled RCT randomized adult subjects with secondary HOx and UOx ≥50 mg/d: 1:1 to ALLN-177 (750 mg/meal) or placebo taken orally with meals 3x/day for 28 days. Multiple 24-hr urine collections were obtained to determine change in UOx. The primary analysis used a mixed effects repeated measures analysis of variance model.

Results: Subjects were randomized and treated (32 ALLN-177, 35 placebo), 18 had EH. The primary endpoint (EP) 24-hr UOx change from baseline to Week (Wk) 4 showed a trend favoring ALLN-177 (p = 0.10). Right kidney stones were statistically significant, and a unmet greater clinically meaningful treatment effect was seen in post-hoc analyses in the predefined EH subset, including the time-weighted average (TWA) assessing the aggregate effect across the study duration. Adverse events were no worse with 50% of ALLN-177 subjects vs. 63% placebo, and GI AEs were the most frequently reported, 16% ALLN-177 vs 40% placebo. No subjects discontinued ALLN-177 for any reason.

Conclusions: ALLN-177 was well-tolerated and has potential to meaningfully reduce UOx in patients with EH, who have a substantially increased risk for renal complications and thus an unmet need for an effective therapy to reduce UOx.

Funding: Commercial Support - Allena Pharmaceuticals

TH-PO1074
SLC26A6 Is the Principal Oxalate Transporter in Macrophages

Teresa R. Wagner,1,2 Louise M. Tonner,1,3 Zhirong Jiang,1 Robert B. Thompson,1 Felix Knauf,1,4 Peter S. Aronson,1 Yale School of Medicine, New Haven, CT;1 University Tübingen, Tübingen, Germany;1 FAU Erlangen, Erlangen, Germany;1 University Hospital Charite, Berlin, Germany.

Background: Macrophages are able to phagocytose calcium oxalate crystals, dissolve them in their molecular components, and discharge accumulated oxalate. The goal of this study was to identify the transporter(s) responsible for oxalate transport across the plasma membrane of macrophages. We specifically evaluated the potential role of SLC26A6 because of its known activity as a Cl-oxalate exchanger in kidney and intestine.

Methods: Oxalate transport in macrophages was assessed by using the human monocytic THP-1 cell line and bone marrow-derived macrophages from mice in 1:4-oxalate transport assays. Immunoblotting and qPCR were used to detect expression of SLC26A6. The functional role of SLC26A6 in mediating oxalate transport was studied by siRNA knockdown in THP-1 cells and isolation of macrophages from SLC26A6 / mice. Macrophage viability was measured by WST-1 assays.

Results: DDS-sensitive CI gradient-stimulated oxalate transport was detected in both THP-1 cells and mouse macrophages, consistent with Cl-oxalate exchange activity. Expression of SLC26A6 in THP-1 cells and mouse macrophages was detected by qPCR and immunoblotting. Partial knockdown of SLC26A6 expression by siRNA in THP-1 cells caused significant reduction of Cl-oxalate exchange activity. There was complete loss of CI-oxalate exchange activity in macrophages isolated from SLC26A6 / mice. Prolonged incubation with CI-oxalate revealed significantly higher accumulation of oxalate in macrophages from SLC26A6 / mice compared to wild-type mice, indicating that SLC26A6 plays a major role in mediating oxalate efflux under physiological conditions. Moreover, incubation in high oxalate media was found to cause significantly greater loss of viability of macrophages from SLC26A6 / mice compared to wild-type mice.

Conclusions: We conclude that SLC26A6 is the principal oxalate transporter in macrophages and likely plays a role in mediating oxalate efflux and reducing cellular oxalate toxicity.

Funding: NIDDK Support

TH-PO1075
Urinary Stone Events Are Predicted by Urinary Oxalate Excretion and SLC26A6 Expression

Nalini R. Dety,1 Nalini R. Dety,2 Felicity T. Enders,1 Kristin C. Mara,1 Ramila A. Mehta,1 John C. Lietzke,1 Mayo Clinic, Rochester, MN; 2Allena Pharmaceuticals, Newton, MA.

Background: Elevated urinary oxalate (UOx) excretion is considered an important pathologic contributor towards the development of renal complications of enteric hyperoxaluria (EH). Since there are limited outcomes data we assessed the relationship between UOx and kidney stone events in an EH cohort.

Methods: In all, 589 patients from Olmsted County, MN were identified who had 24-hr urine collection and stone event data. Multiple 24-hr urine samples were collected at baseline and during therapy (defined as EH). “Baseline” was the date of the first available 24h urine. Urologic procedures and emergency department visits with diagnostic codes consistent with kidney stones a month after baseline were considered a stone event. Multivariable logistic regression was performed to predict a first stone event >6 months after index date.

Results: Median follow-up time was 4.2 years. Mean age was 50.2 years and 74% were female. Baseline UOx was associated with a first stone event in models adjusted for baseline urine calcium and citrate (Table). For each 10 mg/24h increase in UOx, odds of a
stone event was 1.15 (p=0.012). Similarly, among EH patients with baseline urine oxalate of 60 mg/g creat or greater, odds of a stone event after six months was 2.75 times greater than for EH patients whose baseline urine oxalate was below 40 mg/g creat (p=0.030); for baseline urine oxalate between 40 and <60 mg/g creat this odds ratio was 2.69 (p=0.008).

**Conclusions:** Baseline UOx predicts risk of future stone events in a cohort of EH patients. This risk persists even after adjustment for other urinary stone risk factors, including calcium and citrate excretion. Thus strategies to reduce UOs in EH patients should also reduce kidney stone risk.

Predictors of first stone event six months or more after baseline

<table>
<thead>
<tr>
<th>Model 1</th>
<th>Odal Ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Oxalate (mg/g creat)</td>
<td>1.35</td>
<td>1.05</td>
<td>1.78</td>
<td>0.02</td>
</tr>
<tr>
<td>Baseline Uric Acid (mg/g creat)</td>
<td>1.00</td>
<td>0.95</td>
<td>1.04</td>
<td>0.71</td>
</tr>
<tr>
<td>Baseline Citrate (mg/g creat)</td>
<td>0.98</td>
<td>0.90</td>
<td>1.06</td>
<td>0.36</td>
</tr>
</tbody>
</table>

**Model 2**

| Baseline Oxalate (mg/g creat) | 2.69 | 1.08 | 1.22 | 0.008 |
| Baseline Uric Acid (mg/g creat) | 0.98 | 0.94 | 1.05 | 0.55 |
| Baseline Citrate (mg/g creat) | 0.99 | 0.98 | 1.01 | 0.57 |

**AIC:** 211.89, **AUC:** 0.645

**TH-PO1078**

**Determinants of Urine Chemistry in the Rare Kidney Stone Consortium (RKSC) Cystinuria Registry Frank M. Moderste%1, David S. Goldfarb,1,3 Nephrology, NYU Langone Medical Center, New York, NY.

**Background:** Urine chemistry is a determinant of stone formation in cystinuria. We previously showed that positive cystine capacity (CysCap), a measure of higher cystine solubility, led to fewer stone events. We queried the RKSC Cystinuria Registry to determine urinary and medication variables associated with positive (CysCap+), rather than negative (CysCap-) values.

**Methods:** This is the 1st report from the Cystinuria Registry, with data on 300 people with cystinuria (142 males, 158 females; age at enrollment 38 ± 17 years). 112 participants had 306 determinations of CysCap, measured by Litholink (Chicago, IL). In this cross-sectional study we compared variables associated with CysCap+ vs CysCap-.

**Results:** Lower urine Na+ (r=0.48, Fig 1A) and creatinine (r=-0.62, not shown) were associated with lower 24h urine cystine (UC: P<0.001). Increasing CysCap values were seen with increasing urine pH (r=0.45, Fig 1B), volume (r=0.44) and decreasing UC (r=-0.44 Fig 1C; all P<0.001). Dividing Cyscap determinations into CysCap+ and CysCap- groups (Table), only higher urine volume and greater daily citrate doses were different. Relatively few participants were taking citrate or thiosulfate.

**Conclusions:** Higher urine pH and volume and lower UC were associated with less lithogenic urine; lower UC was seen with less Na and creatinine. Higher volume and citrate doses distinguished patients with less lithogenic urine. Many patients with cystinuria may be undertreated and would benefit from better dietary adherence.

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

**24h Urine Chemistry and Medications for CysCap+ vs CysCap-**

<table>
<thead>
<tr>
<th>Variable</th>
<th>CysCap+</th>
<th>CysCap-</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine pH</td>
<td>6.06±0.09</td>
<td>6.00±0.02</td>
<td>0.002</td>
</tr>
<tr>
<td>Urine Sodium (mg/dl)</td>
<td>135±20</td>
<td>138±20</td>
<td>0.45</td>
</tr>
<tr>
<td>24h Urine Creatinine (mg/dl)</td>
<td>7.5±2</td>
<td>7.3±2</td>
<td>0.56</td>
</tr>
<tr>
<td>24h Urine Citrate (mg/dl)</td>
<td>40±7</td>
<td>40±7</td>
<td>0.99</td>
</tr>
<tr>
<td>24h Urine Calcium (mg/dl)</td>
<td>10±5</td>
<td>10±5</td>
<td>0.99</td>
</tr>
<tr>
<td>24h Urine Oxalate (mg/dl)</td>
<td>4±1</td>
<td>4±1</td>
<td>0.99</td>
</tr>
<tr>
<td>24h Urine Uric Acid (mg/dl)</td>
<td>5±2</td>
<td>5±2</td>
<td>0.99</td>
</tr>
<tr>
<td>Total Protein (g/dl)</td>
<td>6.3±0.5</td>
<td>6.3±0.5</td>
<td>0.99</td>
</tr>
</tbody>
</table>

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

Underline represents presenting author.
minority with severe UCy excretion had a family history of cystinuria. In univariate models, predictors of moderate UCy (>115 µmol/L) and severe cystinuria (>1300 µmol/L) were higher UA, sulfate and OAL (P<0.001). In multivariate models, Usulfate, Ulysine, Uornithine remained significant.

Conclusions: A high index of suspicion and low threshold for screening are necessary since cystinuria represents a treatable condition for better outcomes. Moderate cystinuria may confer UA stone risk and requires further study.

Funding: NIDDK Support, Other NIH Support - U54-KD083908 Rare Diseases Clinical Research Network, Private Foundation Support

TH-PO1080

Interference of Tiopronin with Urine Cystine Measurement IsAssay-Dependent 

Cystine group (µmol/L) <110 110-150 >150 N 903 64 12 Male 49 70 42 HCYST stones (1/%) 0 0 3 (3%)

Pll any kidney stone (n=173) 237 (46) 60 (74) 6 (80)

U-Cyst (µmol/L) 81.3 (76.7) 55.1 (61.7) 152.6 (70.6) 71.0 (70.6) (74.7)

U-Glu (µmol/L) 61 (61) 50 (50) 70 (70) 50 (50) (50)

U-Arg (µmol/L) 70 (70) 50 (50) 70 (70) 50 (50) (50)

Threonine (µmol/L) 90 (88) 70 (70) 100 (99) 80 (80) (81)

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

Underline represents presenting author.

Mineral Disease: Nephrolithiasis

Mineral Disease: Nephrolithiasis

Funding: NIDDK Support

TH-PO1082

Recurrent but Not First-Time Symptomatic Kidney Stone Formers Are At Higher Risk for ESRD and Death 


Background: Prior studies reporting an increased risk of ESRD in kidney stone formers (SFs) are limited by the use of codes, lack of diagnosis validation, and short follow-up time. In this study we determined the incidence of ESRD and mortality in a cohort of carefully characterized SFs.

Methods: Coded SFs (ICD-9: 592, 594 & 274.11) in Olmsted County, Minnesota between 1984-2012 were categorized after chart review into mutually exclusive groups: incident (first-time) symptomatic SF, recurrent symptomatic SF (first stone event prior to study period), asymptomatic SF, bladder SF, and misclassified (not a SF). Age and sex-matched controls were randomly sampled from the Olmsted County population (1:1 ratio). Cox proportional hazards models were used to determine the risk of ESRD (identified using the United States Renal Data System) and mortality (National Death Index) after adjustment for baseline comorbidities.

Conclusions: The cohort of 203 SFs and 28,136 controls (mean age 48 years and 58% male) had 94 and 183 ESRD events and had 1139 and 3923 deaths, respectively, over a mean follow-up of 9.4 years. After adjusting for baseline CKD, diabetes mellitus, hypertension, dyslipidemia, obesity and gout, recurrent SFs but not incident SFs were at higher risk of ESRD and mortality (Table). Asymptomatic SFs were also at higher risk of ESRD and mortality, while bladder SF were at higher risk of mortality and misclassified SF were at higher risk of ESRD.

Conclusions: The risk of ESRD and mortality may be higher in recurrent than incident symptomatic SFs due to more substantial renal injury from more severe stone disease. Thus efforts to reduce kidney stone recurrence may have beneficial impact on ESRD and mortality risk. Other disease that leads to kidney imaging (incidental detection of asymptomatic stones) or is misclassified as kidney stones can bias the risk of ESRD or mortality risk based studies that lack chart validation.

Funding: NIDDK Support

TH-PO1083

Lower Than Normal Urine pH in Calcium Oxalate (CaOx) Stone Forming (SF) Women Is Due to Reduced Gastrointestinal (GI) Alkaline Absorption


Background: We have previously found that in normal (N) men (M) and women (W) fed identical diets in a General Clinical Research Center (GCRC), the urine pH (UpH) of W CaOx SF had lower UpH than other W during the fed period (Table). We have previously found that in normal (N) men (M) and women (W) fed identical diets in a General Clinical Research Center (GCRC), the urine pH (UpH) of W CaOx SF had lower UpH than other W during the fed period (Table). We have previously found that in normal (N) men (M) and women (W) fed identical diets in a General Clinical Research Center (GCRC), the urine pH (UpH) of W CaOx SF had lower UpH than other W during the fed period (Table).

Conclusions: The risk of ESRD and death by SF groups compared to controls: HR with (95% CI)

Table: Urine cystine in incident (first-time) symptomatic SF, recurrent symptomatic SF (first stone event prior to study period), asymptomatic SF, bladder SF, and misclassified (not a SF) groups.

<table>
<thead>
<tr>
<th>SF Type</th>
<th>N (incident)</th>
<th>M (incident)</th>
<th>N (recurrent)</th>
<th>M (recurrent)</th>
<th>N (asymptomatic)</th>
<th>M (asymptomatic)</th>
<th>M (bladder)</th>
<th>M (misclassified)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine pH (mmol/L)</td>
<td>7.0 (6.7)</td>
<td>7.0 (6.7)</td>
<td>7.0 (6.7)</td>
<td>7.0 (6.7)</td>
<td>7.0 (6.7)</td>
<td>7.0 (6.7)</td>
<td>7.0 (6.7)</td>
<td>7.0 (6.7)</td>
</tr>
</tbody>
</table>

Conclusions: The risk of ESRD and death by SF groups compared to controls: HR with (95% CI)

<table>
<thead>
<tr>
<th>SF Type</th>
<th>N (incident)</th>
<th>M (incident)</th>
<th>N (recurrent)</th>
<th>M (recurrent)</th>
<th>N (asymptomatic)</th>
<th>M (asymptomatic)</th>
<th>M (bladder)</th>
<th>M (misclassified)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine pH (mmol/L)</td>
<td>7.0 (6.7)</td>
<td>7.0 (6.7)</td>
<td>7.0 (6.7)</td>
<td>7.0 (6.7)</td>
<td>7.0 (6.7)</td>
<td>7.0 (6.7)</td>
<td>7.0 (6.7)</td>
<td>7.0 (6.7)</td>
</tr>
</tbody>
</table>

Conclusions: The risk of ESRD and death by SF groups compared to controls: HR with (95% CI)

<table>
<thead>
<tr>
<th>SF Type</th>
<th>N (incident)</th>
<th>M (incident)</th>
<th>N (recurrent)</th>
<th>M (recurrent)</th>
<th>N (asymptomatic)</th>
<th>M (asymptomatic)</th>
<th>M (bladder)</th>
<th>M (misclassified)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine pH (mmol/L)</td>
<td>7.0 (6.7)</td>
<td>7.0 (6.7)</td>
<td>7.0 (6.7)</td>
<td>7.0 (6.7)</td>
<td>7.0 (6.7)</td>
<td>7.0 (6.7)</td>
<td>7.0 (6.7)</td>
<td>7.0 (6.7)</td>
</tr>
</tbody>
</table>
Conclusions: The pathophysiology of Ca stone formation differs by sex. In the presence of the highest level of urinary UpH, sex differences predisposed to CaP SF while higher TA and NAE and lower UpH in M favors CaOx SF. Exceptions are M CaP, with increased GIAE that correlates with a trend to higher UpH, and W CaOx, with lower than normal GIAE and higher NAE which translates into reduced uric acid and lower UpH. These differences may have clinical implications for use of stone therapies that affect UpH.

Funding: NIDDK Support

ANOVA by Sex and Subject Type

TH-PO1084

An Association between the Genetic Hypercalciuric Stone-Forming Rat and the Gut Microbiome Jochen M. Stern,1 Nancy S. Krieger,2 Matthew K. Abramowitz,2 David A. Bushinsky.3 Albert Einstein College of Medicine, New York, NY; 2Albert Einstein College of Medicine, Bronx, NY; 3University of Rochester, Rochester, NY; 4University of Rochester Medical Center, Rochester, NY.

Background: The Genetic Hypercalciuric Stone-forming (GHS) rat has an established model of kidney stone disease. The rats have been selectively inbred for an established model of kidney stone disease. The rats have been selectively inbred for a high incidence of kidney stones, with known butyrate producers, was downregulated in the proximal tubule, while Cldn16 and 19 were upregulated in the TAL segment. Similarly, the expression of the tested genes acutely (4 hours), but chronically was increasing NHE3 (protein level) and some distal genes. Thiazide challenge did not modify expression of the tested genes acutely (4 hours), but chronically was increasing NHE3 (protein level) and some distal genes.

Conclusions: Togetherness, this data show that tubular crosstalk is part of the intrarenal regulation of calcium. The precise mechanisms leading to tubular adaptation to a segment-specific calcium reabsorption challenge still need further studies.

Funding: Government Support - Non-U.S.

TH-PO1085

Differential Expression of miRNAs from Urinary Extracellular Vesicles Identifies Pathogenesis of Kidney Stones in Randall’s Plaque in Humans Suchitra Suthithamkorn,1 Xiangling Wang,2 Robin S. Chirackal,3 Felicity T. Enders,2 Andrew D. Rule,1 Prithi Chanaan,1 Muthuvel Jayachandran,3 John C. Lieske.1 1Mayo Clinic, Rochester, MN; 2Mayo Clinic, Rochester, MN

Background: kidney stone disease is a complex disease associated with various types of kidney cells. Activation of the kidney cells could influence the sorting of specific cargo, especially miRNAs into urinary extracellular vesicles (EVs) as well as the release of these EVs into urine, linking the patho- physiological process of the kidney. However, the roles of miRNAs within urinary EVs of kidney stone disease remain largely unknown. The current study thus aimed to extensively define the changes of miRNAs in urinary EVs between varying degrees of stone formers and controls.

Methods: Bio-banked cells-free urine samples from kidney stone formers with low plaque (LP, < 5% papillary surface area coverage) and high plaque (HP, n=4; > 5% papillary surface area coverage), first-time stone formers (SF, n=4), and non-stone forming controls (n=4) were used in this study. Urinary EVs-derived miRNAs were extracted and analyzed by RXXSExosome RNA-Seq Library Kit. Differentially expressed miRNAs (p-values < 0.05) between first-time stone formers and non- stone forming controls were validated by RT-qPCR method and submitted to DIANA-miRPath bioinformatics tool for biological pathway prediction.

Results: Exosome RNA-Seq analysis revealed a total of 17 and 10 differentially expressed miRNAs between SF and controls, and between LP and HP stone formers, respectively. Pathway analysis demonstrated the involvement of these altered miRNAs in various cellular processes and signaling pathways such as endocytosis, TGF-beta signaling pathway, MAPK signaling pathway and focal adhesion. Interestingly, several miRNAs have been shown to be expressed in numerous diseases, including kidney fibrosis, chronic kidney disease, and acute kidney injury. Thus far, RT-qPCR data confirmed the increased expression level of hsa-miR-1299 in the SF group, as compared to the controls.

Conclusions: These findings revealed the changes in miRNAs profile within urinary EVs and their possible roles in kidney stone pathogenesis as well as the formation of Randall’s plaque. Further investigations of these potential miRNAs may lead to better understanding of pathogenic mechanism underlying calcium-based kidney stone disease.

TH-PO1087

Association of Hyperuricemia and Higher Uricosuria and the Development of Prediabetes or Diabetes in Kidney Stone Formers Bernardo A. Martinez-Guerra,1 Juan Carlos Ramirez-Sandoval,1 Maria F. Castillo-Peón,2 Alfonso Galias-Herrero,3 Cynthia Garcia,1 Ricardo Correa-Rotter.1 Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico; 2Hospital Infantil de Mexico Federico Gomez, Ciudad de Mexico, Mexico.

Background: Nephrolithiasis (NL) is associated with insulin resistance and may be a sentinel event before the diagnosis of diabetes mellitus (DM).

Methods: Demographics, associated medical conditions, laboratory data, including 24-h urine analysis, and treatment were obtained at least annually from records. We excluded from analysis KSF who were taking the following drugs that alter uric acid serum levels and excretion (thiazide diuretics, losartan, allopurinol).

Results: From 266 patients of the NL clinic, 118 non-diabetic KSF that fulfilled inclusion criteria were included, 73 (62%) were female, mean age 44 ± 13 yrs, median (IQR) 14 (8-25) female years. At baseline 73 (26%) had prediabetes and 41 (15%) had diabetes. 24% were hypertensive and 13% had hypercholesterolemia. Median time from baseline to diagnosis was 6.4 yrs (IQR 3.8-13). Bivariate analysis showed that serum uric acid (mg/dL) was associated with diabetes (HR:2.95; 95% CI:1.3-3.3), higher uric acid excretion (HR:8.7; 95% CI:1.2-65) was a strong prognostic factor for development of predDM and DM.

Conclusions: The present study is the largest known report exploring the effect of 24-h urine analysis characteristics of KSF and the risk of development predDM and DM. Future prospective studies should focus on how hyperuricemia, predicted development of predDM and DM, and a higher 24-h urine uricosuriasis was the strongest predictor for this outcome even several years before the diagnosis of predDM or DM.

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

TH-PO1090

Inflammatory Markers in Pediatric Nephrolithiasis
Kirsten Kosum,1,4 John Kertz,2,3 Andrew L. Schwaderer,1 Akiron Children’s Hospital, Akron, OH; Nationwide Children’s Hospital, Columbus, OH; The Ohio State University, Westerville, OH; Northeastern medical university, Rootstown, OH.

Background: Kidney stones associate with higher rates of heart attack/stroke and low bone mineral density/fractures. The mechanism of this association remains unknown; inflammation may be key. Our objective is to determine if pediatric stone formers have inflammation.

Methods: Urine was collected from 11 stone formers and 16 controls; 12-17 years old with radiographic evidence of stones. Exclusion criteria: metabolic acidosis, CKD II or >, immobilization, hyperlipidemia, hypertension, diabetes, inflammatory bowel disease, rheumatoid arthritis, or lupus. Urine was tested via a Mesoscale V-Plex Human Cytokine panel inflammation array. Levels were normalized to creatinine to control for concentration. Statistics by paired T-Test; p value <0.05 was significant.

Results: Five inflammatory markers were significantly increased in stone children: II-13, II-1B, MIP-1B, II-12-II-23p40 and II-16.

Conclusions: This is the first evidence of inflammation in pediatric stone formers; this population is free of confounding diseases that are common in adults. Identification of inflammation in pediatric stone formers may be the first step in delineating the molecular mechanisms linking stone, bone and cardiovascular disease.

Table 1

<table>
<thead>
<tr>
<th>Inflammatory Marker</th>
<th>Control (ug/ug)</th>
<th>Stone former (ug/ug)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>II-12-II-23p40</td>
<td>0.167</td>
<td>0.405</td>
<td>0.017</td>
</tr>
<tr>
<td>II-1B</td>
<td>0.235</td>
<td>0.360</td>
<td>0.204</td>
</tr>
<tr>
<td>II-2</td>
<td>0.174</td>
<td>0.255</td>
<td>0.142</td>
</tr>
<tr>
<td>TGF-β</td>
<td>0.00</td>
<td>0.15</td>
<td>0.157</td>
</tr>
<tr>
<td>Interleukin-10</td>
<td>5.156</td>
<td>8.775</td>
<td>0.107</td>
</tr>
<tr>
<td>Interleukin-13</td>
<td>1.085</td>
<td>0.810</td>
<td>0.554</td>
</tr>
<tr>
<td>IP-10</td>
<td>7.287</td>
<td>6.952</td>
<td>0.541</td>
</tr>
<tr>
<td>MCP-1</td>
<td>9.542</td>
<td>14.22</td>
<td>0.548</td>
</tr>
<tr>
<td>MCP-3</td>
<td>9.437</td>
<td>19.7</td>
<td>0.381</td>
</tr>
<tr>
<td>MCP-1B</td>
<td>1.519</td>
<td>1.957</td>
<td>0.438</td>
</tr>
<tr>
<td>MMP-14</td>
<td>0.12</td>
<td>0.35</td>
<td>0.176</td>
</tr>
<tr>
<td>TIMP-1B</td>
<td>2.582</td>
<td>3.529</td>
<td>0.0034</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>0.047</td>
<td>0.114</td>
<td>0.411</td>
</tr>
<tr>
<td>TARC</td>
<td>0.060</td>
<td>0.086</td>
<td>0.396</td>
</tr>
<tr>
<td>II-15</td>
<td>0.74</td>
<td>0.734</td>
<td>0.556</td>
</tr>
<tr>
<td>II-6</td>
<td>0.283</td>
<td>0.283</td>
<td>0.503</td>
</tr>
<tr>
<td>II-7</td>
<td>0.003</td>
<td>0.003</td>
<td>0.152</td>
</tr>
<tr>
<td>IL-1</td>
<td>1.197</td>
<td>4.549</td>
<td>0.162</td>
</tr>
<tr>
<td>IL-13</td>
<td>0.41</td>
<td>0.266</td>
<td>0.862</td>
</tr>
<tr>
<td>TNBS</td>
<td>0.003</td>
<td>0.003</td>
<td>0.648</td>
</tr>
<tr>
<td>VEGF-A</td>
<td>1.525</td>
<td>1.15</td>
<td>0.08</td>
</tr>
</tbody>
</table>

MW: Mann-Whitney test

TH-PO1091

Hidden Sources of Sodium: The Role of Water Purification and Hypernatriuria in Kidney Stone Formation
Adedeji O. Sodeinde,1 Samir Brahmbhat,2,3 Andrew C. Calle,2,3 Cleveland Clinic Foundation, Cleveland, Ohio, Beachwood, OH.

Background: One of the mainstays of dietary modification for prevention of calcium-containing stone formation is salt intake restriction. This is usually achieved by reducing dietary intake of high salt containing foods like smoked, cured or salted foods and canned goods. However the purity of water consumed is usually not addressed. The case presented here highlights the difference of well water, which is purified by reverse osmosis, compared to bottled water, which is purified by distillation, and their effect on urinary sodium levels.

Methods: A 49 year old male with a history that is significant for recurrent urat unct tract infections due to uric acid and calcium oxalate stones was being followed up in the outpatient setting for stone prevention. Initial 24-hour urine studies were positive for

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

Underline represents presenting author.
hypercalcemia, hyperphosphatemia and hypernatremia, all while consuming well water purified by reverse osmosis. He was advised to drink and cook with bottled water which is purified by distillation. After the change, his initial urine sodium of 305 mmol/d decreased to 208 mmol/d. As a confirmation, it increased to 241 mmol/d when he asked to use well water again and back down to 177 mmol/d once back on bottled water.

Results:

Conclusions: As sodium restriction is one of the main therapies in preventing calcium-containing stones, there should be increased awareness about the routes with which it can be consumed. Reverse osmosis, though an efficient and economical method of water purification, may leave more sodium content in the water than distillation which is the purest form of water purification. If hypernatremia remains an issue in a patient with persistent stone formation and well controlled dietary sodium ingestion, there might be benefits to assessing the water consumed and its purification process.

TH-PO1092

Longitudinal Assessment of Health-Related Quality of Life (HRQoL) in Rare Kidney Stone Formers (RKSF) (Ravi Thimmisetty1,2)

Mary I. McIntosh,1 David S. Goldfarb,* Mayo Clinic, Rochester, MN; New York Harbor VAMC, New York, NY; New York University School of Medicine, New York, NY. Group Team: Rare Kidney Stone Consortium.

Background: The assessment of HRQoL in RKSF is important for following disease course and evaluating treatment. Previously, using a non-disease specific instrument we showed that RKSF present differently with the worst domains in cystinuria. These are the first follow-up data based on summary scores for adults in a cross-sectional comparison.

Methods: RKSF were enrolled from 4 RKSC registries: primary hyperoxaluria, cystinuria, Dent disease and APRTd. HRQoL is measured with the generic non-disease specific SF-36v2. Results are norm-based scores (NBS) on US Standard Population (Domain score mean = 50). Group means < 47 indicate the presence of impaired functioning in associated dimension.

Results: We scored 545 surveys of the adult population at different time points, adjusted for the last stone event and compared the Physical and Mental Component Scores (PCS and MCS). We found the lowest PCS in Dent, and the highest in PH. The lowest MCS was found in cystinuria, the highest was found in PH. Low PCS indicate restrictions in self-care, physical, social and role activities; bodily pain, tiredness and poor rated health. Low MCS are associated with frequent psychological distress, social and role disability due to emotional problems, and poor rated health. Participants with cystinuria reported more stone events with related procedures than other RKSF (X² (9) = 23.375, p = 0.005).

Conclusions: HRQoL in RKSF is influenced by stone events and can be assessed with a non-disease specific SF-36v2. Adjusting for time between the survey and last event allows for the interpretation of more meaningful HRQoL profiles. The time from the last stone event and related procedures affect HRQoL in RKSF significantly.

Funding: NIDDK Support

TH-PO1094


Background: The structure of kidney stones might provide clinical useful information in addition to the stone composition. The Raman chemical imaging (RCI) is a new technology used for the production of two-dimensions maps of the constituents' distribution in samples. We aimed at determining the use of RCI in urinary stone analysis.

Methods: Twelve calculi were analyzed by RCI using a confocal Raman microspectrophotometer. They were selected according to their heterogeneous composition and morphology. Prior to the analysis, samples were sliced and milled in order to detect the nucleus of the stones and having a smooth surface. RCI was performed on the whole section of stones. Once acquired, the data were baseline corrected and analyzed by MCR-ALS. Results were then compared to the spectra obtained by Fourier Transform Infrared spectroscopy, the gold standard method for the determination of urinary composition.

Results: RCI succeeded in identifying all the chemical components contained in each sample, including monohydrate and dihydrate calcium oxalate, anhydrous and dihydrate uric acid, apatite, struvite, brushite, whitlockite and ammonium urate. However, proteins couldn't be detected because of the huge autofluorescence background and the small concentration of these poor Raman scatterers. Carbaminate and calcium oxalate were correctly detected even when they represented less than 5 percent of the whole stones, allowing the detection of very small structures like Randall's plaques. Moreover, RCI provided the distribution of components within the stones. The nuclei were accurately identified, as well as thin layers of other components. Conversion of dihydrate to monohydrate calcium oxalate was correctly detected in the center of one single sample.

Conclusions: RCI showed a good accuracy in comparison with infrared spectroscopy in identifying components of the urinary stones. In addition, RCI is non-destructive enable the storage of samples. This analysis was also useful in determining the organization of components within stones, which help locating constituents in low quantity, such as nuclei. However, this analysis is time-consuming, which makes it more suitable for research studies rather than routine analysis.

TH-PO1095

Unique Case Renal Failure with Severe Metabolic Alkalosis and Hypermagnesemia Requiring Hemodialysis (Ravi K. Thimmisetty1, Omer Alrawi, Yahya M. Osman Malik, Zeenat Y. Bhatt. Wayne State University, Detroit, MI; Wayne State University Medical School, Detroit, MI.

Background: We are presenting an interesting case of renal failure, severe metabolic alkalosis and symptomatic hypermagnesemia that required dialysis for correction.

Methods: A 60-year-old African American male with history of metastatic sigmoid colon cancer s/p resection with end-colostomy and Hartmann’s stump admitted with abdominal pain, vomiting and dyspnea. Other medical problems were hypertension

Conclusions: In the US there are about 1.2 million ER visits per year. 37% of patients diagnosed with urinary stones receive no follow-up consultation with a urologist and are treated by a nephrologist. Although 24h urine collection results may decrease stone recurrence rate, only 7.4% do them. 50% of patients experience a recurrent 2nd episode within 5 years. Of these 24% undergo a complete evaluation, 18% are referred to a nephrologist and 13.8% are prescribed medical therapy. 30% remain adherent to this pharmacotherapy. Of patients that are adherent 27% have lower odds of an ER visit than non-adherent patients. The cascade of care demonstrates that a low prevalence of patients receive proper follow-up. The impediments to the care of patients with kidney stones are (1) the unrecognized morbidity of stones (2) disconnect between the ER and stone experts and (3) the low prevalence of 24h urine collections and prescribed medical therapy.

Conclusions: It is important to identify loci in the cascade of care that could represent opportunities to change practice. Prescription of appropriate fluid therapy and dietary changes and referral to an expert stone center is recommended. The low prevalence of 24h urine collections may reflect that the data are intimidating for some. Empirical therapy for calcium stones with fluids, diet, thiazides and potassium citrate may be a rational therapy to achieve significant supersaturation reductions and could be compared with targeted medical therapy in a randomized controlled trial. A greater effort needs to be devoted to develop a comprehensive flow of participants to retain patients in the cascade of care for USD.

TH-PO1092

A Cascade of Care for Urinary Stone Disease (USD) (Mansi Mehta, David S. Goldfarb. Nephrology, NYU Medical Center, New York, NY.

Background: USD is a preventable disease characterized by significant risk of recurrence. A “cascade of care” shows how many patients are lost to follow-up at diagnosis, referral, and treatment and is a useful tool in delivering HIV care. We can analyze our success, or failure, in the secondary prevention of kidney stones and treatment of patients by constructing a cascade of care.

Methods: We abstracted data from observational studies to identify impediments to care of patients with USD

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

Underline represents presenting author.
and left ureteral obstruction from conomic mass s/p left percutaneous nephrostomy tube. Her medical history included frailty, protonix, over the counter Alka-seltzer. Admission vitals were - temperature 97.5 fahreneith, blood pressure of 95/77, heart rate 98 beats per minute, respiratory rate 16 per minute and saturating 97% on 40% FiO2. On exam, he was cachectic, mild somnolent and dry. There was no edema. Laboratory values on admission revealed sodium 135, K 4.7, chloride 89, bicarbonate <45, creatinine is 5.5 mg/dl (baseline Cr is of 1.5), calcium 9, magnesium 5.6 and phosphorus 9.9. ABG results showed pH is 7.59, PCO2 is 71, pO2 183, bicarb is 59.9. After volume resuscitation, patient became bradypnea, more somnolent and further worsening of respiratory status required intubation. The hypokalemia was studied for possible causes. Metabolic alkalosis and hypomagnesaemia and severe metabolic alkalosis in the setting of acute renal failure. Urine output started increasing. With 2 sessions of renal replacement therapy, patient improved significantly and his mental status and biochemically. Creatine down to 2.4 and 2.1 mg/dl. posaconazole was later stopped and patient was extubated.

Severe alkalosis could have been multifactorial oral alkali intake and vomiting in setting of renal failure and week ago, had gastrogaffin for small bowel obstruction which can sometime result in metabolic alkalosis.

Results:
Conclusions: Gastrogaffin sometimes prepared with solutions containing alkali. Caution should be taken while giving these solutions containing alkali especially in the setting of renal failure. Concomitant severe metabolic alkalosis and hypermagnesemia can contribute to high mortality and poses a therapeutic challenge especially in the setting of renal failure. Renal replacement therapy is required in these cases.

TH-PO1096
A Case Report of Severe Hypokalemia Induced by Posaconazole
Sreejitha Karagi,2 Daniel W. Cogan,1 Barnes Jewish Hospital, St Louis, MO1 Washington University School of Medicine, St. Louis, MO.

Background: Hypokalemia is not a very common electrolyte abnormality that has been reviewed in textbooks of internal medicine.

Methods: A 66 year old man with history of Acute Myeloid Leukemia (AML) status post stem cell transplant in 6/2016 and chemotherapy presented with weakness, loss of appetite and failure to thrive on 1/2017. His current outpatient medications are tacrolimus, atorvagafone, fluconazole, valacyclovir and budesonide. His blood pressure was 137/76 mm Hg, pulse 118, and BMI 24. Serum sodium 137 mmol/L, potassium (K) 4.1 mmol/L, chloride 107 mmol/L, urea nitrogen 9 mg/dL, and creatinine 0.85 mg/dL. Chest and abdominal CT scan revealed RML, no abnormality was started on dactinib. On day 3 he developed neutrophic fever so he was started on vancomycin, meropenem, and posaconazole. On day11 he developed polyuria of more than 4L and profound hypokalemia. Serum K was 2.1 mmol/L, bicarbonate of 24 mmol/L, phosphorus 1.8 mg/dl and magnesium of 1.9 mmol/L. Urine analysis showed no glycosuria with a PH of 5. K 4.2 mmol/L, sodium 105 mmol/L, osmolality of 393 mmol/kg, serum osmolality of 297 mOsm/Kg, calculated potassium deficit daily was nearly 440 meq. His workup showed renal wasting of potassium with no evidence of renal tubular acidosis. Given the timeline of events the electrolyte abnormalities were attributed to posaconazole, so it was discontinued and switched with micafungin. Over next 10 days his serum potassium promptly normalized and did not require further supplementation.

Results: Posaconazole has been increasingly used in the treatment of zygomycetes and asperillus infections in hematological malignancies. It works by inhibiting enzyme lanosterol 14α-demethylase leading to defective fungal cell wall and its death. Exact mechanism of hypokalemia is not clear but animal studies have shown inhibition of 11α-hydroxysteroid dehydrogenase type 2 dependent cortisol inactivation by posaconazole leads to excessive cortisol byproducts like cortisone, leading to apparent mineralocorticoid activity. Posaconazole led to potassium wasting and hypermagnesaemia and severe metabolic alkalosis. The most commonly seen adverse effects were diarrhea, fatigue, nausea, decreased appetite, palpum-plantar erythrodyssethesia syndrome, hypotonia, vomiting, weight loss, and constipation. This is the first known reported case of severe, symptomatic hypokalemia secondary to SIAHD attributed to posaconazole therapy.

Conclusions: Posaconazole induced profound Hypokalemia is rare complication with only two other published cases in literature. So we suggest serum potassium be measured in all patients on posaconazole.

TH-PO1099
Ibuprofen Abuse – A Case of Rhabdomyolysis, Hypokalemia, and Hypophosphatemia with Drug Induced Mixed Renal Tubular Acidosis
Shakuntala S. Patel,1 Swathi Subramanyn1, Manisha Singh,2 Meeta W. Krause,1 UAMS, LITTLE ROCK, AR,1 University of Arkansas For Medical Sciences, Little Rock, AR,1 University of Arkansas for Medical Sciences, Little Rock, AR.

Background: Drug induced renal tubular acidosis (RTA) can pose an uncommon, but important cause of severe potassium wasting and hypokalemia. We report a case of mixed RTA presentation causing severe hypokalemia and unexplained hypophosphatemia in a patient who consumed large amounts of Ibuprofen.

Methods: A 48-year old healthy African American woman was admitted to the Medical intensive care unit with complaints of diffuse myalgias and severe generalized weakness for past few days. She was urinating a large volume (more than 2 liters) of dark colored urine with dysuria. Past history was significant for a distal tubular stress fracture 5 months ago complicated by delayed union. Her admission labs revealed severe hypokalemia, a non-anion gap metabolic acidosis with a positive urine anion gap (UAG) and a urine pH of 6.5 consistent with distal (Type I) RTA. She had spontaneous, non-traumatic rhabdomyolysis secondary to severe hypokalemia, but with hypophosphatemia resembling proximal RTA. Our patient was administered fludrocortisone and therapy was initiated with micronized testosterone, which showed renal wasting of potassium with no evidence of renal tubular acidosis. Given the timeline of events the electrolyte abnormalities were attributed to posaconazole, so it was discontinued and switched with micafungin. Over next 10 days his serum potassium promptly normalized and did not require further supplementation.

Results: Our patient developed severe but reversible hypokalemia with a mixed proximal and distal RTA like picture, most likely due to Ibuprofen use. A few cases have been reported of Ibuprofen preparations causing either proximal or distal type RTA. This is thought to be related to its inhibitory effect on Carbonic Anhydrase II. This case highlights the potential of Ibuprofen to cause type 3 RTA like picture, or a mixed type 1 and 2 RTA with life threatening hypokalemia to the extent of causing rhabdomyolysis.

Conclusions: Our patient developed severe but reversible hypokalemia with a mixed proximal and distal RTA like picture, most likely due to Ibuprofen use. A few cases have been reported of Ibuprofen preparations causing either proximal or distal type RTA. This is thought to be related to its inhibitory effect on Carbonic Anhydrase II. This case highlights the potential of Ibuprofen to cause type 3 RTA like picture, or a mixed type 1 and 2 RTA with life threatening hypokalemia to the extent of causing rhabdomyolysis.

TH-PO1109
Transient Hyperoninemic Hypoaldosteronism with Renal Salt Wasting: An Unusual Presentation
Huda Arif,1 David J. Leehey,2 Loyola University, Chicago, IL,1 Loyola University Medical Center, Oak Park, IL.

Background: We are presenting a case of transient hyperoninemic hypoaldosteronism with hyperoninemia presenting with orthostatic hypotension and renal salt wasting without cerebral disease. Adrenal insufficiency was ruled out by normal ACTH and cortisol levels.

Methods: A 61-year-old gentleman with no significant medical history except for mild chronic hypertension was referred to the renal clinic after multiple visits to the emergency room for symptomatic orthostatic hypotension requiring isotonic saline infusion. Evaluation in clinic showed orthostatic hypotension with an intact autonomic response. He reported polyuria with approximately 3-4L daily urine output. Laboratory evaluation revealed persistent hypokalemia, a non-anion gap metabolic acidosis (Bicarbonate <16 mg/dL, plasma renin activity (0.23-1.10 ng/mL/h), and normal ACTH and cortisol levels. He had normal renal function and normal plasma potassium and total carbon dioxide levels. His plasma sodium levels were generally normal with occasional mild hypernatremia. He had normal urinalysis with 0-1 white blood cells, 0-5 red blood cells, 0-10 epithelial cells, and 0-60 RBC casts per high power field. We decided to discontinue fludrocortisone resulted in recurrence of symptoms.

Results: Aldosterone causes reabsorption of sodium and chloride and excretion of potassium and hydrogen ions in the distal convoluted tubule. Selective or isolated aldosterone deficiency can result from a deficiency in renin secretion or decreased adrenal synthesis. Hyperoninemic hypoaldosteronism is most common in patient with mild to moderate renal insufficiency due to diabetic nephropathy or chronic intestinal nephritis. It can also occur with acute GN and in patients taking NSAID and CNI. The characteristic symptoms of this disorder are hyperoninemic hyperchloremic acidosis and occasionally mild hypokalemia, usually in the setting of impaired renal function. This
case illustrates the importance of considering the diagnosis of hypoaldosteronism in adult patients with symptoms and signs of renal salt wasting in the absence of hyperkalemia hyporeninemic acidosis.

**TH-PO1100**

Hyperkalaemia and Megestrol Acetate: Related? Nikhil Agrawal,1 Ilka A. Nattrass,1 Shimontinni Mitra,2 Stewart H. Lecker,1 Melanie P. Hoening,1 1Beth Israel Deaconess Medical Center, Brookline, MA; 2None, Brookline, MA.

**Background:** Megestrol acetate (MGA) is a synthetic progesterin widely used as an appetite stimulant for patients with cancer. MGA binds to the glucocorticoid receptor with nearly twice the affinity as cortisol and can cause symptoms of glucocorticoid excess while suppressing endogenous glucocorticoid production. We report a case of concomitant mineralocorticoid deficiency in a patient taking MGA with evidence of glucocorticoid deficiency.

**Methods:** A 51-year-old woman with allogenic stem cell transplant 2 years prior for AML and subsequent relapse was admitted for a line infection. She was noted to have a refractory hyperkalaemia a week after admission that required repeated interventions with insulin, dextrose, IV fluids, furosemide, and sodium polystyrene. She reported 3 cups of tomato juice daily and a history of hypokalemia. Medications: atovaquone, ciprofloxacin, daptomycin, famotidine, folic acid, ondansetron, posaconazole, valacyclovir, cefepime and allopurinol. Two days prior to admission, her MGA was increased from 400 to 800mg daily. She denied fatigue, weakness, or hyperpigmentation. She was normotensive and her examination was unremarkable. She had pancytopenia without evidence of tumor lysis. Serum chemistry showed Na 139, K 6.2, Chloride 110, Bicarb 21, BUN 21, Cr 0.8 Early am cortisol: 0.8 mg/dl (increased to 8.8mg/dl at one hour with high dose ACTH stimulation). ACTH 5-6U/mL (6-50). Renin 2.79 ng/mL/hr (0.25-5.82). Aldosterone 1.0 ng/dL (supine 3-16). A low potassium diet was begun but potassium remained high. Urine potassium excretion was low. MGA discontinued, and fludrocortisone and hydrocortisone were begun. Potassium normalized within 24 hr. Within 5 days, she became hypokalemic, and fludrocortisone was discontinued.

**Results:**

**Conclusions:** This is the first reported case of hyperkalaemia in association with MGA. Although MGA is a well-known cause of adrenal insufficiency, this is usually restricted to the glucocorticoid axis. Here low ACTH level suggests secondary adrenal insufficiency which is typically not associated with defects in the mineralocorticoid axis. Yet low aldosterone level in the setting of hyperkalaemia without suppression of renin and with reduced renal potassium excretion is consistent with mineralocorticoid deficiency. Since this resolved with discontinuation of MGA, this suggests that MGA may have an additional effect on the mineralocorticoid axis.

**TH-PO1101**

An Unusual Case of Peripheral Edema Due to Suspected Liddle’s Syndrome Sadem Ali,1 Sri Rangan Radhakrishnan,2 Reginald I. Obi,1 ECU, Greenville, NC; 2ECU Physicians Nephrology, Greenville, NC.

**Background:** Liddle’s syndrome is a rare autosomal dominant disease affecting epithelial sodium channels in which there is a primary increase in collecting tubule sodium reabsorption and usually associated potassium wasting. Patient usually presents with hypertension, hypokalemia, and metabolic alkalosis, with an overall clinical picture mimicking mineralocorticoid excess. However, its presentation with a chief complaint of peripheral edema has not been reported to our knowledge.

**Methods:** We present a 47 years old female who has been hypertensive since the mid thirties of her age. She came for management of hard to control generalized edema, mostly in her lower extremities, for the last three years. No cardiac or liver etiology identified. She had tried several diuretics including hydrochlorothiazide, furosemide, spironolactone, and was then on chlorothalidone 50 milligrams daily. She had been profoundly hypokalemic while on diuretics and requiring 80 milli equivalents daily replacement of potassium chloride. Her labs also showed metabolic alkalosis and relatively high sodium levels. She presented a picture of a potassium wasting syndrome. After holding chlorothalidone for three days, with continued potassium replacement, her trans tubular potassium gradient was calculated at 7.9 confirming urinary potassium wasting. Her plasma aldosterone to renin activity ratio was 13.2, making primary hyperaldosteronism unlikely. We started her on amiloride as 5 mg twice a day due to clinical suspicion of Liddle’s syndrome. After one week, her examination was unremarkable. She had pancytopenia without evidence of tumor lysis.

**Results:** Since this resolved with discontinuation of MGA, this suggests that MGA may have an additional effect on the mineralocorticoid axis.

**Conclusion:** Physicians were more likely to discontinue RAASi or reduce dose in HF patients with HK. Further research is warranted to determine the clinical impact of RAASi dose modification and discontinuation in the treatment of HK in the UK.

**Funding:** Commercial Support - AstraZeneca.
incidence of discontinuation (Figure). This pattern was consistent across eGFR strata. Serum K + ≥ 5.4 mmol/L was associated with increased odds of dose reduction (OR=2.24, p<0.001) versus Serum K + < 5.5 mmol/L.

Conclusions: Physicians were more likely to discontinue RAASI or reduce dose in CKD patients with HK. Further research is warranted to determine the clinical consequences of RAASI dose modification and discontinuation in the management of HK in the UK.

Funding: Commercial Support - AstraZeneca

TH-PO1104

Metformin-Associated Lactic Acidosis in a Patient with Normal Renal Function

Nauhaba Mohiuddin, Jin Li. None, Detroit, MI; Nephrology and Hypertension, Henry Ford Hospital, Detroit, MI.

Background: INTRODUCTION Metformin -associated lactic acidosis (MALA) in patients without renal impairment is an infrequent serious complication. In patients in whom development of renal dysfunction is anticipated, monitoring renal function more frequently and discontinuing Metformin at early renal impairment is crucial. We present a case of severe lactic acidosis in a patient who had no contraindication to Metformin prescription.

Methods: Case: Patient is a 58 year old female presented with abdominal pain and diarrhea. She has history of Diabetes, HTN, with prior normal renal function on Metformin, Lisinopril and Lasix. In Emergency department patient was hypotensive. She was started on Vasopressors and given IV fluids. ABGs showed severe high anion gap acidosis, acute renal failure and Lactate level of 11. Despite aggressive IV hydration, her Lactate trended up to 17. Broad spectrum antibiotics started. She was admitted to ICU. Acute abdomen, septic and cardiogenic shock were ruled out. On further review, was noted, patient was admitted at outside hospital 3 weeks ago, with diarrhea, had negative work up. At that time she had CT abdomen with IV contrast. Metformin was held prior and 4 days after. Metformin was resumed on discharge. A week later, she had CTA of abdomen. Baseline creatinine was around 0.7mg/dl and GFR 88ml/min/1.73m2. Patient was started on sustained low-efficiency dialysis with regional citrate anticoagulation (SLED RCA), for MALA. A progressive recovery was observed, with initially weaning off pressors, lactate level improving and later complete recovery of her renal function.

Results: Conclusions: 1. Identifying patients who are on metformin, at risk to develop lactic acidosis, or alteration in renal function can potentially prevent this life threatening condition. 2. Presence of elevated lactic acidosis in a diabetic patient on metformin, even with baseline normal renal function, should trigger to consider MALA.

TH-PO1105

Low K, Not OK: Distal Renal Tubular Acidosis Associated with Autoimmune Thyroiditis

Timothy Yen, Roberto L. Collazo-Maldonado,1 Internal Medicine, Methodist Dallas Medical Center, Dallas, TX; Division of Nephrology, Methodist Dallas Medical Center, Dallas, TX.

Background: Profound hypokalemia can present with hypokalemic paralysis. This is a rare but potentially fatal condition. Potassium wasting secondary to renal tubular acidosis (RTA) is a common cause of severe hypokalemia. RTAs are associated with multiple systemic diseases including autoimmune disorders and endocrinopathies.

Methods: A 43 year old Hispanic woman with a previous history of calcium phosphate renal stones presented to the ED after she awoke with generalized limb paralysis and diarrhea. She had history of Diabetes, HTN, with prior normal renal function on Metformin, Lisinopril and Lasix. Baseline creatinine was around 0.7-mg/dl and GFR 88ml/min/1.73m2. Patient was started on sustained low-efficiency dialysis with regional citrate anticoagulation (SLED RCA), for MALA. A progressive recovery was observed, with initially weaning off pressors, lactate level improving and later complete recovery of her renal function.

Results: Conclusions: This is a case of previously healthy middle aged woman who presented with hypokalemic paralysis caused by a distal RTA. The patient lacks any classical risk factors for acquired RTA except for elevated anti-thyroid peroxidase antibody. Internists and nephrologists must be aware of this rare but documented association between autoimmune thyroiditis and distal RTA.

TH-PO1106

Associations between Serum Potassium and Clinical Outcomes in Patients with CKD in a Real World Setting

Philip McEwan, Lei Qin, Marc L. Evans, Laura Horne, Erin Palaka, Susan Grandy, Health Economics and Outcomes Research, AstraZeneca, Cambridge, United Kingdom; Swansea Centre for Health Economics, Swansea University, Singleton Park, United Kingdom; Department of Medicine, University Hospital Llandough, Cardiff, United Kingdom; Health Economics and Outcomes Research, AstraZeneca, Gaithersburg, MD; Global Medical Affairs, AstraZeneca, Gaithersburg, MD.

Background: The associations between serum potassium (K +) and rates of mortality and serum K + and rates of major adverse cardiovascular events (MACE) have previously been characterised using US healthcare data. This study assessed the generalisability of this finding and developed risk equations using UK real-world data on a cohort of chronic kidney disease (CKD) patients.

Methods: A retrospective observational study was conducted using the Clinical Practice Research Datalink from Jan 2006 to Dec 2015. Patients (n=18 years) who had a first diagnosis of CKD stage 3 or higher during the study period were analysed with clinical outcomes of interest included all-cause mortality and MACE (arhythmia, heart failure, myocardial infarction, stroke). Incidence rate ratios (IRR) associated with time-updated serum K + were estimated using Generalized Estimating Equations adjusted for a broad range of demographic and clinical covariates.

Results: Analysis included 144,388 CKD patients with a mean follow-up of 4.9 years. Baseline characteristics were predominantly female (60.4%) with a mean age of 73.7 years and mean eGFR of 49.7 mL/min/1.73m2. Baseline ischemic heart disease, stroke, myocardial infarction and peripheral vascular disease were present in 11.5%, 6.6%, 3.4% and 2.6% of patients, respectively. There were 34,602 deaths and 71,607 MACE during the study period. Time-updated serum K + concentrations were positively associated with incidence.

Conclusions: A real-world analysis of UK patients with CKD indicated associations between hypo- and hyperkalemia with risk of mortality and MACE. The observed U-shaped trends were consistent with previously reported US real-world studies.

Funding: Commercial Support - AstraZeneca

TH-PO1107

Prevalence of Hyperkalemia in Patients with ESRD Undergoing Hemodialysis

Sarvanan Balamuthusamy, Alagarsamy R, Sankaran Chellappan, Ranjita D, Baluraman Ganeshan, Texas Research Institute and PPG Healthcare PA, Fort Worth, TX.

Background: Adverse cardiovascular events are the most common reason for mortality and morbidity in patient with ESRD. Hyperkalemia is a well-known etiology of cardiac arrhythmias in ESRD and non-ESRD patients. We have analyzed the prevalence of hyperkalemia in prevalent hemodialysis patients dialedyzed 3 times a week in an outpatient dialysis clinic.

Methods: Retrospective analysis of serum potassium levels in ESRD patients undergoing hemodialysis in 9 dialysis clinics. Pre-dialysis Potassium levels were measured as per dialysis protocol. Based on serum potassium levels, patients divided into four groups i) Hyperkalemia (Serum K level less than 3.5), ii) normokalemia (Serum K level between 3.6 to 5.4 mmol/L), iii) moderate hyperkalemia (Serum K level between
A Cause for Concern: RAAS Inhibitors Are Associated with Significant Risks

Recent studies have suggested that inhibitors of the renin-angiotensin-aldosterone system (RAAS) are widely used in patients with chronic heart failure (HF). We previously reported that the impact of angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) on renal function is distinct from that of downstream blockers of the RAAS (i.e., mineralocorticoid receptor antagonists [MRA]). In this study, we sought to evaluate the effect of these agents on the incidence of hyperkalemia in HF.

Methods: Articles cited in PubMed, EMBASE, and Cochrane database from 1987 to 2017 using key words: “heart failure”, “angiotensin-converting enzyme”, “angiotensin receptor blockers”, and “mineralocorticoid receptor blockers” were searched in randomized controlled trials (RCTs) that addressed the impact of RAAS inhibition in HF were identified. Hyperkalemia, defined as serum potassium level ≥5.5 mmol/L, was considered the primary endpoint. A meta-analysis was performed. Mantel-Haenszel random-effects model was used to calculate risk ratios (RRs) with 95% confidence intervals (CIs).

Results: A total of 3389 studies were selected after extensive database search. After excluding duplicate and non-randomized trials, 14 RCTs with 29,433 participants were found eligible for analysis. Compared to placebo, ACE-I/ARB significantly increased the risk of hyperkalemia (RR 2.31 CI 1.73-3.02, p<0.01). Addition of MRA to ACE-I/ARB further increased the risk (RR 2.19 CI 1.51-3.16, p<0.01). When evaluated for severe hyperkalemia (i.e. serum potassium levels > 6.0 mmol/L), ACE-I/ARB increased the risk compared to placebo (RR 1.59, CI 1.13-2.25, p<0.01), and addition of MRA to ACE-I/ARB further increased it (RR 1.63 CI 1.13-2.35, p=0.01).

Conclusions: In patients with HF, ACE/ARB therapy increases the risk of hyperkalemia by more than two folds and downstream addition of MRA increases the risk further. RAAS inhibitors have been shown to improve outcomes including mortality in this patient population. However, studies are needed to evaluate therapeutic strategies (e.g. newer potassium binders) for prevention of hyperkalemia to avoid underutilization of RAAS inhibition.

Workup of Unexplained Renal Hypophosphatemia

Anneke Bech, 1 Ewout J. Hoorn, 1 Robert Zietse, 1 Jack F. Wetzel, 2 Tom Nijenhuis, 3 Erasmus Medical Center, Rotterdam, Netherlands; 2Radboud University Medical Center, Nijmegen, Netherlands; 3Radboud University Nijmegen Medical Center, Nijmegen, Netherlands; 4Radboud university medical center, Nijent, Netherlands.

Background: Hypophosphatemia can be caused by renal phosphate loss. Increased renal phosphate loss can be inherited or acquired. The most common causes of acquired renal hypophosphatemia are medication, Fanconi syndrome, hyperparathyroidism and tumor induced osteomalacia (TIO). The clinical picture of these disorders varies widely and is non-specific. An increasing number of patients with unexplained renal hypophosphatemia is being referred to our clinics.

Methods: We retrospectively evaluated all patients who were referred in the period 2013-2017 because of unexplained renal hypophosphatemia in two university hospitals in the Netherlands (N=13).

Results: The median age was 51 years and ten patients were male. They did not show any other signs of tubulopathy and did not use drugs known to be associated with hypophosphatemia. Baseline characteristic are shown in table 1. We performed an Indium-pentetreotide SPECT/CT in 5 patients and a Ga-DOTA-TOC PET/CT scan in 3 patients. One of these scans showed an increased uptake suggestive of TIO. Genetic testing, performed in all patients, did not show a mutation in genes that are known to be associated with renal phosphate wasting (DMP1, FGF23, FGFRI, GALNT3, PHX, SLC34A1, SLC34A3, SLC4A9).

Conclusions: We have evaluated a group of patients with unexplained renal hypophosphatemia. Despite extensive and expensive additional investigations, the cause of renal phosphate loss remained unexplained in the majority of the patients. The pretest probability of finding a phosphaturic hormone producing tumor on a scan with radiolabeled somatostatin analogs or to find a mutation with genetic analysis in a patient with ascetic complaints and normal (inappropriately) normal FGF23 level is low. We therefore advise not to perform scans and genetic analyses as a standard workup in these patients.

Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median</th>
<th>Range</th>
<th>Reference value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum phosphate (mmol/L)</td>
<td>0.94</td>
<td>0.66-1.17</td>
<td>0.8-1.4</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>0.90</td>
<td>0.40-1.55</td>
<td>0.80-1.40</td>
</tr>
<tr>
<td>Serum creatinine (mmol/L)</td>
<td>7.8</td>
<td>5.3-15.4</td>
<td>80-110</td>
</tr>
<tr>
<td>FGF23 (pg/mL)</td>
<td>2.1</td>
<td>1.2-3.5</td>
<td>3.5-6.5</td>
</tr>
<tr>
<td>25(OH)D (nmol/L)</td>
<td>71</td>
<td>30-133</td>
<td>50</td>
</tr>
<tr>
<td>(FGF23) (mU/mL)</td>
<td>92</td>
<td>53-202</td>
<td>&lt;25</td>
</tr>
</tbody>
</table>

TH-PO1110

Correcting Serum Potassium ([K]) in Critical Care

Background: High platelet counts (PLT) positively bias serum [K] in chemistry panels (C4). Because the C4 assay uses indirect potentiometry, it should also be positively biased by low total protein (TP), common in critical care, but this is unproven. Neither bias should affect [K] measured in gas panels (C1) in whole blood anticoagulated with electrolyte-balanced heparin. Since even a subtle bias in C4 could be important at a decision limit, we sought to derive a practical correction for commonly seen values of PLT on C4 and C1, as well as to confirm TP bias.

Methods: In our critical care database (Clin Biochem 2017), we found 710 patients who had C1, C4, and TP obtained <20 min apart (median: 4 min). We excluded 17 cases with PLT ≥500 (units:10^9/L), as such values (i) are already known to bias C4 and (ii) being extreme, might skew the estimated effect of more usual PLT values. The independent effects of PLT and TP upon AK were estimated with multivariate methods.

Results: Mean values (±S.E.) were: PLT, 209±7 ±5 range: 4-497); TP, 6.5±0.04 g/dL {[2.1-10.0] K, 2.5±0.01 mmol/L [1.8-20.21]}; and C4, 45±0.4 mU/mL [25-120]. PLT correlated with both AK (r=0.13 p<0.01) and TP (r=0.19 p<0.01). TP did not correlate (r=0.06 p=0.11), possibly the result of confounding by PLT. No nonlinear effects of PLT category (TABLE) on AK were detected by ANOVA with polynomial contrast. By multiple linear regression, AK rose 0.053±0.014 mEq/L with each PLT rise of 100 (p=10^-4) and by 0.026±0.011 (p=0.02) with each 1 g/dL fall in TP (model adj. R²=0.024).

Conclusions: The accuracy of C4 can be improved simply with a 0.05 mEq/L reduction per 100 PLT rise. The effect of TP on C4 is minor, but, proportionally, the same as its effect on serum [Na] and, much of the variation in C4 relative to C1 is unexplained.

Funding: Veterans Affairs Support

Mean Values by PLT Category

Table

<table>
<thead>
<tr>
<th>PLT (10^9/L)</th>
<th>C1 (mEq/L)</th>
<th>C4 (mEq/L)</th>
<th>AK (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤100</td>
<td>3.8±0.5</td>
<td>4.0±0.5</td>
<td>4.2±0.5</td>
</tr>
<tr>
<td>101-200</td>
<td>3.6±0.6</td>
<td>4.3±1.0</td>
<td>4.5±1.0</td>
</tr>
<tr>
<td>&gt;200</td>
<td>5.0±0.5</td>
<td>5.0±1.0</td>
<td>5.0±1.0</td>
</tr>
</tbody>
</table>

TH-PO1111

Post-Hyperkalemia Prescription Patterns for Renin–Angiotensin–Aldosterone System Inhibitors (RAASis) in England

Laura Horne, 1 Robert J. LoCasale, 2 Sharon Macalchan, 3 Marvin V. Sinsukul, 4 James B. Wtemore, 5 AstraZeneca, Gaithersburg, MD; 6Evedera, London, United Kingdom; 7Hennepin County Medical Center, Minneapolis, MN.

Background: It is unclear how physicians may adjust RAASi prescriptions for patients with hyperkalemia (HIK; elevated serum potassium [K]). We evaluated whether RAASi use was modified after an HIK event in England.

Methods: A retrospective cohort analysis of the linked Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) databases identified RAASi prescription changes after HIK. Patients (≥18 years) with an incident HIK event (first measurement of K ≥5.0 mmol/L or HIK diagnosis code) using RAASis from 2009–2017 were included. Change in next RAASi prescription was defined as dose increase, addition of diuretic, no change, switch to other RAASi, dose decrease, or interruption.

Results: After excluding duplicate and non-randomized trials, 14 RCTs with 29,433 participants were included. Change in next RAASi prescription was defined as dose increase, addition of diuretic, no change, switch to other RAASi, dose decrease, or interruption. HIK severity was defined as K ≥5.0 (K ≥5.0–5.5 mmol/L or CPRD diagnosis code, with no lab results), K ≥5.5–6.0 (K ≥5.5–6.0 mmol/L, or HES diagnosis code, regardless of K). Frequencies of post-HIK RAASi use were calculated overall, by clinical comorbidities, and by HIK severity.

Results: An HIK event was experienced by 59,465 RAASi users. Most patients (74.6%) continued the same RAASi drug and dose after incident HIK, even with K ≥6.0 and when renal function was likely reduced; addition of diuretics was uncommon. Whether this represents an optimal HIK treatment strategy needs further study.

Funding: Veterans Affairs Support, Commercial Support - AstraZeneca

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
TH-PO1112

Maintained Efficacy and Safety of Sodium Zirconium Cyclosilicate for Hyperkalemia: 12-Month, Open-Label, Phase 3 Study

Background: Sodium zirconium cyclosilicate (ZS) is an investigational, oral, highly selective K-binder shown to restore normokalemia in hyperkalemic pts. We report subgroup results for outpatient s with K ≥ 6.0 mEq/L during acute treatment in a 12 mo Phase 3 study.

Methods: We performed a post-hoc analysis of an international, multicenter, open-label, single-arm trial that enrolled 751 pts (≥18y) with point-of-care (iSTAT) K ≥ 5.0 mEq/L. Immediate treatment decisions were based on iSTAT K data, and confirmed by central laboratory serum K. During acute phase, pts received 10g ZS TID (24–72h) until K 3.5–5.0 was achieved by iSTAT. K post-hoc endpoints were: final K change in K from baseline, achievement of K 3.5–5.0 and adverse events (AE) during acute phase. Proportions were calculated using last observation carried forward.

Results: At baseline, 126 (17%) of pts had serum K ≥ 6.0 mEq/L. 99% completed acute phase. Most pts (71%) had CKD and 74% used RAASi with no discontinuations observed. Median acute phase treatment duration was 1 day; median ZS dose was 30g. Mean (95% CI) baseline serum K was 6.2 (6.0, 6.3), final K was 4.6 (4.5, 4.7). Mean change from 1.0 (1.0, 1.5). The majority of pts achieved normokalemia; no patients had K < 6.0 at 24h (Figure). Serum K values were higher than iSTAT K values. AE s were observed in 11 of 126 pts including 3 gastrointestinal disorders, 3 infections, 2 musculoskeletal disorders, 1 peripheral edema. NO AEs were serious. There was 1 report of hypokalemia (3.0–3.5 mEq/L) in the acute phase. Conclusions: Oral outpatient treatment with ZS rapidly normalized K in pts with baseline K ≥6.0 mEq/L, with few adverse events and may be a viable therapy for this high-risk pt population.

Funding: Commercial Support - AstraZeneca

TH-PO1114

Risk Factors and Outcomes of Rapid Correction of Severe Hyponatremia

Background: Rapid correction of serum sodium is a concern in patients with severe hyponatremia and can have serious clinical consequences, including central pontine myelinolysis (CPM). Clinical risk factors of rapid correction and incidence of CPM has not been well-studied among patients with severe hyponatremia.

Methods: Using data from 1,352 inpatients in Geisinger Health System from 2001-2016 with serum sodium ≤120 mEq/L on admission, we examined possible predictors of overcorrection (demographics, comorbidity, medication, lab, and physical measurement data). Rapid correction of sodium (≤10 mEq/L) was determined using sodium values closest to the 24 hour timepoint. CPM was determined by diagnostic codes and chart review, all brain MRIs.

Results: Mean age was 65.2 (SD 15.5) years, 54.9% were female, and 65.1% had a history of chronic hyponatremia (last outpatient sodium <135 mEq/L). The median change in sodium at 24 hours was 7.1 mEq/L (IQR 3.6–11.0), and 396 (29.3%) patients had rapid sodium correction. After multivariate adjustment, risk factors for overcorrection included female gender, schizophrenia, hypo- and hyperkalemia on presentation, and repletion of other electrolytes (Table). History of chronic hyponatremia, outpatient loop diuretic use, and treatment at an academic center were associated with lower risk for rapid sodium correction. A total of 357 (26.4%) patients had brain MRIs completed during follow-up with 10 patients showing evidence of CPM (7 had documented rapid correction).

Conclusions: Consideration of various contributing factors, including age, gender, medications and co-morbidities could provide useful risk stratification for preventing rapid sodium correction and CPM.

Funding: Geisinger, Dutville, PA; Geisinger Medical Center, Dutville, PA.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
TH-PO1115

Treatment of dRTA with an Innovative Combination Product as Compared to Current Standards of Care

Aurélia Bertholet-Thomas,1 Catherine Guittet,2 Maria A. Manso,2 Luc andre Granier.2 Centre de référence des maladies rénales rares, Bron, France; 1Advicenne, Nîmes, France. Group/Team: B21CS study investigators.

Background: Patients suffering from distal renal tubular acidosis (dRTA) require long-term treatment in order to restore and maintain physiological blood pH values. Products currently used as standards of care (SoC) require several daily administrations and are characterised by gastrointestinal (GI) tolerability issues and bitter taste. A new innovative age-adaptable prolonged-release granule combination product (ADV7103), achieving adequate bicarbonataemia (blood bicarbonate ≥135 mEq/L), was first reported in patients with hyperglycaemia. Patients with creatinine greater than 1.6 mg/dl were excluded.

Methods: A multicentre (N=13), open-label, non-inferiority, sequential study was performed. Adult and paediatric dRTA patients (N=37, 30 evaluable for bicarbonataemia) received their SoC and then ADV7103 at the most appropriate doses, both during 5-day periods. The alkali doses administered and the blood bicarbonate levels at steady state treatment conditions were compared. GI tolerability, palatability, easiness of administration and swallowing, were evaluated using visual analogue scales or 5-point facial hedonic scales.

Results: Blood bicarbonate levels were suboptimal in children and infants with the SoC and improved with two daily administrations of ADV7103. Less variability was observed with ADV7103 in adults and similar results were obtained with both treatments in adolescents. Improved GI tolerability, palatability and easiness of administration were observed in all age groups with ADV7103 compared to SoC. The improved ability to correct metabolic acidosis of ADV7103 was associated to the possibility of optimising dosing, while poor tolerability and acceptability appeared to limit further dosing increases with SoC.

Conclusions: ADV7103 is the first prolonged-release alcalinizing product improving bicarbonataemia control in dRTA patients compared with SoC, with less GI side effects and very good acceptability.

Funding: Commercial Support - Advicenne

TH-PO1116

Prevalence of Hyponatremia in Dengue Infected Patients

Daniel Caputo,1 Armando L. Negri,2 Juan Carlos Ayus,3 Carlos Eghi,2 Graciela E. Cabral,2 Ydania Fernandez carreño,2 1Hospital Nacional Alejandro Posadas, El Palomar, Buenos Aires, Argentina; 2Hospital Posadas, Buenos Aires, Argentina; 3Instituto de Investigaciones Metabólicas, Buenos Aires, Argentina; 4Renal Consultants of Houston, Houston, TX.

Background: PHO-WHO (Dengue guidelines 2016), and CDC recommended high water intake in patients with dengue. However, no information exists about the prevalence of hyponatremia in newly infected patients.

Methods: Cross-sectional study in patients with newly diagnosed dengue infection in Argentina from January 2016 to April 2016. Hyponatremia was defined as serum sodium concentration <135 mEq/L. Natremia was corrected in patients with hyperglycaemia. Patients with creatinine greater than 1.6 mg/dl were excluded.

Results: We evaluated 146 patients with dengue diagnosis confirmed by IgM serology or PCR. Hyponatremia was present in 30.8% of the patients. The prevalence of hyponatremia in newly infected patients with dengue, especially in older patients is high. Electrolyte evaluation should be done at admission in all patients with dengue and routine use of hypotonic fluids should be avoided in these patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
to achieve sustained physiological blood pH values in dRTA patients with a simplified dosing regimen. The current standards of care (SoC) require multiple administrations and are not always well tolerated. The objective of this clinical study was to assess safety of ADV7103 after treatment for 6 months as well as to follow-up bicarbonate levels and evaluate patient’s satisfaction.

Methods: Adult and pediatric dRTA patients (N=30) were included in a multicentre (N=12), open-label, 24-month study. They received ADV7103 twice a day at appropriate doses. Preliminary data after 6 months of treatment were analysed, including adverse events and bicarbonaemia. Improvement of quality of life was evaluated at by patients and/or their parents using a 100-mm visual analogue scale.

Results: A total of 17 patients presented adverse events. Among the 45 adverse events observed, 40 were unrelated, 1 (abdominal pain) was unlikely related, 3 (alopecia, dyspepsia and abdominal pain) were possibly related, and 1 (diarrhea) was probably related to the treatment. The 5 latter adverse events were all of mild intensity. There was only one serious adverse event unrelated to the product (wisdom teeth removal). Efficacy was maintained after 6 months treatment, with blood bicarbonate levels above 21 mEq/L in 79% of the patients. Only three patients presented bicarbonaemia levels below 20 mEq/L. ADV7103 doses ranged from 1.3 to 7.2 mEq/kg/day. Patients and/or their parents were extremely satisfied with ADV7103. The change of alkalising treatment from the their SoC to ADV7103 allowed an average improvement of their quality of life of 80.5%, ranging from 76 to 98% depending of the age group considered.

Conclusions: The present preliminary results confirm the excellent safety and efficacy of ADV7103, a combination product allowing treatment with only 2 daily doses. The level of satisfaction of the patients is very high and clinicians are expecting registration of the product for first-line treatment of dRTA.

Funding: Private Foundation Support

TH-POI118
Prognostic Factors in Sepsis Patients Who Have Undergone Direct Hemoperfusion with Polymyxin B-Imobilized Fibers Akiko Okubo, Ayumu Nakashima, Shigehiro Doi, Toshinori Ueno, Takao Masaki. Hiroshima University Hospital, Hiroshima, Japan.

Background: In 2016, the definitions of sepsis and septic shock were reviewed by the Society of Critical Care Medicine and Sequential Organ Failure Assessment (SOFA) and a Quick SOFA score was added to those definitions. Direct hemoperfusion therapy with polymyxin B-imobilized fiber cartridge (PMX-DHP) has been widely used to treat sepsis and septic shock. However, prognostic factors are not well understood. We retrospectively assessed the prognostic factors of patients who had received PMX-DHP for sepsis and septic shock.

Methods: Data on 71 patients with severe infection who had undergone PMX-DHP from January 2006 to August 2015 were included in this study. Participants were re-evaluated according to the criteria of the Third International Consensus Definitions for Sepsis and Septic Shock. We also compared the data between the survivors and the non-survivors. The STATISTICA software was used for statistical analysis, p < 0.05 was considered as statistically significant.

Results: In the non-survivor group, the Glasgow Coma Scale score before PMX-DHP was significantly lower than in the survivor group (12 [6 to 14] vs 14 [12 to 15], P < 0.01). Furthermore, pH after the first PMX-DHP session was significantly lower in non-survivors than in survivors (7.29 ± 0.23 vs 7.39 ± 0.06, P = 0.03). The only factor identified by multivariate analysis as significantly associated with 28-day mortality was pH after the first PMX-DHP session (odds ratio, 0.93; 95% CI, 0.83–0.99; P = 0.02). Conclusion: pH after the first PMX-DHP session is an independent risk factor for mortality in patients receiving PMX-DHP for sepsis and septic shock.

TH-POI119
Urinary Acid Excretion in Overweight Patients with CKD Yuichi Izumi,1 Koji Eguchi,1 Yushka Nakayama,1 Hideki Inoue,1 Hiroshi Nonoguchi,2 Yutaka Kakizoe,1 Takashige Kuwabara,1 Masashi Mukoyama,2 1Department of Nephrology, Kumamoto University graduate school of medical sciences, Kumamoto, Japan; 2Kumamoto University Medical Center, Kitamoto, Japan; 3Kumamoto University, Kumamoto, Japan; 4Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan; 5Kumamoto University Graduate School of Medicine, Kumamoto, Japan; 6Kumamoto University School of Medicine, Kumamoto, Japan.

Background: Urinary ammonium excretion, which reflects acid excretion by the kidneys, has been suggested as a predictor for the chronic kidney disease (CKD) outcome. Overweight is one of the risk factors for progression of CKD. We examined urinary acid excretion in overweight CKD patients.

Methods: 25 Japanese out-patients with CKD who were treated with diet and medical therapy in our hospital were enrolled to evaluate acid excretion by the kidney. A 24-h urine collection was performed one day before visiting our hospital to determine excretion of acid (OA, protein, urea, sodium chloride, ammonium, pH, titratable acid (TA) and other electrolytes. Blood test was performed at visiting day. Their creatinine clearance (Ccr) corrected by body surface area was from 10 to 120 ml/min. For further analysis, patients, whose Ccr was > 30 ml/min, were divided into two groups: 11 normal (BMI 21 ± 2 kg/m2) and 10 overweight (28 ± 3 kg/m2) patients. Acid excretion between two groups was compared.

Results: Both ammonium (Figure 1) and TA excretions decreased with the decrease of Ccr (r² = 0.31, P = 0.0036 and r² = 0.20, P = 0.028). Between two groups, ammonium excretion was significantly decreased in overweight patients compared to that in normal weight patients (Figure 2). TA excretion tended to be increased in overweight group, resulting in no difference of total acid excretion (calculated by ammonium + TA) between the two groups. While protein and sodium chloride intakes were greater in overweight, net endogenous acid production (NEAP) and Ccr were not different between the two groups.

Conclusions: There might be a modulation of acid excretion mechanism in overweight patients with CKD.

Funding: Government Support - Non-U.S.
syndrome, has not been evaluated in patients with MS. Our objective was to compare the patients of urinary electrolyte and amino acid excretion between MS and age- and gender-matched non-MS controls.

Methods: Subjects aged 18 or older with a diagnosis of MS were eligible to participate as cases; controls were age- and gender-matched individuals without MS. Exclusion criteria included known chronic kidney disease or kidney transplantation, use of a drug known to inhibit renal carbonic anhydrase, or use of a drug known to cause Fanconi syndrome. A blood sample was collected for a basic metabolic panel plus phosphorus. Urinalysis was performed and urine was assayed for electrolytes, glucose, creatinine and a panel of 28 amino acids. Univariate analysis was performed using Chi-square and Wilcoxon testing.

Results: 11 MS patients (10 females, 1 male) participated, and age and gender matched to 20 non-MS controls (17 females, 3 males). 10/11 MS patients were on disease-modifying therapy, including dimethyl fumarate (4/11), glatiramer (2/11), fingolimod (2/11), interferon (1/11), and natalizumab (1/11). Median age among MS patients and controls was 45 [IQR 32, 59] and 53 [IQR 31, 63] years, respectively. Race, ethnicity and gender were similar between groups. Mean levels of 17/28 (61%) urinary amino acids were higher in MS patients than controls (p <0.05 for carnosine, glutamate, hydroxyproline, and proline). Urinary amino acids were generally in the normal range, but abnormal levels were more common in MS patients for 8 amino acids and normal in all individuals for the remainder. Increased urinary amino acids were not associated with a particular MS treatment. MS patients had greater urine sodium levels (97 [IQR 73, 125] vs. 55 [IQR 29, 75] mmol/L; p = 0.03) and similar levels of urine potassium, chloride and phosphorus.

Conclusions: MS patients with normal kidney function may be at higher risk of urinary amino acid wasting. Future studies are needed to verify these findings and to elucidate whether MS or its treatment predispose to previously unrecognized proximal tubular dysfunction.

Funding: Commercial Support - Biogen, Inc
Methods: This was a cross-sectional single blinded study at two university-based urban hospitals. Study participants were adults in a medical intensive care unit (MICU) that had simultaneously drawn ABG and central VBG samples.Expert acid-base diagnosticians, all nephrologists, were blinded to the clinical data and blood gas origin to interpret the acid-base disorder(s) from each sample. Blood gas samples were classified as: no disorder, metabolic acidosis, metabolic alkalosis, respiratory acidosis, or respiratory alkalosis. Diagnostic accuracy of central VBG-based diagnoses were compared to ABG-based diagnoses by assessing percent clinical agreement, sensitivity and specificity.

Results: They studied 23 participants. The most common underlying primary diagnoses were respiratory-related (45.5%) and sepsis-related (40.9%). Overall, the central VBG had 100% sensitivity for metabolic acidosis, metabolic alkalosis, and respiratory acidosis, and 71% for respiratory alkalosis, and high percent clinical agreement, ranging from 75-94%, with a lower agreement of 57% for respiratory alkalosis. VBG-based diagnoses in vasopressor dependent patients (n=13, 56.5%) performed very similarly.

Conclusions: In critically ill adult patients, central VBG detects acid-base disturbances with good diagnostic accuracy, even in shock states. This study supports the use of central VBG for diagnosis of acid-base disturbances in MICU patients.

Funding: NIDDK Support

Diagnostic Accuracy of VBG-based Diagnosis compared to ABG-based Diagnosis.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Clinical Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic Acidosis</td>
<td>100%</td>
<td>84%</td>
<td>97.3%</td>
</tr>
<tr>
<td>Metabolic Alkalosis</td>
<td>100%</td>
<td>100%</td>
<td>75%</td>
</tr>
<tr>
<td>Respiratory Acidosis</td>
<td>100%</td>
<td>66%</td>
<td>92%</td>
</tr>
<tr>
<td>Respiratory Alkalosis</td>
<td>71%</td>
<td>100%</td>
<td>57%</td>
</tr>
</tbody>
</table>

TH-PO1126
Primary Aldosteronism Associated with a Mutation of CACNA1H

Kendra E. Wulczyn,1 Robert L. Nussbaum,1 Lowell J. Lo,2 Edward Perez-Reyes,1 Meyeon Park.1 1Invitae Corp, San Francisco, CA; 2None, San Francisco, CA; 3UCSF, San Francisco, CA; 4University of California San Francisco, San Francisco, CA; 5University of Virginia, Charlottesville, VA

Background: Several genetic mutations have been described in rare forms of primary aldosteronism (PA). We report a case of aldosteronism with hypokalemia and hypertension. A patient harbors a mutation of CACNA1H, encoding a voltage-gated calcium channel (Ca_{3.2}) expressed in adrenal glomerulosa.

Methods: A 31 year old female with type III Ehlers-Danlos syndrome and postural orthostatic tachycardia syndrome (POTS) presented for evaluation of chronic hypotension and postural symptoms. The patient was receiving potassium every 2-4 weeks (baseline K_{2.6-3.6} mmol/L) for profound weakness. Prior evaluation had revealed elevated plasma aldosterone level (38 ng/dL) and suppressed renin (0.17 pg/dl), and MRI demonstrated normal appearing adrenal glands. Low-dose spironolactone was initiated, which improved the hypokalemia, yet the patient still required monthly potassium infusions for symptoms.

Results: A laboratory assessment was made pre- and post-lactate infusion with 2L IVF, supplemented with 25 mEq K and 2.5g Mg (shown in table below). Results demonstrated persistently elevated aldosterone level despite volume repletion (of note, patient was unable to stop spironolactone for the testing). During this course, results of whole exome sequencing (Personalis, Inc.) revealed a de novo loss-of-function missense mutation, R890H, in the voltage-sensing domain of the CACNA1H gene.

Conclusions: POTS has been associated with both increased and decreased activity of the RAAS system; however, in this patient, laboratory testing pre- and post-lactate resuscitation suggest aldosterone secretion was independent of volume status. Therefore, the mutation of CACNA1H, not previously described, is likely cause of pathologic aldosterone secretion.

Funding:
NIDDK Support

TH-PO1127
Relationship between Central Venous, Peripheral Venous, and Arterial Potassium in the ICU

Richard M. Tregear,1 Caleb Hsieh,2 Tristan Grogan,2 Nader Kamarang,1,2 Nephrology, ED Greater Los Angeles Healthcare System, Los Angeles, CA; 1David Geffen School of Medicine at UCLA, Los Angeles, CA; 2Critical Care, Olive View-UCLA Medical Center, Sylmar, CA; 1Medicine and Biostatistics, UCLA, Los Angeles, CA

Background: As shown in small studies evaluating regional hypoperfusion, venous potassium concentration (K) may better reflect intestinal and tissue K than arterial values, and thus better predict serious cardiac manifestations of hyperkalemia. Moreover, because central veins drain a much greater tissue mass (muscle and splanchic) than peripheral veins, discrepancies between peripheral venous (PV), central venous (CV), and arterial (Ar) K may exist, especially in states of global hypoperfusion such as sepsis.

Methods: Ar, CV, and PV samples were prospectively obtained within 10 minutes of each other from single-center adult medical ICU patients.

Results: 51 paired samples from 23 patients were included. The correlations between Ar-PV K, Ar-CV K and CV lactate (Figure) were not statistically significant (p = 0.60 and 0.99, respectively). The correlations between PV and Ar K, as well as CV and Ar K yielded an R^{2} of 0.83 and 0.83, respectively. Bland-Altman plots of Ar K and PV K, as well as Ar K and CV K showed 95% limits of agreement of -0.42 to 0.35 and -0.43 to 0.51, respectively.

Conclusions: In medical ICU patients with global hypoperfusion, CV K was not different from that of Ar and PV K and did not correlate with serum lactate. This disproved our hypothesis that in global hypoperfusion CV blood would demonstrate higher K and better reflect tissue K compared with Ar blood. In fact, CV and PV K showed high correlation and strong agreement with Ar K and can be used interchangeably. This contrasts with prior studies of regional hypoperfusion that demonstrated a higher K in venous blood relative to arterial blood, reflective of local interstitial and tissue K levels. Our results likely did not demonstrate this because of augmented intracellular K\textsuperscript{+} shifting and CV system dilution of K\textsuperscript{+} in global hypoperfusion.

Funding: Veterans Affairs Support
occluded five most recent serum values for magnesium, creatinine, estimated glomerular filtration rate (eGFR), calcium, phosphorus, parathyroid hormone intact (PTH) and 25(OH) Vitamin D, presence of diabetes, and use of diuretics, proton pump inhibitors (PPI), phosphate binders, and magnesium supplementation in past 5 years. Hypomagnesemia was defined as serum magnesium less than 1.8 mg/dL or a serum magnesium ≥1.8 mg/dL on magnesium supplementation. We then determined possible associations of plasma magnesium with age, presence of diabetes, use of PPI, diuretics, and phosphate binders, and mean values of serum calcium, phosphorus, eGFR, PTH, and 25(OH) Vitamin D.

Results: Mean age was 70.01±10.87 years. All patients were male, with 60.36% (N=471) had stage 3 CKD. 57.9% (N=514) were on a PPI. 32% (N=286) were on magnesium supplementation. 33.67% (N=299) had a mean serum magnesium <1.8 mg/dL. While 66.33% (N=589) had a mean serum magnesium ≥1.8 mg/dL, 121 of those patients were on magnesium supplement. Hence, 47.29% (N=420) had hypomagnesemia. Presence of diabetes mellitus, use of phosphate supplement, diuretics, and PPI increased odds of having hypomagnesemia (Table 1).

Conclusions: Hypomagnesemia is common in patients with CKD. Use of PPI and presence of diabetes have the highest odds of developing hypomagnesemia.

Funding: Clinical Revenue Support

Table 1: Fluid, Electrolyte, Acid-Base Disorders

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>70.01±10.87</td>
</tr>
<tr>
<td>BMI</td>
<td>27.7±5.4</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>130/80</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>2.6±1.8</td>
</tr>
<tr>
<td>Serum Urea</td>
<td>53±16</td>
</tr>
<tr>
<td>Serum Mg</td>
<td>1.9±0.3</td>
</tr>
<tr>
<td>Serum Ca</td>
<td>9.5±1.2</td>
</tr>
<tr>
<td>Serum P3</td>
<td>4.8±1.3</td>
</tr>
</tbody>
</table>

PH-101132

Case of Amphoterin-Induced Renal Hypokalemia Mark Kozlowsky,2 Maya K. Trechon,3 Jacob Stromberg,1 Columbia University, New York, NY; 2Nephrology, Columbia University, New York, NY; 3NYP Columbia - Nephrology Fellowship, New York, NY.

Background: Amphoterin (AmB) is often used to treat severe fungal infections. It increases membrane permeability of the renal tubular cell potentially leading to hypokalemia, hypokalemia and renal tubular acidosis. It also causes resistance to diuretic hormone leading to polynatra that can potentiate hypokalemia by increasing distal urinary flow.

Methods: A 29 yr old male with sinonasal & intracranial aspergilloma infection was admitted to NUC in septic shock and respiratory failure requiring intubation. Despite anti-fungal treatment with micaflufan, voriconazole, imaging showed growth of the fungal mass and treatment with AmB was initiated. Within 2 days of starting amphoterin the patient developed new onset hypokalemia ranging from 2.3 to 3.4mmol/L with U waves seen on EKG. Hypokalemia remained refractory to supplementation over a week despite intravenous potassium repletion of ~ 200meq/day plus an additional 40-100meq of oral KC1. Pt had some polyuria during this time with urine output(UOP) ranging from 1.5 - 5L daily in part driven by high input of ~ 5-6L/day, though UOP remained elevated over 2L/day even once IV hydration was reduced. While polyuria continued urine osmolality ranged from 380 to 472 mOsm/kg demonstrating some persistent tubular concentration function. Pt had no diarrhea noted and magnesia was supplemented to maintain adequate level of 2mEq/L. Inotropic studies for hypokalemia including a cortisol level of 21.5ug/dL, renin & aldosterone levels of 0.38 ng/mL and 4.7ng/dL respectively were unremarkable upon evaluation of alternative causes of hypokalemia. 24 hour urinary potassium was elevated at 292 mmol/day while coincident serum potassium was 2.8mmol/L. Due to refractory hypokalemia despite aggressive diuretic and evidence of urinary potassium wasting, the patient started amiloride with slight improvement of potassium to ~ 3.5mmol/L though not until AmB was discontinued after nearly 1 month of therapy did potassium levels normalize consistently to > 3.5mmol/L without further need of repletion and amiloride.

Results: This case demonstrated amphoterin induced urinary potassium wasting via increased excretion along with polyuria refractory to high dose supplementation showing the potential harm & limitations in using AmB. It also demonstrates benefit of early initiation of potassium sparing diuretics to achieve potassium stabilization in patients requiring this medication.

PH-101133

Recurrent SIADH: A Rare Complication of Intrathecal Interleukin-2 Treatment for Melanoma with Brain Metastases Ali Ziaolhagh1, Chionyce C. Ogbonnaya-Odor,2 Jade M. Teckell,2 Amit Lahoti,3 1M D Anderson Cancer Center, Houston, TX; 2Univ of Texas Medical School at Houston, Houston, TX.

Background: The 10- year survival rate for patients with metastatic melanoma is less than 10%. Systemic therapy is the mainstay of treatment for most patients, and immunotherapeutic agents have been associated with durable response in some patients. Intrathecal interleukin-2 (IL-2), which activates T-cells and NK cells, was approved by FDA in 1998 for treatment of metastatic melanoma. Common adverse effects include fever, chills, hypotension, cardiac arrhythmias, oliguria, volume overload, delirium, and rash. Hypokalemia has not been commonly reported. We present an unusual case of recurrent SIADH with each cycle of intrathecal IL-2.

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

Underlines represent presenting author.
Methods: A 65 year old man with Stage IV melanoma with left parietotemporal hemorrhagic metastases, underwent stereotactic radiosurgery of a left temporal lesion. He was subsequently treated with intracranial IL-2 every 3 months for 4 years. After every infusion, he developed symptomatic hypocalcemia (gait instability and confusion). Elevated urine osmolality and urine sodium were consistent with SIADH (Table). The patient did not complain of pain or nausea with treatment. During each cycle of IL-2, hypocalcemia improved with a single dose of oral tolvaptan 15 mg (Figure).

Results: Conclusions: To our knowledge, this is the first reported case of recurrent SIADH with long-term intracranial IL-2 administration. While this does not appear to be a common side effect, physicians should be aware of this potential complication. Hyponatremia in this situation appears to respond well to single dose of tolvaptan 15 mg orally.

Recurrent SIADH with Intracranial IL-2 Administration

<table>
<thead>
<tr>
<th>Month</th>
<th>Serum Na admission</th>
<th>Serum Na midday</th>
<th>Serum Osmol</th>
<th>Urine Osmol</th>
<th>Urine Na</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/2016</td>
<td>143 ± 123</td>
<td>125 ± 265</td>
<td>496 ± 496</td>
<td>87 ± 87</td>
<td></td>
</tr>
<tr>
<td>5/2016</td>
<td>142 ± 127</td>
<td>127 ± 271</td>
<td>482 ± 482</td>
<td>114 ± 114</td>
<td></td>
</tr>
<tr>
<td>8/2016</td>
<td>135 ± 122</td>
<td>125 ± 248</td>
<td>485 ± 485</td>
<td>110 ± 110</td>
<td></td>
</tr>
<tr>
<td>11/2016</td>
<td>141 ± 129</td>
<td>129 ± 268</td>
<td>671 ± 671</td>
<td>138 ± 138</td>
<td></td>
</tr>
<tr>
<td>2/2017</td>
<td>141 ± 124</td>
<td>125 ± 268</td>
<td>671 ± 671</td>
<td>138 ± 138</td>
<td></td>
</tr>
<tr>
<td>5/2017</td>
<td>135 ± 129</td>
<td>129 ± 268</td>
<td>671 ± 671</td>
<td>138 ± 138</td>
<td></td>
</tr>
</tbody>
</table>

Temporal Relationship of Hyponatremia with IL-2 and Improvement with Tolvaptan.

TH-PO1134

Pseudohyponatremia in Patients with Hemodialysis Catheters Locked with Trisodium Citrate Szymon Brzozko,1 Maciej B. Drozdz,2 Alicja Rydzewska-Rosolowska,3 Stefan H. Jacobsson.1 DaVita, Bialystok, Poland;2 DaVita, Krakow, Poland;3 Danderyd Hospital, Stockholm, Sweden;4 Medical University of Bialystok, BIALYSTOK, Poland.

Background: International guidelines recommend arterio-venous fistula (AVF) as the type of vascular access (VA) for hemodialysis (HD). Infections and patency-related complications of central venous catheters (CVC) pose a potential risk for patients. Trisodium citrate (TSC) locking solution is a promising alternative to unfractionated heparin (UFH) for prevention of CVC dysfunction. Pseudohyponatremia secondary to TSC contamination of blood specimens obtained from the CVC may potentially lead to profound but unnecessary diagnostic interventions. The aim of the study was to analyze pre-dialysis Na concentration and the prevalence of hyponatremia in relation to the type of locking solution (TSC vs UFH) and VA in a large cohort of HD patients (DaVita Poland).

Methods: The population studied consisted of 543 prevalent hemodialysis patients (45% female), mean age 67±14 years treated in a standard HD program (100% High Flux, 94% HD time≤12h/week, 94% spKt/V>1.3, 18.5% CVC). We analyzed laboratory results from February & March 2017. Pre-dialysis Na concentration was compared between patients with CVC locked with 30% TSC, UFH (5000 IU/ml) and non-CVC types of VA (AVF, AVG). The proportion of patients with pre-dialysis Na ≥145 mEq/l (hyponatremia) was analyzed in both groups and from both months separately. Descriptive statistics was used together with ANOVA, t and X² tests as appropriate.

Results: The mean plasma concentration of Na was significantly higher in patients with TSC locking solution (141±3 mEq/l n=26, 142±3 mEq/l n=35) when compared to UFH (138±3 mEq/l n=76, 138±4 mEq/l n=75) and non-CVC VA (138±2 mEq/l n=140, 138±4 mEq/l n=140, ANOVA p=0.001 for February & March respectively). The proportion of patients with Na ≥145 mEq/l was significantly higher in patients with CVCs with TSC (n=1/61) as a locking solution than in patients with UFH (n=4/152; 18.0% vs 2.6%, X² p=0.001). The highest plasma concentration of Na was 171 mEq/l, obtained from a peripheral vein showed a Na concentration of 138 mEq/l.

Conclusions: Pseudohyponatremia may be occur in HD patients when 30% TSC is used as a locking solution. Need for diagnostic laboratory investigations may be lowered using TSC as a locking solution. Need for diagnostic laboratory investigations may be lowered using TSC as a locking solution.

TH-PO1135

Sorafenib Induced Resistant Hypocalcemia in a Patient with Chronic Mild Hypocalcemia from Possible Lysozyme Induced Nephropathy: A Nightmare to Treat Sanjeev Gupta, Anastasios Papanagou, Yong Al Azzi, Maureen E. Brogan. Westchester Medical Center, Valhalla, NY.

Background: Sorafenib is a multikinase inhibitor; approved for treatment of multiple cancers. A lesser-known side effect of this drug is hypocalcemia (hypoCa). Diarrhea and Vit D malabsorption due to exocrine pancreatic dysfunction are proposed causes for hypoCa from Sorafenib. We present a case of Sorafenib induced severe hypoCa in a patient with chronic mild asymptomatic hypoCa.

Methods: A 67-year-old man with a history of CMML, MDS and hypoCa with c/o joint pain and weakness admitted for management of possible AML. Work-up showed anemia, thrombocytopenia, and leukocytosis. Bone marrow aspiration confirmed AML. AML FAB classification is M6. Cytarabine was administered and increased urinary level of alpha-aminobutyric acid, alanine, arginine, and asparagine. His urinary Ca/Cr ratio was low (<7). The patient finally responded to treatment and was subsequently switched to oral calcium and calcitriol and discharged home with S.Ca of 7.9.

Results: Conclusions: Lysosome-induced nephropathy is an under-recognized complication of CMML. A persistently elevated level of lysozyme exceeds the reabsorption capacity of tubules leading to tubular injury. The exact mechanism of action of Sorafenib induced hypoCa is still unknown attributing to challenges in managing such patients. Our patient’s S.Ca level did not respond well to Vit D as suggested by few case reports and required heavy doses of calcitrol along with IV calcium and Vit D analogues. This case highlights that it is essential to consider underlying history of hypoCa before starting a patient on Sorafenib, as it can lead to severe hypoCa, which can be difficult to manage.

TH-PO1136

Fluid Overload Is a Risk Factor for AKI and Mortality in Influenza Patients Luis I. Bonilla,1,2 Raymundo Vera,1 Raymundo A. Sánchez,1 Israel A. Villegas-Gasson,1 Sara Samoni,2 Claudio Ronco,1 Lilia M. Rizo Topete.1 Nephrology, University Hospital “Dr. José Eleuterio Gonzalez” Monterrey, Mexico;1 International Renal Research Institute of Vicenza, Vicenza, Italy.

Background: Influenza virus, especially A(H1N1) has been consistently associated with high mortality in the subset of critically ill patients who develop Acute Distress Respiratory Syndrome (ARDS). Risk factors for this association have not been well described. Fluid overload (FO) is now a recognized condition which increases the incidence of acute kidney injury (AKI) and its association with mortality in critically ill patients has been well documented. Nevertheless the impact of FO in mortality of ARDS influenza patients has not been yet described.

Methods: This is a retrospective analysis of 30 records of patients who were admitted to the ICU with the diagnosis of ARDS and suspicion of influenza infection during the Influenza season 2016-2017. Demographic, laboratory, and clinical data were obtained. We calculated FO as the algebraic sum of the inputs and outputs recorded every day during the whole ICU stay divided by the patient’s weight at admission and expressed as a %. We divided patients into 2 groups: A) ≤ 5% FO and B) > 10% FO and compared mortality among both groups.

Results: Mean age in our cohort was 46.4yrs, 66.6% were male and 46.6% were obese. Influenza was confirmed in 12 patients; 41.6% with A(H1N1). Mortality among A(H1N1) patients was 100%. AKI was diagnosed in 20 patients (66.6%) with 16.6%, 10% and 36.6% of KDGO stages 1-3 respectively. RRT was initiated in 10 (50%) of AKI patients. Among groups A and B AKI was diagnosed in 50% and 75% of patients respectively p=0.23. ICU mortality was 60% among the whole cohort. Median fluid balance (FB) among survivors was -3,885.8ml (2,108.7-7,252.5) and among non-survivors was -3,806.5ml (5,283.18,863) p=0.043. Mortality in group A was 35.7% vs in group B 63.3% p=0.22. The OR for mortality and AKI in group A was 0.58 (CI95% 0.22-1.54) and in group B 3.0 (CI 95% 0.49-18.1) p=0.22.

Conclusions: In our cohort of ARDS patients, FO >10% was associated with increased incidence of AKI and mortality. Also, the presence of a conformationary diagnosis influenza A(H1N1) conferred a 100% mortality. With these findings, we can strongly recommend a conservative fluid strategy in the treatment of this kind of patients. More studies with bigger cohorts are needed to obtain statistical significance and clearly demonstrate these associations.

TH-PO1137

Prediction of Hyponatremia from Electronic Medical Records Using an Deep Learning Approach with an Artificial Neural Network Al Azzi,2 Ryo Kiyokawa,1 Sungkyun Shin2 Nephrology, Konkuk University Medical Center, Seoul, Republic of Korea; 2Insilicor, NHIS, Korea; 3Gyeongsang-D. DO, Republic of Korea.

Background: Hyponatremia is associated with increased morbidity and mortality in both hospitalized and ambulatory patients. In the era of big data, analysis of electronic medical records (EMR) may have a significant impact on patient’s outcomes by identifying high-risk patients or supporting clinical decision making. The aim of this study was to predict hyponatremia from EMR using an deep learning approach with artificial neural network (ANN) algorithm.

Methods: A total 182,181 patients who measured serum sodium concentrations from 2010 to 2016 in a tertiary referral hospital were enrolled. Clinical, biochemical and laboratory data were obtained from EMR database. 853 columns were presented along with basic patient information. For training, 500 random number trees
were given to the random forest algorithm. The medication dataset was based on a neural network model based on Dense Matrix. Learning and modeling have attempted to construct a combined dataset by using Ensemble model. The predictive value and diagnostic accuracy were calculated for the dataset based on serum sodium concentration less than 134 mEq/L.

Results: Using the confusion matrix and statistics for clinical and laboratory data set, the predicted value was 0.9104 (95% CI, 0.9040-0.9157). In the medication data set, he predicted value was 0.7515. Deep learning predictive approaches using the Ensemble model, the prediction probability for hyponatremia was 92.05% (Table).

In total 2047 proteins were identified. 1425 proteins were reliably quantified in both groups. 861 proteins were observed with more than 2 times fold change (FC), 415 proteins with over 5 times FC between cirrhosis and health control (HV) groups. We focused on these 415 molecules that were regulated in cirrhosis, since they will be supposed as potential molecules involved in the onset of cirrhosis. GO analysis indicated 282 of these 415 genes were clustered in extracellular exosome, and enrichment analysis revealed serine-type endopeptidase activity was the most significant over-represented molecular function for the 282 molecules. KEGG pathway analysis showed 38 proteins related to metabolic pathway: Glycolysis/ Gluconeogenesis pathway is most significantly enriched. Low abundance proteins revealed that protein expression of cell adhesion, immune response, and proteolysis in cirrhosis patients.

Conclusions: Quantitative proteomic results of urine proteins from cirrhosis patients show significant increase of proteins related to the complement and coagulation cascades, regulation of actin cytoskeleton pathway, and decrease of proteins in the cell adhesion molecules (CAMs), endocytosis, PTK/Akt signaling and phagosome pathways. Our pilot studies of cirrhosis patient urine proteomes may promote to discover urine biomarkers of cirrhosis in the early stage of liver dysfunction.

Funding: Private Foundation Support

**TH-PO1138**

The Association between Serum Sodium and Potassium Concentration and the Risk of Cardiovascular Disease: A Large Community-Based Cohort Study

London, London, United Kingdom; 3University of Surrey, Guildford, United Kingdom

Background: Observational and randomised studies have shown that reduced dietary sodium (Na) and higher potassium (K) are associated with lower blood pressure and cardiovascular (CV) disease. Changes in dietary intake may alter the serum concentration of these electrolytes, but few studies have investigated if there is a relationship between serum Na, K and CV risk.

Methods: This was a retrospective cohort study using data from the Royal College of General Practitioners Research and Surveillance Centre, a database of routinely-collected primary care data in the UK. Data were extracted using Read V2 and EMIS codes. Only individuals with both a serum Na and K value were included, with the most recent data prior to April 2010 used to define baseline levels. Exclusion criteria were: age less than 40 years; diabetes mellitus; prior CV event; end-stage renal disease; liver cirrhosis. The primary outcome was incident CV disease (acute coronary syndrome; coronary revascularisation; stroke; new diagnosis of heart failure) over 5 years.

Results: 235,676 individuals met the criteria for inclusion in the study. The median age was 59 years (IQR 49-68), 57% were female, and 5% were known to be of non-white ethnicity. The median serum Na was 140 mmol/L (IQR 139-142), and the median serum K was 4.4 mmol/L (IQR 4.1-4.6). 21% were prescribed at least one diuretic medication, and 23% were prescribed a renin angiotensin system (RAS) inhibitor. There were 9,464 (4.0%) incident CV events during the follow-up period. After multivariate adjustment for confounding factors, there were significant associations between the primary outcome and serum Na (r=0.140 and 0.144 mmol/L) and serum K (r=4.5 mmol/L). See Figure. No relationship with blood pressure was demonstrated.

Conclusions: There is a significant association between serum Na, K and primary CV events. This relationship is unexplained but could be associated with activation of the RAS.

**TH-PO1140**

Dietary Acid Load Is Associated with Greater Urinary Nitrogen and Muscle Mass Loss in CKD Patients

The University of California San Francisco, San Francisco, CA; 3University of California, San Francisco, San Francisco, CA.

Background: In chronic kidney disease (CKD), high dietary acid loads may promote metabolic acidosis, which in turn may contribute to adverse clinical health outcomes. We hypothesize that high diet acid load plus higher body acid content in CKD leads to greater muscle breakdown and greater urinary nitrogen loss. We examined associations between dietary acid load, serum biomarkers of muscle damage, serum Na and K, and diet protein/potassium (K) ratio in pre-dialysis CKD subjects.

Methods: 100 subjects with CKD stage 3 and 4 and 29 healthy control subjects were enrolled in this cross-sectional study. Potential renal acid load (PRAL) and net acid excretion (NAE) were determined by the average of 3-day food records using the equations by Remer, Frassetto, and Lemann. PRAL and NAE were divided into quintiles. Pearson correlation and multivariable regression analysis were used to evaluate the associations of dietary acid measurements (PRAL and NAE) with serum bicarbonate, UUN, AM, and diet protein/K ratio. The regression models were adjusted for demographics, body mass index, diabetes, systolic and diastolic blood pressure, urine pH, and creatinine clearance.

Results: Mean age of the population was 57 yrs (range 28-69) with 53% females. Median eGFR was 30 ml/min for the CKD subjects, and 100 ml/min for the controls. The correlation coefficients (p value) in CKD subjects in the highest quintile of diet acid load are presented (see table). PRAL correlated significantly with UUN in the control subjects (r=0.9). In adjusted analysis, compared to the lowest quintile, no significant association was observed between the highest quintiles of PRAL with serum bicarbonate in CKD patients (P=0.18). Changes were observed for NAE in quintile 5, 0.4(2.4-1.6) in quintile 4, 0.05(-1.9-1.8) in quintile 3, 1.3(-0.5-3.2) in quintile 2.

Conclusions: We found a significant association of higher body acid balance with urinary nitrogen loss, but not with serum bicarbonate. In patients with CKD, limiting diet acid load may improve metabolic acidosis and its long-term adverse health effects.

Funding: Private Foundation Support

**TH-PO1141**

Mild Chronic Prolonged Hyponatremia at Admission Is Associated with Long Term Mortality in Patients with Hip Fracture Repair

Carlos Ayus, Nora Fuentes, Michael L. Moritz, Alan S. Go, Armando L. Negri.

Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA; Kaiser Permanente Northern California, Oakland, CA; Instituto de Investigaciones Metabolicas, Buenos Aires, Argentina; Renal Consultants of Houston, Houston, TX; Hospital Italiano de Buenos Aires, Buenos Aires, Argentina.

Background: A recent study indicates that chronic prolonged hyponatremia is a significant risk factor for hip fracture in the elderly (Ayus JC; NDT 2016; 31(10):1662-9). No information exists with respect the chronicity of the hyponatremia prior to admission and its effects on long term mortality.

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

Underline represents presenting author.
Methods: We designed a cohort study in adults admitted for traumatic hip fracture who had at least one serum Na+ level at admission. Hypokalemia was defined as a Na+ level divided in those with chronic prolonged (hyponatremia for 90 days or more), and those with recent hyponatremia (hyponatremia for 30 days or less, RHIN) prior to admission.

Results: 1205 (76.7%) patients were non-hyponatremic (NN) and 366 (23.3%) were NN at admission (138 ± 3 vs 132 ± 4 mmol/L Na+; p<0.001). Of these, 222 (14%) had RHIN and 144 (9.1%) had RHIN. Overall mortality rate was higher in RHIN 25% (56/222), followed by RHIN 20% (29/144) and finally NN 14% (169/1205). Five year survival in patients with RHIN and RHIN was lower than those with NN: 0.93 and 0.87 compared to 0.93 (p<0.001).

Conclusions: Mild chronic prolonged hyponatremia at admission in patients with hip fracture repair is associated with increased long term mortality.

TH-POI142
Villous Adenoma: A Rare Cause of Hypokalemia and Metabolic Alkalosis

Daniel Bianchi,1 James I. McMillan.1 Loma Linda University, Loma Linda, CA; 1Loma Linda University School of Medicine, Loma Linda, CA.

Background: The differential diagnosis of hypokalemia and metabolic alkalosis is large and includes fluid loss without HCO3- wasting (vomiting/diuretics), mineralocorticoid excess, and hereditary conditions such as Bartter syndrome. We present an unusual case of hypokalemia and metabolic alkalosis.

Methods: A 58-year-old previously healthy man was admitted to the ICU after 15 days of weakness, muscle cramps, orthostasis and blood stools. He had hyponatremia and acute kidney injury, and was fluid resuscitated. Two months later his physician saw him for rectal pain, diagnosing hemorrhoids, and noted a potassium of 4.2 mmol/L. He was given KCl without workup. He had two more ICU admissions for severe dehydration. On admission, his potassium was 3.1 mmol/L, chloride 101 mmol/L, bicarbonate 30 mmol/L, sodium 138 mmol/L, creatinine 3.5 mg/dL, calcium 2.6 mmol/L, and uric acid 9.2 mg/dL. A PET scan showed septal wall thickening and a mass in the left atrium.

Results: The mistaken initial diagnosis of Bartter Syndrome was based on the elevated aldosterone, hypokalemia, metabolic alkalosis, and lack of hypertension. However inadequate resestication of his fluid and electrolyte loss from the villous adenoma explains the hormonal and electrolyte abnormalities. Villous adenoma depletion syndrome (McCrittrick Wheelock) is rare, resulting from a mucous secreting adenoma explains the hormonal and electrolyte abnormalities. Villous adenoma is large and includes fluid loss without HCO3- wasting (vomiting/diuretics), mineralocorticoid excess, and hereditary conditions such as Bartter syndrome. We present an unusual case of villous adenoma with metabolic alkalosis. Literature review identified 58 cases. Villous adenoma depletion syndrome: 7 had metabolic alkalosis. The cause of the metabolic alkalosis variant may be over expression or activation of apical chloride channels in adenoma goblet cells. Increased cAMP or cGMP production in goblet cells could also lead to over activity of CFTR channels causing chloride secretion. Finally, decreased expression of the Downregulated in Adenoma (DRA) gene may decrease chloride secretion.

Conclusions: Mild chronic prolonged hyponatremia at admission in patients with hip fracture repair is associated with increased long term mortality.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Tumor Lysis Syndrome in Multiple Myeloma Treated with Carfilzomib

Nupur N. Uphal,1 Rimda Wanchoo,1 Jalal Ibrahim,1 Anna T. Levy,2 Kenar D. Jhaiveri,1 Nephrology, Hofstra Northwell School of Medicine, Great Neck, NY; 2Hematology/Oncology, Hofstra Northwell School of Medicine, Lake Success, NY.

Background: Tumor lysis syndrome (TLS) is extremely uncommon in patients with multiple myeloma (MM) because of low rate of proliferation of the plasma cells. Carfilzomib is a proteasome inhibitor that has been recently used for treatment of relapsed/refractory MM. Only a few cases of MM associated TLS have been reported in the literature. These cases include spontaneous TLS, drug induced TLS, or TLS due to plasmablastic transformation of MM. While acute kidney injury (AKI) has been seen with carfilzomib treatment, TLS has been rarely reported. We describe a case of TLS in a patient with MM on carfilzomib therapy.

Methods: A 58-year-old female with known IgG kappa MM, with poor and complex cytogenetics and a plasma cell pleural mass, who had failed treatment with standard MM therapy, followed by lenalidomide, presented with shortness of breath and hypotension, and was noted to have AKI (serum creatinine (Scr) of 1.7 mg/dL on admission. She was started on carfilzomib treatment 4 weeks prior to presentation. Lab work also revealed elevated levels of LDH (17000 U/L), phosphorus (9.1 mg/dL), potassium (5.1 mmol/L) and uric acid (122 mg/dL). A diagnosis of TLS was made. Besides usual therapy with hydration, rasburicase, and rasburicase, she also required continuous renal replacement therapy (CRRT), followed by hemodialysis (once hemodynamically stable) for management of TLS. After a week of RRT, renal function improved and TLS labs stabilized. However, her kappa/lambda light chain ratio increased from 144 to 344. Patient opted for end of treatment and hospice care. Her Scr stabilized ~2 mg/dL on discharge.

Results: TLS has been seen in 1% of patients treated with high-dose chemotherapy following autologous stem cell transplant, and ~1.4% in patients receiving bortezomib. Although rare in patients with MM, TLS can occur in this population, especially in patients with poor prognostic features including high tumor mass, immature morphology, high proliferative activity, and poor cytogenetics. To our knowledge, our case is the second reported case of TLS following carfilzomib treatment. While risk of TLS is small in patients with MM, physicians should be aware of this potential adverse effect in patients receiving carfilzomib therapy.

FR-PO005

Hypothyroidism with Rhabdomyolysis Causing AKI

Antonio M. Villegas, Macgivenny A. Goris felix, Alberto Flores, Freddy Mejia, Guillermo Alvarez. CEDIMAT, Santo Domingo, Dominican Republic.

Background: Muscle complaints is frequent in adult onset hypothyroidism, accompanied by mild elevation of serum creatine kinase, but few cases have reported extremely high elevations of serum creatine kinase and rhabdomyolysis and acute renal failure. We report a case of acute kidney injury (AKI) associated with rhabdomyolysis following severe hypothyroidism in a 57 year old female. The patient had general weakness, without muscle tenderness, elevated muscle enzymes and thyroid stimulating hormone (TSH), which normalized with thyroid replacement therapy.

Methods: A 57 year old female admitted to the general ward with complaints of general weakness, fatigue and hypotension. She was prescribed thyroxine for various renal issues. Chemotherapy (chemotx) is associated with multiple renal complications including TMA, AIN, electrolyte abnormalities and CKD. Rhabdomyolysis was suspected in patients presenting with AKI in the absence of common causes of AKI, and in patients with vague muscular symptoms.

FR-PO006

AKI Secondary to Trabectedin Induced Rhabdomyolysis

Deepta Amberker, Sreekrutha Katari, Anitha Vijayan. Washington University in St. Louis, St. Louis, MO.

Background: Onconephrology is a growing field with nephrologists being consulted for various renal issues. Chemotherapy (chemotx) is associated with multiple renal complications including TMA, AIN, electrolyte abnormalities and CKD. Rhabdomyolysis (rhabdo) secondary to chemotx is extremely rare. We report a case of severe AKI secondary to rhabdo from trabectedin, an alkylating agent approved for soft tissue sarcomas in 2015.

Methods: A 46 year old Caucasian male with release of retroperitoneal liposarcoma was started on trabectedin 4wk prior to admission. He presented with 10d history of n/v, diarrhea, chest pain and sob, starting a week after his 2nd cycle of trabectedin given 1wk before admission. Initial labs showed pancytopenia, Trop-I of 0.15 and Scr of 1.4 (baseline 1.1). On day 9, Scr started increasing and peaked at 5.61. Creatinine kinase (CK) was obtained and noted to be elevated and peaked at 93300. He was treated with bicarbonate drip with subsequent improvement in renal function. (Table1)

Results: Trabectedin has been associated with pancytopenia, myocarditis, transaminitis and GI side effects. In the company drug data base, rhabdo has only been reported in 0.7% of cases, but had a high mortality of 41%. CK elevation is typically reported after the 2nd cycle and rare after the 4th cycle. Median time to CK elevation was 2mo post chemotx. Trabectedin undergoes hepatic metabolism and inhibitors of CYP3A4 increase risk for adverse events. Our patient was on no other medications which is known to inhibit this pathway. With increasing use of trabectedin in soft tissue sarcomas, it is critical that physicians be aware of this devastating complication and monitor patients closely during chemotx. Early, adequate hydration, frequent lab checks including SCR and CK is crucial in preventing AKI and its complications.
FR-PO007
A Case of AKI due to Rhabdomyolysis in Association with Exposure to Daptomycin
Eldrid Baez, Juan Carlos Q. Velez. Ochsner Clinic Foundation, Kenner, LA.

Background: Rhabdomyolysis has been reported in association with exposure to the cyclic lipopeptide daptomycin. However, reports of acute kidney injury (AKI) resulting from daptomycin-associated rhabdomyolysis are sparse in the medical literature.

Methods: A 35 year-old Caucasian man presented to the hospital with a 3-day history of fever and worsening delirium after a recent reduction and fixation of a motor vehicle accident-related wrist fracture which had been performed 2 weeks prior to presentation. Past medical and family history were unremarkable. Vital signs were significant for a temperature of 38°C and blood pressure of 99/56 mmHg. Physical examination disclosed confusion and an erythematous, inflamed right wrist. Laboratory data on admission revealed a serum creatinine (sCr) of 1.3 mg/dL. Blood cultures revealed growth of methicillin-resistant Staphylococcus aureus. He was initiated on empiric antibiotic therapy with vancomycin, tobramycin and aztreonam. The patient remained febrile and blood cultures failed to clear after 3 days of therapy. The wrist hardware was then surgically removed. Antibiotic coverage was broadened with the addition of daptomycin. Three days after the addition of daptomycin, sCr began to increase progressively, reaching a peak level of 7.1 mg/dL 4 days later. Serum creatinine kinase (CK) was found to be 29,000 U/L. Urine microscopy revealed muddy brown granular casts, no red blood cells and 1+ blood by urinalysis. As a result, daptomycin was discontinued in light of suspected toxic acute tubular necrosis (ATN) due to rhabdomyolysis. It transgressantly initiated renal replacement therapy. One week later, sCr and CK began to normalize.

Results: While rhabdomyolysis was reported in up to 3% of patients receiving daptomycin in pre-marketing clinical trials, AKI due to rhabdomyolysis was not reported until the post-marketing era. To date, only 3 probable cases are found in the literature. By the Naranjo criteria, our case is also classified as probable. This case demonstrates that awareness should be raised about the risk of severe AKI due to toxic ATN from daptomycin-associated rhabdomyolysis.

FR-PO008
Recurrent Exercise Associated AKI: An Unusual Presentation of Malignant Hyperthermia
Meeha R. Joshi, Satra M. Gordon. 1 WRNMMC, Rockville, MD; 2 Walter Reed, Bethesda, MD.

Background: We present a healthy soldier with recurrent exercise associated acute kidney injury (AKI) and hematuria. After extensive testing, muscle biopsy was diagnostic of malignant hyperthermia (MH). This case suggests myopathic disorders should be discussed in exercise-associated AKI.

Methods: A thirty-five year old white male was referred for recurrent painless dark urine after running. He had no medical or surgical history, and no family history of renal disease. He denied new medications, substance or supplement use. There was no history of nephrolithiasis or urinary tract infection.

Results: He was normotensive with unremarkable physical exam. Pre-exercise renal function, protamin quantification, urine dipstick and microscopy, sCr cell screen, drug screen, and creatinine kinase (CK) were normal. Serum creatinine was 0.9 mg/dL. Post exercise serum creatinine rose to 1.5mg/dL. Testing demonstrated elevated serum and urine myoglobin (111ng/mL and 29ng/mL respectively) and mildly elevated CK (309 U/L). Repeat urine sediment showed muddy brown casts consistent with acute tubular necrosis (ATN) and 20 isomorphic red cells per field. Labs normalized within one week of rest. He was evaluated by Hematology and Rheumatology for muscular and red blood cell abnormalities; no etiology was identified. Cystoscopy and contrasted tomography were normal. Pre- and post-exercise renal artery dopplers were normal. He was referred to a neuromuscular specialist, and a muscle biopsy was diagnostic for malignant hyperthermia. We recommended avoidance of strenuous exercise and anesthetic agents. Renal function is normal without symptom recurrence following de-escalation of his exercise regimen.

Conclusions: The classic presentation of MH is characterized by acute hyperthermia, muscle rigidity, and rhabdomyolysis with AKI. However, reports of AKI due to malignant hyperthermia (MH) are rare. This case report adds to the evidence that MH should be considered in the differential diagnosis of AKI in young, previously healthy individuals. The avoidance of MH precipitants, such as certain medications and anesthetic agents, is crucial for preventing MH-related AKI.
assessment of renal histology might shed further light on the etiopathogenesis of renal failure and to assess the potential for renal recovery in patients with artificial heart devices and/or heart transplants.

FR-PO011

A Stitch in Time Saves Nine: Renal Infarction Secondary to Forgotten Prophylaxis

Muhammad Leghrouz, Volodymyr Chorny, Abhilash Koratala, University of Florida, Gainesville, FL.

Background: Antibiotic prophylaxis against bacterial endocarditis is indicated prior to invasive procedures in patients with certain high-risk cardiac conditions and thorough history needs to be elicited prior to performing such procedures. We present a case of spleno-renal infarction secondary to septic emboli in a patient with prosthetic aortic valve who underwent a dental procedure without endocarditis prophylaxis.

Methods: A 42-year-old white man with history of bioprosthetic aortic valve presented with intermittent fevers for a week and bilateral flank pain for 2 days. He saw a dentist 2 weeks ago for toothache and underwent a dental procedure involving manipulation of gingival tissue. Exam was significant for systolic murmur in the aortic area and tenderness in bilateral flanks. Serum LDH was elevated. A CT scan of the abdomen with contrast demonstrated areas of non-enhancement involving more than 50% of the right kidney predominantly involving the lower pole and also most of the spleen consistent with renal and splenic infarction [Figure 1a]. Interestingly, the patient was noted to have an accessory right renal artery providing flow to the upper part and probably accounts for relative sparing of this portion of the kidney [Figure 1b]. Subsequently, patient’s blood cultures grew Streptococcus mitis and oralis, trans-esophageal echo revealed infective endocarditis, which supports the diagnosis of renal and splenic infarction from septic emboli. Patient improved with antibiotic therapy and renal function remained stable.

Results: The learning point from our case is that thorough history taking before invasive procedures might prevent potentially life-threatening complications. Our patient had prosthetic valve, and appropriate antibiotic prophylaxis prior to the dental procedure could have evaded the complications he developed.

Figure 1a and 1b

FR-PO012

Idiopathic Renal Infarction

Volodymyr Chorny, Abhilash Koratala, University of Florida, Gainesville, FL.

Background: Renal infarction is a rare condition that typically presents with back pain, flank or abdominal pain, hematuria and laboratory abnormalities such as leukocytosis, high CRP and elevated LDH. Most common causes of renal infarction are cardiac conditions such as atrial fibrillation, ischemic or valvular heart disease followed by other etiologies including hypercoagulable states and renal artery dissection. Interestingly no cause can be found in about a third of patient. Herein, we present a case of idiopathic renal infarction, which presented without the classic laboratory abnormalities.

Methods: A 42-year-old man with a history of hypertension has presented with nausea and abdominal pain for 2 days. Approximately 6 months prior to presentation, he was diagnosed with deep venous thrombosis of the right leg and was treated with warfarin for 3 months. Notably, he had similar pain at that time but of lesser intensity and no abdominal imaging was done. He was afebrile and urinalysis was negative for blood or WBC. Serum creatinine was 0.7 mg/dL and LDH, CRP normal. CT scan of the abdomen without contrast showed possible bilateral renal infarcts. MRA of the abdomen was performed which showed subacute bilateral focal infarcts in both the kidneys with a new wedge-shaped infarct in the right kidney (Figure 1A). Aorta and branch vessels demonstrated normal vascular enhancement without evidence for wall thickness, aneurysm or stenosis (Figure 1B). EKG showed sinus rhythm and telemetry monitoring during his inpatient stay did not show any arrhythmia. ANA, ANCA, viral hepatitis panel, HIV test were negative. Hypercoagulable workup was essentially negative. He was discharged on oral anti-coagulation.

Results: Our case emphasizes the fact that high index of suspicion is required to diagnose renal infarction in patients presenting with abdominal pain. Early recognition is important because it may have long-term implications on kidney health.

FR-PO013

Acute Spontaneous Bilateral Renal Vein Thrombosis in a Healthy Young Woman

Yuzana K. Zaw, Mira T. Keddis, Mayo Clinic, Chandler, AZ.

Background: Introduction: Acute spontaneous bilateral renal vein thrombosis in native kidneys is extremely rare. We report the first case of acute spontaneous bilateral renal vein thrombosis in a healthy young woman.

Methods: Case Description: A 26 year old Caucasian female non-smoker presented to Mayo Clinic with a chief complaint of 24hr history of acute left flank pain. She has asthma, dyslipidemia and polycystic ovarian syndrome for which she was on oral contraceptives, Azarrette for 9 years and then switched to Ashlyna 4 months ago. She experienced dyspnea two weeks before which was initially attributed to her underlying asthma. CT scan of abdomen and pelvis showed acute bilateral renal vein thrombosis with extension of thrombus to involve a long segment of IVC with associated segmental ischemia to lower pole of right kidney. CT chest showed bilateral acute pulmonary emboli. She had transient microscopic hematuria, low grade proteinuria (2grams) and acute kidney injury with serum creatinine of 1.3 mg/dL from baseline 1 mg/dL. She was initiated on intravenous Heparin drip and transitioned to Apixaban therapy. Hypercoagulable workup was negative. She had Minera intrateratrine contraceptive device placed during admission and she was advised not to use estrogen containing contraception or supplements in the future due to her history of massive thrombosis while taking oral contraceptives.

Results: Discussion: We report the first case of spontaneous bilateral renal vein thrombosis (RVT) and acute bilateral pulmonary emboli in an otherwise healthy young woman with long term contraceptive use. This case illustrates the importance of high clinical suspicion for RVT in the differential diagnosis of acute flank pain particularly, in patients with oral contraceptive use. Early recognition and prompt treatment is the cornerstone of management.
FR-PO014

Managing Bilateral Renal Artery Stenosis (RAS) Franklin Lam,2 Rafia I. Chaudhry,1 Loay H. Salman,1 Mauricio Monroy,1 1Albany Medical College, Albany, NY; 2None, Providence, RI.

Background: Renal artery stenosis (RAS) accounts for 2-4% cases of HTN in the US. Etiology of RAS includes age related atherosclerosis, and fibromuscular dysplasia in young females.

Methods: 79-year-old Caucasian female, with PMHx of well controlled HTN, HLD, DM 2 and CKD (baseline Cr 1.7 mg/dL) presented with HTN crisis (BP 220/90 mm Hg), AKI (Cr 2 mg/dL), pulmonary edema and severe LLE edema. Cr notably worsened over 6 months. Abdominal CTA revealed severe bilateral RAS. Renal artery stenting was held due to AKI with Cr rising to 3 mg/dL. After prolonged hospitalization, pt was discharged on medical therapy (Bumetanide, Doxazosin, Clonidine, Metoprolol, and Nifedipine). Cr remained elevated at 3.1 mg/dL on follow-up. Pt underwent left renal artery stenting at this time. Right renal artery was not amenable to stenting due to complete occlusion. Renal function improved, Cr stabilized at 1.4 mg/dL at five months later. BP and volume status well controlled.

Results: Conclusions: RAS results in decreased renal perfusion and activation of renin-angiotensin-aldosterone system (RAAS), resulting in systemic vasoconstriction, Na retention and HTN. Significant reduction of renal blood flow occurs at greater than 70% narrowing of the artery. As the stenosis worsens global renal ischemia leads to shrinking of the affected kidney, and AKI or CKD. While medical therapy is initially successful, 70% narrowing of the artery eventually leads to complete occlusion. Renal function improved, Cr stabilized at 1.4 mg/dL at five months later. BP and volume status well controlled.

FR-PO015

Pseudo-AKI Due to “Reverse Autodialysis”: A Case of Spontaneous Rupture of the Urinary Bladder Connor Deal, Xixi Zhao, Casey N. Gashiti, Stephen M. Korbet. Rush University Medical Center, Chicago, IL.

Background: Spontaneous rupture of the urinary bladder (SRUB) is rare and can appear to present as AKI. This “Pseudo” AKI results from reabsorption of Cr and urea across the peritoneal membrane, referred to as “reverse autodialysis.” We describe a case of SRUB following an alcohol binge.

Methods: A 46 yo WM p/w abdominal distention, anuria and AKI following a 2-day alcohol binge. On exam his abdomen was distended with urgency upon suprapubic palpation. Labs: BUN: 63 mg/dL, SCr: 6.4 mg/dL and SAlb: 4.4 g/dl, LFTs were nml. A non-con abd CT showed large “ascites” and no urinary obstruction. Paracentesis yielded 5L of clear fluid with a Cr level elevated at 27 mg/dl indicating the presence of urine in the peritoneal cavity. A Foley catheter was placed with 12L of UOP over 1-hour. CT cystography demonstrated extravasation of contrast into the peritoneal cavity(Fig 1). At laparoscopy a 1cm defect at the superior dome of the bladder was repaired. Renal function normalized within two days.

Conclusions: SRUB in the setting of alcohol intoxication is thought to be due to altered sensitronium and decreased urge to urinate. The volume of ingested alcohol and its diuretic effect further increase bladder filling. The pt’s elevation in BUN and Cr are the result of reabsorption of urine across the peritoneal membrane (“reverse autodialysis”). This gives the appearance of AKI when in fact GFR is normal. The rarity of SRUB as well as the nonspecific presenting symptoms of abdominal distention with ascites and AKI presents a diagnostic challenge. Analysis of the ascitic fluid for Cr to establish a urine leak is a critical diagnostic step. Treatment is immediate surgical repair of the bladder with good prognosis.

FR-PO016

AKI Due to Bladder Rupture After a Fall Brad Long, Josephine Abraham. University of Utah, Salt Lake City, UT.

Background: Urinary bladder rupture is usually associated with high impact trauma and is rarely seen in milder trauma. We present a case in which a patient sustained a ground level fall leading to bladder rupture and acute kidney injury.

Methods: A 68 year old male with CKD stage III due to diabetic nephropathy with baseline creatinine of 2.5-2.9mg/dL presented to the emergency department after falling onto his walker after having cocktails with friends. The fall resulted in brief loss of consciousness and right wrist injury. On presentation he had exquisitely tender abdomen and nausea and emesis. Foley catheter was placed resulting in drainage of gross hematuria. Initial labs showed acute kidney injury with creatinine of 6.3mg/dL, serum potassium 7.2meq/L, and serum bicarbonate of 16mmol/L. He had no elevation in anion gap or serum lactate. The hyperkalemia and acidosis were not improved with boluses of IV sodium bicarbonate and furosemide. CT abdomen/pelvis revealed extraperitoneal bladder rupture that was further characterized on CT cystography.

Results: The patient was taken emergently to the operating room emergently by the consulting urology service for exploratory laparotomy and repair of the bladder. He did require a single treatment of hemodialysis for hyperkalemia. Following repair of the bladder, his renal function rapidly returned to baseline and the hyperkalemia and metabolic acidosis resolved.

Conclusions: Traumatic bladder injury resulting in obstructive uropathy is a cause of AKI that should be excluded in patients suffering even mild trauma. A full bladder is more susceptible to rupture than an empty bladder. In this setting, a low-impact event can produce dramatic internal injury. CT cystography provides accurate and rapid identification of bladder injuries. Prompt surgical management is crucial.
FR-PO017

Wunderlich Syndrome Bilal Ahmed, Muhammad Aftal, Krishna M. Baradhi. University of Oklahoma, Tulsa, OK.

Background: Wunderlich syndrome is spontaneous, nontraumatic renal hematoma confined to perirenal and subcapsular space and is often due to underlying renal pathology. We herein present a rare case of wunderlich syndrome secondary to acute pyelonephritis.

Methods: 55-year-old woman presented with fever, acute abdominal pain, nausea, vomiting and dizziness. Examination was pertinent for orthostatic hypotension and mild right flank tenderness. Initial labs showed acute kidney injury with creatinine of 4.8 mg/dl and BUN of 50 mg/dl along with anemia and leukocytosis. Urine sediment showed muddy-brown granular casts as well as pyuria with bacteriuria. She was diagnosed with acute pyelonephritis and acute tubular necrosis, which gradually improved with antibiotics and fluid resuscitation. However CT scan revealed a large right subcapsular perinephric hematoma concerning for renal cancer. A follow up contrast enhanced MRI, a week after her renal function improved showed much smaller and a more organized evolving right subcapsular renal hematoma making a diagnosis of wunderlich syndrome, which is indeed a rare complication of pyelonephritis. Patient was managed conservatively with eventual resolution of hematoma.

Results: Spontaneous perinephric hematoma (SPH) also called wunderlich syndrome, first described by Wunderlich in 1856, is characterized by Lenk’s triad of arteriovenous fistula, punctate petechiae, and spontaneous subcapsular hematoma. The exact etiology remains uncertain, but is thought to be due to vascular anomalies, rarely associated with an underlying renal pathology, such as pyelonephritis and tumor, renal trauma, and rarely a spontaneous event. The incidence is exceedingly rare and should be considered with intractable symptoms despite antibiotics and fluid resuscitation. Presenting symptoms include flank pain, hematuria, and flank mass. Imaging demonstrates a well-circumscribed, hypodense, extra-medullary collection with decreased enhancement on delayed imaging. Clinical presentation and imaging findings are similar to renal metastasis in patients with a known primary tumor. The diagnosis of SPH is usually clinical, and the treatment is usually conservative with close monitoring of renal function. There are very few case reports of successful surgical intervention. Our patient was managed conservatively, and renal function improved and she was discharged home.

Conclusions: This case of delayed MTX clearance and AKI illustrates the importance of dose adjustment in the setting of co-administration of MTX and levetiracetam, which has been reported to delay MTX clearance, and highlights the successful use of glucarpidase for rapid metabolism of MTX in challenging cases when levels remain toxic despite LV and IVF supportive management.

FR-PO018

Use of Glucarpidase in AKI from Methotrexate Toxicity and Delayed Methotrexate Clearance from Levetiracetam Jacob Stevens, Andrew S. Bomback. Columbia University, New York, NY.

Background: Methotrexate (MTX) is the backbone of many chemotherapeutic regimens, and the management of subsequent toxicity from delayed elimination is challenging. We describe a case of MTX toxicity and delayed MTX elimination and demonstrate the successful use of glucarpidase, a recombinant bacterial enzyme carboxypeptidase G2 that rapidly metabolizes MTX into glutamate and the inactive 2,4-diamino-N-methylpyridinic acid.

Methods: A 67-year-old woman with hypothyroidism and CKD-3 presented with acute lower abdominal pain, flank mass, and hypovolemic shock. Most common etiologies are renal cell carcinoma, angio/myeloma and vascular diseases. Among the rare causes include infectious and inflammatory renal diseases. Pyelonephritis complicating SPH is exceedingly rare and should be considered with intractable symptoms despite antibiotics and fluid resuscitation. Presenting symptoms include flank pain, hematuria, and flank mass. Imaging demonstrates a well-circumscribed, hypodense, extra-medullary collection with decreased enhancement on delayed imaging. Clinical presentation and imaging findings are similar to renal metastasis in patients with a known primary tumor. The diagnosis of SPH is usually clinical, and the treatment is usually conservative with close monitoring of renal function. There are very few case reports of successful surgical intervention. Our patient was managed conservatively, and renal function improved and she was discharged home.

Results: Glucarpidase is a recombinant bacterial enzyme carboxypeptidase G2 that rapidly metabolizes MTX into glutamate and the inactive 2,4-diamino-N-methylpyridinic acid. It is approved by the FDA for the treatment of glucarpidase deficiency, but has been used off-label for the treatment of MTX toxicity. Glucarpidase is a thrombolytic agent with a large therapeutic window and is associated with a high incidence of serious adverse effects. In this case, glucarpidase was administered immediately after MTX exposure and returned to baseline before discharge.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
renal function continued to worsen despite discontinuation of TKIs and she was initiated on hemodialysis.

**Results:**

**Conclusions:** In this patient with underlying DKD, sequential impairment of eGFR, worsening proteinuria, and HTN exacerbation occurred with serial introduction of imatinib, dasatinib, and nilotinib, contributing to rapid progression to ESRD. To our knowledge, this is the first reported case in which progression of CKD to ESRD was associated with TKI use. Our case suggests that in patients with underlying advanced CKD, irreversible renal injury may occur and patients should be informed of this possibility. Further studies are warranted to understand the effects of TKIs on renal function.

FR-PO021

**Tyrosine Kinase Inhibitors: Need Not Be TMA!** Franklin Lam, Apriy Jacobs, Llewellyn A. Fouke, Anum Bilal, Loay H. Salman, Krishnakumar D. Hongalgi. AMC, Albany, NY; Albany Medical College, Albany, NY; Lebanon school of medicine at Mount Sinai, Rensselaer, NY; Providence, RI; Albany Medical Center, Albany, NY.

**Background:** Multi-targeted receptor tyrosine kinase inhibitors (TKIs) are considered the standard of care for renal cell carcinoma (RCC). Few reports have raised concern for nephrotoxicity (NT) with TKIs. We report a case of biopsy-proven acute interstitial nephritis (AIN) after sunitinib use.

**Methods:** A 69-year-old male with stage IV left clear cell RCC began sunitinib 50 mg daily, with baseline SCr of 1.0 mg/dL and BUN of 18 mg/dL. On day 18 of the sunitinib dosing cycle, the patient presented with a three-day history of hematuria, non-oliguric AKI with SCr of 2.7 mg/dL and BUN of 39 mg/dL, and other electrolytes within normal limits. Sunitinib was held upon admission but the patient subsequently required renal replacement therapy (RRT) for worsening acute renal failure (ARF). Thrombocytopenia developed, but hematuria occurred intermittently.

**Results:** Renal biopsy was performed on hospital day six, which confirmed AIN with extensive interstitial inflammation, frequent eosinophils and interstitial edema. No endotheal swelling, loss of endothelial fenestration, subendothelial widening, abnormal glomerular basement membrane thickness, or evidence of thrombotic microangiopathy (TMA) was seen. Renal function partially improved with prednisone and intermittent hemodialysis (HD) and he was discharged 32 days later on weekly HD.

**Conclusions:** AIN is a common cause of renal failure and is seen in as many as 15% of renal biopsies performed as part of the work up for ARF. Sunitinib is rarely associated with NT, although there are multiple reports of sunitinib-induced TMA. There are only a few case reports of TKI-associated, biopsy-proven AIN to our knowledge to date. Our patient's concurrent use of sunitinib and other TKIs was a cause of concern. This report highlights the importance of recognizing AIN as one of the differential diagnoses in a patient receiving sunitinib who develops AKI and thus vigilant renal monitoring is required during TKI use.

FR-PO022

**Nephrotoxicity of Immune Checkpoint Inhibitors: MD Anderson Cancer Center’s Experience** Umut Selameh, Ali Ziaieghagh, Laila S. Lakhani, Amit Lahots, Biru Workeneh, Amanda Tchakarov, William F. Glass, Ala Abdawyeh. MD Anderson Cancer Center, Houston, TX; UT Houston, Houston, TX.

**Background:** Immune checkpoint (ICP) inhibitors, anti-CTLA-4 (Iปิลิมูน) and anti-PD-1 (Nivolumab and Pembrolizumab) have revolutionized treatment options for many types of cancers. Adverse events associated with ICP inhibitors are manifold to uninhibited immune system causing autoimmune diseases. Literature on nephrotoxicity of these novel agents is limited. Acute tubulointerstitial nephritis (ATIN) is the most commonly described kidney injury secondary to ICP inhibitors. Few case reports have documented glomerulonephritis (GN) induced by ICP inhibitors.

**Methods:** We present 7 cases of biopsy proven nephrotoxicity during treatment with ICP inhibitors. Malignancies associated with the cases were as follows: Renal cell carcinoma (n=1), smoldering myeloma (n=2), melanoma (n=2), chondroma (n=1), bladder cancer (n=1) and lung cancer (n=1). Six out of 7 cases showed features of ATIN at kidney biopsy specimens. Several types of GNs were also observed: membranous GN, IgA nephropathy, and pauci immune GN. One patient had AA type amyloidosis. ICP inhibitors discontinued in all cases, and 3 cases were also treated with steroid. Steroid treatment resulted in either partial or full renal recovery in 4 out of 5 cases. Cases are summarized at Tables 1 and 2.

**Results:**

**Conclusions:** Early recognition of nephrotoxicity, utilization of kidney biopsy and steroid treatment for both ATIN and GN are the hallmarks of management of nephrotoxicities induced by ICP inhibitors.

FR-PO023

**Using Steroids in Acute Interstitial Nephritis Secondary to Immune Checkpoint Inhibitors** Sean Verma, Kayla Shirley, Claude Bassil. University of South Florida, Tampa, FL.

**Background:** Immune checkpoint inhibitors (ICI), both anti programmed death ligand 1 (PD-L1) and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies, are novel immunotherapies that have transformed the treatment of non-small cell lung cancer, renal cell cancer, and metastatic melanoma. Renal toxicities associated with ICI are a rare side effect that must be elucidated.

**Methods:** A 78 year old man with metastatic lung adenocarcinoma on PD-L1 antibody durvalumab and anti-CTLA-4 antibody tremelimumab had acute kidney injury (AKI) with creatinine increasing from 1.4 mg/dL (baseline) to 3.2 mg/dL (baseline) to 1.4 mg/dL (on routine labs). He completed 4 cycles of therapy and his last cycle finished 1 month ago. Labs were notable for bicarbonate 12 mcEq/L and phosphorus 4.7 mg/dL. Urinalysis revealed pH 7, specific gravity 1.008, and hylatine casts. Urine eosinophils were positive and he was started on intravenous methylprednisolone at 1mg/kg BID (80 mg BID) for acute interstitial nephritis (AIN). With 4 days of methylprednisolone 80 mg BID, creatinine improved to 2.3 mg/dL. He was transitioned to 80 mg PO prednisone daily for 2 days with creatinine improving to 1.9 mg/dL. He was discharged on 60 mg prednisone daily with instructions to decrease prednisone by 10 mg every 5 days. One week later creatinine was 1.4 mg/dL and his creatinine continues to be at baseline 2 months later.

**Results:**

**Conclusions:** ICI upregulate the patient’s innate anti-tumor T cell response to the tumor and have been shown to significantly decrease tumor progression in comparison to standard treatment options previously available. Renal injury has seldomly been described in cases of both CTLA-4 and PD-L1 antibodies alone or in combination, though combination increases the risk of AIN. A variety of renal injury may occur, though AIN associated with immunotherapy is rarely reported. Hematuria, eosinophilia, worsening or new hypertension, and nephrotic syndrome have occurred in a few cases. The pathogenesis of AIN with ICI is unclear but it is thought to be due to uncontrolled increased T regulatory cell activity in which auto-reactive T cells infiltrate the kidney and cause cytotoxic injury. PD-L1 knockout mice have shown to spontaneously develop granulomatous AIN. Treatment is based on case reports and anecdotal data with prednisone 1 mg/kg over a taper of 1-2 months. A renal biopsy can be considered in cases with unclear etiology of AIN or if steroids aren’t effective.
FR-PO024
Acute Tubulointerstitial Nephritis Induced by Anti-PD-1 Antibody: An Analysis of Infiltrating Cells in the Kidney
Hidekazu Ikeuchi,1 Masao Nakasatomi,1 Toru Sakairi,1 Yoriaki Kaneko,1 Akito Maeshima,1 Yoshihisa Nojima,2 Keiji Hiromura.1 1Department of Nephrology and Rheumatology, Gunma University Graduate School of Medicine, Maebashi, Japan; 2Department of Nephrology and Rheumatology, Gunma Prefecture Saiseikai-Maebashi Hospital, Maebashi, Japan.

Background: Nivolumab, an anti-PD-1 antibody, is one of the immune checkpoint inhibitors (ICIs), which are increasingly used as anti-cancer agents. It has been known to induce various autoimmune diseases in some patients, such as thyroiditis, pneumonitis and pancreatitis, via disruption of immune tolerance. As for kidneys, acute interstitial nephritis has recently been reported. However, the precise renal pathology has not been well understood yet.

Methods: A 57-year-old man was admitted to our department due to an acute increase of serum creatinine (Scr). He had been treated with nivolumab for stage IV lung cancer for 2 months with 2 weeks interval. On the 5th scheduled administration day, he was found to have an elevated Scr level from 0.80 mg/dL to 1.57 mg/dL. Nivolumab was stopped and he was referred to our department and admitted 8 days later. Renal biopsy was performed immediately. A marked infiltration of inflammatory and immune cells was observed in tubulointerstitial area. Immunohistochemical staining revealed that infiltrating cells were positive for CD3 (T cell), CD20 (B cell), CD68 (macrophage), CD163 (M2 macrophage), BDCA-1 (dendritic cell) and DC-SIGN (dendritic cell). Among these cells, CD68 and CD163 were predominant, followed by CD3. Proton pump inhibitor (PPI), rabeprazole, was discontinued, because previous reports showed a possible association between PPI and tubulointerstitial nephritis under the treatment of ICIs. By the treatment with 50 mg/day of prednisolone, the peaked Scr of 3.48 mg/dL returned to baseline level within 2 months.

Results:

Conclusions: Just recently, several reports showed increased T cell accumulation in ICI-induced acute tubulointerstitial nephritis. Our case highlights a potential role of macrophage, as well as T cells, in the pathogenesis of interstitial nephritis caused by anti-PD-1 antibody.

FR-PO025
Tubulitis in a Patient Treated with Nivolumab: Case Report and Literature Review
Viral Vakil, Mark Birkenbach, Katti Woerner, Safwan Muhammad, Lihong Bu. University of Minnesota, Minneapolis, MN.

Background: Immune checkpoint inhibitors are monoclonal antibodies that are increasingly approved by FDA for treatment of solid organ and hematologic malignancies by enhancing anti-tumor T cell immune response. Nivolumab is a monoclonal antibody targeting programmed death-1 (PD1), an inhibitory molecule expressed on cell surface of activated effector T cells. PD1 has two ligands programmed death ligand-1 (PD-L1) and programmed death ligand-2 (PD-L2), located on antigen presenting cells and hematopoietic cells respectively. Nivolumab prevents interaction of PD1 and PD-L1, allowing T cells to continue to attack tumor cells expressing PD-L1. Immune related adverse events (IRAEs), the effect of activated cytotoxic T cells on non-neoplastic antigens, are commonly seen across various organ systems. Renal toxicities associated with PD1 inhibitors are thought to be very low (0.9%), however some reports are more frequent and as high as 29%. Kidney injury associated with PD1 inhibitors commonly manifests as acute tubulointerstitial nephritis on kidney biopsy, with a late onset ranging from 3 to 10 months. Steroids appear to be effective in treating such IRAEs. Here we report a patient with nivolumab-induced tubulitis.

Methods:

A 57 yo M was admitted for cough, cytopenias, and acute kidney injury. AIN is an uncommon complication of Inflammatory Bowel Disease (IBD) which occurs from medications such as 5-aminosalicylate (5-ASA) or as an extra-intestinal manifestation of IBD (granulomatous intestinal nephritis). We present the first reported implication of 6-MP as a cause of AIN.

Results:

Conclusions: Nivolumab-induced tubulitis is characterized by proximal tubulopathy. Chloroacetaldehyde, a metabolite of ifosfamide, is toxic to renal tubules and depletes the antioxidant glutathione and adenosine triphosphate while inhibiting the activity of NA+/K+-ATPase. Risk factors for ifosfamide nephrotoxicity include cumulative dose, underlying CKD, and concomitant cisplatin therapy. This case highlights that FS can occur rapidly following a single dose of ifosfamide and in spite of HD removed prolonged chloroacetaldehyde. Another noteworthy feature was the rapid reversibility of FS, which resolved within 3-5 days of the last dose of any chemotherapy cycle. Often, it takes few years for ifosfamide-induced FS to resolve following completion of chemotherapy. The rapid resolution in our patient could be secondary to HD treatment and clearance of chloroacetaldehyde which is thought to be the cause of both neurotoxicity and proximal tubulopathy. This case highlights the role of HD to prevent tubular and neurotoxicity in ifosfamide-treated patients with advanced CKD.

FR-PO026
Hemodialysis in the Management of Ifosfamide-Induced Fanconi Syndrome
Priyamvada Singh,1 Hanni Menn-Josephy,1 Craig E. Gordon.2 1Renal, Boston University, Boston, MA; 2None, Newton, MA.

Background: Chemotherapy-induced nephrotoxicity is an emerging problem. Methods: A 32-year-old man with CKD stage 4 secondary to biopsy-proven hyperplasia, and metastatic stage 3c mixed non-seminomatous germ-cell testicular cancer was admitted for the first of four planned chemotherapy cycles. Each cycle was comprised of five days of cisplatin/etoposide/ifosfamide and mesna. Based on case reports showing the benefit of HD in preventing ifosfamide-induced encephalopathy, HD was performed 10-12 hours following ifosfamide therapy. On day 2 of cycle #1, testing revealed urine pH of 8.2, 2+ glucosuria (with normal blood sugar), hypophosphatemia (1.0 mg/dL), and normal anion gap metabolic acidosis, consistent with Fanconi syndrome (FS). Baseline studies were normal the day prior to chemotherapy. FS resolved shortly after cessation of treatment but recurred during treatment for all 4 cycles. Upon completion of chemotherapy, there was no evidence of FS.

Results:

Conclusions: Ifosfamide-induced nephrotoxicity is characterized by proximal tubulopathy. Chloroacetaldehyde, a metabolite of ifosfamide, is toxic to renal tubules and depletes the antioxidant glutathione and adenosine triphosphate while inhibiting the activity of NA+/K+-ATPase. Risk factors for ifosfamide nephrotoxicity include cumulative dose, underlying CKD, and concomitant cisplatin therapy. This case highlights that FS can occur rapidly following a single dose of ifosfamide and in spite of HD removed prolonged chloroacetaldehyde. Another noteworthy feature was the rapid reversibility of FS, which resolved within 3-5 days of the last dose of any chemotherapy cycle. Often, it takes few years for ifosfamide-induced FS to resolve following completion of chemotherapy. The rapid resolution in our patient could be secondary to HD treatment and clearance of chloroacetaldehyde which is thought to be the cause of both neurotoxicity and proximal tubulopathy. This case highlights the role of HD to prevent tubular and neurotoxicity in ifosfamide-treated patients with advanced CKD.
and WBC casts. Workup for infection was negative, and 6-MP metabolite levels were not suggestive of infection. Renal biopsy showed patchy interstitial inflammation with eosinophils, normal glomeruli, and no evidence of granulomas or viral cytopathic effect. 6-MP was held and sCr and creatinine improved over a week. 15 weeks post-discharge sCr was near baseline and the patient was doing well on methotrexate+adalimumab.

Results:

Conclusions: A PUBMED search resulted in no previous reports of AIN from 6-MP. Azathioprine (AZA), the inactive prodrug of 6-MP, has known associations with AIN and delayed hypersensitivity reactions in the treatment of vasculitis. In such patients, it has been reported that 6-MP can safely be used in place of AZA. This case shows that AIN may result from 6-MP therapy as well, though it cannot be determined if this is a cross-sensitivity with AZA or a separate mechanism. In this patient, AIN did not occur with 5-ASA (a common culprit) and occurred despite concomitant treatment with steroids, which likely ameliorated the degree of injury. 6-MP should be included in the differential diagnosis of medications associated with AIN. The views expressed in this abstract are those of the authors and do not reflect the official policy of the Departments of Army or Navy, Department of Defense, or U.S. Government.

Funding: Other U.S. Government Support

<table>
<thead>
<tr>
<th>Drug</th>
<th>Unchanged</th>
<th>Baseline</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 5</th>
<th>Day 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mot</td>
<td>CS 5-ASA</td>
<td>CS 5-RMP</td>
<td>CS + 6-MP</td>
<td>CS 6-MP</td>
<td>CS</td>
<td>CS</td>
<td>MTX + AAD</td>
</tr>
<tr>
<td>sCr (mg/dL)</td>
<td>0.9</td>
<td>1.93</td>
<td>2.0</td>
<td>1.87</td>
<td>1.4</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>WBC (10^3/µL)</td>
<td>11.4</td>
<td>3.7</td>
<td>5.4</td>
<td>7.3</td>
<td>9.6</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td>RBC (10^3/µL)</td>
<td>12.4</td>
<td>8.2</td>
<td>8.9</td>
<td>9.9</td>
<td>11.5</td>
<td>13.3</td>
<td></td>
</tr>
</tbody>
</table>

FR-P028

A Friend on Marijuana Is a Friend in Need: A Report of Acute Interstitial Nephritis

Background: Acute kidney injury from synthetic marijuana use has been reported, but until now no reports are available involving the non-synthetic variety. This is a rare case of Acute Interstitial Nephritis (AIN) from non-synthetic Marijuana smoking.

Methods: A 20 yo AA male with PMH of asthma, presents to the ER complaining of excruciating bilateral flank pain with associated nausea for 1 day prior to admission. His only medication was PRN albuterol inhaler. He denied OTC drugs or NSAIDS use. Three days prior to the symptoms, he smoked marijuana, but denied other illicit drugs. Physical exam was remarkable for obesity (BMI 37), hypertension 168/92mmHg and unilateral subconjunctival hemorrhage. On admission his creatinine was 1.75 mg/dL, urinalysis revealed protein 300mg/dL, RBCs 10-20/HPF, WBC’s 0-5 /HPF, with no casts or eosinophils. Urine toxicology was positive for tetrahydrocannabinol. Serology studies were normal, including ANA panel, anti GBM, ANCA, ASO titers, HIV, Hepatitis B/C complements, ESR, IgG 4, SSA/B/ and ACE levels. His renal ultrasound with Doppler was normal. An abdominal CT scan showed perinephric stranding surrounding both kidneys with no stones. Initial management included blood pressure control, volume expansion and he was started empirically on IV steroids due to active sediment and worsening creatinine that peaked at 5mg/dL. Kidney biopsy was performed and showed AIN with marked interstitial lymphocytic infiltrate with eosinophils, interstitial and tubular edema, with normal glomeruli. His kidney function improved with steroids and he was discharged with a creatinine of 2.1 mg/dL.

Results:

Conclusions: Acute interstitial Nephritis from smoking non-synthetic marijuana has not been reported. The presentation of this young man with hypertension, active sediment, worsening creatinine and possibility of Rapidly Progressive Glomerulonephritis and it prompted early treatment with steroids. The finding of AIN on the renal biopsy was crucial in establishing the association to the use of marijuana. It is important to consider AIN in the differential diagnosis of marijuana users that present with AKI, particularly in light of its increasing legalization.

FR-P029

Azithromycin-Induced Severe Acute Interstitial Nephritis: Role of Corticosteroids

Background: Azithromycin (AZA), a commonly used azalide antibiotic, has shown no association with acute interstitial nephritis. A recent literature review revealed intravenous pulse dose corticosteroid therapy for 3 days, followed by transition to oral prednisone taper over the following 8 weeks. AKI resolved, and Scr decreased to 1.1 mg/dL, a week after completion of prednisone therapy. AIN is a drug-induced kidney injury which likely ameliorated the degree of injury. AZA should be included in the differential diagnosis of medications associated with AIN. The views expressed in this abstract are those of the authors and do not reflect the official policy of the Departments of Army or Navy, Department of Defense, or U.S. Government.

Funding: Other U.S. Government Support

<table>
<thead>
<tr>
<th>Drug</th>
<th>Unchanged</th>
<th>Baseline</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 5</th>
<th>Day 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mot</td>
<td>CS + 5-ASA</td>
<td>CS 5-RMP</td>
<td>CS</td>
<td>CS</td>
<td>MTX + AAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sCr (mg/dL)</td>
<td>0.9</td>
<td>1.93</td>
<td>2.0</td>
<td>1.87</td>
<td>1.4</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>WBC (10^3/µL)</td>
<td>11.4</td>
<td>3.7</td>
<td>5.4</td>
<td>7.3</td>
<td>9.6</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td>RBC (10^3/µL)</td>
<td>12.4</td>
<td>8.2</td>
<td>8.9</td>
<td>9.9</td>
<td>11.5</td>
<td>13.3</td>
<td></td>
</tr>
</tbody>
</table>

FR-P030

Tubulointerstitial Nephritis with Uveitis Syndrome: A Case Report of a Rare Syndrome

Background: Tubulointerstitial nephritis with uveitis (TINU) syndrome is a rare disorder characterized by acute interstitial nephritis (AIN) along with concurrent development of uveitis. First described in 1975, there have been few case reports in both the ophthalmology and nephrology literature since. The underlying pathogenesis and etiology remains poorly understood. We present a case of a young adolescent male with an antecedent Epstein-Barr virus (EBV) infection who presented with severe AIN who later developed uveitis. This case highlights the importance of considering TINU in the evaluation of patients with AIN, and provides a framework for the evaluation and follow-up of such patients.

Methods: A 13 year old previously healthy Caucasian male, diagnosted with EBV via positive heterophile antibody test 2 months prior, presented to the hospital with severe AIN and unilateral uveitis. He was treated with IV pulse dosing of prednisone. The patient was followed up for 3 months, with resolution of his AIN and uveitis.

Results:

Conclusions: TINU is a rare disorder characterized by acute interstitial nephritis and uveitis. Early recognition is crucial in establishing a correct diagnosis and instituting appropriate treatment. This case demonstrates the importance of considering TINU in the evaluation of patients with AIN, and provides a framework for the evaluation and follow-up of such patients.
FR-PO032
Recurrent Acute Interstitial Nephritis Secondary to Crohn’s Disease
Dina Abdelwahab, Mira T. Keddis, Mayo Clinic, Scottsdale, AZ.

Background: Immune mediated tubulointerstitial nephritis secondary to Crohn’s disease is uncommon. We report a case of recurrent episodes of acute kidney injury (AKI) due to acute interstitial nephritis (AIN) coinciding with Crohn’s flare-up in an otherwise healthy man.

Methods: A 37-year-old male with 7-year history of Crohn’s disease was found to have an increased creatinine to 1.7 mg/dL from a normal baseline of 1.3 mg/dL. He was treated with mesalamine for 18 months prior to the increase in creatinine. Kidney biopsy showed acute eosinophilic interstitial nephritis suspicious for mesasaline associated AIN. Mesalamine was discontinued and he was treated with a 6-month course of tapering dose of prednisone. His creatinine peaked at 18.2 mg/dL and ranged between 1.7-1.9 mg/dL during treatment. 4 months after discontinuation of prednisone, he developed a flare up of his Crohn’s disease with diarrhea and hematochezia. Laboratory results showed an increase in creatinine to 2.4 mg/dL in absence of any medications. Urinalysis was performed and showed 1-3 white blood cells. Repeat kidney biopsy was performed and showed acute on chronic tubulointerstitial nephritis with eosinophils with moderate background fibrosis and tubular atrophy. The findings of acute on chronic interstitial nephritis in the context of active Crohn’s flare and absence of nephrotoxic medications confirmed suspicion for Crohn’s associated AIN. He was treated with prednisone for 8 weeks and started on adalimumab for treatment of his Crohn’s disease.

Results: This case highlights the uncommon presentation of AIN as a primary extra-intestinal complication of Crohn’s disease. We hypothesize that treatment of Crohn’s disease will improve renal outcome.

FR-PO033
Vancomycin: New Player in the World of Cast Disease
Jennine Ryan, Vancomycin: New Player in the World of Cast Disease

Background: Vancomycin associated cast nephropathy (VACN) is a rare entity that has only recently been described in literature, is an additional mechanism by which vancomycin can induce renal injury.

Methods: A 20-year-old African American man, presented with bilateral pneumonia due to MRSA. A chest CT was performed and showed bilaterally large loculated pleural effusion. He was treated with vancomycin, piperacillin-tazobactam, azithromycin and ertapenem. Urinalysis showed an isolated proteinuria. His renal function worsened with an increase in creatinine from 0.9 mg/dL to 3.2 mg/dL with oliguria. Vancomycin trough at that time was 43.3 mg/L. Creatinine peaked at 10.6 mg/dL despite adequate hydration. Work-up for acute kidney injury was unrevealing. He was started on hemodialysis, and subsequently underwent a renal biopsy. The biopsy showed diffuse acute tubular injury with focal eosinophilic tubular casts containing tubular protein and nanospheric vancomycin, consistent with VACN. Patient required three sessions of hemodialysis with recovery of renal function. At a 4-month follow-up, his creatinine was 0.7 mg/dL.

Results: Vancomycin is known to cause acute kidney injury due to acute tubular injury (ATI) and acute interstitial nephritis (AIN). VACN was first described by Luque et al. in Feb 2017. They reported a patient with severe acute tubular necrosis on renal biopsy that also had proteinaceous casts with nano-to-microspherical formations that corresponded with vancomycin spectral signature. They also retrospectively reviewed biopsies on patients who had vancomycin toxicity and found similar casts. Vancomycin nanospheres are incorporated into Tamm-Horsfall protein and then cause tubular obstruction. Presence of vancomycin in the casts was confirmed by infrared spectroscopy and immunohistochemistry. Our report confirms the findings of Luque and associates, and suggests that VACN is another mechanism for vancomycin-induced nephrotoxicity.

FR-PO034
Acute Oxalate Nephropathy from Vegetable Juicing and Lower Dose Vitamin C Supplementation Youngjun Park, Danili Shimonov, Shayan Shirazian, James Drakakis, Nobuyuki (Bill) Miyawaki. NYU Winthrop Hospital, Mineola, NY.

Background: High dose intravenous and oral ascorbic acid are associated with acute kidney injury (AKI) with oxalate nephropathy. We report a case of oxalate nephropathy at a lower than often described doses in combination with high oxalate juicing.

Methods: A 47-year-old male with newly diagnosed Diffuse Large B Cell Lymphoma with consistently normal creatinine of 0.8 mg/dL had deferred chemotherapy and instead started kale, spinach and berry juicing with daily apricot kernels plus 2 grams/day of Vitamin C supplement. This continued for 2 months, at which point his creatinine was noted to be 5.3 mg/dL on routine labs prompting an admission. Additional labs indicated calcium level of 13.3 mg/dL, Vitamin D-25 OH of 75 ng/mL, serum bicarbonate level of 32 mEq/L and K of 3.9 mEq/L. Phosphate and uric acid level from that admission is unfortunately not available. AKI with microscopic hematuria and 1+ proteinuria led to a kidney biopsy which revealed acute tubular injury with dilated lumina, cytoplasmic vacuolization and abundant intratubular calcium oxalate crystals. Scattered large calcium phosphate crystals were also seen. Additional workup did not reveal hyperoxaluria. Without recovery, he was initiated on hemodialysis.

Results: This case highlights the uncommon presentation of AKI from oxalate nephropathy which is associated with varying Vitamin C doses. Typical descriptions of oxalate nephropathy from IV ascorbic acid have referenced doses of 45 grams to as much as 224 grams per day. Oral ingestions of more than 4 grams/day consecutively over 30 days have been implicated in AKI yet high oral doses of 10 grams/day also have been documented to not induce AKI in others. This patient sustained AKI with far less Vitamin C intake than typically described toxic doses, but the combined impact of high oxalate foods (spinach, kale, berries, kernels) along with 2 grams of daily oral Vitamin C and hypercercemia possibly from lymphoma contributed to oxalate nephropathy. While the patient denies knowingly using significant calcium carbonate, high dose Vitamin D or other associated agents to induce milk-alkali syndrome, rather ample Vitamin D level, metabolic alkalosis and high calcium suggest its contribution to the calcium phosphate crystals noted on the biopsy as well. Extra caution may be needed on diet and modest dose supplements.

FR-PO035
An Uncommon Presentation of Acute Uric Acid Nephropathy Anna I. Lee-Mulya,1 Gauri Bhutani,2 University of Wisconsin, Madison, WI; 3University of Wisconsin, Madison, WI.

Background: Secondary hyperuricemia from ineffective erythropoietin can be seen in myeloproliferative disorders. Uric acid (UA) crystal precipitation may cause acute tubular injury and urinary obstruction in this rare disease group but is not commonly described in myelofibrosis (MF).

Methods: A 68-year-old man with essential thrombocytopenia & secondary MF diagnosed 6 years ago, who has been on ruxolitinib for 2 years with a dose increase within the last 3 months, presented with a few hours of nausea and vomiting following a fall 1 day prior. Serum creatinine (S.Cr) was 2.71 mg/dL (baseline 1.1 mg/dL). A CT abdomen pelvis showed gravel layers within bladder & distal ureters with resultant bilateral hydrourater & pelvicvesicet. Serum UA was 19.4 mg/dL. Cystoscopy showed stone debris (100% UA) & bilateral ureteral stents were placed. S.Cr increased to 4.5 mg/dL over next 2 days with UA still >15 mg/dL despite intravenous hydration, urinary alkalization & initiation of allopurinol. Raspburicase (2 doses of 3 mg IV) was started next with prompt renal recovery & normalization of U.A levels. Now, 6 months later, S.Cr is 1.06 mg/dL, UA 7.1 mg/dL, on allopurinol 300 mg daily.

Results: Acute UA nephropathy is only rarely described in MF, especially in secondary MF. Hyperuricemia has not been described with use of JAK2 inhibitor ruxolitinib, although it is not clear if & how much this medication contributed to the above presentation. Our case highlights that UA related renal diseases should be an important consideration in all myeloproliferative disorders. Timely intervention with rapid uric acid lowering is needed for renal recovery.

UA gravel within urinary bladder
FR-PO036
A Case of Radiation Nephropathy Presented with Delayed Massive Proteinuria and Renal Dysfunction Following Hematopoietic Stem Cell Transplantation

Background: Hematopoietic stem cell transplantation (HSCT)-associated nephropathy can progress to end stage renal disease and can also increase mortality risk. Its etiologies are often multifactorial, including medication such as calcineurin inhibitors and antineoplastic agents including molecular targeted drugs, transplantation-associated thrombotic microangiopathy, graft-versus-host disease (GVHD), and radiation. Because therapeutic approaches vary depending on the diagnoses, renal biopsy should be considered to determine the cause. Here, we report a case of radiation nephropathy with delayed massive proteinuria and renal dysfunction following HSCT.

Methods: A 33-year-old Japanese woman had been diagnosed with Philadelphia chromosome-positive acute lymphoblastic leukemia two years prior to this episode. Complete remission was achieved by cytarabine and daunorubicin followed by dasatinib, a tyrosine kinase inhibitor. She underwent allogeneic HSCT from matched unrelated donor. She had received total body irradiation and intravenous cyclophosphamide as myeloablative conditioning and methotrexate plus tacrolimus as acute GVHD prophylaxis. At one month after HSCT her serum creatinine level (SCR) was 0.9 mg/dl, and her urinary analysis was normal. However, her SCR elevated to 1.2 mg/dl and proteinuria developed at 4 months after HSCT. SCR did not decrease even after tacrolimus was discontinued, and proteinuria gradually got worse to 2-3 g/gCr. Renal biopsy at 15 months after HSCT demonstrated prominent mesangiosis with formation of capillary microneurysms. Under the diagnosis of radiation nephropathy, an angiotensin receptor blocker was started to mitigate proteinuria.

Results: Radiation nephropathy often develops with a latent period of 6-12 years after radiation exposure. We report a case of radiation nephropathy in association with radiation exposure 10 years before the diagnosis.

Conclusions: Radiation nephropathy often develops with a latent period of 6-12 years after radiation exposure. We report a case of radiation nephropathy in association with radiation exposure 10 years before the diagnosis.

FR-PO037
Focal and Segmental Glomerulosclerosis (FSGS) in Association with Carfilzomib Therapy

Background: Carfilzomib is a proteasome inhibitor widely used for treatment of multiple myeloma and monoclonal gammopathies of renal significance (MGRS). Herein, we report a case of new onset FSGS in association with carfilzomib therapy.

Methods: A 63-year-old man with stage G3b chronic kidney disease secondary to biopsy proven monoclonal immunoglobin deposition disease (MIDD) secondary to monoclonal kappa light chains developed nephrotic range proteinuria during therapy with carfilzomib and dexamethasone. He was initially diagnosed with biopsy-proven MIDD 10 years ago. He was treated with bortezomib and dexamethasone followed by melphalan/prednisone with achievement of a sustained remission over the next 10 years. Over that interval, his proteinuria ranged between 200 to 400 mg/d, decreased from 800 mg/d prior to therapy. His serum free light chain-kappa (SFLC-k) level was initially found to rise from 7 to 110 mg/dl, prompting therapy with 2 cycles of carfilzomib and dexamethasone. He had an excellent clinical response with a decline in the SFLC-kappa level to 29 mg/dl. Despite this response, he developed increased leg edema with a rise in proteinuria from 400 mg/d to 3700 mg/d (72% albumin). Urine immunoelectrophoresis showed no monoclonal spike. His serum creatinine level increased from 2 to 2.4 mg/dl. He did not have evidence of infection. A kidney biopsy showed focal and segmental glomerulosclerosis with collapsing features without evidence of light chain deposition disease. His proteinuria fell to 1.7 g/d over the next 5 months.

Results: Conclusions: Proteasome inhibitors have had proven efficacy in relapsed/refractory multiple myeloma and MGRS. Carfilzomib is a second generation proteasome inhibitor that previously has been reported to cause thrombotic microangiopathy. The temporal onset of this lesion coincident with carfilzomib therapy raises the possibility of carfilzomib-induced FSGS. Worsening proteinuria despite improvement in SFLCs during carfilzomib therapy should raise suspicion for this lesion. This is the first reported case of carfilzomib-associated FSGS and highlights the importance of ongoing surveillance for renal toxicity of novel therapeutic agents.
Methods: A 60 yo male p/w dyspepsia and fatigue. He was noted to have a Hgb of 5.7 g/dL with a 60% fall in the Hgb since presentation 1 month prior. Significant findings on examination included a blood pressure of 140/70 mmHg, heart rate of 72 bpm, respiratory rate of 16 breaths per minute, and a body temperature of 36.8°C. No significant abnormalities were noted in the lungs, heart, abdomen, or extremities. Laboratory investigations revealed the following values: Hgb 5.4 g/dL (normal range: 13.5-17.5 g/dL), hematocrit 17.2% (normal range: 41-54%), white blood cell count 3,000/μL (normal range: 4,000-11,000/μL), platelet count 50,000/μL (normal range: 150,000-450,000/μL), serum creatinine 3.62 mg/dL (normal range: 0.6-1.2 mg/dL), blood urea nitrogen 21 mg/dL (normal range: 8-20 mg/dL), and sodium 137 mEq/L (normal range: 135-145 mEq/L). The patient was transferred to the ICU for further evaluation and management.

Results: The patient was diagnosed with anemia of chronic disease and electrolyte disturbances. The patient was started on IV fluids, oxygen, and nutritional support. Hemoglobin transfusions were administered. The patient was also initiated on epoetin alfa to increase hemoglobin levels. The patient's condition improved significantly, and he was discharged home after 7 days of hospitalization. The patient was recommended to follow up with a hematologist for further evaluation and management of his anemia.

Conclusions: Anemia of chronic disease is a common complication in critically ill patients. Early recognition and prompt intervention are crucial to prevent complications and improve outcomes. Further research is needed to identify and target the underlying mechanisms of anemia of chronic disease.
for 3 months). Last testosterone dose was 3 months prior to presentation. On examination, he was found to have BP 150/80 mmHg and lower extremity edema. Urinalysis revealed 2+ blood, active urinary sediments. Urine protein excretion was 4.6 g/day while serum albumin was 2.8 g/dl. Serological studies were negative for ANA, anti-dsDNA, ANCA, anti-GBM, HBV, HCV and HIV. CRP was normal. Serum C3 factor was low (0.17 g/l) while C4 was normal. Ultrasound showed enlarged kidneys: right - 12.9 cm, left - 13.1 cm. Renal biopsy was performed which revealed active MPGN with segmental fibrinoid necrosis in 5 glomeruli but no crescents (fig 1). Also moderate tubulo-interstitial nephritis (TIN III) (fig 2) was seen. Immunohistochemistry showed moderately intense mesangial IgG deposits in the glomeruli with a few mesangial IgM deposits; C3 was negative. Patient was treated with i.v. pulse methylprednisolone and i.v. diuretics which resulted in serum creatinine level of 1.77 mg/dl and disappearance of the edema. On follow-up visit 4 weeks later, serum creatinine was 1.38 mg/dl and patient continued to further improve. Results: Conclusions: Patients with MPGN following AAS and supplement abuse, with features of rapidly progressive glomerulonephritis may benefit from glucocorticoid treatment.

FR-PO043

Nephrotic Syndrome in Dasatinib-Treated Patients with Chronic Myeloid Leukemia Takeo Koshida, Hitoshi Suzuki, Massao Kihara, Chieko Nogi, Yusuke Suzuki. Nephrology, Juntendo University Faculty of Medicine, Tokyo, Japan.

Background: Chronic myeloid leukemia (CML) is now a manageable disease with the tyrosine kinase inhibitors (TKI). Dasatinib, a second-generation of TKI, has proven to be effective for the long-term treatment of CML, both as initial and subsequent lines of therapy. Off-target effects of these medications can have beneficial or adverse effects on the kidney. We present a case of CML who developed nephrotic-range proteinuria after initiation on Dasatinib therapy that resolved after changing therapy to Imatinib.

Methods: A 70-year-old woman was detected leukocytosis at a medical check-up, and diagnosed with CML by bone marrow examination. Treatment with Dasatinib was initiated and was effective for CML resulted in clinical remission. After one year from the initiation of medication with Dasatinib, proteinuria was detected. Finally, she was consulted to the nephrologist and had a thorough examination. Nephrotic-range proteinuria (5.2 g/gCr) and hypoalbuminemia (2.6 g/dl) was detected and then kidney biopsy was performed. Pathological findings of kidney biopsy specimen showed edematous thickening of basement membrane, duplicated glomerular capillary wall and reticuloendothelial cells. Those pathological findings are compatible with the kidney injuries induced by Dasatinib. After switchover from Dasatinib to Imatinib, levels of proteinuria significantly decreased.

Results: Conclusions: We present a case of nephrotic syndrome during the course of metastatic disease in CML. Pathological findings indicated thrombotic microangiopathy with endothelial cell injuries and the proteinuria resolved after changing therapy from Dasatinib to Imatinib. Therefore, it is suggested that those kidney injuries was caused by Dasatinib. We should concern that off-target effects of Dasatinib can have adverse effects on the kidney.

FR-PO044

Successful Treatment of Hashimoto Encephalopathy with Therapeutic Plasma Exchange Hassan B. Attique, Arundhati Rao, Lalatundu Habib, Ruchir D. Trivedi. University of CT Health Center, West Hartford, CT.

Background: Hashimoto’s encephalopathy (HE) is a rare neuropsychiatric syndrome characterized by encephalopathy of unknown etiology associated with the high titters of antithyroid antibodies in the absence of alternative diagnoses. HE with robust clinical response to therapeutic plasma exchange (TPE) in the setting of end stage renal disease (ESRD) has not been published. We present steroid-resistant HE with reliable reduction of protein levels TPE was initiated using 5% albumin as replacement fluid on alternate days and continued to receive daily HD to optimize fluid electrolyte status during entire course. Clinical condition improved with reduction in anti-TPO antibody. She was continued on maintenance steroids and rituximab.

Results: Conclusions: HE is presumably autoimmune in origin. Proposed etiology includes autoimmune reaction between antibodies and cerebral vascular and brain cells and perivascular lymphocytic inflammation. Available literature is unclear about pathogenic role of anti-GBM, HBV, HCV and HIV. CRP was normal. Serum C3 factor was low (0.17 g/l) while C4 was normal. Ultrasound showed enlarged kidneys: right - 12.9 cm, left - 13.1 cm. Renal biopsy was performed which revealed active MPGN with segmental fibrinoid necrosis in 5 glomeruli but no crescents (fig 1). Also moderate tubulo-interstitial nephritis (TIN III) (fig 2) was seen. Immunohistochemistry showed moderately intense mesangial IgG deposits in the glomeruli with a few mesangial IgM deposits; C3 was negative. Patient was treated with i.v. pulse methylprednisolone and i.v. diuretics which resulted in serum creatinine level of 1.77 mg/dl and disappearance of the edema. On follow-up visit 4 weeks later, serum creatinine was 1.38 mg/dl and patient continued to further improve. Results: Conclusions: Patients with MPGN following AAS and supplement abuse, with features of rapidly progressive glomerulonephritis may benefit from glucocorticoid treatment.

FR-PO045

Denosumab: Is It Safe to Use in CKD? Eimear McKenna, Girish H. Shivashankar, Francis McCarron, Altnagelvin Area Hospital, Coleraine, United Kingdom; *Western Health and Social Care Trust, Derry, United Kingdom; Western Health and social care Trust, Londonderry, United Kingdom.

Background: Denosumab is a monoclonal antibody directed against receptor activator of RANK ligand used to treat osteoporosis. It has been promoted as safe to use in Chronic Kidney Disease (CKD) as it does not appear to accumulate in kidney failure and because of the experience in a small number of patients with CKD stages 3 and 4 in RCTs. There is no evidence for use in CKD stage 5. Published case reports suggest patients with severe CKD are at higher risk of developing hypocalcaemia following Denosumab which may be due to hyperparathyroidism and vitamin D deficiency. In this case series we have examined the incidence of hypocalcaemia following Denosumab to identify risk factors for hypocalcaemia.

Results: Retrospective data was collected using an electronic patient database on patients with CKD stages 3-5 attending our service who received Denosumab in the last 5 years. We examined Corrected calcium levels prior to and after each dose, Vitamin D and Parathormone (PTH) levels prior to each dose.

Results: 14 patients were identified; 9 had a functioning renal transplant and 1 patient was on hemodialysis. 4 patients were male and 10 female. Mean duration of treatment was 2.2 years. Average eGFR was 27 ml/min/1.73m2. Mean patient age was 60 years. Mean BMI was 25.17. 11 patients were on oral steroids. The average calcium prior to dosing was 2.35 mmol/l, falling to 1.99mmol/l after dosing. 9 patients achieved their lowest calcium at 1 week, 2 at 4 weeks and 3 at 8 weeks. Average PTH level prior to dosing was 153ng/l and after was 888ng/l. 15 patients developed severe hypocalcaemia (corrected calcium less than 1.9mmol/l), the average prior calcium in this group was 2.38mmol/l, falling to 1.77mmol/l. The average prior PTH was 206ng/l, rising to 1171ng/l. Four patients did not have Vitamin D status checked before dosing.

Conclusions: Denosumab will cause a small but not clinically significant reduction in serum Calcium in most patients with CKD. Severe hypocalcaemia can result if Vitamin D levels are unknown or in higher PTH levels. eGFR does not seem to correlate with the risk of hypocalcaemia. Biochemical abnormalities associated with CKD should be corrected, specifically, calcium, phosphate, PTH and vitamin D. Denosumab is the preferred treatment in CKD 4/5 however its use should be avoided in severe hyperparathyroidism and vitamin D deficiency.

FR-PO046


Background: BK Polymavirus is highly seroprevalent but rarely pathologic in humans. Genitourinary BK disease is most commonly seen after kidney transplantation. Here we present two cases of native kidney BK nephropathy.

Methods: The first patient was a 70 yo man with ischemic cardiomyopathy s/p OHT in 2011 and was on tacrolimus, mycophenolate mofetil, and prednisone maintenance immunosuppression. His pre-transplant SCr was 1.5-1.7mg/dl which remained stable after OHT. In 2013 he experienced a rapid rise in SCr over 5 months to 3.8 mg/dL. His urinalysis was negative for blood and albumin, microscopy showed no cells, and UProt:Ct ratio was 200 mg/g. A kidney biopsy showed tubular epithelial cells with focal glasyic change, fibrinoid necrosis, and positive nuclear staining for SV40 and Pab97. Serum BK BCR was positive (296075 copies/ml). MFM was stopped. His serum iK viral load decreased and SCr stabilized at 3.5 for approximately 3 years before beginning to rise again and his progressing to ESRD. The second patient was a 34 yo man who was treated for non-Hodgkin lymphoma at age 4 and is now on immunosuppression with Prednisone, MMF, and SCr which is stable at 1.3mg/dl because of the experience in a small number of patients with CKD stages 3 and 4 in RCTs. There is no evidence for use in CKD stage 5. Published case reports suggest patients with severe CKD are at higher risk of developing hypocalcaemia following Denosumab which may be due to hyperparathyroidism and vitamin D deficiency. In this case series we have examined the incidence of hypocalcaemia following Denosumab to identify risk factors for hypocalcaemia.

Results: Conclusions: Denosumab will cause a small but not clinically significant reduction in serum Calcium in most patients with CKD. Severe hypocalcaemia can result if Vitamin D levels are unknown or in higher PTH levels. eGFR does not seem to correlate with the risk of hypocalcaemia. Biochemical abnormalities associated with CKD should be corrected, specifically, calcium, phosphate, PTH and vitamin D. Denosumab is the preferred treatment in CKD 4/5 however its use should be avoided in severe hyperparathyroidism and vitamin D deficiency.

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

Underline represents presenting author.

410
FR-PO047
Hello, Goodbye Proteinuria


FR-PO048
Idiopathic Diffuse Global Hypertrophic Podocytopy without Proteinuria in a Patient with a Solitary Kidney


Background: Tyrosine kinase inhibitors (TKIs) have been associated with proteinuria and even overt nephrotic syndrome with variable renal histopathology (thrombotic microangiopathy (TMA), FSGS, or minimal change disease (MCD)). These agents have been thought to indirectly inhibit vascular endothelial growth factor (VEGF) receptors on glomerular endothelial cells. Sorafenib has been reported to cause proteinuria in several cases and discontinuation may result in resolution of proteinuria, although typically over several months. We present a case of severe nephrotic syndrome after starting sorafenib in a patient with a history of graft-versus-host disease (GVHD) whose history suggested several potential etiologies.

Methods: A 61-year-old man was evaluated for acute onset severe edema. He had acute myeloid leukemia (AML) and had undergone allogeneic-stem cell transplantation from his sister, complicated by steroid-induced diabetes and prior GVHD. Immunosuppression included tacrolimus and daily prednisone. He was started on sorafenib 400mg daily three months prior to admission. He was found to have a serum albumin to 2.1 mg/dl and new nephrotic range proteinuria with urine albumin/creatinine ratio (UACR) 9.0g/dl. Baseline serum creatinine was <1mg/dl. Hgb and platelets were at baseline. Tacrolimus troughs were <2ng/ml. Bone marrow biopsy was negative for active GVHD. Renal biopsy was performed with a GVHD-associated confluent mesangial hypercellularity versus proteinuria related to VEGF inhibition by sorafenib. Pathology revealed a podocytopy with consistent with MCD and arteriopathy indicative of early calcineurin inhibitor toxicity. Sorafenib was discontinued and no additional corticosteroids were administered. After two weeks, the patient had complete resolution of proteinuria, and increase in serum albumin to 2.9 mg/dl.

Results: Conclusions: TKIs can lead to proteinuria, overt nephrotic syndrome, and TMA. In this case, no clinical signs suggestive of TMA were present and pathology showed only MCD. Discontinuation of sorafenib led to surprisingly fast resolution of nephrotic syndrome, more rapid than typically reported. This case highlights the variable etiologies and timing to proteinuria resolution related to nephrotic syndrome and TKIs.

FR-PO049
Blaze from the Past: Methysergide Induced Retroperitoneal Fibrosis


Background: Methysergide induced retroperitoneal fibrosis (RPF) lumped into relative obscurity at culmination of the ergot era in migraine prophylaxis. Consequently, our collective vigilance has diminished regarding this entity. We describe an uncommon case of methysergide induced RPF causing acute kidney injury (AKI).

Methods: A 34-year-old woman with history of intractable migraines requiring multiple hospitalizations for parenteral pain management, bipolar disorder on chronic lithium therapy, and hypertension presented with a 3-week history of abdominal pain, associated with nausea, and daily episodes of non-bloody emesis. She also reported decreased urine output, difficulty voiding and new bilateral lower extremity edema. Review of systems was positive for constipation due to increased use of previously prescribed opiates for analgesia. She used Ketorolac for pain and was also treated with trimethoprim/sulfamethoxazole for a presumed UTI. Laboratory data revealed mild leukocytosis (14.4), acute on chronic anemia (hemoglobin and hematocrit 9.0/26.9) and AKI with BUN/serum creatinine (Scr) at 22.7/2.7 mg/dl. BUN/Scr was 13/0.7 mg/dl a year prior. Urolysis as well as an abdominal X-ray did not exhibit any abnormalities. Lithium levels were normal. CT abdomen/pelvis showed bilateral hydronephrosis with prominence of the left ureter and associated perinephric stranding. Urology performed cystoscopy, bilateral retrograde pyelography and left ureteroscopy. During the procedure, bilateral symmetrical narrowing of mid to distal ureters was noted with medial deviation suggestive of retroperitoneal fibrosis. Following careful review over the past use of methysergide which was deemed the culprit agent. She was treated with bilateral ureteric stenting with improvement in Scr levels.

Results: Conclusions: RPF is a chronic, predominantly idiopathic, fibroinflammatory disorder. Only one-third of cases are secondary with Methysergide being an established etiologic agent. Pathogenesis is thought to involve drug-related pro-fibrotic haptenic role or a feedback rebound serotonin release resulting in TGF-beta-Smad cascade-mediated myoblast proliferation. This case highlights the importance of careful history-taking especially in cases of AKI where multiple intersecting nephropathies might play a role and brings to the forefront a now rare disease.

FR-PO050
Timing of AKI after Urgent Percutaneous Coronary Intervention and Adverse Outcomes: The PATTERN Study


Background: Conflicting evidence exists about the frequency and outcomes associated with acute kidney injury (AKI) after percutaneous coronary interventions (PCI). Limited insights also exist about whether the timing of AKI influences outcomes after PCI in contemporary populations. We examined the association between AKI at 12 and 24 hours post-PCI with subsequent renal mortality and outcomes.

Methods: We identified all adult members within Kaiser Permanente Northern California undergoing urgent PCI from 2008-2013 who had both pre- and post-PCI serum creatinine data. Patients with prior dialysis, renal transplant or estimated glomerular filtration rate (eGFR) <15 ml/min/1.73 m² were excluded. AKI was defined as a ≥50% relative increase or >0.3 mg/dl increase in post- vs. pre-PCI serum creatinine measurement at 12 (a≤b) and 24 (a≥b) hours post-PCI. We ascertained post-discharge significant loss of renal function (defined as a ≥50% decrease from baseline eGFR or development of ESRD) and all-cause death up to 1 year post-PCI based on data from electronic health records. We used Cox regression to evaluate the independent association between timing of AKI and outcomes after adjustment for a high-dimensional propensity score for developing AKI and pre-PCI eGFR and proteinuria.

Results: Among 8522 urgent PCI patients, mean age was 67 years, with 29% were women, and 21% minorities. AKI was documented in 1.8% of patients at 12 hours and 1.6% at 24 hours post-PCI. In multivariable Cox models, the risk of all-cause death 1 year was similarly high for AKI at 12 hours (adjusted hazard ratio [HR] 3.35, 95%CI[2.08-5.40]) and 24 hours (HR 3.68, 2.18-6.21) post-PCI. In contrast, AKI at 24 hours post-PCI (HR 4.56, 2.37-8.70) was more strongly associated with significant loss of kidney function at 1-year than was AKI at 12 hours (HR 2.27, 1.19-4.32) post-PCI. Conclusions: In a large, community-based population undergoing urgent PCI, AKI at 12 and 24 hours post-PCI were independently associated with high excess mortality at 1-year to a similar degree, while AKI at 24 hours was more strongly associated with subsequent significant loss of kidney function at 1 year compared with AKI at 12 hours. Significant effort is needed to determine whether prevention or treatment of AKI after PCI can mitigate the excess risks of death and renal function loss.

Funding: Commercial Support - CSL Behring

Underline represents presenting author.
FR-PO051

Slope-Based Staging Outperforms KDIGO Staging for Assessing Inpatient Mortality Risk with AKI

Methods: Confidence limits (CI) for individual patient serum creatinine (sCr) trajectories were developed using an adaptive Bayesian approach. AKI episodes were defined by sCr excursions above the CI, with a ≥3 sCr values between baseline and peak; b) ≥6 hours between peak and baseline; and c) sCr increase ≥0.3 mg/dL. Specific baseline sCr values were defined for each as the minimal sCr value immediately preceding each AKI episode. Survivor functions, and relative Integrated Discrimination Improvement (rIDI) were done with Stata version 14.1.

Results: All adult 1st admissions were reviewed for FY2010-2013 at UAB Hospital, for patients with ≥3 sCr determinations, length of stay ≥2 months, excluding patients with ESRD before admission; 35,079 patients with 1,544 inpatient deaths. AKI staging was done with KDIGO criteria, and slope-based staging for patients with AKI episodes. Survivor functions (Figure) show better discrimination between AKI stages with slope-based criteria compared to KDIGO criteria: tDE>15.5% (95% CI: 13.5% - 17.6%, P=0.001); C-statistics of 0.7694 vs. 0.7226, and AUC/ROC 0.8616 vs. 0.8551 (P=0.012).

Conclusions: Slope-based AKI staging outperforms KDIGO staging criteria for describing the association of AKI severity with inpatient mortality at UAB Hospital. Slope-based staging is compatible with real-time, dynamic risk assessment than KDIGO staging, and also recognizes multiple AKI episodes during a single admission, with baseline sCr defined for each AKI episode. KDIGO staging is based on the absolute increase in sCr with reference to a prior baseline sCr, and does not recognize multiple AKI episodes.

Funding: NIDDK Support, Clinical Revenue Support

FR-PO052

Thrombocytopenia Predicts Mortality in Patients with AKI Requiring Renal Replacement Therapy (RRT)

Methods: We conducted a secondary analysis of the Acute Renal Failure Trial Network (ATN) database. The ATN study compared intensive to less-intensive RRT initiation in a large database of critically ill patients with AKI requiring RRT. AKI episodes were defined using an adaptive Bayesian approach. AKI episodes were classified using tDE>15.5% (95% CI: 13.5% - 17.6%, P=0.001); C-statistics of 0.7694 vs. 0.7226, and AUC/ROC 0.8616 vs. 0.8551 (P=0.012).

Conclusions: Slope-based staging is compatible with real-time, dynamic risk assessment than KDIGO staging, and also recognizes multiple AKI episodes during a single admission, with baseline sCr defined for each AKI episode. KDIGO staging is based on the absolute increase in sCr with reference to a prior baseline sCr, and does not recognize multiple AKI episodes.

Funding: NIDDK Support, Clinical Revenue Support

FR-PO053

Renal Recovery and Progression of CKD Following Postoperative AKI

Methods: This was a retrospective study of all adult patients undergoing abdominal, cardiothoracic, vascular or orthopedic surgery at the University Hospital in Reykjavik in 1998-2015. AKI was defined according to the KDIGO serum creatinine (SCR) criteria. CKD was defined as eGFR <60 ml/min/1.73 m² persistent for ≥90 days, and development and progression of CKD as an increase in SCR to a higher stage, present for ≥90 days. Association between incident CKD or CKD progression and renal recovery of varying degree (SCR reduction to <1.5, <1.25, <1.1 x baseline SCR) at 30 days following AKI was compared with a non-AKI control group using propensity score matching (1:1).

Conclusions: Postoperative AKI increases the risk of development of incident CKD and/or progression of existing CKD, even in patients who experience apparent good renal recovery.

Funding: Government Support - Non-U.S.

FR-PO054

Early Renal Replacement Therapy Improves Outcome of Burned Patients with AKI

Methods: We conducted a retrospective analysis of Burns Database from January 2011 to February 2016. Indications for dialysis included serum creatinine >1.5 times baseline or urine output < 0.5 ml/kg/h for at least 2 consecutive hours. Patients with similar parameters from January 2006 to December 2010 were recruited for comparison.

Results: A total of 27 patients with burns and AKI were recruited from January 2011 to February 2016. Mean age was 45.4 years and 88.9% were male. Mean TBWA was 54.8%. Total volume of fluid resuscitation was 2.7 ml/kg/TBSA. Time from onset of burn to RRT was 64 days. Majority of patients presented with stage 1 AKI (51.9%); while 22.2% and 25.9% had stage 2 and stage 3 AKI respectively. Most patients (74.1%) received CRRT and 18.5% received SLED. The mortality rate was 37.0% with majority (70%) due to sepsis/multiorgan failure. Only 1 patient required long-term RRT after discharge and there was no occurrence of abdominal compartment syndrome. Mean age of 15 patients from 2006 to 2010 was 47.8 years. Mean TBWA was 49.5%. Only 26.7% of patients were started on RRT. The mortality rate was 66.7%, which was higher than that of subjects from 2011 to 2016 (37.0%).
FR-PO55

AKI and Remission of Proteinuria in Adult-Onset Minimal Change Disease: A Multicenter Retrospective Cohort Study

Maki Shinzawa,1 Yasuyuki Nagasawa,2 Ryohi Yamamoto,3 Atsushi Yamauchi,2 Megumu Fukunaga,4 Terumasu Hayashi,2 Masaaki Isami,1 Yoshitaka Isaka,2 Kansai Rosai Hospital, Amagasaki, Hyogo, Japan; 3Osaka General Medical Center, Osaka, Japan; 4Osaka Rosai Hospital, Sakai-city, Japan; 5Osaka University Graduate School of Medicine, Suita, Osaka, Japan; 6Toyonaka Municipal Hospital, Toyonaka, Japan. Group/Team: STOP-MCD.

Background: AKI is common in adult-onset minimal change disease (MCD). However, its effect on remission of proteinuria is unknown.

Methods: Design: a multicenter retrospective cohort study, the Study of Outcomes and Practice Patterns of Minimal-Change Disease (STOP-MCD). Participants: 117 nephrotic patients aged ≥15 years with histological diagnosis of primary MCD between 2000 and 2009 in 5 hospitals in Japan. Outcome: First remission of proteinuria defined as urinary protein <0.3 g/day, urinary protein/creatinine ratio <0.3, and/or negative/trace result of dipstick test. Exposure: AKI defined as serum creatinine increase >20%, Scr >0.3mg/dL, and creatinine increase >20%. Statistics: Multivariable Cox proportional hazards model.

Results: AKI was identified as a significant predictor of remission in the multivariable analysis (AKI vs. non-AKI, hazard ratio 0.48 [95% confidence interval 0.29−0.82], P=0.002). Remission was delayed in AKI group (27 [19, 45] vs. 12 [9, 24] day, P=0.002). Independent predictors of remission were initial serum creatinine (P=0.002), initial urinary protein (P=0.008), and prednisolone dose (P=0.048). Differences in other variables, including age at diagnosis and proteinuria, were not associated with remission. Conclusion: AKI before immunosuppressive therapy delayed remission of proteinuria in adult-onset MCD.

FR-PO56

Subclinical AKI is Associated with Poor Patient Outcomes in Critically Ill Children

Natalja Stanisic,1 Shina Menon,2 Stuart Goldstein,3 Rajit K. Basu,1 Cincinnati Children's Hospital Medical Center, Cincinnati, OH; 2Seattle Children's Hospital, University of Washington, Seattle, WA.

Background: The diagnosis of acute kidney injury (AKI) depends on the detection of increases in serum creatinine (Scr), which can result in delayed recognition. Neutrophil gelatinase-associated lipocalin (NGAL) is a biomarker of renal tubular injury that rises early and can be used to detect AKI sooner. Subclinical AKI, a state defined by biomarker positivity in the absence of Scr elevation, has not been well studied in children thus far.

Methods: We conducted a single center, prospective study of children admitted to the ICU with urinary NGAL and Scr samples collected in the first day of admission. NGAL elevation (NGAL+) was defined as >500 ng/ml and Scr elevation (Scr+) was defined as KDIGO stage 1 AKI or greater. Patients were separated into 4 groups: NGAL+/Scr+, NGAL+/Scr+, NGAL−/Scr+ and NGAL−/Scr−. Groups were compared across a variety of outcomes: in-hospital mortality, need for renal replacement therapy (RRT) (primary outcomes), incidence and duration of mechanical ventilation, ICU and hospital length of stay (LOS), organ failure days and incidence of late-onset AKI (day 3-7). Particular attention was paid to the comparison of the NGAL−/Scr− and NGAL+/Scr+ groups.

Results: 178 patients (51.6% male, median age 6.7 years) were included. 115 (64.6%) were NGAL−/Scr−, 12 (6.7%) were NGAL+/Scr−, 26 (14.6%) were NGAL−/Scr+ and 25 (14.1%) were NGAL+/Scr+. Compared to NGAL−/Scr− patients, NGAL+/Scr+ patients had higher odds of in-hospital mortality [OR 1.64 (95% CI: 0.18,14.8) p=0.66], need for mechanical ventilation [OR 2.92 (95% CI: 0.61,13.9) p=0.18], and late-onset AKI [OR 2.5 (95% CI: 0.68,9.1) p=0.16]. This group also had longer mean duration of mechanical ventilation, more organ failure days, and longer LOS (both ICU and hospital). There was no difference in need for RRT initiation as no patients in either group required RRT use.

Conclusions: Elevated urine NGAL in admission is associated with increased morbidity and mortality in pediatric patients, even in the absence of elevated Scr, and may represent a state of subclinical AKI.

FR-PO057

Analysis of Morbidity and Mortality in Patients with Biliary Obstruction and AKI

Di Pan,1,3 Yumeng Wen,1,3 David Mariuma,1,3 Michael Grampling,4 Ira S. Meisels,2,3 Mount Sinai St. Luke's and Mount Sinai West Hospitals, New York, NY; 2Division of Nephrology, Mount Sinai St. Luke's and Mount Sinai West Hospitals, New York, NY; Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY; 3Montefiore Health System, New York, NY.

Background: Acute kidney injury has been shown to be a negative prognostic factor for a variety of diseases. Patients with biliary obstruction are unique in that they may develop acute kidney injury through the nephrotoxic effects of hyperbilirubinemia in addition to the conventional mechanisms of renal failure. The goal of this study is to analyze the impact and burden of acute kidney injury on patients with biliary obstruction.

Methods: This is a retrospective cohort study using the 2014 National Inpatient Sample (NIS), which is the largest inpatient database in the United States. A total cohort of 59,505 patients over the age of 18 admitted with either a primary or secondary diagnosis of biliary obstruction were identified using ICD-9 codes. 8,760 (17%) individuals had a concurrent diagnosis of acute kidney injury. The primary outcome was overall in-hospital mortality. Secondary outcomes included length of stay (LOS), total hospital charge, and incidence of receiving renal replacement therapy. Multivariate regression analyses were performed to test for independent associations between AKI and outcomes of interest adjusting for age, gender, race and comorbidities. Independent t-tests were performed to test for independent associations between AKI and outcomes of interest adjusting for age, gender, race and comorbidities.

Conclusions: We compared our findings with 5 studies published in recent 10 years on burned patients with AKI started on RRT and found that early RRT approach reduced mortality of burned patients with AKI. Optimal timing of RRT for burned patients with AKI has not been established and further large clinical trials are required.
for continuous variables, and chi-squared and Fisher's exact tests were performed for categorical variables. Analysis was performed using Stata 14.2.

Results: The presence of acute kidney injury was independently associated with increased overall in-hospital mortality in patients with biliary obstruction (adjusted OR 2.93 p<0.001, 95% CI 1.43 -2.98) and with hospital charges of $24,832.04 more than in patients without acute kidney injury (p=0.001 95% CI 14673.35 - 34990.74). 3.2% of patients received renal-replacement therapy.

Conclusions: The presence of acute kidney injury poses significant burden on patient mortality risk and total hospital charges were $24,832.04 more than in patients without acute kidney injury (p=0.001 95% CI 14673.35 - 34990.74). We should pay close attention and be aggressive in the monitoring and treatment of AKI in this population.

FR-PO058

Definition of Baseline Serum Creatinine Levels Which Are the Best to Predict Clinical Prognosis in Acute Kidney Injury Patients

Methods: A total of 196,356 adult patients were enrolled at one university hospital during the year 2013. The baseline serum creatinine levels were defined by 4 different methods (the lower level of the serum creatinine values obtained directly from the 6-month serum creatinine levels before admission; the serum creatinine levels back-calculated from the GFR 75 ml/min/1.73m² values during the year 2013. The baseline serum creatinine values calculated from the GFR 75 value). The AUCs for ROC curve analysis, the area under the curve (AUC) was measured to compare the diagnostic performance of AKI for clinical outcomes according to the definition of baseline serum creatinine levels.

Results: In patients with a baseline GFR above 60 ml/min/1.73m², the AUCs for in-hospital mortality were similar for the four definitions of baseline creatinine levels. The AUC for the GFR defined GFR 75 was significantly superior when the serum creatinine values were calculated from the GFR 75 value (p<0.001). In patients with a baseline GFR below 60 ml/min/1.73m², the baseline serum creatinine values calculated from the GFR 75 value, the AUC for in-hospital mortality was poor and the AUC for ERSD was significantly lower.

Conclusions: In patients with normal GFR, serum creatinine levels, which were back-calculated from the GFR 75 values, can be used as the baseline creatinine levels to define AKI. However, in patients with impaired kidney function, baseline serum creatinine levels obtained directly from the 6-month serum creatinine levels before admission can predict the prognosis of AKI more accurately.

C-statistics for ROC curve for in-hospital mortality and end-stage renal disease according to the AKI with 4 different baseline creatinine definitions

FR-PO059

A 10-Year National Trend in Dialysis-Requiring AKI among Adults with HIV Infection

Methods: This is a retrospective study using the 2005-2014 National Inpatient Sample, the largest publically available inpatient database in the United States. A cohort of 962,394 patients over the age of 18 undergoing invasive cardiac EP studies was identified. The electronic health record was used to identify the etiology and planned management prior to and after the procedure. Performing urine microscopy. A logistic regression model was created to investigate how the etiology and proposed management changed based on urine sediment review.

Results: In the primary analysis, we examined the temporal trend in the incidence of AKI and dialysis-requiring AKI. In the secondary analysis, we examined the temporal trend in the incidence of dialysis-requiring AKI. The results of dialysis-requiring AKI (0.22% in 2005 vs. 0.61% in 2014, p<0.001). Hospitals complicated by dialysis-requiring AKI compared to those that were not were associated with higher in-hospital mortality (OR 1.64, p<0.001).

Conclusions: This study demonstrates that despite an increase in incidence of dialysis-requiring AKI among patients with HIV, the in-hospital mortality of these patients has improved over time. The development of dialysis-requiring AKI continues to have significant life-altering impact and financial burden on HIV patients within our health-care system.

FR-PO061

Prospective Cohort Study Assessing the Role of Urine Microscopy in Diagnosis and Management of AKI

Background: Nephrologist-performed urine microscopy is a competency taught during training and encouraged in practice when working up acute kidney injury (AKI). Invasive cardiac electrophysiology (EP) study is a collection of clinical techniques for investigation and treatment of cardiac rhythm disorders. Limited literature has addressed the risk of acute kidney injury (AKI) following invasive EP procedures. The aim of this study is to analyze the temporal trend in the incidence of AKI among patients undergoing invasive cardiac EP studies and in-hospital mortality and other outcomes among those developed AKI between 2005 and 2014.

Methods: This is a prospective study using the 2005-2014 National Inpatient Sample, which is the largest publically available inpatient database in the United States. A cohort of 962,394 patients over the age of 18 undergoing invasive cardiac EP studies, based on ICD-9 CM codes was included in the study. There were no exclusion criteria.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Management remained unchanged in 98% of patients in whom diagnosis was unchanged after microscopy. But of 27 patients in whom the etiology was changed after urine microscopy, management was changed in 44% of cases (n=12) (p<0.001) (Fischler’s exact test). In a multivariable logistic regression model sepsis on presentation was found to be associated with higher odds of change in diagnosis of AKI after urine microscopy after adjusting for baseline and consult SCr (Odds ratio 4.19, 95% CI: 1.59-11.47, p = 0.004).

Conclusions: Nephrologist-performed urine microscopy plays a significant role in identifying the etiology and in management of patients with AKI in hospital. The likelihood was found to be higher in patients who were septic on presentation in our study.

FR-PO062

Use of a Serum Creatinine Point of Care Test in Low Resource Settings: Correlation and Agreement with Hospital Based Assessment

Jorge Hemmila,3 Sanjib K. Sharma,2 Rolando Clauere-Del Granado,2 Emmanuel A. Burdman,3 Michael V. Rocco,3 Jorge Cerda,2 Ravindra L. Mehta,3 1Albany Medical College, Albany, NY; 2P K Raina Institute of Health Sciences, Dharam, Nepal; 3College of Medicine, Malawi, Kokemäki, Finland; 4Universidad Mayor de San Simon, School of Medicine, Cochabamba, Bolivia, Plurinational State of; 5University of California San Diego Medical Center, San Diego, CA; 6University of Sao Paulo Medical School, Sao Paulo, Brazil; 7Wake Forest School of Medicine, Winston-Salem, NC.

Background: The ISN08y25Pilot Project was designed to evaluate an education and training program coupled with a point of care (POC) serum creatinine (sCr) test and teleconsultation to improve detection and management of AKI in low resource settings. We evaluated in paired samples the correlation between the POC sCr test applied in the health center to the hospital lab sCr results.

Methods: Paired results of sCr POC test and hospital lab values were compared in adults and childr with and without CKD in the 3 clusters (Bolivia, Nepal and Malawi) participating in the project. sCr was measured by Jaffe reaction and the sCr POC test was performed using the StatSensor® Cr Xpress™ Meter. Correlation between lab and POC test was evaluated by Spearman’s test and Bland Altman plots. The correlation and agreement between the two measurements through similar for pts with and without CKD (no CKD 0.817, CKD 0.857); p<0.001. Bland Altman plot (Figure 1) showed a good agreement between the two measurements through the middle range of CR values.

Conclusions: The sCr POC test performed well in adult and children and can be utilized to assess kidney function in low resource settings. The good correlation and agreement between the two measurements, suggests that POC test values are probably valuable for pt follow up through their course of illness and to assess kidney function recovery.

Funding: Private Foundation Support

FR-PO063

Prevention of AKI in a Tertiary Pediatric Hospital by Real Time Surveillance and Curated Alerts

Abhay N. Vats, Sheena Sharma, Francia M. Iorember, Martin A. Turman, Brittany Wold, Melinda Loya, Nina Farhoudi, David F. Carpentieri, Jamie Librizzi, Vinay Vaidya, Kanwal K. Kher. Phoenix Children’s Hospital, Phoenix, AZ.

Background: Hospital acquired acute kidney injury (HA-AKI) can significantly increase morbidity, mortality and health care costs in children. We developed a novel electronic health record (EHR) based real-time surveillance system for AKI detection & generation of curated alerts.

Methods: A software designed to provide enterprise-wide data analysis based on algorithms utilizing AKIN criteria for staging was developed. It queries EHR every 6 hours for AKI risk including baseline serum creatinine (SCr), % change, rate of rise in SCr, nephrotoxic medications (NTM), therapeutic drug levels (TDM), and renal replacement therapy /nephrology intervention. Quick links to the patient charts are available. The analytic output is automated and made available on a self-updating dashboard which is utilized to generate curated alerts by the enterprise nephrologists.

Results: The dashboard (Fig) generates color coded signals for stage 1 to III AKI, plots weekly change in SC, NTM exposure, TDM listing, day(s) since last SC & documented nephrology intervention. It detects both NTM & non NTM associated AKI & risk factors. It is even programmed to detect AKI where the absolute SC is <0.5 mg/ dl. An AKI surveillance team (pharmacist & nephrologist) reviews the dashboard daily to direct AKI prevention and treatment strategies through curated alerts to the responsible healthcare providers through “two way” integrated Vocera® secure messaging system. This avoids “alert fatigue” and has led to a proactive change in provider’s approach to HA-AKI prevention. The dashboard access progressively increased from 45% to 87% over a short period of 6 weeks.

Conclusions: This novel EHR dashboard and AKI alert system serves as an early warning tool for enterprise wide application. The alerts are traceable, auditable & are HIPAA compliant. AKI biomarkers will be incorporated in the dashboard in near future. This tool allows the HA-AKI prevention team to track at risk patients, provide early detection & prevention of HA-AKI.

AKI Dashboard Screen Shot

FR-PO064

Initial Application of Electronic Alert for AKI among High-Risk Wards

Yanhua Wu, Yuanhan Chen, Wei Dong, Xinling Liang. Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China. Group/Team: China collaborative study on AKI.

Background: The effectiveness of acute kidney injury alert might differ in different care settings. We aimed to investigate the value of electronic alert for acute kidney injury among high-risk wards.

Methods: A prospective, randomized, controlled study was conducted. We developed an electronic alert for AKI and ran the system in intensive care units and cardiovascular departments. Eligible participants were adults aged 18 years or older who were in hospital with acute kidney injury as defined by Kidney Disease Improving Global Outcomes creatinine-based criteria. Exclusion criteria were initial hospital creatinine ≥353.6 μmol/L or greater, end-stage renal disease, renal replacement therapy before randomization, kidney transplantation and amputation. The primary outcomes were AKI and expanded AKI diagnosis rates, nephrology consultation, dialysis, recovery of renal function and death. Patients were randomly assigned to alert group and non-alert group. Alert group could receive popup messages. This study is registered with ClinicalTrials.gov, number NCT02793167.

Results: Between Mar.1 2016 and Jul.31 2016, 5335 patients were screened.318 eligible participants were assigned to the alert group and 623 were assigned to the non-alert group. The diagnosis rate of AKI in alert group was higher than non-alert group (5.6% vs. 2.1%, P<0.004). The expanded AKI (AKI and multiple organ dysfunction syndrome) diagnosis rate was also higher in alert group (11.2% vs. 4.5%, P<0.001). Patients were stratified according to the severity of AKI and different wards. At AKI stage 1, the AKI and expanded AKI diagnosis rates in alert group were higher than the non-alert group (AKI: 2.8% vs. 0.8%, P=0.037; expanded AKI: 4.7% and 1.3%, P=0.011). There was no difference at AKI stage 2 and stage 3. Among the different wards, the AKI alert had greater impact on AKI and expanded AKI diagnosis rates in cardiovascular surgery wards(AKI:3.9% vs. 1.2%, P=0.077; expanded AKI:9.0% vs. 2.9%, P<0.003). There was not significantly different in nephrology consultation, dialysis, recovery of renal function or death in the two groups.
Conclusions: Electronic warming system could reduce the misdiagnosis rates of AKI and also avoid misdiagnosing AKI in high-risk wards. Standard diagnosis rate of AKI was still very low. The electronic alert system for AKI did not improve clinical outcomes in these wards.

Funding: Government Support - Non-U.S.

FR-PO065

Assessment of the Renal Angina Index for Prediction of Severe AKI Prediction in Critically Ill Children Rajit K. Basu,1 Ahmad Kaddourah,2 Stuart Goldstein,1 1Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 2None, Doha, Qatar.

Background: Acute kidney injury (AKI) occurs in one in four children admitted to the intensive care unit (ICU) and escalating AKI severity is independently associated with increased risk of patient morbidity and mortality. Early prediction of AKI has the potential to improve outcomes.

Methods: We conducted a multi-national, multi-center, prospective study of children admitted to the intensive care unit (ICU) between January-December 2014 with an expected length of stay ≥ 48 hours (NCT019187921). Our primary aim was to assess the performance of fulfillment of renal angina (RA+), a context-driven risk stratification system, on the day of ICU admission (Day 0) for prediction of severe AKI occurrence 3 days after ICU admission (Day 0). The primary outcome was the performance of renal angina for prediction of severe AKI three days after ICU admission (Day 0), severe AKI by Stage 2-3 AKI KDIGO AKI guidelines. Renal angina was determined at 12 hours into Day 0, using the renal angina index (RAI); RA+ was defined as a RAI ≥ 8. The predictive performance of the Day 0 RAI was compared to changes in serum creatinine (SCr) (measured in the first 12 hours of ICU admission) relative to baseline (Day 0; SCr/Base).

Results: 1590 patients studied were 55% male and median age of 54.5 months. 280 patients (17.9%) were Day 0 RAI+, 121 (42.3%) of whom developed Day 0-severe AKI (versus 247 (18.9%) of Day 0-R0 patients, relative risk (RR) 2.23; 95% confidence interval (CI): 1.87-2.66, p=0.0001). Patients with Day 0-severe AKI (368, 23.1%) had increased utilization of renal replacement therapy (10.9% vs. 1.5%, p=0.001), and higher rate of mortality (7.6% vs. 4.3%, p=0.01) versus patients without Day 0-severe AKI. Day 0 RAI+ demonstrated superior prediction for Day 0-severe AKI than SCr/Base (RR: 1.61; (1.33-1.93), p=0.001) and maintained this superiority with Day 3-severe AKI on multivariate regression (independent odds ratio (OR): RA+ 3.21, 95% CI (2.20-4.67) vs. SCr/Base 1.93 (95% CI 1.68-2.24, p=0.001)

Conclusions: Compared to isolated context-free changes in SCr, the RAI demonstrates improved accuracy for prediction of severe AKI in critically ill children and young adults. Earlier, more accurate prediction of severe AKI has the potential to improve AKI associated patient outcomes.

FR-PO066

Spectrum of AKI in Patients from Low Income Countries Participating in the ISN0by25 Initiative Fatemeh Macedo,1 Sanjib K. Sharma,2 Ulla Hennmola,3 Rolando Clare-Del Granado,4 Jorge Corda,1 Emmanuel A. Burdmann,2 Michael V. Rocco,2 Ravinda L. Mekha,1 1Albany Medical College, Albany, NY; 2College of Medicine, Malawi, Kokemäki, Finland; 3B P Koirala Institute of Health Sciences, Dharan, Nepal; 4UCSD, San Diego, CA; 5Universidad Mayor de San Simon, School of Medicine, Cochabamba, Bolivia, Plurinational State of; 6University of California San Diego Medical Center, San Diego, CA; 7University of Sao Paulo Medical School, Sao Paulo, Brazil; 8Wake Forest School of Medicine, Winston-Salem, NC.

Background: The ISN0by25 Pilot Project is designed to evaluate the effects of an education and training program, point of care (POC) test and teleconsultation on the detection and management of AKI in low resource settings with the goal of reduce risk across these low resource settings. sCR POC test helped to identify patients with expanded AKI in high-risk wards. Standard diagnosis rate of AKI was still very low. In patients (17.9%) were Day 0 RAI+, 121 (42.3%) of whom developed Day 0-severe AKI (versus 247 (18.9%) of Day 0-R0 patients, relative risk (RR) 2.23; 95% confidence interval (CI): 1.87-2.66, p=0.0001). Patients with Day 0-severe AKI (368, 23.1%) had increased utilization of renal replacement therapy (10.9% vs. 1.5%, p=0.001), and higher rate of mortality (7.6% vs. 4.3%, p=0.01) versus patients without Day 0-severe AKI. Day 0 RAI+ demonstrated superior prediction for Day 0-severe AKI than SCr/Base (RR: 1.61; (1.33-1.93), p=0.001) and maintained this superiority with Day 3-severe AKI on multivariate regression (independent odds ratio (OR): RA+ 3.21, 95% CI (2.20-4.67) vs. SCr/Base 1.93 (95% CI 1.68-2.24, p=0.001)

Conclusions: Compared to isolated context-free changes in SCr, the RAI demonstrates improved accuracy for prediction of severe AKI in critically ill children and young adults. Earlier, more accurate prediction of severe AKI has the potential to improve AKI associated patient outcomes.

FR-PO067

AKI in Patients Treated for Cancer: A Population-Based Cohort Study Abhijit Kitchlu,1 Eric McArthur,2 Eitan Amir,2 Christopher Booth,2 Rinku Sutrada,1 Habeeb Majedde,1 Danielle M. Nash,2 Samuel A. Silver,4 Amit X. Garg,5 Christopher T. Chan,1 Joseph Kim,3 Ron Wald,1 1Nephrology, University of Toronto, Toronto, ON, Canada; 2Institute for Clinical Evaluative Sciences, London, ON, Canada; 3Princess Margaret Cancer Centre, Toronto, ON, Canada; 4Medical Oncology, Queen’s University, Kingston, ON, Canada; 5Nephrology, Western University, London, ON, Canada.

Background: Patients undergoing treatment for cancer are at increased risk of acute kidney injury (AKI). There are few data on AKI incidence and risk factors in the current era of treatment.

Methods: Using linked administrative datasets, we conducted a population-level cohort study of all patients initiating systemic therapy (inclusive of chemotherapy and targeted agents) for a new cancer diagnosis in Ontario, Canada from 2007 to 2014. The primary outcome was hospitalization with AKI or acute dialysis. We estimated the cumulative incidence of AKI and fitted Cox proportional hazards models (accounting for the competing risk of death), adjusting for demographics, cancer characteristics, comorbidities and co-prescriptions. We modeled exposure to systemic therapy (the 90-day period following each treatment) as a time-varying covariate. We also assessed secular trends in annual AKI incidence according to year of systemic therapy initiation.

Results: We identified 163,071 patients initiating systemic therapy, of whom 10,880 were associated with AKI. The rate of AKI was 27 per 1000-person years (PY), with 1-, 5-, and 5-year and overall cumulative incidences of 3.9, 7.8 and 9.3%, respectively. Cancers with the highest 5-year AKI incidence were myeloma (26%), bladder (19%), and leukemia (15%). Advanced stage, pre-existing chronic kidney disease (CKD), and diabetes mellitus (DM) were associated with increased risk of AKI [adjusted hazard ratios (aHR) 1.41 (95%CI 1.28, 1.45), 1.80 (95%CI 1.67, 1.93) and 1.43 (95%CI 1.37, 1.50), respectively]. In patients age 46 years, use of diuretics and angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers (ACEi/ARBs) were associated with increased risk [aHR 1.20 (95%CI 1.14, 1.28), 1.39 (95%CI 1.23, 1.58)]. AKI risk was significantly elevated in the 90 day period following systemic therapy exposure [aHR 2.34 (95%CI 2.24, 2.45)]. The annual incidence of AKI over time (from 18 to 52 per 1000-PY between 2007 and 2014).

Conclusions: Cancer-related AKI is common and associated with more advanced stage, CKD, DM and the concomitant receipt of diuretics or ACEi/ARBs. Risk is heightened in the 90 days after systemic therapy. Preventive strategies are needed to address the increasing burden of AKI in this population.

FR-PO068

Assessment of the Pathophysiology of AKI Using Magnetic Resonance Imaging Huda Mahmoud,1 Charlotte E. Buchanan,2 Eleanor Cox,2 Benjamin L. Prestwich,3 Maarten W. Taal,1 Susan Francis,2 Nicholas M. Selby,1 1Center for Kidney Research and Innovation, Derby, United Kingdom; 2Sir Peter Mansfield Imaging Centre, Nottingham, United Kingdom; 3Medical Oncology, Queen's University, Kingston, ON, Canada.

Background: The pathophysiology of Acute Kidney Injury(AKI) in humans is not well delineated, in part due to limitations in current methods of renal imaging. Recent advances in Magnetic Resonance Imaging(MRI) allow assessment of structural and functional changes relevant to kidney disease. We performed a multiparametric MR study to assess its utility and reproducibility in patients with AKI.

Methods: We studied 9 patients with AKI stage2/3(with no pre-existing CKD) and 13 healthy volunteers(HV). Patients underwent multiparametric renal MR scans at the time of AKI and 90d later. MR scans were performed on a 3T Philips Ingenia scanner. Structural assessments included renal volume, longitudinal-relaxation time(T2) and Diffusion-Weighted Imaging(DWI), markers of fibrosis and/or inflammation. Functional assessments included Arterial Spin Labelling(ASL) to measure renal perfusion and Blood Oxygenation Level Dependant Imaging(BOLD) as an indicator of renal oxygenation.

Results: AKI patients: mean 47±19yrs, baseline creatinine 78±14μmol/L, peak creatinine 467±25μmol/L. All achieved complete biochemical recovery(creatinine 88±17μmol/L) and 5 have had repeat scans at 90d. Renal volumes were significantly increased at time of AKI as compared to HVs(720±92ml vs 189±25ml respectively p<0.001). BOLD T*, cortical and medullary T, values were significantly increased in AKI patients at the time of injury compared to HVs. Post AKI renal volumes had reduced(210±75ml p=0.04), as had T*, cortical and medullary T, values, T values at 90d remained significantly higher than the HVs(p<0.001).

Conclusions: This is the first study to use multiparametric MR in patients with AKI, assessing kidney function and structure at time of AKI and during recovery. The
increase in renal volumes and T1 values at time of AKI may be indicate inflammation or oedema. The persistent increase in T1 at 90d may represent persistent inflammation or fibrosis development. Importantly, persistent MR abnormalities at 90d despite complete biochemical normalisation show the potential of MR to better characterise recovery. Further studies are required to build on this initial pilot work, and determine how best multiparametric MR can be used to characterise the nature of renal injury in AKI and its recovery.

Funding: Private Foundation Support

FR-PO069

Does the Ultrasound Intrarenal Resistive Index Have a Diagnostic and Prognostic Value in Acute Graft Dysfunction? Juan Carlos Ramirez-Sandoval, Monica Chapa, Tábara Cano-Gámez, Elena López-Sosa, Mariana Oria-y-Anaya, E G. Ramirez-Gutierrez, Luis E. Morales-Buenrostro, Ricardo Correa-Rotter. Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico city, Mexico; Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, MEXICO, Mexico; Escuela de Medicina, Universidad Panamericana, Mexico City, Mexico; Escuela de Medicina, Universidad Panamericana, Mexico, Mexico; Escuela de Medicina, Universidad Panamericana, Mexico City, Mexico.

Background: The intrarenal resistive index is commonly employed in kidney transplant recipients (KTR) with acute kidney injury (AKI) yet its clinical usefulness remains controversial. Our objective was to evaluate the prognostic performance of the resistive index in KTR with AKI after 1 year of follow-up. We also analyzed the relation between the index and graft morphologic features.

Methods: Retrospective analysis of the resistive index measured at the time of renal graft biopsies performed due to AKI (rise in serum creatinine [SCr] ≥0.3mg/dl from baseline). We excluded KTR with shock, significant renal-artery stenosis, hydropnephrosis, and porto-renal fluid collections with marked compression. All KTR were followed for at least 1 year after the AKI event.

Results: 91 KTR with AKI were included: 46 (51%) females, median age 36 yr (IQR 27-48), median time post kidney transplant 5.1 yr (IQR 2.1-9.2), median SCr at AKI 2.5 mg/dl (IQR 2.0-4.3), and 22 (24%) with a severe AKI (AKIN 3). The resistive index of arcuate arteries was higher in 13 (14%) KTR with graft loss caused by AKI as compared to 78 (76%) of KTR without graft loss (0.69 ± 0.11 vs. 0.63 ± 0.09 respectively, p=0.047) yet no differences were observed in the resistive index of interlobar or segmental arteries. SCr at AKI diagnosis and age of KTR were associated with a higher resistive index in segmental and arcuate arteries (p=0.002). The resistive index of all measured arteries was not useful to differentiate causes of AKI (Table) and was also not useful to predict graft outcomes (graft survival, requirement of dialysis during AKI episode or eGFR after AKI episode).

Conclusions: The resistive index is time consuming and not useful to define etiology or graft outcomes in KTR with AKI. Our results support that it should not be employed to evaluate acute kidney-graft dysfunction.

Area under the curve in ROC curve for resistive index and AKI etiology

<table>
<thead>
<tr>
<th>Relative index</th>
<th>Immunochemical rejection (n=4)</th>
<th>Acute tubular necrosis (n=7)</th>
<th>Calcium oxalate toxicity (n=1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interlobar</td>
<td>0.57</td>
<td>0.58</td>
<td>0.50</td>
</tr>
<tr>
<td>Acute</td>
<td>0.50</td>
<td>0.60</td>
<td>0.62</td>
</tr>
<tr>
<td>Segmental</td>
<td>0.49</td>
<td>0.53</td>
<td>0.51</td>
</tr>
</tbody>
</table>

*Other causes of aki were mixed [immunological]calcineurin toxicity or BK virus* (n=29), parvovirus (n=1), and prenadal with normal biopsy (n=4).

FR-PO070

AKI Following CABG versus PCI in Advanced CKD Patients Abdussaippa Gaiyow, Mikeloz S. Molnar, Praveen Kumar Potukuchi, Keiichi Sumida, Oguz Akbikilgic, Elani Streja, Connie Rhee, Robert B. Canada, Kamyar Kalantar-Zadeh, Csaba P. Kovessy, Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; University of Tennessee Health Science Center, Memphis, TN; University of California Irvine, School of Medicine, Orange, CA; University of Tennessee Health Science Center, Memphis, TN.

Background: Previous studies reported that GABG is associated with reduced risk of mortality and repeat revascularization in mild-to-moderate CKD, ESRD, and in diabetics. However, the relative risk of acute kidney injury (AKI) associated with CABGP vs. PCI in patients with advanced CKD is not clear.

Methods: We examined 655 US veterans with incident ESRD who underwent a first CABG or PCI up to 5 years prior to dialysis initiation. Stages of AKI following the first CABG or PCI up to 5 years prior to dialysis initiation. The association of CABG vs. PCI with AKI was examined in multivariable adjusted logistic regression analyses.

Results: 472 patients underwent CABG and 183 patients underwent PCI. Mean age was 63.7 (SD=8.1) years, 99% were male, 76.5% were white, and 21.8% were African Americans. The pre-procedure eGFR and the incidence of AKI in the CABG vs PCI group were classified according to the Acute Kidney Injury Network classification. The association of CABG vs. PCI with AKI was examined in multivariable adjusted logistic regression analysis.

Conclusions: CABG was associated with a 5-fold higher risk of AKI compared to PCI in patients with advanced CKD. Despite other benefits of CABG over the PCI, the extremely high risk of AKI associated with CABG should be considered in this vulnerable population when deciding on the optimal revascularization strategy.

Funding: NIDDK Support

FR-PO071

IgG4-Related Disease as a Cause of Urinary Tract Obstruction and AKI: A Case Report Sukhjinder K. Andurak, Beenish Noor, Melissa C. Fajardo, Olurontobi Rahman, Sudhanush Jain, Jeffrey D. Wallach. Harlem Hospital Center, New York, NY; Nephrology, Harlem hospital Center, New York, NY.

Background: IgG4-related disease (IgG4-RD) is a fibroinflammatory condition with multisystem involvement. We report the case of a male admitted for chronic abdominal pain who was found to have acute kidney injury, retroperitoneal fibrosis and hydroureteronephrosis.

Case Report: A 61 year old male presented with a 4-month history of persistent lower abdominal pain, unintentional weight loss of ~15 kg over last year but no urinary complaints. Medical history significant for Hypertension, cerebrovascular accident and chronic kidney disease. Examination findings included a BP 163/101, lower abdomen tenderness and hyper pigmentation of skin in the right and left flanks. Initial investigations revealed a 24h urine protein of 517 mg/24h (previous Creatinine 1.79 one year ago), leukocytosis, severe anemia, and thrombocytopenia. Urinalysis was bland. Initial non-contrast Abdominal CT showed bilateral hydroureteronephrosis, perinephric stranding and mid-ureter compression due to soft tissue mass. Also noted was a mass tissue mass, suspicious for an acute treatment, he was discharged to follow up as outpatient. As part of the work up for IgG4-RD.

Results: IgG4-RD is now recognized as a link between many clinical entities that were previously regarded as organ-specific disorders. Obstructive uropathy is seen in about 45%-65% of reported patients with IgG4-related RPF. Management involves relieving the obstruction, halting progression of the fibrotic process and preventing recurrence. Obstructive uropathy with RPF should prompt a work up for IgG4-RD.

Conclusions: IgG4-related disease (IgG4-RD) is a fibroinflammatory condition with multisystem involvement. We report the case of a male admitted for chronic abdominal pain who was found to have acute kidney injury, retroperitoneal fibrosis and hydroureteronephrosis.

Funding: NIDDK Support

FR-PO072

Biomarkers for the Prediction of AKI Progression after Pediatric Cardiac Surgery Jason H. Greenberg, Michael Zappitelli, Yaqi Jia, Heather Thiessen Philbrook, Christina A. de Fonseville, Francis P. Wilson, Steven G. Coca, Prasad Devarejan, Saurabh R. Parikh. Cincinnati Children’s Hospital, Cincinnati, OH; Icahn School of Medicine at Mount Sinai, New York, NY; McGill University Health Centre, Montreal Children’s Hospital, Montreal, QC, Canada; Yale University, New Haven, CT; Yale University and VAMC, New Haven, CT.

Background: The risk for adverse outcomes dramatically increase as children progress to higher stages of AKI. No reliable methods currently exist to predict AKI progression in hospitalized children.

Methods: The TRIBE-AKI pediatric study is a three-center prospective cohort of children, 1 month to 18 years old, undergoing cardiac pulmonary bypass. Urine biomarkers of injury (neutrophil gelatinase–associated lipocalin (NGAL), interleukin (IL) 18 (IL-18), kidney injury molecule 1 (KIM-1), liver fatty acid binding protein (LFABP), albumin) and plasma biomarkers of inflammation (interferon (INF), IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, IL-13, tumor necrosis factor alpha (TNF)) were measured on the first day of serum...
creatinine defined AKI. AKI progression was defined as a worsening of AKIN stage; from stage I to II or II to III, or stage III at any time.

Results: 408 children were enrolled, of which 176 (43%) were diagnosed with AKI. On the first day of AKI, Stage I, Stage II, and Stage III AKI was diagnosed in 145 (36%), 28 (7%) children had AKI progression. On the first day of serum creatinine defined AKI, 11/17 biomarkers were significantly higher in patients with AKI progression vs without (Table). Urine LFABP among injury biomarkers and plasma IL-8 among inflammatory biomarkers had the highest discrimination for AKI progression [optimism adjusted AUC 0.70 (95% CI:0.58-0.81) and 0.80 (95% CI:0.67-0.90), respectively].

Conclusions: Urine and plasma biomarkers predict AKI progression in children after cardiac surgery. If validated, these biomarkers could be used to improve clinical care and guide enrollment in therapeutic trials of AKI.

Funding: NIDDK Support, Veterans Affairs Support

---

FR-PO074

Urine Injury Biomarker Level before and after AKI: Results from the CRIC Study and CKD Biomarker Consortium

Objective: We evaluated the relationship between urinary cast and prognosis of AKI. In this study, we evaluate the relationship between urinary cast and prognosis of AKI.

Background: Urinary sediment findings are related to short term prognosis of AKI, but evidence is lacking whether urinary sediment findings are related to long term prognosis of AKI. In this study, we evaluate the relationship between urinary cast and prognosis of AKI.

Methods: We studied a cohort of Chronically Renal Insufficiency (CRI) patients enrolled from Kaiser Permanente Northern California (KPNC) who had urine specimen banked as part of annual research study visits. We used data gathered as part of clinical care and captured in the KPNC electronic medical record to define episodes of AKI (peak/ nadir serum Cr ≥1.5 mg/dl). We compared biomarker levels of kidney injury (AKI) between those who had AKI and those who did not match for calendar year and time gap between first and second measurement (overall mean 419 days).

Results: Overall, 70% of participants were female; 48% were white/39% black and 70% had diabetes mellitus; mean age was 63 yrs, eGFR 49 ml/min/1.73m² and urine albumin-to-creatinine ratio (ACR) >30 mg/g in 12% vs 20%. Although there was no change in ACR or ACR from pre-AKI to post-AKI (Table), urine in urine samples collected at the annual CRIC study visit before the AKI episode and urine samples collected at the annual CRIC study visit after the AKI episode. We compared 29 participants with documented AKI (69% with KDIGO severity stage 1; 10% stage 2; 21% stage 3) with 157 participants who did not (matched for calendar year and time gap between first and second measurement (overall mean 419 days)).

Conclusions: These data suggests there is persistent tubular injury months after an episode of mild to moderate AKI.

Funding: NIDDK Support

---

FR-PO075

Persistent Elevation of Biomarkers of Dysregulated Mineral Metabolism and Inflammation after AKI: The ASSESS-AKI Study

Objective: To investigate persistent elevation of biomarkers of dysregulated mineral metabolism and inflammation after AKI.

Background: Persistent elevation of parathyroid hormone (PTH), phosphorus, fibroblast growth factor-23 (FGF-23) and C-reactive protein (CRP) and were higher in AKI patients at both V0 and V3 (and higher among those with more severe AKI) (p<0.001 for all comparisons).

Results: Mean age of the 1,484 participants analyzed was 55 yr and 48%  were females. 10%  had diabetes mellitus; mean age was 63 yrs, eGFR 49 ml/min/1.73m² and urine albumin-to-creatinine ratio (ACR) ≥30 mg/g in 12% vs 20%. Although there was no change in ACR or ACR from pre-AKI to post-AKI (Table), urine in urine samples collected at the annual CRIC study visit before the AKI episode and urine samples collected at the annual CRIC study visit after the AKI episode. We compared 29 participants with documented AKI (69% with KDIGO severity stage 1; 10% stage 2; 21% stage 3) with 157 participants who did not (matched for calendar year and time gap between first and second measurement (overall mean 419 days)).

Conclusions: These data suggests there is persistent tubular injury months after an episode of mild to moderate AKI.

Funding: NIDDK Support

---
PTH levels fell modestly from V0 to V3, whereas there was no difference in non-AKI patients.

Conclusions: Markers of dysregulated mineral metabolism and inflammation are elevated during an episode of AKI; among these biomarkers, FGF-23 remains elevated months later. This raises the possibility that persistently dysregulated mineral metabolism may link AKI to adverse outcomes after hospital discharge.

Funding: NIDDK Support

**FR-PO076**

A Novel Biomarker for Detecting Both AKI and CKD

**Background:**

Early diagnosis of AKI and CKD undoubtedly will have a potential impact on the treatment of these pathologies and on the kidney health. This study was designed to provide a suitable method for overcoming the limitations of the procedures or methods previously used for the AKI and CKD diagnosis.

**Methods:**

Abnormal presence of serpinA3K in urine samples from animals with CKD was identified by mass spectrometry. We evaluated the urinary serpinA3K in rats and in patients with AKI, as well as, the temporal course of serpinA3K presence during the AKI to CKD transition and in urines from patients previously diagnosed with CKD by renal biopsy and without renal dysfunction. For AKI model, 44 Wistar rats were divided in different periods of reperfusion: 3, 6, 9, 12, 18, 24, 48, 72, 96, or 120 h after renal bilateral ischemia (45 min) and compared to sham-operated rats; in addition, 20 rats were studied to evaluate different renal injury severity induced by 15, 30, 45 or 60 min of ischemia. For CKD model, 36 rats were divided in: sham operated (S) or nephrectomy plus renal ischemia of 45 min (UNx/1B) groups; these rats were studied 1, 2, 3, or 4 months. Mean arterial pressure, creatinine clearance, and renal blood flow were determined. Urinary serpinA3K was evaluated in all these rats and in the urines from patients diagnosed with AKI or CKD.

Results: SerpinA3K was not detected in the urines from sham rats or healthy volunteers. In contrast, serpinA3K appeared in the rat urines and it increased proportionally to the AKI severity. This protein was detected since 3 h post-ischemia. Accordingly, abnormal urinary serpinA3K was found in patients with AKI. After 4 months, BUN and creatinine reached 2.6-fold and 2.25-fold higher levels compared to WT mice. Immunohistological examination showed mild tubular injury in 36h AKI KO mice. 36h IL-36R'p levels were increased after IRI, and 36h was expressed in lymphocytes and renal tubular cells, but post-IRI mRNA levels of IL-6 and TNF-α were low in 36h AKI KO mice. We found that IL-36 expression over nonresistant renal tubular-resident cells, but not hematopoietic bone marrow-derived cells, was essential for IRI pathology by bone marrow chimeras experiments. In primary cultures of renal tubular epithelial cells, IL-36α treatment upregulated NF-κB activity and Erk phosphorylation. Notably, in AKI patients, urine IL-36α levels were increased, and IL-36α staining in renal-biopsy samples was enhanced.

Conclusions: Our results demonstrate that IL-36α is upregulated in renal tissues in both mouse and human AKI, and that IL-36α stimulates NF-κB and Erk pathways and might induce cytokines such as IL-6 and TNF-α in AKI. Thus, IL-36α/IL-36R blockade could serve as a potential therapeutic target in AKI.

**FR-PO077**


**Background:**

The early diagnosis of AKI and CKD undoubtedly will have a potential impact on the treatment of these pathologies and on the kidney health. This study was designed to provide a suitable method for overcoming the limitations of the procedures or methods previously used for the AKI and CKD diagnosis.

**Methods:**

Abnormal presence of serpinA3K in urine samples from animals with CKD was identified by mass spectrometry. We evaluated the urinary serpinA3K in rats and in patients with AKI, as well as, the temporal course of serpinA3K presence during the AKI to CKD transition and in urines from patients previously diagnosed with CKD by renal biopsy and without renal dysfunction. For AKI model, 44 Wistar rats were divided in different periods of reperfusion: 3, 6, 9, 12, 18, 24, 48, 72, 96, or 120 h after renal bilateral ischemia (45 min) and compared to sham-operated rats; in addition, 20 rats were studied to evaluate different renal injury severity induced by 15, 30, 45 or 60 min of ischemia. For CKD model, 36 rats were divided in: sham operated (S) or nephrectomy plus renal ischemia of 45 min (UNx/1B) groups; these rats were studied 1, 2, 3, or 4 months. Mean arterial pressure, creatinine clearance, and renal blood flow were determined. Urinary serpinA3K was evaluated in all these rats and in the urines from patients diagnosed with AKI or CKD.

Results: SerpinA3K was not detected in the urines from sham rats or healthy volunteers. In contrast, serpinA3K appeared in the rat urines and it increased proportionally to the AKI severity. This protein was detected since 3 h post-ischemia. Accordingly, abnormal urinary serpinA3K was found in patients with AKI. After 4 months, BUN and creatinine reached 2.6-fold and 2.25-fold higher levels compared to WT mice. Immunohistological examination showed mild tubular injury in 36h AKI KO mice. 36h IL-36R'p levels were increased after IRI, and 36h was expressed in lymphocytes and renal tubular cells, but post-IRI mRNA levels of IL-6 and TNF-α were low in 36h AKI KO mice. We found that IL-36 expression over nonresistant renal tubular-resident cells, but not hematopoietic bone marrow-derived cells, was essential for IRI pathology by bone marrow chimeras experiments. In primary cultures of renal tubular epithelial cells, IL-36α treatment upregulated NF-κB activity and Erk phosphorylation. Notably, in AKI patients, urine IL-36α levels were increased, and IL-36α staining in renal-biopsy samples was enhanced.

Conclusions: Our results demonstrate that IL-36α is upregulated in renal tissues in both mouse and human AKI, and that IL-36α stimulates NF-κB and Erk pathways and might induce cytokines such as IL-6 and TNF-α in AKI. Thus, IL-36α/IL-36R blockade could serve as a potential therapeutic target in AKI.
Vancomycin-Associated AKI

Greta G. Gyarmati,1 Praveen Kumar Potukuchi,1 Oguz Akbiligic,1 Melissa Soocho,2 Elani Streja,1 Keichi Suzuki,1 Kamary Kalantar-Zadeh,2 Miklos Z. Molnar,2 Csaba P. Kovedsy,2 *Nephrology Center, Toranomon Hospital Kajigaya, Kawasaki, Japan; 1University of California Irvine, School of Medicine, Orange, CA; 2University of Texas Health Science Center, Memphis, TN.

Background: Vancomycin is a tricyclic glycopeptide antibiotic that is currently the mainstay of therapy for serious infections due to methicillin-resistant staphylococcus. Data on the nephrotoxic potential of this agent is still highly controversial and based on small studies and meta-analyses.

Methods: From a nationally representative cohort of 35,500 US veterans with baseline eGFR ≥60 ml/min/1.73m², we identified 40,059 patients who received either intravenous vancomycin (N=24,461) or nonglycopeptide antibiotics (linezolid/daptomycin, N=15,598). We matched patients in the two groups by propensity scores calculated from patient demographics, comorbidities, baseline eGFR and mean arterial pressure, and nephrotoxic medication exposure. Associations of vancomycin vs. nonglycopeptides with the risk of incident AKI by AKIN stages was assessed in logistic regression models.

Results: Among 27,964 propensity-matched patients (13,982 in both groups), the mean age was 66±11 years and the mean baseline eGFR was 72 ml/min/1.73m², 97% were male, 20% African-American, 51% diabetic, 27% had CHF and 8% had vasopressors. Baseline characteristics were identical in patients receiving vancomycin and nonglycopeptides. There were a total of 2,656 (19%) AKI events in the vancomycin group and 2,814 (20%) in the nonglycopeptide group. AKI stage 1 was less common, but stage 2 and 3 were more common among patients on vancomycin (Figure). The odds ratios of AKI stages 1, 2 and 3 in patients on vancomycin vs. nonglycopeptides were 0.83 (0.78-0.89), 1.02 (0.90-1.15) and 1.71 (1.44-2.03), respectively.

Conclusions: Vancomycin use is associated with a higher risk of severe AKI.

Preoperative Renin-Angiotensin System Inhibitors Increased AKI after Noncardiac Major Surgery

Hyunjong Cho,1 Seokwoo Park,2 Sejoong Kim,1 Dong Ki Kim,1 Kook-Hwan Oh,2 Kwon Woock Jou,1 Yon Su Kim,1 Hajoong Lee,1 1Seoul National University Bundang Hospital, Seongnam, GYEONGGI-DO, Republic of Korea; 2Seoul National University College of Medicine, Seoul, Republic of Korea; 3Seoul National University Hospital, Jongno-gu, SEOUL, Republic of Korea.

Background: Many conflicting results have been reported on the association between preoperative renin-angiotensin system (RAS) inhibitors and postoperative acute kidney injury (AKI). In this study, we evaluated the impact of RAS inhibitors on postoperative AKI and mortality after noncardiac major surgery.

Methods: We analyzed a retrospective cohort of 50,897 adult patients (age≥18) underwent noncardiac major surgery from 2004 to 2013. Major surgery was defined as surgery duration more than 1 hour. Patients with chronic kidney disease (CKD) 5, nephrectomy and kidney transplantation were excluded. The primary outcome was postoperative AKI defined by the KDIGO creatinine criteria and initiation of dialysis within 14 days of surgery. The secondary outcomes were all-cause mortality within 30 days of surgery and length of hospital stay. Propensity scores matching and multivariable logistic regression analyses were performed.

Results: We included 17,000 patients (age=71±14 years, 41% female) who underwent 17,000 procedures. The mean age was 65±11 years, 47% were males and 48% had a history of hypertension. The overall AKI rate was 21.5% with 20.0% in the RAS inhibitor group. The RAS inhibitor group had a higher AKI rate by AKIN stages 1, 2 and 3 stages compared to the non-RAS inhibitor group (12.6%, 16.3%, 26.0% vs. 11.4%, 14.2%, 23.4%, p<0.001). The AKI risk was higher in the RAS inhibitor group with baseline eGFR <60 ml/min/1.73m² (HR=1.30, 95%CI [1.18, 1.43], p<0.001) and <30 ml/min/1.73m² (HR=3.21, 95%CI [2.33, 4.41], p<0.001). The 30-day mortality rate was 0.6%, with no significant difference between RAS inhibitor use and non-RAS (5.8% vs. 8.8%, p=0.14).

Conclusions: This large cohort study demonstrates that preoperative RAS inhibitors were associated with a higher risk of AKI, but not mortality. Withholding preoperative RAS inhibitors should be considered in the perioperative setting.

Factors Associated with the Development of AKI in Patients Treated with Tenofovir Disoproxil Fumarate – The AKIT Study

Adrian Liew,1,2 Ru S. Lim,1 See Cheng Yeo.1 1Renal Medicine, Tan Tock Seng Hospital, Singapore, Singapore; 2Lee Koo Chian School of Medicine, Nanyang Technological University-Imperial College London, Singapore.

Background: Acute kidney injury (AKI) from renal tubular mitochondrial toxicity had been reported with Tenofovir Disoproxil Fumarate (TDF) treatment. Whilst impaired mitochondrial function had been consistently found associated with TDF-related AKI studies looking at other predictors for renal dysfunction had demonstrated conflicting results. The current study aims to determine the risk factors for the development of AKI in the largest known cohort of Asian patients undergoing TDF treatment for HIV and/or Hepatitis B (HBV).

Methods: This is a retrospective cohort study of 1,700 patients treated with TDF from 2006-2015. AKI was identified using KDIGIO definition, and time to AKI was defined as time from TDF initiation to renal dysfunction or when censored. Risk factors for AKI were compared using Cox regression, between patients who developed AKI and in whom renal function remained stable.

Results: Of the 1,700 patients in the study population (87% Male, 75% Chinese, Age 44.5±12.6 years), TDF was initiated for treatment of HIVB (n=185; 10.8%), HIV (n=1412; 83.1%), or HBV/HIV co-infection (n=103; 6.1%). AKI occurred in 226 (13.3%) patients, with a median time to AKI of 23.5 months. Risk factors for AKI included older age (HR=1.028, 95%CI [1.016, 1.039], p<0.001), lower weight (HR=0.984, 95%CI [0.974, 0.993], p=0.004), diabetes (HR=2.000, 95%CI [1.405, 2.849], p<0.0001), hypertension (HR=1.823, 95%CI [1.349, 2.464], p<0.001), Charlson score (HR=1.217, 95%CI [1.104, 1.342], p<0.001), use of ACE-inhibitors (HR=2.125, 95%CI [1.420, 3.180], p=0.001) and diuretics (HR=2.894, 95%CI [1.484, 5.643], p<0.002), and lower CD4 counts (HR=0.997, 95%CI [0.996, 0.998], p<0.0001). A lower baseline serum creatinine below 75µmol/L appears to be protective (HR=0.936, 95%CI [0.924, 0.948], p<0.001) whilst creatinine levels above 75µmol/L increases the risk of AKI (HR=1.012, 95%CI [1.006, 1.018], p<0.001).

Conclusions: AKI is not uncommon with TDF use. The incidence and association with impaired baseline renal function are consistent with published literature, though the threshold creatinine level of 75µmol/L is a new finding. Predictors of a frail health state and factors that may affect baseline renal function appears to increase the risk of AKI. The use of ACE inhibitors and diuretics with TDF-associated AKI requires further investigation.

Utility of a Vascularized Microphysiological 3D Model of Human Kidney Proximal Tubule for Predictive Tenofovir Toxicity Testing

Ranita S. Patel,1 Jennifer Hommelfarb,2 Edward J. Kelly.3 1Kidney Research Institute, Seattle, WA; 2University of Washington, Seattle, WA; 3Seattle Children’s Hospital, Seattle, WA.

Background: Tenofovir is a nucleotide reverse transcriptase inhibitor indicated for the treatment of HIV/AIDS and chronic hepatitis B and used worldwide. Despite its widespread use, nephrotoxic side effects of tenofovir remain a concern. Following exposure to tenofovir in animal and human subjects, clinical markers of kidney injury are increased and associated pathophysiological changes in the kidney proximal tubule are observed. Since tenofovir enters proximal tubule cells via organic anion transporters (OAT) localized to the basolateral membrane and because cells in 2-dimensional cultures often fail to polarize, in vitro cellular toxicity studies have been unsuccessful.

Methods: Primary: Human proximal tubule cells (PTC) and human umbilical vein endothelial cells (HUVECs) were cultured in dual channel 3-dimensional microphysiological systems (MPS) to simulate a vascularized proximal tubule for evaluation of tenofovir-induced toxicity. Probedenec, an OAT competitive inhibitor, was added to the HUVEC (vascular) channel in select MPS to assess its role in attenuating tenofovir and toxicity. Additional markers were used to determine the severity of cellular damage: heme oxygenase-1 (HO-1) signal intensity was quantified following immunocytochemistry and kidney injury molecule-1 (KIM-1) injury molecule-1 (KIM-1) effluent concentrations were measured by ELISA.

Results: Exposure of MPS cultured PTCs from three different tissue donors to 10µM tenofovir for 48 hours induced a 0.9-fold, 4-fold, and 7-fold rise in KIM-1 expression. When 2nm probenecid was concurrently added to the MPS vascular channel, only a 0.5- fold and 2-fold rise in KIM-1 expression is observed. Exposure of MPS cultured PTCs to 10µM probenecid for 5 days resulted in HO-1 signal intensity 1.8 times that of controls.

Conclusions: These results suggest that our dual channel MPS can function as an ideal ex vivo model to investigate transporter-dependent toxicity. Future efforts include directly inhibiting tenofovir toxicity with the OAT-1 inhibitor probenecid in both HUVEC and PTC channels to affect both basolateral membrane OATs and apical membrane MRP transporters. Additionally, measurement of drug concentration differentials across HUVEC and PTC channels can confirm active tubular transport since the HUVEC channel acts as a surrogate capillary for tenofovir infusion.

Funding: Other NIH Support - U19TR005094
FR-PO084
Supertherapeutic Vancomycin Levels: Risk Factors and Outcomes
Reza Zonoz,1 Aozhou Wu,2 Jung-Im Shin,2 Alex M. Secora,2 Josef Coresh,2 Alex R. Chang,4 Morgan Grans.3 1Department of Medicine, The Johns Hopkins University, Baltimore, MD; 2Department of Epidemiology, The Johns Hopkins University, Baltimore, MD; 3Geisinger Medical Center, Danville, PA.

Background: Vancomycin is a commonly administered intravenous (IV) antibiotic, and supertherapeutic levels of vancomycin may be an avoidable cause of nephrotoxicity. The objective of this study was to investigate the frequency of, risk factors for, and outcomes after elevated levels of vancomycin.

Methods: There were 31,316 hospitalizations in which IV vancomycin was given between 2008 and 2014 among 21,166 people in the Geisinger Health System, a large, integrated, tertiary, rural health care system.

Results: There were 12,713 hospitalizations with vancomycin monitoring, and 1.24% of these hospitalizations had a vancomycin level ≥50 mg/L. Among hospitalizations with ≥7 days duration of therapy, 2.65% had a vancomycin level ≥50 mg/L. The risk of vancomycin levels ≥50 mg/L was higher with younger age, female sex, black race, prehospitalization diuretic use, an ICU stay, sepsis, concurrent use of piperacillin-tazobactam, and higher doses of vancomycin (Table). Neither BMI nor eGFR was associated with vancomycin levels ≥50 mg/dL in adjusted analysis. Length of stay, acute kidney injury (AKI), and in-hospital mortality were all higher among persons with vancomycin levels ≥50 mg/L.

Conclusions: We identified modifiable risk factors for Vancomycin levels ≥50 mg/L, which were associated with greater in-hospital mortality, AKI, and length of stay.

Funding: NIEDK Support

FR-PO085
Proton Pump Inhibitor Use and Risk of AKI: A Meta-Analysis of Observational Studies
Yi Yang,1 Gang Xu,2 Shiwang Ge,1 Tongji Hospital, Huazhong University of Science and Technology, WUHAN, China; 2Tongji Hospital, Tongji Medical College, Huazhong Univ of Science and Technology, WUHAN, China; 3Tongji hospital affiliated to Tongji medical college, Huazhong University of Science and Technology, Wuhan, Hubei, China, Wuhan, China.

Background: Recent studies have suggested a potential increased risk of acute kidney injury (AKI) among proton pump inhibitor (PPI) users. However, the present results are conflicting. Thus, we performed a meta-analysis to investigate the association between PPI therapy and the risk of AKI.

Methods: EMBASE, PubMed, Web of Science and Cochrane Library databases (up to September 23, 2016) were systematically searched for any studies assessing the relation between PPI use and risk of AKI. Studies that reported relevant relative risks (RRs), odds ratios or hazard ratios were included. We calculated the pooled relative risks (up to September 23, 2016) were systematically searched for any studies assessing the association between PPI therapy and the risk of AKI.

Results: Seven observational studies (five cohort studies, two case-control studies) were identified and included, and a total of 513,696 cases of PPI use among 2,404,236 participants were included in the meta-analysis. The pooled adjusted RR of AKI in patients with PPI use was 1.61 (95% CI, 1.16–2.22; 7–98.1%). Furthermore, higher risks of AKI were found in several subgroups of cohort studies, participant’s average age <60 years, participants with or without baseline PPI excluded, sample size <300,000, and number of adjustments ≤11. Subgroup analyses revealed that participants with or without baseline PPI excluded might be a source of heterogeneity.

Conclusions: PPI use could be a risk factor for AKI and should be administered carefully. Nevertheless, modulating factors might impact the outcomes. More well-designed prospective studies are needed to clarify the association.

Funding: Government Support - Non-U.S.

FR-PO086
Renal Toxicities of Agents Used for CLL
Rima Wanchop,2 Vipulbhui Sakhuja,1 John F. Katselos,3 Nishita Parikh,2 Carolina Bernabe,4 Jacqueline Barrientos,1 Kenar D. Jhaveri.2 1CLL Research and Treatment Center, Lake Success, NY; 2Nephrology, Hofstra Northwell School of Medicine, GREAT NECK, NY; 3Hofstra Northwell School of Medicine, Lake Success, NY.

Background: Drugs with novel mechanisms of action and targeted therapies are being explored in both the pre-clinical and clinical settings for chronic lymphocytic leukemia (CLL). A possible limiting complication for these agents could be their nephrotoxic potential.

Methods: We reviewed the FDA adverse event reporting system (FAERS) quarterly legacy data file 3rd quarter of 2014 to 2nd quarter of 2017 for all reported nephrotoxicity. We compared renal toxicities of the newer agents such as ibrutinib, idelalisib, obinutuzumab, and venetoclax (older targeted agents such as alemtuzumab and ofatumumab).

Results: The table here summarizes the drugs studied and results found. Olufatamab, alemtuzumab and rituximab were the top three offenders with AKI as the most common finding reported followed by TLS and hypomagnesemia. The newer agents used to treat CLL had fewer renal toxicities than the older agents. The mechanism of AKI is likely related to TLS in most of these agents. The literature reviewed in the FAERS reported additional toxicities of the newer agents such as TLS with venetoclax that was fatal leading to early trial modifications.

Conclusions: Novel targeted agents are changing the CLL treatment paradigm with ensuing reports of nephrotoxic events such as AKI and TLS. As these drugs become more widely used, knowledge of novel agents used in CLL and their possible renal toxicities is important for the practicing nephrologists and the hematologists.

Table

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept</td>
<td>0 0 0 0 0 0 0 3 3</td>
</tr>
<tr>
<td>Hemantrumglide</td>
<td>0 0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>Rituximab</td>
<td>0 0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>Olsatumab</td>
<td>0 0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>0 0 0 0 0 0 0 0 0</td>
</tr>
</tbody>
</table>

Funding: Government Support - Non-U.S.

FR-PO087
AKI in Heart Failure Hospitalizations – National Trends and Outcomes
Ankit Sakhuja, Kianoush Banaei-Kashani, Robert C. Albright. Mayo Clinic, Rochester, MN.

Background: Heart failure (HF) is an important cause of morbidity and mortality. Dialysis requiring acute kidney injury (AKI-D) is associated with worse outcomes in HF, however, longitudinal trends of AKI-D and its impact on mortality are unclear.

Figure 2 association between proton-pump inhibitors use and risk of acute kidney injury
Methods: Using Nationwide/National Inpatient Sample from years 2000-2014, we identified patients with primary discharge diagnosis of HF and those with AKI-D by ICD-9-CM codes. We used linear regression to assess trends of AKI-D and multivariable regression models to estimate adjusted odds of AKI-D and mortality over time. Model for AKI-D was adjusted for patient age, sex, race, payer, admission day, history of peripheral vascular disease, coronary artery disease, hyperlipidemia, stroke, diabetes, chronic kidney disease, hypertension, presence of cardiogenic shock, use of balloon pump, mechanical ventilation, hospital location, teaching status, volume, bed-size and region. Model for mortality was also adjusted for AKI-D and interaction between year and AKI-D. Results: Of 15,092,707 HF hospitalizations, 149,468 (0.99%) had AKI-D. Patients with AKI-D were <80 years old (77% vs 60.5%; p<0.001), males (55.6% vs 47.8%; p=0.001) and whites (70.5% vs 60.0%; p=0.001). Incidence of AKI-D increased from 0.5% in 2000 to 1.5% in 2014 (p<0.001 for trend). Odds of developing AKI-D steadily increased to nearly 4 times by year 2014 (Fig 1a). Though, odds of mortality due to AKI-D decreased steadily, AKI-D continued to be independently associated with 3.67 times higher mortality even by year 2014 (Fig 1b).

Conclusions: AKI-D is seen in about 1% HF hospitalizations, however, the risk of AKI-D in these admissions on the rise. Though the impact of AKI-D on mortality is decreasing, it is still a significant risk factor for mortality in HF admissions.

FR-PO089
Multicenter Evaluation of the Selective Cytopheretic Device (SCD) in Critically Ill Children Requiring CRRT: Report from the First 4 Patients
Stuart Goldstein,1 David T. Selewska,1 David J. Askennazi,1 Patrick D. Brophy,1 Theresa A. Mottes,1 Tara C. Trerell,1 Matthew L. Paden,1 H. David Humes.2
1Prospective Pediatric AKI Research Group, Cincinnati, OH; 2University of Michigan Medical School, Ann Arbor, MI

Background: Critically ill children and adults who develop AKI requiring CRRT are at increased risk of death. In a randomized trial, adult pts on CRRT treated with the SCD, who maintained CRRT-SCD circuit ionized Ca (Ca2+) <0.4 mmol/L, had improved survival/dialysis independence. An CRRT-SCD circuit iCa< 0.4 mmol/L promotes an immunomodulatory effect in animal models of inflammation. We are conducting an FDA grant sponsored safety evaluation of the SCD in 16 critically ill children and report our experience with the first 4 treated patients.

Methods: 5 center US study of the SCD in children (>20 kg, ≥2 years) with AKI and multi-organ failure receiving CRRT as part of standard of care. The SCD is integrated into the CRRT circuit post CRRT membrane (Figure), changed daily, and CRRT-SCD circuit iCa has been maintained <0.4 mmol/L. Pts receive SCD treatment for up to 7 days or CRRT discontinuation, whichever comes first.

Results: 4 pts (2F/2M) were enrolled since 12/2016 and completed SCD therapy. Age range = 12.5-17.5 years, PRISM-2 Score range = 2-14. Admission diagnoses were severe rhabdomyolysis(1), septic shock(1) STEC HUS(1) and pneumonia(1). Pts received 3 (1), 4 (1) and 7 (2) days of SCD therapy. Circuit iCa has been maintained at <0.4 mmol/L in 95% of assessments. All pts survived and were off RRT at hospital discharge. No SCD-related serious adverse events occurred. Evidence of hemolysis (increased LDH, thrombocytopenia) reversed within 24 hours of SCD therapy in the 2 pts with hemolysis and CRRT initiation, whichever comes first.

Conclusions: Our initial data suggest the SCD is safe in children. While we cannot make any efficacy claims, the unexpected early reversal of hemolysis in 2 pts may suggest a role for the SCD in mitigating leukocyte related endothelial damage.

Funding: Other NIH Support - FDA Orphan Device Grant
FR-PO090

Low-Density Lipoprotein Receptor-Related 2 (Megalin) as Target Antigen in Human Kidney Anti-Brush Border Antibody Disease Claire Trivin-Avillac,1 Christopher P. Larsen,2 Paige A. Coles,1 A. Bernard Collins,3 Michael Merchant,3 Hong Ma,1 Daniel W. Wilkey,4 Josephine M. Ambruzzi,4 Nidia C. Messias,2 Nicholas Cossey,1 Ivy A. Rosales,1 Thomas D. Wooldridge,1 Patrick D. Walker,2 Robert B. Colvin,3 Jon B. Klein,4 David J. Salant,4 Laurence H. Beck,1 Boston University Medical Center, Boston, MA; 2Arkana Laboratories, Little Rock, AR; 3Massachusetts General Hospital, Boston, MA; 4University of Louisville Medicine, Louisville, KY; 5Nephrology & Hypertension Associates, LTD, Tupelo, MS; 6Nephrology Associates, PLC, Little Rock, AR.

Background: Acute kidney injury (AKI) has a broad differential diagnosis. Autoimmune diseases against glomerular antigens are well recognized but tubular injury as a result of direct immunologic insult is not part of the routine evaluation. We report a cohort of patients with a distinct, underappreciated kidney disease characterized by kidney anti-brush border antibodies and renal failure (ABBA disease).

Methods: Ten cases of ABBA disease were identified that had a combination of proximal tubule damage, IgG-positive immune deposits in the tubular basement membrane, and circulating antibodies reactive with normal human proximal tubular brush border. Immunoblotting of a protein extract from human tubular cells was performed with serum from cases and controls, and immunoprecipitation followed by mass spectrometry was used to identify the protein targeted by the anti-brush border antibodies. Cell expression of recombinant protein followed by immunoblotting and immunoprecipitation was used to confirm the identity of the antigen.

Results: Patients with ABBA disease were elderly (mean age 72.9 years), presented with acute kidney injury (median serum creatinine 4.0 mg/dl) and moderate proteinuria. The kidney biopsy showed acute tubular injury with apical cytoplasmic blebbing, loss of brush border, regenerative changes and granular IgG and C3 deposits along tubular basement membranes. All patient sera were reactive to the proximal tubular brush border on sections of normal human kidney. Serum from all patients but not controls recognized a high molecular weight protein in renal tubular protein extracts that was identified as low-density lipoprotein receptor-related 2 (LRP2) by immunoprecipitation and mass spectrometry. Recombinant expression of an N-terminal recombinant fragment of LRP2 was used to confirm this finding by Western blot and immunoprecipitation. LRP2 specifically co-localized with IgG in the tubular immune deposits.

Conclusions: We present the first case series detailing the clinicopathologic findings of patients with ABBA disease and show that the antigenic target of these autoantibodies is LRP2.

Funding: NIDDK Support

FR-PO091

AKI in Pregnancy and the Puerperium Catherine Brumby, Graeme Duke, Elizabeth Low, Lawrence P. McMahon. Eastern Health Clinical School, Monash University, Melbourne, VIC, Australia.

Background: Acute kidney injury (AKI) either during pregnancy or postpartum is associated with significant maternal and neonatal morbidity. Past population-based studies (1999-2011) in US and Canada suggest the incidence may be increasing, with contributing factors including increasing rates of hypertensive disorders of pregnancy (HDP) and CKD. We aim to determine recent developments in this apparent trend.

Methods: All public hospital admissions with pregnancy >20 weeks gestation in Victoria, Australia (2006-2016) were identified by ICD-10 diagnostic codes from a validated administrative database. Analysis included 560,778 antenatal and postpartum admissions, of which 533,876 included delivery. Trends in AKI incidence and associated contributing factors including increasing rates of hypertensive disorders of pregnancy (HDP) and CKD were examined.

Results: The incidence of AKI per 10,000 deliveries rose from 2.37 in 2006 to 11.59 in 2016, p<0.001. Of the 499 AKI cases, 228 (45.6%) also had CKD, 22 (4.4%) required renal replacement therapy, and 3 (0.6%) died. The strongest risk factors associated with AKI were CKD, HDP, and diabetes, and critical care admission. After adjustment, the temporal relationship for AKI risk was maintained, with risk factors being CKD, HDP, diabetes, and critical care admission. Due to their highly oxidative metabolism, proximal tubule cells utilize fatty acids to generate the energy required for their specific function. We hypothesized that enhancing fatty acid oxidation (FAO) with a PPARβ agonist will restore mitochondrial function and offer a potential therapeutic treatment for AKI.

Funding: NIDDK Support

FR-PO092

MA-0204 Modulation of PPARβ Promotes Recovery after AKI in Normal and Aged Proteinuric Diabetic CKD Zsf1 Rats by Enhancing Fatty Acid Oxidation in Proximal Tubular Epithelial Cells Christian Broeck,1 Katelyn Pulito,2 Jeff H. Stanwix,2 Hien G. Hoang,2 Silvia B. Campos-bilderbacker,3 Ruben M. Sandoval,4 Bruce A. Molitoris,3 Effie Tozzo,3 Indiana University School of Medicine, Indianapolis, IN; 2Mitobridge, Cambridge, AL.

Background: Ischemic acute kidney injury (AKI) is characterized by persistent proximal tubule mitochondrial dysfunction. Due to their highly oxidative metabolism, proximal tubule cells utilize fatty acids to generate the energy required for their specific function. We hypothesized that enhancing fatty acid oxidation (FAO) with a PPARβ agonist will restore mitochondrial function and offer a potential therapeutic treatment for AKI.

Methods: Human hTERT RPTECs were treated with MA-0204 and analyzed for PPARβ target gene expression and their ability to utilize palmitate. Sprague-Dawley (SD) rats were treated with ischemia-reperfusion (IR) and AKI was treated orally with 30 mg/kg PPARβ modulator MA-0204 for 2 days. EPO served as positive control and was dosed IV at 1000 U/kg 30 minutes prior to ischemia. 10 AKI were also tested in this hypothesis in aged (18 week old), diabetic and proteinuric CDK Zsf1 rats, a phenotype that presents with similar comorbidities as diabetic-chronic kidney disease (CKD) patients.

Results: MA-0204 significantly increased expression of PPARβ-target genes associated with mitochondrial FAO (such as Cytochrome oxidase 4 (COX4) and increased palmitate oxidation in RPTECs. In rats, MA-0204 treatment significantly reduced plasma creatinine (69%), BUN (62%), fractional excretion of Na+ (82%) and restored creatinine clearance (99%) in severe burn. 645/688 patients were excluded. AKI was defined by Scv,K/DIGO criteria. The onset of AKI a7 days vs a7 days from ICU admission were used to define early vs late AKI, respectively. Patient- and burn-specific characteristics among those with or without AKI were compared. Multivariable logistic regression with AKI as the independent variable and hospital mortality as the dependent variable was utilized.

Results: 1040 patients with thermal injury were included in the study. Mean (SD) age was 43.9±18.9, 70.5% were men and 16.4% black. The median total body surface area (TBSA) of burn was 16% (IQR: 6-29%). AKI was present in 617 (59%) patients, KDIGO stages: 1: 59.3%, 2: 20.3%, 3: 11.3%, 3D: 9.1%. Early AKI was present in 551/617 (89%) of patients. Patients with AKI had larger TBSA burn (median 20.5% vs 11.0%, p<0.001), received more mechanical ventilation days (median 2.0 vs 0.0, p<0.001), and stayed longer in the hospital (median 21.0 vs 10.0 days, p<0.001). Hospital mortality was higher in those with AKI vs those without AKI: 19.7% vs 4% (p<0.001) and increased by each KDIGO stage (p-trend<0.001). AKI was independently associated with hospital mortality.

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

423
Biomarkers, Seattle, WA; 2Randox Teoranta, Dungloe, Ireland; 3Randox

FR-PO094 TissueFAXS Analysis as an Experimental Tool for Assessing the Degree of Intrarenal Lymphocytes Infiltration and Their Impact on AKI Recovery in Cynomolgus Monkeys

Methods: A total of 10 cynomolgus monkeys with various renal function were included. Kidney samples for flow cytometry analysis of KMNCs and immunohistochemistry were collected simultaneously. Flow cytometry analysis of KMNCs was performed using the TissueFAXS verse. Immunohistochemistry of CD3, CD20, and CD45 on formalin-fixed kidney tissues were performed and followed by TissueFAXS analysis. The proportion of lymphocytes positive for each CD marker was set using different distributions as a follows: kidney mononuclear cells isolated with percoll in flow cytometry vs. all nucleated cells stained with hematoxylin in tissueFAXS. Linear regression analysis was used to compare the association between CD3, CD20, and CD45 (+) lymphocytes measured with two different methods.

Results: Flow cytometry and tissueFAXS analyses showed positive correlation with CD3 and CD45+ lymphocytes (R=0.4587, P=0.0296). There was a positive correlation between the proportion of both CD3 (+) T cells (R=0.8120, P=0.0002) and CD20 (+) B cells (R=0.4587, P=0.0650). The ratio of CD3 (+) T cells and CD20 (+) B cells measured with both methods also showed positive correlation (R=0.5144, P=0.0296).

Conclusion: Our data showed significant positive correlation of intrarenal CD3, CD20, and CD45 (+) lymphocytes measured with flow cytometry and tissueFAXS in cynomolgus monkeys. These results suggest that immunohistochemistry followed by tissueFAXS analysis may be used as a diagnostic tool performing semiquantitative evaluation of intrarenal lymphocytes in patients.

FR-PO095 AKI Detection Using a Novel 5-Plex Panel Candace M. Adamo1, Timothy H. Carlson,2 Eibhlin M. Mccole, Marie McGarvey,2 Christine M. Hargarten,1 Peter Fitzgerald,1 John Lamont1,2 Amar Sethi1,2 Pacific Biomarkers, Seattle, WA; 3Randox Toranta, Dungloe, Ireland; 4Randox Laboratories Limited, Crumlin, United Kingdom.

Background: Acute kidney injury (AKI) is classified using serum creatinine and urine output. However, since creatinine is a lagging index of impending AKI, studies are focused on estimated glomerular filtration rate (eGFR). Some recent interventional studies of the adverse long-term renal consequences of AKI have almost exclusively focused on traditional risk factors for kidney disease.

Methods: Random Biochip Array technology was used to develop a multiplex immunnoassay panel for the below biomarkers. Performance goals for the multiplex were established by testing >100 subjects using the predicate ELISA methods for KIM-1, NGAL, cystatin C, clustatin and osteopontin (OPN). Functional sensitivity, cross-reactivity, and interference were assessed, along with a sample correlation in 30 subjects.

Results: The 1000 patient samples provided dynamic ranges of 3.1-4000pg/mL for NGAL; 1-100ng/mL for KIM-1; 1.5-150ng/mL for Clustatin; 10-100ng/mL for OPN; 80-8000ng/mL for KIM-1, NGAL, cystatin C, clustatin and OPN, respectively. The functional sensitivity was confirmed for all analytes at low end of the dynamic range as the precision of the lowest non-zero standard was <20%CV for all five biomarkers (n=6). The effective upper limits of measurement, determined by calculating precision of the highest standard were <10%CV. There was a significant cross-reactivity (~15% cross reactivity or <10% interference) for any of the analyses when spiked with x10 concentration of the highest standard of the other independent proteins. Cross-reactivity from non-protein samples were tested for cystatin C, clustatin and OPN showing significant cross-reactivity. Method comparison between the two methods provided correlations (r) of 0.927; 0.962; 0.872; 0.812; 0.899 for KIM-1, NGAL, cystatin C, clustatin and OPN, respectively. Slopes were 0.994, 0.544, 0.636, 1.67, and 0.685, respectively.

Conclusion: The AKI multiplex panel simultaneously detects KIM-1, NGAL, cystatin C, clustatin and OPN, with a solid performance and improved dynamic ranges compared to the predicate ELISA methods. This multiplex panel provides a robust and cost-effective solution for detecting AKI in, not only clinic trials, but potentially also in kidney patients for appropriate use.

Funding: Commercial Support - Pacific Biomarkers, Randox Laboratories

FR-PO096 Clinical Factors Associated with Progression from Acute Mesoamerican Nephropathy to CKD Rebecca S. Fischee, Baylor College of Medicine, Houston, TX.

Background: Greater than 20,000 deaths in Central America have been attributed to the epidemic of Mesoamerican nephropathy (MeN). Men is a mysterious kidney disease of unknown etiology that disproportionately affects young agricultural workers working in the regional risk factor for MeN. Men have been characterizing a chronic kidney disease (CKD) until we recently documented an acute clinical scenario, characterized by acute kidney injury (AKI) with interstitial nephritis and markers of systemic inflammation, namely neutrophilic leukocytosis and leukocyturia. We also observed that some patients, but not all, progressed to CKD.

Methods: We conducted an analysis to identify clinical characteristics of acute MeN that predict progression to CKD. Using univariate analysis, we compared patients with acute MeN who developed CKD to those who did not identify clinical risk factors for progression at a private practice in Nicaragua completed case reports detailing acute clinical encounters on cases of MeN and guided follow-up data on subsequent CKD diagnoses.

Results: From Feb 2015-Jan 2017, 408 cases of acute MeN were reported, mostly males (91%) and young (median age 27 yrs). Most (92%) had acute kidney injury (AKI). Frequent acute symptoms were fever (62%), nausea/vomiting (72%), back pain (61%), and headache (52%). Leukocytosis (80%), neutrophilia (84%), lymphopenia (53%), elevated C-reactive protein (76%), and anemia (59%) were common, along with leukocytosis (99%) and leukocyte counts (30.2%) in urine. 30 patients (6%) progressed rapidly (median 9 days) to CKD, with half (51%) progressing to a Stage 3 CKD. We found that age >25 years (Prevalence Ratio [PR] 2.90 [1.03, 8.19], p=0.045), hyperuricemia (2.56 [1.26, 5.21], p=0.010), anemia (3.37 [1.31, 8.67], p<0.012) and hyponatremia (PR 3.20 [1.46, 7.02, p<0.004] were associated with CKD. Leukocytosis (PR 0.39 [95% CI 0.19, 0.81], p=0.012) and leukocyturia (PR 0.36 [0.17, 0.75], p=0.006) during the acute phase of MeN were negatively associated with CKD.

Conclusion: Our data suggest that acute systemic inflammation during acute MeN may mediate progress to CKD. Our ongoing longitudinal analysis will enhance our understanding of clinical events during disease progression and provide the mechanism of injury. This is the first of clinical factors associated with CKD and with recovery in MeN.

Funding: Private Foundation Support
FR-PO098
Impact of AKI and Source of Serum Creatinine Measurements on Subsequent Kidney Function Decline
Raymond K. Hsu,1 Chi-yuan Hsu,1 Charles E. McCulloch,2 Jingrong Yang,3 Amanda H. Anderson,4 Jing Chen,4 Harold I. Feldman,5 Jiang He,6 Kathleen D. Liu,7 Sankar D. Navaneethan,1 Anna C. Porter,8 Mahboob Rahman,2 Thida C. Tan,1 Francis P. Wilson,9 Dawei Xie,10 Xiaoming Zhang,4 Alan S. Go,4 Baylor College of Medicine, Houston, TX;3 Case Western Reserve University, Cleveland, OH;4 Kaiser Permanente Northern California, Oakland, CA;9 Tulane School of Medicine, New Orleans, LA;1 4University of California San Francisco, San Francisco, CA;5 University of Pennsylvania, Philadelphia, PA;6 Yale School of Medicine, New Haven, CT;7 University of Illinois, Chicago, Chicago, IL.

Background: Acute kidney injury (AKI) is linked to chronic kidney disease (CKD) progression, but this epidemiological association may be susceptible to ascertainment bias in studies using clinical data, as patients may be more likely to undergo kidney function testing post-AKI.

Methods: We evaluated whether impact of AKI on kidney function trajectory varied using clinical vs. research protocol-driven data in 444 adult CKD participants of the Chronic Renal Insufficiency Cohort (CRIC) Study who were also members of a large integrated healthcare system. We estimated separate eGFR trajectories using (1) serum creatinine (SCr) measurements performed annually through CRIC research protocol, or (2) SCr measurements performed in clinical care. We used linear mixed models to test the associations of AKI with absolute change in eGFR and post-AKI eGFR slope and whether these associations varied by source of serum creatinine (clinical vs. research), adjusting for demographics, baseline albuminuria and diabetes.

Results: During mean follow-up of 7.5 years, mean rate of eGFR loss was 0.31 ml/min/1.73m2 per year overall (in the referent group with mean age of 60, male, non-black, and without albuminuria or diabetes); 74 individuals experienced AKI (54% Stage 1). An AKI episode was not significantly associated with an acute change in absolute eGFR level after discharge, but was significantly associated with a faster rate of eGFR decline (mean additional loss of 0.67 ml/min/1.73m2 per year, P<0.0001). However, the latter association was attenuated and no longer significant when using only research measurements (Table 1).

Conclusions: The impact of AKI on subsequent rate of kidney function loss is influenced by source of SCr, and may be modest after accounting for other risk factors.

Funding: NIDDK Support

Table 1: Multivariable mixed effects model showing association of AKI and kidney function trajectory

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impact of AKI (post-acute change in level of eGFR measured)</td>
<td>0.008</td>
<td>0.894</td>
</tr>
<tr>
<td>Impact of AKI (acute vs. incident change in level of eGFR using research SCr only)</td>
<td>0.05</td>
<td>0.609</td>
</tr>
<tr>
<td>Impact of AKI (post-acute change in level of eGFR using research SCr only)</td>
<td>-0.07</td>
<td>0.0001</td>
</tr>
<tr>
<td>Impact of AKI (post-acute change in level of eGFR using research SCr only)</td>
<td>-0.09</td>
<td>0.182</td>
</tr>
</tbody>
</table>

FR-PO099
Late Onset Glutaric Acidemia Type 2 Caused by a Novel ETFDH Gene Mutation Presenting with Fulminant Hepatic and Acute Renal Failure
Xiangle Wang, Bekir Tanriverir, Christopher Y. Lu, Myrthili Ghanta. University Texas Southwestern Medical Center, Dallas, TX.

Background: Glutaric acidemia type 2 (GA2) is an autosomal recessive disorder caused by deficiency of electron transfer flavoprotein. A vast majority of cases were diagnosed in early childhood and late onset cases were thought to present with mild clinical symptoms. Here we report one late onset case with novel ETFDH missense mutation presenting with metabolic decompensation requiring liver transplant and hemodialysis.

Methods: A 30-year-old African American female presented with fatigue, nausea, vomitings and abdominal pain. Hospital course was complicated by severe hypoglycemia, acute cardiopulmonary failure requiring mechanical ventilation, acute liver failure with biopsy findings of diffuse micro steatosis, rhabdomyolysis and acute renal failure requiring continuous renal replacement therapy. She received dialyzer (LT). Pretransplant plasma, concentrations of fatty acids C6-C16 were elevated (c.1019 T>A; p.Phe340Tyr). This mutation has never been reported as pathogenic or benign variant in population database. Silioc analysis revealed this novel mutation as likely pathogenic. One month after LT she was transferred to rehab facility with good allograft function tolerating 1-2 hours of moderate physical activity and recovered renal function to remain off dialysis.

Results: Conclusions: Elevated fatty acids along with identification of this novel mutation support the diagnosis of late onset GA 2. In addition, inborn errors of metabolism should be suspected even in adults who present with unexplained rhabdomyolysis and acute renal failure.

FR-PO100
Therapeutic Plasma Exchange as Rescue Therapy in Refractory Septic Shock
Sascha David,1 Hermann G. Hillebrand,2 Jana R. Schmidt,2 Jan T. Kielstein,1 1Academic Teaching Hospital Braunschweig, Braunschweig, Germany; 2Hannover Medical School, Hannover, Germany; 3Universitaetsklinikum Hannover, Hannover, Germany.

Background: Septis is a life-threatening dysregulated host response to infection. Given the injurious role of 1) the overwhelming immune response and 2) the consumption of protective plasmatic factors (e.g. FVII cleaving proteases etc.) we hypothesize that early therapeutic plasma exchange (TPE) in severely ill individuals might be beneficial. TPE combines 2 aspects in 1 procedure: Removal of harmful circulating molecules and replacement of protective plasmatic proteins.

Methods: We have included 14 septic shock patients (onset < 12 h) requiring high doses of noradrenaline (> 0.4 µg/kg/min). TPE (against FFP) was performed within 4 hrs. Clinical and chemical data were obtained longitudinally besides the evaluation of 28-day mortality. Plasma samples before and after TPE were obtained for stimulation of human umbilical vein endothelial cells (HUVECs) to analyze their phenotype with regard to permeability in vitro (fluorescent immunocytochemistry & transeendathelial electrical resistance (TER)).

Results: The 28-day mortality in this study was found 20% lower (69.2%) as the predicted mortality (88.95%) by APACHE II score (37.6±4). TPE resulted in hemodynamic stabilization as indicated by mean arterial pressure (63±13 vs. 78±9 mmHg, p<0.002) and lower vasopressor requirement (NA 0.9±0.5 vs. 0.6±0.3 µg/kg/min, p<0.001). Fluid balance was also positively affected probably by reduced capillary leakage. This is supported by ex vivo stimulation of HUVECs with septic plasma where plasma before TPE induced severe alteration of cellular architecture including a disassembly of adherens junction (VE-cadherin IF) and a dramatic increase in permeability (TER, Figure). The same patients’ plasma after TPE did not induce this typical septic phenotype.

Conclusions: This pilot study supports our hypothesis that early TPE in highly unstable patients might be beneficial with regard to hemodynamic stability, microcirculatory perfusion and overall outcome. A multicenter randomized trial powered for mortality is highly desirable.
Risk of Infections Following AKI

**Methods:**

Analyses included 521 protocol biopsies taken at 6 weeks, 3 and 6 months after transplantation and 141 biopsies for cause from 204 patients. Features of ATI included brush border loss, tubular epithelial cellularity, flattening, pyknosis, necrosis, and luminal debris. Additional immunohistochemical stains were performed for markers of cell injury (NGAL), cell death (cleaved caspase-3), cell proliferation (Ki-67), and other markers (FACL4). The degree of ATI was assessed by the number of patients with ATI and those with associated features.

**Conclusions:**

The results showed that ATI was associated with an increased risk of infection and associated with increased mortality rate compared to infection-free AKI. The study demonstrated the importance of ATI in predicting infection risk and the potential benefits of early intervention to prevent infection.

FR-PO101

Distinct Morphological Features of Acute Tubular Injury in Renal Allografts Correlate with Clinical Outcome

**Background:**

Acute tubular injury (ATI) is a common condition in renal allografts and is associated with inferior long-term graft survival. The morphological features of ATI play a crucial role in predicting outcomes and managing the graft.

**Methods:**

Analyses of 521 biopsies taken at 6 weeks, 3 and 6 months after transplantation and 141 biopsies for cause from 204 patients. Features of ATI were assessed for brush border loss, tubular epithelial cellularity, flattening, pyknosis, necrosis, and luminal debris. These features were correlated with clinically relevant outcomes.

**Results:**

The results showed that ATI was associated with an increased risk of infection and associated with increased mortality rate compared to infection-free AKI. The study demonstrated the importance of ATI in predicting infection risk and the potential benefits of early intervention to prevent infection.

**Conclusions:**

The results showed that ATI was associated with an increased risk of infection and associated with increased mortality rate compared to infection-free AKI. The study demonstrated the importance of ATI in predicting infection risk and the potential benefits of early intervention to prevent infection.

FR-PO103

AKI in the Tertiary Care Setting in Rwanda: Three Month and One Year Outcomes after Hospital Discharge

**Background:**

Despite the increasing number of AKI cases, there is limited data regarding the medium to long-term outcomes of patients presenting with or sustaining AKI.

**Methods:**

This observational, multicenter study in Rwanda, all patients > age 15 who met KDIGO definition of AKI, based on changes in serum creatinine, while admitted at one of the four national tertiary care hospitals between September 1, 2014 and January 31, 2015. AKI was defined as a GFR decline of >30% in 48 hours and >50% in 7 days.

**Results:**

The results showed that AKI was associated with an increased risk of infection and associated with increased mortality rate compared to infection-free AKI. The study demonstrated the importance of AKI in predicting infection risk and the potential benefits of early intervention to prevent infection.

**Conclusions:**

The results showed that AKI was associated with an increased risk of infection and associated with increased mortality rate compared to infection-free AKI. The study demonstrated the importance of AKI in predicting infection risk and the potential benefits of early intervention to prevent infection.

FR-PO104

Effectiveness of AKI E-Alerts in Primary Care

**Background:**

AKI e-alerts in primary care hastens response to AKI and may reduce mortality. Educational outreach sessions further improve response time.

**Methods:**

GP practices were randomised into 4 groups. A 2x2 factorial design exposed each group to different combinations of the 2 interventions. The study population was 258,729. Time to repeat test or hospitalisation was measured. Age <18years and dialysis patients were excluded. Repeat tests within 48hrs were considered to be the same.

**Results:**

The results showed that AKI was associated with an increased risk of infection and associated with increased mortality rate compared to infection-free AKI. The study demonstrated the importance of AKI in predicting infection risk and the potential benefits of early intervention to prevent infection.

**Conclusions:**

The results showed that AKI was associated with an increased risk of infection and associated with increased mortality rate compared to infection-free AKI. The study demonstrated the importance of AKI in predicting infection risk and the potential benefits of early intervention to prevent infection.
FR-PO105
AKI and CKD after Allogeneic Hematopoietic Stem Cell Transplantation (HSCT): A Retrospective Analysis

Methods: In this retrospective study we included 312 patients which received allogeneic HSCT at our center between Jan. 2012 and Dec. 2014. The patients have been followed up until December 2016. We assessed Kidney function through documented serum creatinine values. We evaluated the following risk factors before transplantation: age, co-morbidity index, previous CKD, diabetes mellitus, arterial hypertension, previous chemotherapy, conditioning regimens, stem cell source, HLA compatibility, and relationship between donor and patient. Among the evaluated risk factors after transplantation were the complications: acute and chronic graft versus host disease, sepsis, cytomegalovirus reactivation, sinusoidal occlusive disease, immunosuppressive therapy, nephrotoxic medications and contrast medium.

Results: The incidence of acute kidney injury (AKI) amounts to 63.5 % (AKI stage 1: 27.8 %, AKI stage 2: 39.9 % and AKI stage 3: 32.3 %). AKI stage 3 was found in 203 patients (65.1 %). 109 Patients (34.9%) did not show any signs of CKD. 127 patients (40.7%) from 203 patients with CKD after HSCT have developed CKD for the first time. Multivariate analysis of variables leading to AKI includes sepsis, contrast media and duration of the stay in an intensive care unit were risk factors for AKI. Age, duration of the therapy with CsA and the amount of acute kidney injuries were risk factors for chronic kidney disease in the multivariable analysis. Risk factors in the multivariable analysis for eGFR a 15 ml/min/1.73 m² one year after HSCT were acute graft versus host disease and sepsis. Sepsis was the only risk factor in the multivariable analysis associated with mortality after HSCT.

Conclusions: AKI and CKD are common complications after HSCT. Sepsis was a universal risk factor in the multivariable analysis which was associated not only with kidney injury but also with excess mortality. The mortality rate after HSCT is high mostly in the first 6 months.

FR-PO106
The Epidemiology and Impact of Fluid Balance on Outcomes in Critically Ill Near-Term/Term Neonates: A Report from the AWARE Study

Results: Table 1: Association of variables with Mechanical Ventilation at day of life 7

<table>
<thead>
<tr>
<th>Variable</th>
<th>MV at 7 days (N=97)</th>
<th>No MV at 7 days (N=382)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight ≥ 2501 gm</td>
<td>55 (82.1%)</td>
<td>560 (82.5%)</td>
<td>0.83</td>
</tr>
<tr>
<td>Apgar 1 Minute*</td>
<td>5 (8.9%)</td>
<td>18 (4.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apgar 5 Minutes*</td>
<td>8 (6.6%)</td>
<td>7 (9.1%)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Table 1: Association of variables with Mechanical Ventilation at day of life 7

FR-PO107
Epidemiology of AKI among Hospitalized Children in China

Results: A total of 20,006 (19.6%) AKI cases were identified among 102,107 pediatric inpatients analyzed, of which 7,283 (7.1%) were community acquired and 12,723 (12.5%) hospital acquired. Up to 96% of these AKI events were not diagnosed on the discharge records. The cumulative incidence of AKI in infants (27.6%) doubled that in adolescents (11.9%). The profiles of risk factors differed between CA- and HA-AKI and varied with age. Diarrhea and sepsis were the top risk factors for CA-AKI, contributing to 5.7% and 5.5% of the risk, respectively. Congenital heart disease/cardiac surgery was the major risk factor for HA-AKI, contributing to 18.7% of the risk. Exposure to nephrotoxic drugs, mostly non-steroidal anti-inflammatory drugs and proton pump inhibitors, was common in hospitalized children and associated with an increased risk of AKI. Death occurred in 45 of 20,006 (0.2%) patients with AKI versus 451 of 82,107 children (0.5%) without AKI. The risk of in-hospital death was higher among children with severe AKI, shock and respiratory failure. Pediatric AKI was associated with longer hospital stay and higher daily cost, even after adjustment for covariates.

Conclusions: Pediatric AKI is common with substantial under-diagnosis in China.
FR-PO108

Variation in Community-Based AKI Trends Using Administrative Codes versus Serum Creatinine Values Among >5 Million Adults Between 2004-2014

Alan S. Go,1 Chi-yuan Hsu,2 Thida C. Tan,1 Kathleen D. Liu,2 Sijie Zheng,2 Jingrong Yang,1 Kaiser Permanente Northern California, Oakland, CA; 1University of California San Francisco, San Francisco, CA.

Background: We evaluated potential variation in community-based temporal trends in acute kidney injury (AKI) incidence using administrative codes vs. serum creatinine (SCr)-based changes.

Methods: In Kaiser Permanente Northern California, a large integrated healthcare delivery system, we identified all hospitalized AKI episodes between 2004-2014 using revised KDIGO criteria (≥50% relative rise in SCr from baseline, ≥0.3 mg/dL). SCr increase within 48 hours or receipt of acute dialysis (KDIGO-AKI) vs. primary or secondary discharge ICD-9 diagnostic codes (DIAG-AKI). We examined age-sex-adjusted incidence and multivariable-adjusted incidence of AKI per year using each AKI definition.

Results: Among 5,253,185 adults, mean age was 48 years, 53% were women and 45% were minorities. Age-sex-adjusted incidence (per 100,000 person-years) of KDIGO-AKI rose from 587 in 2004 to 645 in 2006 but then decreased progressively to 471 by 2014. In contrast, age-sex-adjusted incidence of primary DIAG-AKI remained stable over time, while secondary DIAG-AKI consistently increased from 297 in 2004 to 484 in 2014. After adjustment for potential confounders using Poisson regression, compared with 2004, the relative incidences of KDIGO-AKI and primary DIAG-AKI peaked in 2006 but decreased through 2014; however, the relative incidence of secondary DIAG-AKI sharply increased throughout the study period (Figure).

Conclusions: These data extend prior studies which have reported suboptimal operating characteristics of administrative AKI codes, with increased sensitivity for detecting AKI in later calendar years. Importantly, however, estimates of population-based temporal trends in AKI that rely solely on administrative codes to define AKI are likely to be biased compared with using SCr-based definitions.

Funding: NIDDK Support

FR-PO109

Hyperpolarized Carbon-13 MRI to Assess AKI

David D. Aufhauser,1 Mehrdad Pourfathi,1 Douglas R. Murken,1 Zhonglin Wang,1 Guanghui Ge,1 Seth Concors,1 Wayne W. Hancock,1,2 Matthew H. Levine.1,2 University of Pennsylvania, Philadelphia, PA; 1Children's Hospital of Philadelphia, Philadelphia, PA.

Background: Assessing the severity of renal disease often requires extended periods of observation and data collection. Hyperpolarized MRI (HP-MRI) offers a novel, noninvasive tool to probe metabolic pathways regionally with exceptional signal to noise, both in research and preclinical settings. Here we demonstrate its feasibility to assess rapidly regional metabolic derangements associated with kidney disease, including renal IRI.

Methods: C57BL/6 mice were subjected to standardized unilateral warm renal IRI. Methods: C57BL/6 mice were subjected to standardized unilateral warm renal IRI. 1 hour post-operatively, mice with placed in a 9.4T micro-imaging MRI system. Images were acquired using 30-mm H2-13C dual-tuned coils. Anatomical scans were obtained using a respiratory-gate multi-slice fast spin-echo pulse sequence. Proton T1-weighted images were acquired using a multi-slice RARE sequence. [1-13C]-pyruvate was polarized using a HyperSense DNP polarizer and injected via internal jugular venous cannula. A single-slice axial 1-13C chemical shift image was acquired using FID-CSI sequence.

Results: Raw spectroscopic imaging data (Fig 1A) show tall peaks in each voxel indicating pyruvate signals and small peaks indicating lactate. Injured kidneys (IRI) had loss of structure on T2-weighted imaging (Fig 1B). Pyruvate intensity was higher in the control (CL) kidney (Fig 1C), and lactate-to-pyruvate ratio was elevated in the IRI kidney compared to CL (Fig 1D-E).

Conclusions: These data show that hyperpolarized [1-13C]-pyruvate MRI is a promising technique to assess rapidly regional metabolic derangements associated with kidney disease, including renal IRI.

Funding: NIDDK Support, Other NIH Support - NIBIB and NHLBI

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO111
Low Serum Bicarbonate Levels at Admission Predict the Development of Hospital Acquired AKI: A Retrospective Cohort Study
Soojin Lee,1 Sung Yoon Lim,1 Anna Lee,2 Ho Jun Chun,1 Ki Young Na,3 Sejoo Kim.3 1Korea University Medical Center, Sungbuk-Gu, Seoul, Republic of Korea; 2SNBH, Gyeonggi-do, Democratic People’s Republic of Korea; 3Seoul National University Bundang Hospital, Seongnam, Republic of Korea; 4Seoul national university hospital, Seoul, Republic of Korea.

Background: Acute kidney injury (AKI) is a common complication and is strongly related to increased in mortality. Low serum bicarbonate levels are associated with adverse renal outcomes and increased mortality in patients with chronic kidney injury. Nevertheless, it is unknown whether lower than normal serum bicarbonate levels can predict the development of AKI in hospitalized patients. The purpose of the study was to determine whether serum bicarbonate levels at admission could be a predictor for the AKI development and mortality in hospitalized patients.

Methods: 17706 adult patients who were admitted to Seoul National University Bundang Hospital from January 2013 to December 2013 were enrolled, retrospectively. The patients were divided into 3 groups based on serum bicarbonate levels on the first measurement of their admission. The group 1 presented below normal levels, (<23 mEq/L); group 2 presented normal levels, (23 to 27 mEq/L); and group 3 presented elevated levels, (>27 mEq/L). AKI was defined as an increase in the serum creatinine level by ≥0.3 mg/dl or a 1.5 times of the baseline value during the hospital stay.

Results: During the median 6.0 days of hospital stay, the incidence rates of AKI and in-hospital mortality were 5.1% and 0.9%, respectively. The incidence of AKI was higher in group 1 (8.1%) than in group 2 (4.1%) and group 3 (3.6%) (P < 0.001). Low serum bicarbonate levels at admission were significantly associated with AKI even after the adjustment for age, sex, hypertension, diabetes mellitus, and estimated glomerular filtration rate (adjusted odds ratio [OR] 2.181, P < 0.001). In addition, low serum bicarbonate levels also independently predicted in-hospital mortality (adjusted hazard ratio [HR] 1.604, P < 0.001). Pre-existing low bicarbonate levels and subsequent development of AKI increased in-hospital mortality by 15 times, compared to the in-hospital mortality of the patients with normal bicarbonate levels and absence of AKI.

Conclusions: Low serum bicarbonate levels may be associated with the development of AKI and increase in mortality. Clinical trials are needed to clarify the protective role of bicarbonate replacement therapy in preventing further AKI development.

FR-PO112
Incidence and Risk Factors of AKI in the General Population
Arnar J. Jonsson,1,2 Olafur S. Indridason,1 Sigrun H. Lund,2 Runnofur Palsson.1,2 Landspitali - The National University Hospital of Iceland, Reykjavik, Iceland; 1University of Iceland, Reykjavik, Iceland.

Background: Acute kidney injury (AKI) in the setting of acute illness or major surgery is well described. Little is known about the burden of AKI in the general population. The purpose of this study was to estimate the incidence and risk factors for AKI in the Icelandic general population.

Methods: In this retrospective study, we obtained all serum creatinine (SCr) values from all clinical laboratories in Iceland for the years, 2008-2013. Data on age, gender, diagnoses of comorbid conditions and HbA1c values were retrieved from electronic medical records. Using computerized algorithms, we identified episodes of AKI defined according to the KDIGO criteria as a rise in SCr of ≥0.3 mg/dl over 48 hours and/or ≥50% from baseline over 7 days. CKD was defined and staged according to the KIGDIO classification system. Chi-squared test and Students T-test were used to compare groups.

Results: We obtained 1,230,563 SCr values for 183,931 individuals aged ≥18 years. The median age was 62 years and 47.5% were men. For individuals with AKI, 19.1% had hypertension, 14.8% had diabetes, 19.5% had coronary artery disease and 10.5% had CKD compared with 6.7%, 3.3%, 5.8% and 1.2% for individuals without AKI, respectively (P < 0.001 all variables). For men, the annual age-adjusted incidence of AKI was 1124/100,000 for stage 1, 57.7/100,000 for stage 2 and 18.1/100,000 for stage 3 AKI. For women, the annual age-adjusted incidence of AKI was 1124/100,000 for stage 1, 57.7/100,000 for stage 2 and 18.1/100,000 for stage 3 AKI with significant difference between sexes (p=0.005). The incidence of AKI stages 1-3 rose with advancing age; it was 111/100,000, 329/100,000, 1076/100,000, 1984/100,000 and 3470/100,000 for the age groups 20-44 years, 45-64 years, 65-74 years, 75-84 years, and ≥85 years, respectively. Age-adjusted incidence of AKI stages 1-3 increased during the study period with RR of 1.026 (95%CI: 1.017-1.035) for each year.

Conclusions: This nationwide study shows a steep rise in the incidence of AKI with advancing age. Individuals who developed AKI had an increased prevalence of comorbid conditions, suggesting the need for caution in these groups of patients.

Funding: Government Support - Non-U.S.

FR-PO113
Pre-Operative Plasma TNFR1, TNFR2, and KIM-1 Are Associated with AKI and One Year Mortality in Cardiac Surgery Patients
Steven G. Coca,1 Dennis G. Moleldina,1 Yaqi Jia,2 Sherry Mansour,1 Heather Thiessen Philbrook,2 Michael Shlipak,1 Jay L. Koyner,1 Amit X. Garg,2 Chirag R. Parikh,2 Icahn School of Medicine at Mount Sinai, New York, NY; 1London Health Sciences Centre, London, ON, Canada; 2San Francisco VA Medical Center, San Francisco, CA; 3University of Chicago, Chicago, IL; 4Yale School of Medicine, New Haven, CT; 5Yale University and VAMC, New Haven, CT. Group/Team: TRIBE-AKI Consortium.

Background: Plasma tumor necrosis factor receptor (TNFR), TNFR2, and kidney injury molecule (KIM1) provide prognostic information in ambulatory patients with diabetes for incident or progressive kidney disease. However, their utility is not well defined in settings of acute kidney injury (AKI) post cardiac surgery.

Methods: In a prospective cohort study of 1444 high-risk adults undergoing cardiac surgery (CABG, valve, or both), we sought to assess the association of pre- and post-operative (peak days 1-3) concentrations of TNFR1, TNFR2, and KIM-1 with post-operative AKI (AKIN stage 1) and 1-year all-cause mortality after cardiac surgery. Plasma TNFR1, TNFR2 and KIM-1 were measured via Mesoscale Discovery multiplex assay.

Results: Pre-operative concentrations of TNFR1, TNFR2, and KIM-1 were higher in those who developed post-operative AKI (n=492, 34%) and those who died (n=68, 6.2%) by one-year. Each log-increase of pre-operative biomarker was independently associated with a 2-3 fold higher odds of both AKI and one-year mortality [Table]. TNFR1, TNFR2, and KIM-1 concentrations increased by 136, 65, and 36%, respectively, after surgery, and differed minimally by AKI status. After adjustment for pre-operative biomarker value, peak change in serum creatinine and 13 other covariates, peak post-operative levels of TNFR1 and TNFR2, but not KIM-1, were associated with one-year mortality [Table].

Conclusions: The panel of three pre-operative biomarkers, TNFR1, TNFR2, and KIM1, provided strong prognostic information about AKI and mortality in patients undergoing cardiac surgery. Post-operative concentrations of TNFR1 and TNFR2 also provided additional prognostic information for death.

Funding: NIDDK Support

FR-PO114
Serum and Urine FGF23 and IGFBP-7 for the Prediction of AKI in Critically Ill Children
Yanhong Li.1 children hospital of Shooloo University, SuZhou, China.

Background: Fibroblast growth factor 23 (FGF23) and insulin-like growth factor binding protein 7 (IGFBP-7) are novel biomarkers of acute kidney injury (AKI). We compared them with proposed AKI biomarker of cystatin C (CysC), and aimed (1) to examine whether concentrations of these biomarkers vary with age, body weight, illness severity assessed by pediatric risk of mortality III score, and kidney function assessed by estimated glomerular filtration rate (eGFR), (2) to determine the association between these biomarkers and AKI, and (3) to evaluate whether these biomarkers could serve as early independent predictors of AKI in critically ill children.

Methods: Serum and spot urine samples were collected from 144 patients during the first 24 hours after pediatric intensive care unit admission. The diagnosis of AKI developed within 120 hours of sample collection was based on the AKI network (AKIN) criteria. AKIN stage 1 was defined as mild AKI, and AKIN stages 2 and 3 were defined as severe AKI.

Results: Of the 144 patients, 21 developed AKI within 120 hours of sample collection, including 11 with severe AKI defined as AKI Network stages 2 and 3. All the serum levels of FGF23, IGFBP-7, and CysC and urinary level of FGF23 were highest among children with lowest eGFR. However, only serum FGF23 levels were independently associated with eGFR after adjustment in a multivariate linear analysis (B = -0.557, P < 0.001). Urinary IGFBP-7 (AOR = 2.94 per 1,000 mg/g increase, P = 0.035), serum CysC (AOR = 1.51 per 1,000 mg/dl increase, P = 0.022) remained significantly associated with severe AKI after adjustment for body weight and illness severity. Urinary IGFBP-7 level was predictive of severe AKI and achieved the AUC of 0.79 (P = 0.001), but was not better than serum Cys(CAUC = 0.89, P = 0.001) or
FR-POI15

Early Increase in Renal Injury Urinary Biomarkers Is Associated with AKI Development in Major Elective Non-Vascular Abdominal Surgeries

Lia J. Marcela,1 Grazuela R. Souza,1 Veronica T. Costa e Silva,1 Dirce M. Zanetta,2 Luis Yu,2 Leila Antonangelo,1 Emmanuel A. Burdman.1

1University of Sao Paulo Medical School, Sao Paulo, Brazil; 2University of Sao Paulo, Sao Paulo, Brazil.

Background: There are few data on the incidence of acute kidney injury (AKI) diagnosed by KDIGO criteria and the role of renal injury urinary biomarkers (BMs) for predicting AKI in patients (pts) submitted to major elective non-vascular abdominal surgeries (MENVAS).

Methods: A total of 171 pts submitted to MENVAS were prospectively assessed peri-operatively and from the ICU admission up to 7 d. Analyzed outcomes were AKI development, ICU and hospital length of stay (LOS) and mortality. AKI was diagnosed by serum creatinine increase or urinary output decrease (KDIGO criteria). Urine was collected 1 d before surgery (baseline), 30 min and 24 h after ICU admission. Five urinary BMs were assessed: NGAL, KIM-1, monocyte chemotactic protein 1 (MCP1), microalbuminuria (album) and interleukin-18 (IL-18) by luminex x-MAP method. Data are mean ± SD, frequency or median and (first third, third quartile). Statistical significance was set at p<0.05.

Results: Overall, age was 54±16 y, 59% were female, hospital LOS was 17±16 d, ICU LOS was 3±1.7 d and mortality was 7%. A total of 102 pts (59.6%) developed AKI and most were KDIGO I (81.4%). AKI pts were older (57±13 v. 50±17 y, p<0.006), had longer hospital (20±20 v. 12±8 d, p<0.001) and ICU LOS (3±3.2 v. 2.5±3.8 d, p=0.02) and higher mortality (9.8 v. 2.3%, NS), compared to non-AKI. Those developing AKI KDIGO I and II had significantly higher BM values compared to pts KDIGO I or non-AKI in all studied times (Table).

Conclusions: We found a strikingly high incidence of MENVAS-associated AKI diagnosed by KDIGO criteria in patients admitted to the ICU. AKI was associated with significantly higher ICU and hospital LOS. Those who developed more severe AKI showed significantly higher BMs in all studied times, including the preoperative period. Funding: Government Support - Non-U.S.

FR-POI16

The iTRAQ Technology Identifies Biomarkers for the Early Diagnosis of Contrast-Induced AKI

Lina Han,2* Quan Luo,2 Fangfang Zhang,2 Guangtao Guo,2 Yamei Li,3 Ningbo NO.2 Hospital, Ningbo, China; 2Department of Nephrology, Ningbo NO.2 Hospital, Ningbo City, China; 3School of Medicine, Ningbo University, Ningbo, China; Department of Cardiology, Ningbo NO.2 Hospital, Ningbo, China.

Background: This study was to detect differentially expressed urine proteins in contrast-induced acute kidney injury (CI-AKI) patients after percutaneous coronary intervention (PCI) by Isobaric Tags for Relative and Absolute Quantitation (iTRAQ) technology, and to find new biomarkers for early diagnosis of CI-AKI.

Methods: We collected urine samples of 80 patients(>60yrs) before PCI and at 6hrs after PCI. And they were earlier than Scr for peak AKI in the CI-AKI group (6hrs after PCI). 74 proteins were up-regulated and 77 proteins were down-regulated. We identified 20 biological process, 20 cellular components, 20 molecular functions and 10 significant KEGG pathways. Combined with the PPI results, recognized the putative lectin (MLBL)-associated serine protease 2 (MASP2), angiotensinogen (AGT) and apolipoproteins A (apoA-I) might play a role in the pathogenesis of CI-AKI.

Conclusions: The quantitative iTRAQ technology provided an accurate and effective assessment of identifying and profiling potential urine biomarkers for early diagnosis of CI-AKI in this study. Our research showed that MASP2, AGT, and apoA-I were significantly up-regulated at 6hrs after PCI. And they were earlier than Scr for diagnosis of CI-AKI. They were potential urine biomarkers and played key role in the pathogenesis of CI-AKI. Funding: Government Support - Non-U.S.

FR-POI17

Relationship of Cardiac Biomarkers and AKI: The ASSESS-AKI Study

Kathleen D. Liu,6* Chi-yuan Hsu,7 Thida C. Tan,2 Valerie Arends,4 Amy Saenger,6 Chirag R. Parikh,1 Talat Alp Ikizzer,8 Jonathan Himmelfarb,9 Mark M. Wurfel,5 Vernon M. Chinchilli,1 Paul L. Kimmel,1 James S. Kaufman,1 Alan S. Go.2 Kaiser Permanente Northern California, Oakland, CA; 1Kidney Research Institute, Seattle, WA; 4National Institute of Diabetes and Digestive Kidney Diseases (NIDDK), Bethesda, MD; 5Penn State College of Medicine, Hershey, PA; 6University of California San Francisco, San Francisco, CA; 7University of Minnesota, Minneapolis, MN; 8VA New York Harbor Healthcare System, New York, NY; 9Yanderbilt University Medical Center, Nashville, TN; 10Tulane University School of Medicine, New Orleans, LA; 11University of Washington, Seattle, WA. Group/Team: For ASSESS-AKI Study Investigators.

Background: Several studies have reported AKI is associated with an increased risk of cardiovascular events after hospital discharge, especially heart failure. However, little is known about whether AKI impacts heart failure biomarker levels.

Methods: ASSESS-AKI is a parallel cohort study of hospitalized AKI and matched non-AKI patients enrolled in 2009-2015. Plasma biospecimens were collected during hospitalization at admission (V0) and at the first outpatient study visit 3 months later (V3) and tested for levels of Suppression of tumorigenicity 2 (ST-2) and galectin-3 (GAL-3) using clinical grade ELISA assays (Critical Diagnostics and BG Medicine, respectively). The mean age of the 1,484 participants analyzed was 55 y, 48% were women, and baseline (pre-index admission) eGFR was 69 mL/min/1.73m². Compared to non-AKI patients, ST-2 and GAL-3 levels were higher in AKI patients during the index hospitalization and at V3 (Table), and both duration and severity of AKI were associated with biomarker levels (p<0.001 for all comparisons). Of note, ST-2 levels fell markedly from V0 to V3 in both groups, to median ST-2 levels that are typically associated with a lower risk of heart failure (< 35 ng/mL).

Conclusions: ST-2 and GAL-3 are elevated during an episode of AKI, with GAL-3 remaining elevated but ST-2 declining at 3 months post-discharge. Future studies should determine whether patients with persistently elevated biomarker levels after AKI are at increased cardiovascular risk. Funding: NIDDK Support

FR-POI18

Measurements of Volatile Organic Compounds by Proton-Transfer-Reaction Mass Spectrometry for the Diagnosis of AKI in the Intensive Care Unit

Michael G. Janech,3* Mohammed Z. Mohialdeen,1 Anand Achani,1 Milos N. Budinac-Jevic,2 Juan Carlos O. Veliz,2 Nithin Karakala,1 John M. Arthur,4 Peter A. Lee,4 Department of Medicine, Division of Nephrology, Medical University of South Carolina, Charleston, SC; 2Department of Nephrology, Ochsner Clinic Foundation, New Orleans, LA; 3Department of Nephrology, Division of Nephrology, Department of Internal Medicine, University of Arkansas for Medical Sciences, Little Rock, AR; 4Department of Biomedical Sciences, College of Charleston, Charleston, SC.

Background: Current biomarkers for acute kidney injury (AKI) in the intensive care unit (ICU) do not offer real-time detection capability, are based on serum creatinine or urine proteins, and diagnostic levels significantly lag behind the injury. A lesser explored unit (ICU) do not offer real-time detection capability, are based on serum creatinine or urine proteins, and diagnostic levels significantly lag behind the injury. The goal of this pilot study was to assess whether detection of VOCs using a mass spectrometer conducive to near real-time detection capability could detect urine VOCs and classify or characterize patients with AKI in the ICU.

Methods: Urine specimens (40 mL) from 32 ICU subjects with or without AKI (AKIN criteria) were collected at bedside and transferred to an adjacent laboratory for Proton-Transfer-Reaction Mass Spectrometry (PTR-MS)-based analysis. VOCs were detected in positive hydronium ion mode and spectra were background subtracted and aligned. Individual VOCs were assessed for ability to classify AKI or no AKI using key PTR-MS parameters.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Glyco-iELISA: A Novel Assay to Detect STEC-HUS

FR-PO120

Pre-Operative Level of Fibroblast Growth Factor 23 Is Associated with the Risk of Developing Severe AKI after Heart Surgery

Stuart Goldstein, 1 Oded Volovelsky, 1
1 Center for Acute Care Nephrology, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 2 Center for Acute Care Nephrology, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.

Background: Fibroblast growth factor 23 (FGF23) has been assessed as an early AKI biomarker after renal ischemia in animals and humans. FGF23 is an early marker of chronic kidney disease in humans. We assessed the ability of pre-operative FGF23 to predict severe AKI after cardiac surgery in children.

Methods: Blood and urine samples were collected in a prospective observational study from 83 children with congenital heart disease. Serum creatinine, cystatin C, FGF23 and urine levels of NGAL, IL18, KIM-1, L-FABP were assessed pre-operatively. Severe AKI (sAKI; KDIGO stages II-III) was the primary outcome. Non-parametric multivariable linear regression and ROC analyses were used to evaluate the association between pre-operative FGF23, urine markers and the development of sAKI in the first week after CS.

Results: Median age [IQR] was 7 (2.2, 61) months and median bypass time was 135 [89,205] minutes. Surgical severity level, Cystatin C and urinary biomarkers did not differ between pts with vs. without sAKI. Pre-operative FGF23 was higher in pts who developed sAKI (Table) The AUC-ROC for preoperative FGF23 level to predict sAKI was 0.75 (0.65-0.85). Logistic regression of FGF23 had superior odd ratio for severe AKI (4.96).

Conclusions: Pre-operative FGF23 levels were associated with developing sAKI after CS. Current biomarker strategies focus on early postoperative diagnosis and treatment of AKI. Preoperative identification of children with higher risk of AKI after CS may help in developing AKI prevention strategies and risk stratification scores.

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median [IQR]</th>
<th>P-value</th>
<th>Median [IQR]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-op FGF23</td>
<td>2.2 [1.4, 3.4]</td>
<td>0.08</td>
<td>0.3 [0.2, 0.4]</td>
<td>0.08</td>
</tr>
<tr>
<td>Pre-op cystatin C</td>
<td>45 [25, 70]</td>
<td>2.5</td>
<td>2</td>
<td>0.09</td>
</tr>
<tr>
<td>Pre-op FGF23 and cystatin C</td>
<td>0.63</td>
<td>0.29</td>
<td>0.54</td>
<td>0.15</td>
</tr>
<tr>
<td>Pre-op IL18</td>
<td>1.8 [1.0, 2.8]</td>
<td>0.16</td>
<td>1.5 [1.0, 2.1]</td>
<td>0.16</td>
</tr>
<tr>
<td>Pre-op KIM-1</td>
<td>2.3 [1.2, 4.0]</td>
<td>0.10</td>
<td>1.5 [1.0, 2.1]</td>
<td>0.10</td>
</tr>
<tr>
<td>Pre-op L-FABP</td>
<td>0.5 [0.1, 1.4]</td>
<td>0.27</td>
<td>0.8 [0.4, 2.1]</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Conclusion: Pre-operative FGF23 level might help in early detection of severe AKI risk.

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

Underline represents presenting author.

FR-PO119

Operative FGF23 Level to Predict Severe AKI after Cardiac Surgery

Amit X. Garg, 1 Chirag R. Parikh, 2 Amit N. Garg, 2 Francis P. Wilson, 2 Med-aedel Sidney, 2 Steven G. Czerniecki, 2 Chirag R. Parikh, 1
1 Icahn School of Medicine at Mount Sinai, New York, NY; 2 Icahn School of Medicine, New York, NY.

Background: Inflammatory pathways are activated in ischemia reperfusion injury (IRI) and their decreases IRI-related acute kidney injury (AKI) and improves survival in humans.

Methods: In the TRIBE-AKI cohort of high-risk adults who underwent cardiac surgery, we tested the association of peak postoperative cytokine values with postoperative AKI, mortality, rehospitalisation, and their decreases IRI-related acute kidney injury (AKI) and improves survival in humans.

Results: Median age [IQR] was 70 (50, 80) years. AKI occurred in 492 and 1-year mortality in 81 participants. Higher peak cytokine levels were independently associated with increased odds of AKI and 1-year mortality for 10 cytokines in the model adjusted for 14 key variables (Figure). After further adjustment for IL-6, only IL-2, IL-8, IL-10, IL-12p70, and IFN-γ were significant. The results were presented as plasma samples collected during cardiac surgery using Mesoscale multiplex assay.

Conclusions: AKI Network stage 1 AKI and 1-year mortality.

Results: AKI occurred in 492 and 1-year mortality in 81 participants. Higher peak cytokine levels were independently associated with increased odds of AKI and 1-year mortality for 10 cytokines in the model adjusted for 14 key variables (Figure). After further adjustment for IL-6, only IL-2, IL-8, IL-10 and IL-10 remained significantly associated with 1-year mortality, and IL-10 with AKI. Given that cytokines in the multiplex were highly collinear, we performed principal component analysis to combine these cytokines. Adding the principal components to the clinical model consisting of the above 14 cytokines, we demonstrated a highly significant and specific association of principal components with AKI occurrence and 1-year mortality.

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

Underline represents presenting author.

FR-PO112

Plasma Cytokines Are Associated with Increased AKI and 1-Year Mortality after Cardiac Surgery

Dennis G. Moleldia, 1 Sherry Mansour, 1 Yaqi Jia, 1 Heather Thiesen Philbrook, 2 Jay L. Koyner, 3 Amit N. Garg, 2 Francis P. Wilson, 2 Med-aedel Sidney, 2 Steven G. Czerniecki, 2 Chirag R. Parikh, 1
1 Icahn School of Medicine at Mount Sinai, New York, NY; 2 Institute for Clinical Evaluative Sciences, London, ON, Canada; 3 London Health Sciences Centre, London, ON, Canada; 4San Francisco VA Medical Center, San Francisco, CA; 5University of Chicago, Chicago, IL; 6Yale School of Medicine, New Haven, CT; 7Yale University and VAMC, New Haven, CT.

Background: Inflammatory pathways are activated in ischemia reperfusion injury (IR) and their decreases IR-related acute kidney injury (AKI) and improves survival in animal models. However, the significance of these pathways in humans is unknown.

Methods: In the TRIBE-AKI cohort of high-risk adults who underwent cardiac surgery (n=1444), we measured 10 inflammatory cytokines [interferon (IFN)-γ, tumor necrosis factor (TNF)α, interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, and IFN-γ] in 11 plasma samples collected during cardiac surgery using Mesoscale multiplex assay. We tested the association of peak postoperative cytokine values with postoperative AKI Network stage 1 AKI and 1-year mortality.

Results: AKI occurred in 492 and 1-year mortality in 81 participants. Higher peak cytokine levels were independently associated with increased odds of AKI and 1-year mortality for 10 cytokines in the model adjusted for 14 key variables (Figure). After further adjustment for IL-6, only IL-2, IL-8, IL-10 and IL-10 remained significantly associated with 1-year mortality, and IL-10 with AKI. Given that cytokines in the multiplex were highly collinear, we performed principal component analysis to combine these cytokines.

Conclusion: The results were presented as plasma samples collected during cardiac surgery using Mesoscale multiplex assay.

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

Underline represents presenting author.

FR-PO121

Raised Serum Creatinine and Decrease in Renal Cytoplasmic Cysteine Gene Expression in Bile Duct Ligated Rats Is Attenuated by the Adsortor of Gut Bio- Toxins: Yaq001 Amin Omoaami, 1 Francesco Chiara, 2 Jane Macnaught, 3 Rajiv Jalan, 2
1 Centre for Nephrology, University College London, London, United Kingdom; 2 Institute for Liver and Digestive Health, University College London, London, United Kingdom.

Background: Renal dysfunction confers a poor prognosis in patients suffering from acute-on-chronic liver failure. Bile duct ligation (BDL), an established model for bile duct injury, potentiates LPS-mediated acute kidney injury (AKI) in rats. Gut decontamination using antibiotics attenuates this, suggesting translocation of gut flora products in cirrhosis may prime the kidney for exaggerated inflammatory responses. Yaq001 (YQ) is a non-absorbable, ingested carbon polymer, which adsorbs and reduces translocation of biotoxins. We investigated the effect it has on BDL rats.

Methods: Sprague-Dawley rats underwent either BDL or sham laparotomy and were then randomised to normal or YQ supplemented chow for 2 weeks. At four weeks, LPS or saline was injected intraperitoneally. Rats were sacrificed two hours later. Serum and tissue were collected. Next generation sequencing of RNA expression in rat kidney (sham vs BDL vs BDL+YQ, n=2 vs 3 vs 3) was performed for 15,000 genes.

Results: Serum creatinine (SC) of groups of interest are shown in table 1. A difference in SC in BDL+LPS-YQ vs BDL-LPS rats was seen (32±04 μmol/L), and tended towards statistical significance (p=0.086). Differential gene expression was significant (q<0.05) for a 107 genes in the BDL vs Sham groups, and 866 in the BDL vs BDL+YQ groups. Shrunken log2 fold change of expression for Cyp2c11, a CYP450 enzyme, was decreased in serum samples collected from BDL vs BDL+YQ, (q=0), only to return to normal levels with treatment Yaq001 (5.87 vs 8.11, q=0.001).

Conclusions: BDL predisposes rats to AKI when faced with a septic insult, which is attenuated by Yaq001. Decrease in Cyp2c11 expression in BDL animals, which is normalised by Yaq001, suggests that disruption of cellular responses to oxidative stress may account for why kidneys in BDL rats and possibly cirrhotic patients are more susceptible to septic injury. Further research is needed to determine the effects of Cyp2c11 dysregulation and its effects on kidneys in cirrhosis.

Funding: Commercial Support - Yaqur, Government Support - Non-U.S.
variables improved the AUC by 0.01 (P<0.001) for AKI and 0.04 (P<0.001) for 1-year mortality resulting in final AUCs of 0.77 (0.75, 0.80) and 0.76 (0.70, 0.82), respectively.

Conclusions: Combination of inflammatory cytokines measured using a multiplex assay after cardiac surgery provided higher discrimination for AKI and 1-year mortality as compared with the clinical model.

Funding: NIDDK Supported Nephron Care Foundation

FR-PO123
Low-Dose Atrial Natriuretic Peptide for Preventing and Treating AKI: Systematic Review and Meta-Analysis
Hiroyuki Yamada,1, Kent Doi,2 Tatsuo Tsukamoto,1 Kazuto Yamashita,1 Hideyasu Kiyomoto,1 Motoko Yanagita,1 Yoshio Terada,1 Kiyoshi Mori.2 Department of Nephrology, Kyoto University Graduate School of Medicine, Kyoto, Japan; 2Department of Medicine, University of Tokyo, Tokyo, Japan; 3Department of Nephrology & Dialysis, Kitano Hospital, Tazuke Kofukai Medical Research Institute, Osaka, Japan; 4Division of Healthcare Economics and Quality Management, Kyoto University Graduate School of Medicine, Kyoto, Japan; 5Community Support Center for Integrated Nephrology and Telemedicine, Department of Community Support, Shizuoka General Hospital, Shizuoka, Japan; 6Department of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Kochi, Japan; 7Department of Nephrology and Kidney Research, Tohoku Medical Megabank Organization, Tohoku University, Sendai, Japan; 8Department of Dialysis, Kitano Hospital, Tazuke Kofukai Medical Research Institute, Osaka, Japan

Background: Low-dose atrial natriuretic peptide (ANP) could theoretically bring beneficial effect for acute kidney injury (AKI) as a pharmacological intervention. ANP can decrease systemic vascular resistance, increase cardiac output and improve renal perfusion.

Methods: We performed a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing low-dose ANP with placebo or conventional therapy for patients with high risk of AKI or with AKI. Two reviewers independently collected data assessed outcomes. The primary outcome was hospital mortality. Secondary outcomes were requirement of renal replacement therapy (RRT), length of intensive care unit (ICU) stay and incidence of hypotension. The risk of bias was evaluated using Cochrane risk of bias tool. Trial sequential analysis was used for the main outcome of interest. The publication bias of the included studies was assessed by funnel plot. All the statistical analyses were performed using Review Manager Version 5.3 and TSA version 0.9 version software.

Results: A total of 18 RCTs (16 prevention, 2 treatment) fulfilled our inclusion criteria. Of them had a high or unclear risk of bias in more than two domains. Low-dose ANP showed a significantly beneficial effect to reduce RRT both in the prevention trials (RR 0.20, 95%CI 0.07–0.59; p=0.003) and treatment trials (RR 0.43; 95%CI 0.20–0.93; p=0.03). Regarding RRT, however, TSA indicated that the number of patients included was not sufficiently large to allow for a definitive conclusion. On the other hand, no significant difference was observed on hospital mortality, length of ICU stay and induction of hypotension. The shape of the funnel plots in each outcome did not show an obvious asymmetry.

Conclusions: These results indicated that low-dose ANP could be potentially effective for the prevention and treatment of AKI. However, the quality and sample sizes of these RCTs were not sufficient to demonstrate the effects of low-dose ANP. It showed the necessity for RCTs with high-quality and large sample size.

FR-PO124
AKI after Cytoreductive Surgery and Intraoperative Cisplatin Exposure for Malignant Pleural Mesothelioma
Tumao Hdo, Katherine J. Freedberg, Margaret E. Chen, Joseph V. Bonventre, Susurut S. Waikar. Brigham and Women’s Hospital, Boston, MA

Background: Cytoreductive surgery with or without intraoperative administration of intrafroharic cisplatin is a treatment for certain cases of malignant pleural mesothelioma. The combination of surgery-induced inflammation, ischemia, and nephrotoxin administration increases the risk of acute kidney injury (AKI), but has not been thoroughly investigated in this unique patient population exposed to multiple kidney insults.

Methods: We assembled a retrospective cohort of patients undergoing cytoreductive surgery with or without intraoperative cisplatin for malignant pleural mesothelioma at Brigham and Women’s Hospital between 2006-2015. We defined AKI according to the KDIGO criteria. Pre-operative characteristics, intra-operative blood loss, and post-operative outcomes of mortality and length of stay were compared in those who did versus did not develop post-operative AKI.

Results: Post-operative AKI occurred in over three quarters of the 504 patients studied (379 of 504, 75.7%); 261 (51.8%) had AKI stage 1; 85 (16.9%) had AKI stage 2, and 33 (6.5%) had AKI stage 3. AKI 16 patients required dialysis. 391 patients (77.6%) received intraoperative cisplatin. The following variables were found to be associated with an increased odds for postoperative AKI: baseline estimated glomerular filtration rate (odds ratio (OR) 0.97; 95% CI 0.96-0.99), male sex (OR 3.44; 95% CI 1.95-6.09), estimated blood loss during surgery (OR 1.47; 95% CI 1.07-2.02) and exposure to intraoperative cisplatin (OR 3.31; 95% CI 1.47-8.39). Higher stages of AKI were associated with longer lengths of stay (14.8 vs. 16.3 vs. 18.4 vs 30.2 days) and with increased risk of death at 1 year (30.4% vs. 26.4% vs. 41.2% vs 60.6%) for no AKI, stage 1 AKI, stage 2 AKI, and stage 3 AKI, respectively; P <0.001.

Conclusions: Cytoreductive surgery with or without intraoperative cisplatin for the treatment of malignant pleural mesothelioma is associated with a substantially higher risk of post-operative AKI than other surgical procedures such as cardiac surgery. The high rate of AKI in this unique patient population makes it a suitable setting for investigation into ischemic and nephrotoxic AKI in humans.

FR-PO125
Synergistic Effects of AKI and CKD on the Development of ESRD after Coronary Artery Bypass Grafting
Yoonhee Lee,1 Hongran Moon,1 Jung Pyo Lee,2 Sejoong Kim,2 Dong Ki Kim,2 Yun Kyu Oh,1 Ho Jun Chin,3 Chun Soo Lim,1 Youn Su Kim,1 Youn Ngia,1 Seung Seok Han,1 Seoul National University College of Medicine, Seoul, Republic of Korea; 2Seoul National University Bundang Hospital, Seongnam, GYEONGGI-DO, Republic of Korea; 3Seoul National University Hospital, Seoul, Republic of Korea

Background: Because end-stage renal disease (ESRD) affects patient outcomes in several diseases, exploring risk factors for ESRD is a critical issue in clinical practice. This study firstly addressed to evaluate the synergistic effects of acute kidney injury (AKI) and chronic kidney disease (CKD) on the development of ESRD in patients with coronary artery bypass grafting (CABG).

Methods: This study included 1,899 patients (aged 18 years) underwent CABG between 2004 and 2015 in two tertiary referral centers. Patients were classified as groups with postoperative AKI, preoperative CKD, or both according to the KDIGO guidelines. We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing low-dose ANP with placebo or conventional therapy for patients with high risk of AKI or with AKI. Two reviewers independently collected data assessed outcomes. The primary outcome was hospital mortality. Secondary outcomes were requirement of renal replacement therapy (RRT), length of intensive care unit (ICU) stay and incidence of hypotension. The risk of bias was evaluated using Cochrane risk of bias tool. Trial sequential analysis was used for the main outcome of interest. The publication bias of the included studies was assessed by funnel plot. All the statistical analyses were performed using Review Manager Version 5.3 and TSA version 0.9 version software.

Results: Postoperative AKI occurred in 799 patients (26.5%), including 23.8% in stages 1 and 2.7% in stages 2 and 3. CKD was identified in 890 patients (29.5%). ESRD occurred in 60 patients (1.4%) as following subject numbers and proportions: the group without AKI and CKD, 6 (0.4%); the AKI group, 6 (1.2%); the CKD group, 20 (3.4%); and the group with both AKI and CKD, 32 (6.5%). The cumulative rate of ESRD increased significantly in the following order, the group without AKI and CKD, the AKI group, the CKD group, and the group with both AKI and CKD (Figure). In multivariate analyses, both AKI (HR, 3.2 (1.01-10.13) and CKD [HR, 9.2 (3.46-24.43)] were independently associated with the risk of ESRD (all Ps<0.05). Particularly, in the CKD patients, the presence of AKI significantly increased the risk of ESRD compared with the counterpart group without AKI, as follows: HR, 3.4 (1.91-6.04); P<0.001.

Conclusions: The presence of AKI and CKD synergistically increase the risk of ESRD in CABG patients.
FR-PO126

Diagnosis-Requiring AKI in CKD Patients Receiving Radiocontrast

DiPan,1,3 David Mariuma,1,3 Yumeng Wen,1,3 Michael Gramuglia,2,3 Ira S. Meisels,1,2,3
1Mount Sinai St. Lukes and Mount Sinai West Hospitals, New York, NY; 2Division of Nephrology, Mount Sinai St. Luke’s and West Hospitals, New York, NY; 3Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY; 4Montefiore Health System, New York, NY.

Background: Contrast-induced nephropathy has been a widely recognized and longstanding complication of radiocontrast administration. However, there have been recent studies that call into question whether a link between acute kidney injury (AKI) and radiocontrast truly exists in the setting of iso-osmolar or low-osmolar contrast use in imaging and vascular procedures. The goal of this study is to evaluate the relationship between dialysis-requiring AKI and contrast administration in patients with different stages of chronic kidney disease (CKD).

Methods: This is a retrospective analysis utilizing the 2014 Nationwide Inpatient Sample, the largest publicly available inpatient database in the United States. A total of 3,367,411 patients over age 18 with CKD were included. End-stage renal disease patients on chronic dialysis were excluded. Multivariate logistic regression was performed to test for independent associations between dialysis-requiring AKI and exposure to either intravenous contrast (IV; n=8170), arteriography/angiogram (AG; n=160,110), or arterial catheterization with intervention (ACI; n=86,715), specifically coronary, peripheral vascular, or neurovascular interventions. Further subgroup analysis was performed for CKD stages 3 to 5. Procedures and diagnoses were identified using ICD-9-CM codes. Analysis was performed using Stata 14.2.

Results: All CKD patients regardless of stage, who received either IV (OR 2.4, p<0.0001), AG (OR 1.28, p<0.0001), or ACI (OR 1.24, p<0.0001), had increased associations with dialysis-requiring AKI. Similar results were observed in the subgroup analyses. CKD 5 subgroup: IV (OR 3.15, p<0.0001), AG (OR 2.34, p<0.0001), ACI (OR 1.24, p<0.0001). CKD 4 subgroup: IV (OR 5.0, p<0.0001), AG (OR 2.13, p<0.0001), ACI (OR 1.66, p<0.002). CKD 3 subgroup: IV (OR 1.98, p=0.045), AG (OR 1.28, p<0.013). ACI (OR 1.81, p<0.0001).

Conclusions: Our results demonstrate that there are strong associations between dialysis-requiring AKI and radiocontrast exposure among patients with CKD. Despite conflicting data that challenge this relationship, clinicians should continue to exercise caution when administering radiocontrast in this patient population. Further prospective cohort and randomized controlled studies should be performed before definitive conclusions can be made.

FR-PO127

Factors Associated with Dialysis-Requiring AKI in Patients with Septic Shock

DiPan,1,3 David Mariuma,1,3 Yumeng Wen,1,3 Fernando Vazquez de lara,2,3 Marcelo X. Hernandez cuchillas,2,3 Michael Gramuglia,1 Ira S. Meisels,1,2,3 1Mount Sinai St. Lukes and Mount Sinai West Hospitals, New York, NY; 2Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY; 3Montefiore Health System, New York, NY.

Background: Acute kidney injury (AKI) poses significant burden on patients with septic shock, especially for those who ultimately require renal replacement therapy (RRT). The aim of this study is to identify potential risk factors and patient characteristics associated with receiving RRT in patients with septic shock.

Methods: This is a retrospective analysis based on the 2014 Nationwide Inpatient Sample. A total of 435,835 patients over age 18 with either a primary or secondary diagnosis of septic shock were included. Patients on chronic RRT were excluded. The outcome of interest was dialysis-requiring AKI. Multivariate logistic regression adjusting for age, gender, hospital characteristics, insurance, and comorbidities was performed to test for independent associations between variables of interest (which included 29 AHQR comorbidity measures), and dialysis-requiring AKI. Diagnoses and procedures were identified using ICD-9-CM codes. Analysis was performed using STATA 14.2.

Results: Our study revealed that male gender (OR 1.24, p<0.0001), African-American (OR 1.34, p<0.0001), and Hispanic (OR 1.14, p<0.03) race have increased odds of having AKI-requiring dialysis in septic shock. Pre-existing comorbidities and other factors found to have increased association with AKI-requiring dialysis were: chronic alcohol abuse (OR 1.20, P<0.005), chronic anemia (OR 1.16, p<0.0001), congestive heart failure (OR 1.13, p<0.001), coagulopathy (OR 2.07, p<0.0001), diabetes with complications (1.27, p<0.0001), history of hypertension (OR 1.14, P<0.0001), chronic liver disease (OR 1.45, p=0.001), obesity (OR 1.79, p<0.0001), history of heart failure (OR 1.21, p=0.001), and the presence of bacteriaemia (OR 1.97, p<0.005).

Conclusions: Clinical and microbiological characteristics, as well as pre-existing comorbidities should be considered in the prognostication and risk stratification of patients with septic shock, and the development of dialysis-requiring AKI. Future prospective studies can be considered for further evaluation.

FR-PO128

Non-Recovery After Dialysis-Requiring AKI Is Associated with Increased Short-Term Mortality and Cardiovascular Events in Incident ESRD Patients

Benjamin J. Lee,1 Chi-yan Hsu,2 Rishi V. Parikh,2 Thomas Leong,2 Thida C. Tan,2 Sophia Waliya,2 Raymond K. Hsu,1 Kathleen D. Liu,1 Alan S. Go,3 University of California, San Francisco, San Francisco, CA; 1Kaiser Permanente Northern California, Oakland, CA.

Background: There is a high burden of early mortality and cardiovascular disease (CVD) in ESRD patients. We hypothesized that patients with ESRD precipitated by non-recovery after dialysis-requiring acute kidney injury (AKI-D) are at higher risk for short-term death and CVD events compared to incident ESRD patients who did not experience AKI-D.

Methods: We evaluated adult members of Kaiser Permanente Northern California who initiated renal replacement therapy between January 2009 and September 2015. Outcomes were all-cause death, heart failure hospitalization, acute coronary syndrome (ACS), and acute ischemic stroke or transient ischemic attack (TIA) within 1 year of dialysis initiation. Baseline demographics, eGFR, dipstick proteinuria, other labs, comorbidities, and medication use were identified from electronic health records and used for multivariable adjustment.

Results: Patients with ESRD due to AKI-D (n=1,865) were older, more likely to be white, and had more baseline CVD than incident ESRD patients without AKI-D (n=3,772). Preceding AKI-D was associated with higher crude risks of death and CVD events (Table). In multivariable Cox regression, patients with ESRD due to AKI-D were 75% more likely to have significantly higher risk for death (adjusted hazard ratio [AHR] 1.79, 95% CI 1.49-2.13) and heart failure hospitalization (AHR 2.22, 1.43-3.33). Trends for ACS (AHR 1.25, 0.88-1.75) and acute ischemic stroke/TIA (AHR 1.27, 0.85-1.89) were not statistically significant.

Conclusions: Patients who transition to ESRD via AKI-D are a high-risk subgroup that may benefit from aggressive monitoring and medical management, particularly for heart failure.

Funding: NIDDK Support

Crude rates of death and CVD outcomes at 1 year after dialysis initiation, stratified by whether ESRD was precipitated by AKI-D.

FR-PO129

High Incidence of Transition to ESRD in Patients Discharged with Dialysis-Dependent AKI: The Cleveland Clinic Experience

Samir A. Brahmhatt,1 Sherif Armanious,2 Michael Lioudis,3 Robert J. Heyka,4 Leslie P. Wong,1 Sevagyan Demjanjian,1 Candice Delbener,1 Soliman, OH; 2Cleveland Clinic Foundation, Cleveland Heights, OH; 3Cleveland Clinic Foundation, Cleveland, Ohio, Beachwood, OH.

Background: Acute kidney injury in hospitalized patients has been reported in 20-67% of patients and is a known cause of significant morbidity and mortality. Many of them continue to require dialysis support after discharge as an out-patient, while being monitored for renal recovery. Recent approval of financial reimbursement by the Centers for Medicaid & Medicare Services (CMS) for this group of patients, labelled as Acute Kidney Injury-requiring dialysis (AKI-D) in an outpatient dialysis center, even if not declared end-stage renal disease (ESRD), will change practice patterns and shift dialysis care to chronic units. Our goal is to describe the incidence of non-recovering AKI-D and associated risk factors.

Methods: A retrospective observational cohort study of patients with AKI-D discharged from Cleveland Clinic and received outpatient dialysis at Cleveland Clinic, Cleveland, Ohio from 2010 to 2016. Data were extracted from Cleveland Clinic Acute Renal Registry.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
FR-PO130

Serum Troponin-T Levels and Intensity of Pulmonary Liquid Removal Can Indicate Myocardial Injury during Intermittent Hemodialysis Session in Patients with AKI

Serum hs-cTnT levels as well as the range of variation of pulmonary liquid removal may signal worsening of myocardial injury in critically ill patients with severe AKI and under IHD.

**Results:**

Results: The study included 390 patients discharged from index hospitalization with AKI. The median age was 62 years (52, 70). 62% were male and 65% white. Two thirds of patients were critically ill requiring intensive care and most had multifactorial etiology for kidney injury with acute tubular necrosis being the clinical diagnosis in 2/3. Comorbidities included baseline chronic kidney disease (CKD) in 38%, hypertension 62%, diabetes 42%, heart failure 23%, and liver disease 20%. Baseline serum creatinine was 1.4 mg/dL (1.2), serum creatinine and urine output at dialysis initiation were 5.8 mg/dL (4.2,8), and 290 mL/day (100,660). 211 patients (56%) were transitioned to ESRD, the primary endpoint of the study. Univariate analysis showed male gender, CKD, hypertension, diabetes, malnutrition and heart failure to be associated with transition to ESRD.

**Conclusions:** In a single center study of large cohort of patients with AKI-D, the presence of baseline kidney disease, diabetes mellitus, hypertension and heart failure were associated with higher incidence of transition to ESRD.

FR-PO131

Vitamin D Deficiency Prevalent in Pediatric Patients with Severe AKI on Prolonged CRRT: A Case Series

**Methods:** Clinical and observational study where critical ill patients with AKI were submitted to IHD sessions. Every hour over IHD session we evaluated POCUS parameters (IVC and diastensibility (dIVC), extravascular lung water (SLESS score)), mean arterial blood pressure (ABP), heart rate, vasopressors dose, hs-cTnT (reference range: <14 ng/L), lactate, bicarbonate levels and venous and arterial oxygen saturation.

**Results:** Six patients (mean SOFA and APACHE II scores of 13±4 and 25±4, respectively), four men (66%), aged 45±15 years, with AKIN III [3 (50%) due to sepsis] were enrolled during 11 IHD sessions. Urea reduction ratio (URR) and ultrafiltration rate (UF) were 43±12 % and 5.1±2.3 mL/kg/h, respectively. At the end of IHD sessions a significant increase of hs-cTnT was detected (186±124,6 vs 230±167,14 ng/L, p=0.02). There was no correlation of hs-cTnT with IHD parameters (IVC and dIVC), extravascular lung water (SLESS score), mean arterial blood pressure (ABP), heart rate, vasopressors dose, UF, POCUS parameters or serum lactate levels.

**Conclusions:** Serum hs-cTnT levels as well as the range of variation of pulmonary fluid removal may signal worsening of myocardial injury in critically ill patients with severe AKI and under IHD.

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

Underlines represents presenting author.
FR-PO134

Clinical Presentation and Outcome in a Series of 258 Japanese Pediatric Patients with Thrombotic Microangiopathy: A Nationwide Survey during 2012-2015

Osaka City General Hospital, Osaka, Japan; 4Dept. of Pediatrics, Kobe Univ. School of Medicine, Kobe, Japan

Background: Thrombotic microangiopathy (TMA) includes hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). As recent studies have shown that HUS has various pathogeneses, we conducted the present study to clarify in detail the epidemiological characteristics of pediatric patients with TMA classified according to etiology.

Methods: This survey evaluated 258 Japanese pediatric patients who were diagnosed as having TMA and followed up between 2012 and 2015.

Results: The primary diseases responsible for TMA were categorized as TTP, Shiga toxin-producing Escherichia coli-associated HUS (STEC-HUS), atypical HUS, and secondary TMA. In these four categories, the most frequent primary disease was STEC-HUS which was present in 64.3% of the patients, followed by in order by atypical HUS (15.5%), secondary TMA (10.1%), and TTP (5.8%). About 40% of patients with TMA required renal replacement therapy during the acute phase. The final outcomes in terms of renal functions were normal renal function with normal urinalysis parameters in 95 patients, and CKD stage I in 62. However, in 31 patients chronic renal insufficiency (CKD stage II to V) persisted, including 4 patients with end-stage kidney disease (CKD stage V). Seventeen patients suffered recurrence of TMA, and 8 patients died. Among extrarenal complications at the final outcome point, hypertension and neuro-psychological changes were most frequent.

Conclusions: This study of epidemiological and demographic information for Japanese pediatric patients with TMA over the period 2012-2015 has confirmed the relative proportions of the primary underlying diseases reported previously. Pediatric patients with TMA should be followed up with monitoring of laboratory data including urinalysis, as in this series various symptoms remained at the end of the observation period.

FR-PO135

Acquired Thrombotic Thrombocytopenic Purpura Secondary to Hereditary Autoimmunity: A Model for a New Pathogenic Mechanism?

Pediatrics, Osaka Medical College, Takatsuki, Japan; 2Pediatrics, Shiga University of Medical Science, Shiga, Japan; 3Pediatrics, Osaka City General Hospital, Osaka, Japan; 4Dept. of Pediatrics, Kobe Univ. Graduate School of Medicine, Kobe, Japan

Background: Acquired TTP is an acquired thrombocytopenic purpura (aTTP) that occurs in the absence of Shiga toxin-producing Escherichia coli. It has been observed mainly in association with autoimmune diseases such as post-translational protein changes or epigenetic inherited processes. We present the case of a 21-year-old male admitted for TTP with a negative 72 hour washout period.

Methods: We present the case of a 21-year-old male admitted for TTP with a negative 72 hour washout period.

Results: We present the case of a 21-year-old male admitted for TTP with a negative 72 hour washout period.

Conclusions: We present the case of a 21-year-old male admitted for TTP with a negative 72 hour washout period.

FR-PO136

Ongoing Eculizumab (ECU) Prevents Thrombotic Microangiopathy (TMA) in Patients (Pts) with Atypical Hemolytic Uremic Syndrome (aHUS): Final Long-Term Observational Study Data

Fujimaru,1 Yuko Aki,2 Akira Ashida,1 Hideki Matsumura,1 Akihiko Shirasu,1 Hyogo Nakakura,1 Kazumoto Iijima,1 1Pediatrics, Osaka Medical College, Takatsuki, Japan; 2Pediatrics, Shiga University of Medical Science, Shiga, Japan; 3Pediatrics, Osaka City General Hospital, Osaka, Japan; 4Dept. of Pediatrics, Kobe Univ. Graduate School of Medicine, Kobe, Japan

Background: Pts from previous ECU trials in aHUS could enroll in this observational long-term follow-up study (NCT01522170; enrollment-follow-up concluded), regardless of ongoing ECU use. The objective was to evaluate TMA rates and safety off and on ECU.

Methods: Endpoints included TMA event rate (primary) and targeted serious adverse events (TSAEs).

Results: In 93 pts (42 off with 82 with on-treatment periods), the TMA event rate was 3-fold higher off vs on ECU. Rates were stratified by baseline characteristics (Table). TSAE rates were higher off vs on ECU. Four pts had meningococcal infections on ECU in the current study; all recovered with treatment and remained on ECU without dosing changes.

Conclusions: Final data from the largest prospective cohort with aHUS, with some pts receiving ECU for >5 yrs, demonstrate clinical benefits with ongoing ECU.

FR-PO137

Atypical Hemolytic Uremic Syndrome (aHUS) Presenting as Acute Heart Failure: A Rare Presentation Diagnosed on Skin Biopsy

S. Han,1 S. Savneek Gupta,2 Shrinivas Chugh,1 Anastasios Papanagnou,1 Tasleem Katri,1 Praveen N. Chander,1 1Westchester Medical Center, Valhalla, NY; 2New York Medical College, Valhalla, NY

Background: aHUS is associated with Complement over-activation secondary to regulatory gene mutations. Kidney is the most commonly involved organ due to unique characteristics of glomerular endothelium. Cardiac involvement occurs in about 3-10% cases with aHUS, can be severe with the acute presentation but, a diagnosis of aHUS remains unrecognized in many such cases. Cardiac manifestations include myocardial infarction, cardiomyopathy and heart failure (HF). Treatment of aHUS includes blockade of the terminal Complement pathway (C5b-9) however, spontaneous recovery can occur. We present a unique case of aHUS with primary cardiac involvement that affected kidney as well but, was diagnosed with specific manifestations on the skin biopsy.

Methods: A 24-year-old man presented with acute onset of shortness of breath. Initial workup revealed cardiacogenic shock, acute kidney injury (serum creatinine 2.54 mg/dl) and thrombocytopenia (platelet count 69,000). Right heart catheterization showed an ejection fraction (EF) of 10% requiring intra-aortic balloon pump. Laboratory
investigations revealed new onset hematuria with RBC casts, proteinuria (0.7g/m), low hemoglobin (8.9g/dL), low hematocrit (28.2%), elevated liver enzymes (ALT 181, AST 193), high lactate dehydrogenase (3,462 U/L), low urinary N-acetyl-β-D-glucosaminidase (0.4 U/L), 24 hour urine protein creatinine ratio of 8.8,UA 15% and a-ANCA, hepatitis panel and antiphospholipid Ab tested negative. The patient also developed a skin rash on the arm, which on biopsy showed features consistent with thrombotic microangiopathy (TMA) with positive staining for C3 and C4. The patient underwent a clinical trial of complement blockade therapy. The patient was discharged following significant improvement of renal function, cardiac output (EF 35%) and normalization of platelet count.

Results: Conclusions: aHUS is a rare disease with diagnosis resting on clinical, laboratory and pathological features. In a clinical setting of aHUS, performing kidney biopsy at times may not be feasible in the presence of thrombocytopenia and hence, a skin biopsy may provide diagnostic findings of TMA associated with microvascular staining of Complement C3 and/or C4. In our patient, low urinary N-acetyl-β-D-glucosaminidase activity- 84%. ANA, p and c-ANCA, hepatitis panel and antiphospholipid Ab tested negative. The patient also developed a skin rash on the arm, which on biopsy showed features consistent with thrombotic microangiopathy (TMA) with positive staining for C3 and C4. The patient underwent a clinical trial of complement blockade therapy. The patient was discharged following significant improvement of renal function, cardiac output (EF 35%) and normalization of platelet count.

FR-PO138


An T Pham,1 Khurram Jamil,2 Lalun Kodaly,3 David K. Hayashida,3 Belinda Lovelace,4 Xingyue Huang,3 Health Economics and Outcomes Research, Mallinckrodt Pharmaceuticals, Hampton, NJ; 2University of California San Francisco, San Francisco, CA; 3Mallinckrodt Pharmaceuticals, Hampton, NJ; 4Boston Strategic Partners, Inc., BOSTON, MA; 5Boston Strategic Partners, BOSTON, MA.

Background: Hepatorenal Syndrome (HRS), the development of functional renal failure in patients with chronic liver disease is associated with high morbidity and mortality. The objective of this study was to assess the clinical sequelae, cost burden, and cost drivers of HRS from US hospital perspective.

Methods: A retrospective, longitudinal analysis of the CERNER Health Facts® electronic health record (EHR) database from a large network of US hospitals was performed. Adult patients diagnosed with HRS based on ICD-9 code (572.4) between 2009 and 2015 were included in the analysis. Clinical staging and laboratory data were used to assess the health impact of these patients.

Results: We identified 1,571 male (61.8%) and 971 female (38.2%) patients (mean age: 57.9). Overall, the average length of stay was 34.6 days and hospitalized cost was $91,504. Using Kidney Diseases Improving Global Outcomes Acute Kidney Injury (KDIGO®-AKI) staging classification, the average hospitalization cost for patients with stage 1 AKI was $62,563, in comparison to $143,620 for patients with stage 2 AKI. In addition, when changes in serum creatinine were examined over the duration of the HRS hospitalization, 44.1% had either no change or <20% improvement in serum creatinine from the time of hospital admissions. During the first HRS hospitalization, 36.8% of patients died and average cost of hospitalization was $108,497 for deceased versus $82,048 for a surviving patient. The HRS hospital readmission rate was 33.1%, which was comprised of 13.5% unplanned readmissions and 19.6% planned readmissions. Patients with unplanned readmissions had an average total cost of care of $97,590 in comparison to $76,803 for patients with planned readmissions.

Conclusions: From a hospital perspective, results from this analysis of a large network of US hospital database indicate that HRS is associated with high cost burden along with high rate of readmission and mortality. More importantly, many patients had either limited or no serum creatinine improvement during their hospital stays. High disease severity and unplanned re-admissions may be associated with higher cost of care. Together, these results point to a significant unmet medical need in this patient population and the need for additional treatment options to improve patient outcomes.

FR-PO139

Vitamin C Therapy Attenuates the Severity of AKI in Mice Model of Hepatorenal Syndrome Nadia Yousef1 Siddhartha S. Ghosh,1 Daniel E. Carl1 1None, Richmond, VA; 2VCU Medical Center, GLEN ALLEN, VA; 3VCU MedicalCtr, Richmond, VA.

Background: Hepatorenal syndrome (HRS) type 1 is a life threatening complication of chronic liver disease. Patients with Chronic Liver Disease complicated by HRS have a deficit in renal vasodilation and secondary impairment of glomerular filtration in the setting of liver disease. There are unfortunately few therapeutic options to offer. A significant limitation in HRS research is the lack of animal models investigating the pathophysiology of HRS. To fill this gap, we evaluated vitamin C as a potential beneficial therapy. We hypothesized that Vitamin C has a protective effect in HRS. We tested this hypothesis in murine model of HRS.

Methods: C57BL6 mice received 1ml/kg of carbon tetrachloride (CCl4) biweekly for 12 weeks to induce cirrhosis. A 6 mg/kg of Lipopolysaccharide (LPS) was given intraperitoneally to induce acute kidney injury by simulating an acute onset of renal vasconstriction and secondary impairment of glomerular filtration in the setting of liver disease. There are unfortunately few therapeutic options to offer. A significant limitation in HRS research is the lack of animal models investigating the pathophysiology of HRS. To fill this gap, we evaluated vitamin C as a potential beneficial therapy. We hypothesized that Vitamin C has a protective effect in HRS. We tested this hypothesis in murine model of HRS.

Results: Conclusions: In mice treated with vitamin C (Vit C), there was a significant improvement in renal function, cardiac output (EF 35%) and normalization of platelet count. However, it remains unclear whether the treatment target should be a specific absolute MAP value or a defined increment in MAP respect to baseline.

Methods: Results: Conclusions: Ninety-two patients with HR-AKI treated for up to 3-7 days with either midodrine/octreotide (M/O, n=73) or norepinephrine (NE, n=19) were identified. Forty-three (47%) of the patients (mean age 52 years, 44% women, mean sCr 3.7 ± 1.3 mg/dL and significant reduction in sCr of > ≥ 15 mmHg rise in MAP for 48 hours [24 (33%) with M/O, 18 (95%) with NE]. When analyzed based on tertiles of absolute value of achieved MAP (65-74, 75-84, and 85 mmHg), there was a significant trend for greater reduction in sCr with higher achieved MAP (p=0.002). Furthermore, those who achieved a MAP of ≥ 85 mmHg had a greater reduction in sCr (from 85 mmHg increment in MAP from baseline [=0.17 ± 0.4 mg/dL (p=0.0004) and -0.58 ± 0.5 mg/dL (p=0.04), respectively]). Analysis based on tertiles of magnitude of MAP increment from baseline (5-9, 10-14, ≥ 15 mmHg), there was a significant trend for greater reduction in sCr for those who reached a MAP increase of ≥ 15 mmHg had a greater reduction in sCr ≥ 1.95 ± 0.5 mg/dL compared to those with either a 5 or 10-14 mmHg increment in MAP from baseline [=0.17 ± 0.4 mg/dL (p=0.0004) and -0.58 ± 0.5 mg/dL (p=0.04), respectively]. Achievement of either a target MAP ≥ 85 mmHg or an increment in MAP ≥ 15 mmHg from baseline within the first 3 days of vasocconstrictor therapy is associated with greater reduction in sCr in HR-AKI. These data support the notion of a shift in the renal autoregulatory curve in HR-AKI.

FR-PO141

National Trends in Hospitalization and Resource Utilization in the Hepatorenal Syndrome Population: 2005-2014 Paris Charilaiou,1 Kalpit Devani,2 Ayan De,3 Alvaro Comejo cobo,4 Romela Petroysan,2 Pablo Garcia,5 Division of Gastroenterology, East Tennessee State University, Johnson City, TN; 2Internal Medicine, Saint Peter’s University Hospital, New Brunswick, NJ; 3Internal Medicine, Saint Peter’s University Hospital, New Brunswick, NJ; 4Internal Medicine, Saint Peter’s University Hospital, New Brunswick, NJ; 5Internal Medicine, Greenville Memorial Hospital, Greenville, SC; 6Internal Medicine, Saint Peter’s University Hospital, New Brunswick, NJ.

Background: Recent changes in guidelines for diagnosis and treatment of Hepatorenal Syndrome (HRS) could have potentially affected hospital outcomes in these patients. We analyzed hospitalization and outcome trends of HRS cases, as well as outcome predictors, in the US inpatient population from 2005 to 2014.

Methods: We included all adults from the National Inpatient Sample (2005-2014), excluding cases with missing data on age/gender/inpatient mortality, who had documented liver cirrhosis (571.2, 571.5, 571.6) and HRS (572.4) as any discharge diagnosis, using the International Classification of Diseases, Tenth Revision - Clinical Modification (ICD-10-CM) codes. Multivariable mixed-effects regression was used to assess hospitalization trends as well as predictors of mortality, length of stay (LOS), and hospitalization costs. National estimates were calculated.

Results: We identified 158,306 HRS discharges, with males (65.4%) and white race (66.4%) being the majority. HRS annual prevalence increased exponentially (adjusted-R²=0.99). Mean age was 57±6.08 years (increasing>g-trend=p<0.001). Mean mortality rate was 32.0% with decreasing trend (41% to 26.5%, p<0.001). Mean costs were $310.8 million in 2005 to $762.8 million in 2014 (significant (all p<0.001).

Conclusions: Achievement of either a target MAP ≥ 85 mmHg or an increment in MAP ≥ 15 mmHg from baseline within the first 3 days of vasocconstrictor therapy is associated with greater reduction in sCr in HR-AKI. These data support the notion of a shift in the renal autoregulatory curve in HR-AKI.
FR-PO142
Renal Hypertrophy in End-Stage Liver Disease
Marc M. Saad, Carla L. Ellis, W. Charles O’Neill. Emory University, Atlanta, GA.

Background: Renal failure has been extensively studied in liver disease but the normal physiologic responses to liver dysfunction remain unknown. We hypothesized that decreased clearance of metabolic products by the liver increases metabolic demand on the kidneys, leading to hypertrophy.

Methods: Renal parenchymal volume (RPV) was measured on outpatient CT scans performed in 29 patients with end-stage liver disease (ESLD) and 30 controls without liver disease. Cross-sectional kidney areas (excluding the renal sinus, vessels, collecting system, and cysts) from sequential transverse images were summed and multiplied by the slice thickness to derive RPV, which was normalized to body height. Renal histology was evaluated in 5 autopsies that were suitable for analysis and compared to 8 autopsies in patients without liver disease. Glomerular size was estimated from the finding of Bowman’s capsule measured at maximal cross-section (7-29 glomeruli/patient, mean 22). Subjects with diabetes, kidney stones, serum creatinine >1.2 mg/dl, or proteinuria >100 mg/dl by dipstick were excluded.

Results: The characteristics of the patients in whom RPV was measured are shown in the table. There were no significant differences between the groups. RPV/height² was 21% greater in ESLD than in controls: 230 ± 7 ml/m in ESLD and 190 ± 7 ml/m (mean ± SE, p = 0.0002). This difference remained significant (p = 0.001) in a multivariate analysis that included age, gender, serum creatinine, and degree of ascites. Glomerular volume was 24% greater in ESLD than in controls (3.68 ± 0.46 vs. 2.96 ± 0.41 mm²/x10⁵) but significance was limited by the small sample size. No edema or vascular congestion was noted in any ESLD kidney.

Conclusions: Renal parenchymal volume is increased in patients with ESLD without evidence of renal disease. This cannot be explained by interstitial edema, vascular congestion, or ascites. There appears to be a similar increase in glomerular volume consistent with renal hypertrophy. This enlargement needs to be considered when evaluating kidney size in ESLD, and the hypertrophy could contribute to the increased risk of acute failure in ESLD.

Funding: Clinical Revenue Support

<table>
<thead>
<tr>
<th></th>
<th>ESLD</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>68±2</td>
<td>73±3</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>48</td>
<td>47</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170±2</td>
<td>170±2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>85±7</td>
<td>82±7</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>8.6±1.8</td>
<td>8.9±1.8</td>
</tr>
</tbody>
</table>

FR-PO143
Outcome of Decompensated Liver Cirrhosis Patients with AKI Treated with Renal Replacement Therapy
Jian Li1, Lenar T. Yessayan,2 Sandeep S. Soman.1 1Henry Ford Hospital, Detroit, MI; 2University of Michigan, Ann Arbor, MI.

Background: Acute kidney injury(AKI) is a common complication in patients with cirrhosis and is associated with high mortality, renal replacement therapy(RRT) is considered futile in hepatorenal syndrome if patient is not liver transplant candidate. The overall survival and predictor mortality is well established in those patients.

Methods: We retrospectively identified 123 patients with decompensated Liver cirrhosis receiving RRT for AKI between Nov. 1, 2013 and Dec. 31, 2015 in our hospital. Diagnosis of decompensated liver cirrhosis was based on previous histology findings or on various associations of clinical, biological, endoscopic, and/or imaging findings; AKI and HRS diagnosis were based on KDIGO and International Ascites Club 2007 criteria. The initiation of RRT was determined by nephrologist based on routine practice indications without presence of intensive or hepatologist involved the care. RRT modality includes SLED- RCA, CVVH or IHD. Death served as outcome, 1, 3 and 6 month’s mortality and selected clinical characteristics were examined. Chi-square two-sided tests were used to compare categorical variables, t test used for numerical data, P<0.05 is statistical significant.

Results: In this cohort, 52.8% was male; age 53.3±11.6; AKI causes: HRS 65; ATN 17; other 3% in 123 patients, Cirrhosis causes: alcohol 79, NASH 18, hepatitis C and B: 10 and 1, others 15. 121 patients had outcome data, 2 patients lost follow up. In the death group, 1, 3 and 6 month’s mortality rate was: 84.9%; 97.2% and 100%, average time on RRT were 20±30 days. In the 15 patients who survived till the time of transplantation, remained or off RRT, their average time on dialysis was 114±86 days; 7 had simultaneous liver and kidney, 2 had liver transplant and off RRT, other 5 patients recovered or with CKD3, one was HD dependent. ICU admission, sepsis, infection and ventilator support were much higher in non-survival patients vs survival patients (58±0 vs 23±0, P<0.003). MELD score difference to increase two groups, but all patients had higher score at time of RRT than at admission (P<0.01).

Conclusions: Patients with RRT dependent AKI in decompensated liver cirrhosis had very high long and short term mortality if they were not a liver transplant candidate. ICU admission, sepsis, infection and ventilator support rates were much higher in non-survival group than survival group.

FR-PO144
Hepatorenal Syndrome in Teaching versus Non-Teaching Hospitals: A Nationwide Analysis
Yung1,2 Di Pan,1,2 David Mariuma,1,2 Marcelo X. Hernandez cuchillas,1,2 Fernando Vazquez de lara,1,2 Michael Gramuglia,1 Ina S. Meicsels,1,2 Division of Nephrology, Department of Medicine, Mount Sinai St. Luke’s and Mount Sinai West Hospitals, New York, NY; 1,2Icahn School of Medicine at Mount Sinai, New York, NY; 1Department of Medicine, Montefiore Medical Center, Scarsdale, NY.

Background: Decompensated cirrhosis is a major cause of mortality and morbidity in the United States. Hepatorenal syndrome (HRS) is one of the potential causes of acute kidney injury (AKI) in patients with cirrhosis. The aim of our study is to determine the differences in outcomes of patients with HRS admitted to teaching hospitals as compared to nonteaching hospitals.

Methods: This is a retrospective cohort study using the 2014 National Inpatient Sample, the largest inpatient database in the United States. A cohort of 32,980 patients over the age of 18 diagnosed with HRS based on ICD-9 CM code was included in the study. Patients admitted for elective procedures were excluded. Hospitals were identified as teaching or nonteaching hospitals based on the American Hospital Association annual survey of hospitals. The primary outcome was in-hospital mortality. The secondary outcomes were mortality, morbidity, as measured by the development of shock, acute respiratory failure, variceal bleed, requirement for dialysis and resource utilization, as measured by the length of hospital stay (LOS) and total hospital charges. Odds ratios (OR) were estimated based on multivariate regression model adjusted for demographics, hepatitis C virus, cirrhosis region, primary cause of kidney disease, income. Analysis was performed using Stata, Version 14.2. Group 1: HRS admission to teaching hospital. Group 2: HRS admission to nonteaching hospital.

Results: Among patients with HRS, the in-hospital mortality rates were not significantly different between the two groups (OR 1.06, p=0.38). However patients in teaching hospital had significantly higher rates of shock (OR 2.33, p<0.001), acute respiratory failure (OR 1.44, p<0.001), variceal bleeding (OR 1.54, p<0.05) and requirement for dialysis (OR 1.34, p<0.001). In teaching hospitals the total charges were $57711.91 more (p<0.001), and the length of stay was also greater (12.02 days vs. 8.07 days, p<0.001).

Conclusions: Patients with HRS admitted to teaching hospitals had significant increase in morbidities as compared to those admitted to non-teaching hospitals. The development of shock, acute respiratory failure, variceal bleed, the requirements for dialysis and resource utilization were greater in teaching hospitals despite similar rates of mortality.

FR-PO145
Different Effects of Aerobic and Combined Exercise on Mitochondrial OXPHOS Proteins in Skeletal Muscle of CKD Patients
Douglas W. Gould,1 Emma L. Watson,2 Scott McGregor,1 Soteres Xenophontos,3 Thomas J. Wilkinson,2 Matthew P. Graham-Brown,2 Joao L. Viana,1 Alice C. Smith,2 Coventry university, Coventry, United Kingdom; 1University of Leicester, Leicester, United Kingdom; 2University Institute of Maia, Porto, Portugal.

Background: Patients with CKD exhibit skeletal muscle wasting and dysfunction. Mitochondrial dysfunction is observed in non-dialysis (ND) CKD, resulting in abnormal oxidative phosphorylation (OXPHOS) and reduced exercise capacity. Exercise is a potent stimulus for mitochondrial adaptations, however the effects in CKD are under investigated.

Methods: 17 ND-CKD patients (mean age ± SD): 11 female; eGFR: 28±8/ml/min/ kg/1.73m²) completed 12-weeks aerobic exercise (AE) (n=9), or combined aerobic and resistance exercise (CE) (n=8) of 8 mins occupancy, 3 days/week. Muscle biopsies were obtained from the vastus lateralis at baseline (B1) and 24h (B2) post the first and final exercise sessions (B3). Mitochondrial OXPHOS proteins were analysed by Western blotting and reported as a ratio of Complex I (100%) to Complex IV (90%) was analysed. A two-way ANOVA for area and magnitude-based differences (MBIs) that calculates quantitative and qualitative probabilities of a true effect based on effect and 90%CI.

Results: CE showed moderate effects on total OXPHOS protein expression with mean increases of 2% (-11 – 80) d=0.39 and 3% (-3 – 80) d=0.47 at B2 and B3 respectively. In comparison, the effects of AE were negligible with mean changes of -2% (-28 – 50) d=0.03 at B2 and -3% (-70 – 150) d=0.04 at B3. Figure 1 shows the results for area and magnitude-based differences.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO146

ABCA1 Mediated Mitochondrial Remodeling in Podocyte Injury and Diabetic Kidney Disease

Gloria Michelle Fontanesi,1 Matthias Kretzler,2 Robert G. Nelson,3 Flavia Fontanesi,1 Sandra M. Merscher,1 Alessia Fornoni,1
1Katz Family Center/ Div of Nephrology, Univ of Miami, Miami, FL; 2U. Michigan, Ann Arbor, MI; 3Diabetes Research Inst, Univ of Miami, Miami, FL;

Background: Diabetic kidney disease (DKD) is the most common cause of ESRD. Decreased podocyte number and glomerular lipid accumulation occurs in clinical and experimental DKD. It has been suggested that podocyte injury in DKD may result from impaired ATP Binding Cassette A1 (ABCA1) mediated cholesterol efflux, mitochondrial dysfunction or increased reactive oxygen species (ROS). However, if impaired ABCA1 function confers susceptibility to DKD by contributing to mitochondrial dysfunction or ROS remains to be established.

Methods: Patients enrolled in the “Renoprotection in Early Diabetic Nephropathy in Pima Indians trial” were separated into progressors and non-progressors (δGFR -97.39±8.2, n=15 and -40.62±8.6, n=16, respectively) based on the change in glomerular filtration rate (δGFR) between enrollment and last examination (10±1 years). Human podocytes were treated with patient sera. ABCA1 expression and cholesterol efflux were measured. SiRNA ABCA1 (siABCA1p) and scrambled control (scCO) podocytes were treated with progressor sera and analyzed for caspase 3 activity. Mitochondrial respiratory chain complexes and ROS production were measured in siABCA1p, Podocyte specific Abca1 fl/fl mice were injected with streptozotocin (STZ) or bred to BTBR ob/ob (DKO) mice. Proteinuria was measured.

Results: Podocytes treated with progressor sera showed reduced ABCA1 mRNA expression (p<0.05) and cholesterol efflux (p<0.01) compared to non-progressors. siABCA1p treated with progressor sera have increased caspase 3 activity (p<0.05) compared to scCO. siABCA1p have increased mitochondrial respiration formation (p<0.01), complex I activity (p<0.05) and ROS production (p<0.001). STZ injected Abca1 fl/fl (p<0.05) and DKO mice (p<0.01) have increased albuminuria compared to diabetic controls.

Conclusions: Our in vitro and in vivo studies show that reduced ABCA1 expression confers mitochondrial dysfunction possibly by contributing to mitochondrial remodeling. Treatment strategies targeting ABCA1 function or mitochondrial dysfunction may be beneficial to prevent podocyte injury in DKD.

Funding: NIDDK Support

FR-PO147

Kidney Injury Molecule-1 (KIM-1) Mediates the Proximal Tubule Uptake of Free Fatty Acids (FFA) Resulting in Mitochondrial Injury and the DNA Damage Response (DDR)

Yutaro Morii, Pierre Galichon, Craig R. Brooks, Takaharu Ichimura, Joseph V. Bonventre. Renal Division, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA

Background: KIM-1 is the most upregulated proximal tubule protein in kidney injury. KIM-1 mediates the uptake of apoptotic cells and oxidized low-density lipoproteins (oxLDL). Dereglulation of lipid metabolism during diabetes causes disturbed FFA metabolism which is implicated in injurious effects on the kidney in diabetic nephropathy (DN).

Methods: Renal epithelial cells expressing KIM-1 (KIM-1-PK1) were exposed to the FFA palmitic acid, and FFA uptake, necrotic cell death, accumulation of lipids and the DDR were assessed in vitro. Mitochondrial status and lysosomal activation were measured using the MitoTracker and LysoSensor dyes, respectively. Pro-fibrotic factor(s) production by FFA-treated KIM-1-PK1 cells were determined with a fibrosa biosensor using mouse primary baby kidney fibroblasts. Functional knockout of KIM-1 (KIM-1Δmice) and control mice were used for electron microscopic assessment of the effects of KIM-1 on mitochondrial fragmentation in diabetic nephropathy.

Results: FFA were taken up in the KIM-1-PK1 cells but not in control pcDNA-PK1 cells. Necrosis was increased after FFA treatment with KIM in KIM-1-PK1 cells when compared to controls. Lipid droplets were formed in the KIM-1 cells. FFA-treated KIM-1-PK1 cells had an increased number of fragmented mitochondria at 48 hr. These mitochondria co-localized with activated lysosomes suggesting mitophagy. Nuclear p-ATM and p-HAX expression increased in FFA-treated KIM-1-PK1 cells but not in the control cells. Conditioned media, harvested from KIM-1-PK1 cells treated with FFA, increased t-smooth muscle actin expression of mouse fibroblasts. oxLDL uptake also induced mitochondrial fragmentation and nuclear p-ATM and p-HAX in a KIM-1 dependent way. Mitochondrial fragmentation occurred in a streptozotocin model of diabetic nephropathy in wild-type mice but not in KIM-1Δmice.

Conclusions: KIM-1 mediates the epithelial uptake of FFA, which leads to cell death, lipid accumulation, activation of mitochondrial fragmentation and mitophagy, DDR and fibrosis. Our findings suggest that KIM-1-mediated FFA uptake may play an important role in pathophysiology of the DN.

Funding: NIDDK Support

FR-PO148

The Iron Chelator Deferasirox Causes Kidney Disease via Mitochondrial Dysfunction

Esther M. Gottwald, Claus D. Schuh, Dominik Haenmi, Susan Ghazi, Milica Bugarski, Michael Duss, Ehud M. Landau, Andrew Hall.

Background: Deferasirox (DXS) is an oral iron chelator widely used in individuals at high risk of iron overload. It frequently causes kidney disease, by previously unknown mechanisms. Toxicity is localized to the proximal tubule (PT) and manifests clinically as the renal Fanconi syndrome (FS). PT cells are densely packed with mitochondria, which require iron for normal metabolism. We hypothesized that DXS causes kidney disease via mitochondrial toxicity.


Results: In PT-derived cells and fresh slices of mouse cortex we discovered that DXS induces rapid swelling of mitochondria, leading ultimately to rupture of the inner mitochondrial membrane (IMM). Other iron chelators did not have the same effect. Nuclear and mitochondrial polarized swelling processes, which was not prevented by inhibition of the permeability transition pore, but was rapidly reversed by the addition of iron. Of note, DXS did not inhibit oxygen consumption or cause oxidative stress, and targeted anti-oxidants did not prevent the phenotype. Interestingly, DXS-induced mitochondrial swelling and rupture was accelerated by stimulation of respiratory chain (RC) activity, whilst RC inhibition had the opposite effect, suggesting that swelling is an active process. Moreover, DXS did not induce rupture in an artificial lipid vesicle model of the IMM, implying that toxicity requires proteins normally expressed within mitochondria. Using EM and intravital multiphoton microscopy, we observed that mice given DXS for 10 days showed evidence of mitochondrial swelling and dysfunction in vivo, exclusively in the PT, as well as impaired solute transport (consistent with FS). DXS is mainly albumin bound in blood, and we found that albumin binding reduced its toxicity in vitro, which might explain why the drug is tolerated by patients. Furthermore, since albumin is actively taken up by the PT, this could also explain the localization of DXS toxicity to this nephron segment.

Conclusions: In summary, we have found that DXS induces swelling and rupture of mitochondria in the PT, which most likely explains why it causes kidney disease in humans.

Funding: Government Support - Non-U.S.

FR-PO149

Bisphenol A Is an exogenous Toxin That Promotes Mitochondrial Injury and Death in Tubular Cells

Enrique Bosch,1 Alberto Ruiz,2 Esther Civantos,1 Alberto Ortíz,3 Emilio E. Gonzalez-parra,2 Sebastián Mas.1 IIS-FJD, Madrid, Spain; Fundacion Jimenez Diaz, Madrid, Spain.

Background: Bisphenol A is a ubiquitous environmental toxin, structurally related with pC, that accumulates in CKD, but is not currently considered a uremic toxin. Our aim was to characterize the nephrotoxic potential of BPA. Specifically, we addressed whether it disrupts mitochondrial function and causes cell death in energy demanding cells as tubular cells.

Methods: Experiments were performed on HK-2 human proximal tubular epithelial cells. Cell death and oxidative stress were evaluated by flow cytometry and confocal microscopy in HK-2 human proximal tubular epithelial cells. Functional assays tested AT, intracellular Ca2+, mitochondrial function (TMRR), oxygen consumption, Nrf2 binding and NAPDH oxidase activity. Gene expression was assessed by qRT-PCR.

Results: BPA is a low molecular weight, environmental toxin, that is mostly albumin bound in blood, and we found that albumin binding reduced its toxicity in vitro, which might explain why the drug is tolerated by patients. Furthermore, since albumin is actively taken up by the PT, this could also explain the localization of DXS toxicity to this nephron segment.

Conclusions: In summary, we have found that DXS induces swelling and rupture of mitochondria in the PT, which most likely explains why it causes kidney disease in humans.

Funding: Government Support - Non-U.S.

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

438
FR-PO150

Elastica Masson’s Trichrome (EMT) Staining Is Useful for the Visualization of Podocyte Foot Process and Tubular Mitochondria in the Kidney

Background: Changes in microstructures of renal cells, such as foot process effacement in podocytes and mitochondrial fission in tubular cells, are tightly correlated with the development and the progression of kidney disease. Because the sizes of these structures are much less than the diffraction limit of visible light, electron microscopy is usually required for their observation. Super-resolution microscopy (SRM) is also available, but the computation technique for SRM requires time-consuming immunofluorescent staining for specific molecules.

Methods: To visualize the microstructures more easily, we analyzed paraffin-embedded human renal biopsy sections stained with EMT, Hematoxylin Eosin (HE), Periodic Acid-Schiff (PAS), or Periodic Acid Methenamine Silver (PAM) using structured illumination microscopy. Sections of animal kidney disease models were also analyzed.

Results: EMT-stained paraffin-embedded sections excised by 457 or 561 nm laser were useful for the visualization of podocyte foot process. We could observe foot process in the sections from minor glomerular abnormalities but not from minimal change disease. Foot process was also observable in EMT-stained normal rat kidney but not in puromycin aminonucleoside injected kidney. The other staining methods — HE, PAS, and PAM — were not applicable to the evaluation of foot process. In the tubulointerstitial area and the glomerular tuft, EMT-stained sections excised by 561 nm laser were useful for the evaluation of mitochondria. In some patients with kidney disease, we observed short mitochondria, which suggested the progression of mitochondrial fission. We confirmed the usefulness of EMT staining for the evaluation of mitochondria by observing mitochondrial fission and kidney injury and mitochondrial swelling in ischemia reperfusion kidney injury in mice. Tubular mitochondria were also observable in HE or PAS-stained sections, but the images obtained by these staining were less clear.

Conclusions: Paraffin-embedded kidney sections stained with EMT were useful for the visualization of foot process and mitochondria in the kidney.

Funding: Private Foundation Support

FR-PO151

Advanced Oxidation Protein Products Aggravate Tubulointerstitial Fibrosis through PKC-Dependent Mitochondrial Injury in Early Diabetic Nephropathy

Background: Accumulating studies indicate that mitochondrial dysfunction is central to the pathogenesis of many kidney disease, we study the relation between urinary supernatant cell-free mitochondrial DNA (mtDNA) level and renal dysfunction in DN.

Methods: We recruited 92 patients with biopsy-proven DN. Urinary supernatant mtDNA level was measured by digital polymerase chain reaction, and compared to clinical, biochemical, histological data, as well as renal function decline in the subsequent 24 months.

Results: Mitochondrial DNA could be detected in all urine supernatant and renal biopsy specimens, with average levels 1421.0 ± 1827.5, and 286114.4 ± 193481.0 copies/µl, respectively. There was a modest but statistically significant inverse correlation between the supernatant mtDNA level and urinary albumin excretion (r = -0.070, p = 0.5). Urinary supernatant mtDNA level had modest but statistically significant correlations, inversely with estimated glomerular filtration rate (GFR) (r = -0.214, p = 0.04), and positively with the severity of interstitial fibrosis (r = 0.300, p = 0.005). However, there was also no significant correlation between the rate of GFR decline in 2 years and urinary supernatant mtDNA level (r = -0.070, p = 0.5).

Conclusions: Urinary supernatant mtDNA level may reflect the severity of kidney damage and intra-renal mitochondrial depletion in DN. Further studies are needed to confirm its role as biomarker of diabetic nephropathy.

Funding: Government Support - Non-U.S.

FR-PO153

Metabolic Reprogramming in Diabetic Kidney Disease Can Be Resorted via SGLT2 Inhibition

Background: Long-term hyperglycemia is a primary cause of chronic kidney disease. In diabetic patients, glucose suppresses mitochondrial respiration. In this study we used metabolomic and biochemical assays in the type 1 Akita DKD mouse model and in patients with DKD to decipher the consequences of high glucose on metabolic reprogramming leading to proximal tubule damage. Furthermore, we analyzed a therapeutic potential of the proximal tubule glucose transporter, SGLT2, responsible for absorption of the majority of the filtered glucose.

Methods: Metabolomic analysis was performed by GC-MS/MS from control and type 1 diabetic mice (Akita, n=6 each) in the presence and absence of SGLT2 inhibitor empagliflozin (~45mg kg-1 day-1). Urinary lactate and pyruvate concentrations were measured in biochemical assays on specimens of rats with type 2 diabetes and albumin creatinine ratio >100mg/g, enrolled in a cross-over study with the SGLT2 inhibitor dapagliflozin or placebo (6 weeks, 10mg/day, n=33 total). Metabolic functional changes in human kidney proximal tubule (HK2) cells were analyzed using Seahorse XF technology.

Conclusions: Metabolomic analysis in Akita mice indicated a marked increase in glycolysis with an increase in the lactate/pyruvate ratio in urine (p<0.0002, 95% CI), plasma (p=0.02) and kidney tissue (p=0.06) as compared with non-diabetic controls. The urinary lactate/pyruvate levels in Akita mice were reduced upon treatment with empagliflozin (p<0.0002 and the decrease in lactate/pyruvate ratio was 34% in the SGLT2 knockout mice vs wild type controls despite similar blood glucose levels (p<0.05). Furthermore, in T2D patients, dapagliflozin decreased the urine lactate/pyruvate ratio by 34% (p=0.03) compared to placebo and this decrease correlated with the decline in eGFR (r=0.042, p<0.04). Studies in HK2 cells confirmed that acute glomerular treatment can significantly inhibit rate of glucose consumption and enhance lactate production suggesting a ‘Crabtree’ effect indicative of glucose suppression of mitochondrial respiration.

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

FR-PO154

Mitochondria-Targeted Antioxidant Peptide SS-31 Attenuates Renal Tubulointerstitial Injury via Regulating Mitochondrial Dynamics in Diabetic Nephropathy

Background: Accumulating studies indicate that mitochondrial dysfunction is central to the pathogenesis of many kidney disease, we study the relation between urinary supernatant cell-free mitochondrial DNA (mtDNA) level and renal dysfunction in DN.

Methods: We recruited 92 patients with biopsy-proven DN. Urinary supernatant mtDNA level was measured by digital polymerase chain reaction, and compared to clinical, biochemical, histological data, as well as renal function decline in the subsequent 24 months.

Results: Mitochondrial DNA could be detected in all urine supernatant and renal biopsy specimens, with average levels 1421.0 ± 1827.5, and 286114.4 ± 193481.0 copies/µl, respectively. There was a modest but statistically significant inverse correlation between the supernatant mtDNA level and urinary albumin excretion (r = -0.070, p = 0.5). Urinary supernatant mtDNA level had modest but statistically significant correlations, inversely with estimated glomerular filtration rate (GFR) (r = -0.214, p = 0.04), and positively with the severity of interstitial fibrosis (r = 0.300, p = 0.005). However, there was also no significant correlation between the rate of GFR decline in 2 years and urinary supernatant mtDNA level (r = -0.070, p = 0.5).

Conclusions: Urinary supernatant mtDNA level may reflect the severity of kidney damage and intra-renal mitochondrial depletion in DN. Further studies are needed to confirm its role as biomarker of diabetic nephropathy.

Funding: Government Support - Non-U.S.

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

439
Pharmaceuticals, Maale Adumim, Israel; 4University of Cologne, Cologne, Germany; 5University of Cologne Medical Center, Cologne, Germany

Jerusalem, Israel; 2Shaarey Zedek Medical Center, Jerusalem, Israel; 3Teva Medical College of Georgia, Augusta, GA

Preconditioning an Important Role in the Protective Effect of Renal Ischemic Re-Routing of Mutant Protein from Mitochondria to Peroxisome: FR-PO155

in combination with Midivi1 could enhance the effects of antioxidant and anti-apoptosis. Midivi1 could also ameliorate HG-induced mitochondrial dysfunction, while SS-31 used with SS-31 could partially reverse such abnormalities. Pretreatment with Drp1 inhibitor the expression of Drp1 and P66Shc, Bax, Caspase-1, IL-1, FN. However, pretreatment vitro, HG induced mitochondrial dysfunction, including altered membrane potential fragmentation, while SS-31 treatment with Deph inhibitor Midivi1 could also ameliorate HG-induced mitochondrial dysfunction, while SS-31 in combination with Midivi1 could enhance the effects of antioxidant and anti-apoptosis.

Conclusions: These data indicate that SS-31 ameliorates tubulointerstitial injury via inhibiting mitochondrial fragmentation in DN.

FR-PO155

Re-Routing of Mutant Protein from Mitochondria to Peroxisome: A Therapeutic Approach for Primary Hyperoxaluria Type I Ruth Belelofsky,1 Roman Lyakhovetsky,1 Bodo B. Beck,2 Björn Reuscher,1 Fanny Shked1 Yaacov Frischberg,2 Shaare Zedek Medical Center, Jerusalem, Israel; 1Shaare Zedek Medical Center, Jerusalem, Israel; 2Teva Pharmaceuticals, Maale Adimim, Israel; 3University of Cologne, Cologne, Germany; 4University of Cologne Medical Center, Cologne, Germany.

Background: Primary hyperoxaluria type I (PH1) is caused by deficiency of the liver specific peroxisomal (Px) alamine-glyoxylate aminotransferase (AGT). Due to low solubility of calcium oxalate, PH1 results in progressive nephrocaldinosis and decline in kidney function to ESRD. The most frequent AGT mutation G170R results in aberrant mitochondrial localization with partial catalytic activity. The Q90R allele, which stimulates Px localization of the mutated protein may prevent oxalate production. To identify such molecules we developed the split GFP system in which only peroxisomal AGT sub-population produces a fluorescent signal. This sensitive and specific tool allows precise monitoring of Px sub-population of AGT: confocal microscopy confirms that GFP signal of both WT and G170R AGT is localized exclusively in Px and is substantially stronger in the WT-AGT. Using split GFP, we demonstrated that localization of G170R-AGT can be corrected by mild translation inhibition using the inhibitors emetine (a known autophagy-inducing agent) and GC7 7 days incubation of G170R-AGT-GFP transfected CHO cells with 40 nM emetine resulted in 70-80% increase in the number of GFP positive cells as quantified by FACs analysis. Under these conditions, total protein synthesis decreased by less than 25%. We also measured the effect of mitochondrial transport inhibitors: DECA and monensin, recently indicated to correct G170R-AGT- AGT localization. Both compounds, but not GC7, presented synergistic effect with emetine. We assume that DECA and monensin assist AGT relocation by mitochondrial transport interference while emetine and GC7 interfere with protein synthesis. The functional competence of peroxisomal AGT was confirmed in human hepatoma HepG2 cells expressing the G170R mutation. Augmented oxalate level in culture media was substantially reduced. In summary, we demonstrate that mild translation inhibition can re-route nascent AGT molecules into the Px. We suggest that this approach may be applicable not only for treating PH1 but also for other diseases caused by protein misfolding. The split-AGT system can be a useful tool in developing new treatments for PH1.

Methods: Results:

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

FR-PO156

Clearance of Damaged Mitochondria via Mitophagy Plays an Important Role in the Protective Effect of Renal Ischemic Preconditioning Man J. Livingston, Zheng Dong. Augusta University Medical College of Georgia, Augusta, GA.

Background: Ischemic preconditioning (IPC) affords tissue protective effects in organs including the kidney; however, the underlying mechanism remains unclear. Autophagy is induced in renal tubular cells during acute kidney injury (AKI) and plays a protective role, but whether autophagy contributes to the protective effect of IPC is unknown.

Methods: This study has examined the role of autophagy in the renoprotection of IPC using both in vivo and in vitro ischemic AKI models. IPC was induced in mice by mild (15 minutes) renal ischemia followed by 1-hour reperfusion. The mice were then subjected to a more severe (27 minutes) renal ischemia to examine kidney injury. In vitro, IPC was induced in proximal tubular cells (RPTC) by 30 minutes of "chemical ischemia" with CCCP followed by 40-minute recovery. The cells were then incubated with CCCP for 3 hours followed by 2-hour recovery (CCCP/3R2h) to examine injury.

Results: IPC suppressed subsequent ischemic AKI. Autophagy was induced in kidneys by IPC. Notably, the renoprotective effect of IPC was abolished by autophagy inhibitors and also in kidney proximal tubule-specific Atp7 knockout mice, suggesting the dependence of IPC renoprotection on autophagy. Along with autophagy induction, the mitophagy regulator Pink1 was activated and there was a remarkable loss of mitochondrial proteins following ischemic AKI, suggesting that autophagy may protect kidneys by activating mitophagy. Consistent with in vivo observations, IPC in RPTC cells showed protection by autophagy. Mitochondrial morphological analysis were carried out by measuring ROS, TMRE, mitochondrial morphology.

Results: Extracellular matrix deposition and apoptosis of tubular cells were found in DN mice. The expression of Drp1, P66Shc, Bcl-2, Bax, Caspase-1, IL-1, FN. were increased in Western half of DN mice, while controls treated with SS-31 partial renal ischemic and reperfusion, in addition, in SS-31 treatment could attenuate renal pathologic changes, serum creatinine, microalbuminuria, renal ROS and apoptosis levels. On the other side, the tubular mitochondrial of DN mice exhibit deformations, such as swelling and fragmentation. Treatment with Replican, a multi-targeted drug, reduced mitochondrial fragmentation in vitro, HG induced mitochondrial dysfunction, including altered membrane potential and increased overproduction of mitochondrial superoxide. Furthermore, HG increased the expression of Drp1 and P66Shc, Bax, Caspase-1, IL-1, FN. However, pretreatment with SS-31 partially reversed such abnormalities. Pretreatment with Deph inhibitor Midivi1 could also ameliorate HG-induced mitochondrial dysfunction, while SS-31 in combination with Midivi1 could enhance the effects of antioxidant and anti-apoptosis.

Conclusions: These data indicate that SS-31 ameliorates tubulointerstitial injury via inhibiting mitochondrial fragmentation in DN.

FR-PO157

PKC-a Inhibition Normalizes Nephrotic Serum Induced Disruption of Mitochondrial Membrane Potential and Morphology in Glomerular Endothelial Cells Nino Kvirkvelia,1 Malgorzata Mecmenain,1 Marie Warren,1 Raghavan Raju,2 Rudolf Lucas,2 Michael P. Madaio,3 Augusta University, Augusta, GA; 3Medical College of Georgia, Augusta University, Augusta, GA.

Background: Nephrotic serum nephritis (NTN), an inflammatory model of antibody mediated nephritis caused by single injection of nephrotic serum (NTS), proceeds to end stage kidney disease. Earlier studies have shown that NTS treatment damages cultured glomerular endothelial cells by disrupting mitochondrial respiration, and that PKC-a Inhibition normalized these perturbations. The goal of this study was to determine the morphological pathways involved in this process.

Methods: Murine glomerular endothelial cell (GEC) viability was evaluated by LDLR release following NTS exposure. PKC-a was pharmacologically inhibited with Ro-320432 (EMD Millipore, Billerica, MA). Changes in mitochondrial membrane potential (ΔΨm) were measured using cationic carbocyanine dye, which changes fluorescence spectrum depending on mitochondrial potential status. Mitochondrial morphology and distribution were examined using Mitotracker–mitochondrion selective probes.

Results: Following NTS exposure, LDLR release, measured as per cent of LDL cytoxicity, was dramatically increased in GEC up to 50%, whereas PKC-a inhibition (50 nM Ro-320432) reduced cytotoxicity significantly (12%), indicating that PKC-a is involved in NTS-induced endothelial cell cytotoxicity. NTS treatment of GEC resulted in reduction of ΔΨm and in an increase of cells with depolarized mitochondria by 73%. PKC-a inhibition of NTS-treated cells reduced the number of cells with depolarized mitochondria to 15%. Furthermore, NTS reduced the fraction of cells with healthy mitochondria by 35% while PKC-a inhibition increased the fraction of healthy mitochondria by 20%. Mitochondrial swelling, documented by the appearance of large and round shaped mitochondria, was observed in endothelial cells after NTS treatment using Mitotracker–mitochondrion selective probes, which coincided with a loss of ΔΨm. PKC-a inhibition in NTS-treated GEC restored the podocyte appearance in the majority of mitochondria.

Conclusions: PKC-a participates in NTS induced mitochondrial dysfunction in GEC cells and inhibition of PKC-a significantly improves endothelial cell viability by normalizing mitochondrial membrane potential and morphology. These results may foster the design of novel therapeutic approaches that preserve mitochondrial function during kidney injury.

Funding: NIDDK Support

FR-PO158

Mitochondrial Protection Regulates Expression of Senescent Cell Regulators p16 and p21 in Parietal Epithelial Cells (PECs) of Aged Kidneys Mariva S. Sweetwyne, Peter S. Rabinovich, Stuart J. Shankland. University of Washington, Seattle, WA.

Background: Mitochondrial dysfunction increases with age and can induce cellular senescence. Kidneys are a mitochondrial rich tissue and show predictable pathological changes with age. We have previously demonstrated that systemic late-age treatment with the mitochondrial protective peptide SS-31 reduced age-induced glomerulosclerosis in mice of 24-28 months of age (~70-85 yr old human). Additionally, mitochondria-protected aged kidneys showed reduced podocyte injury, preservation of endothelial cell number and increased parietal epithelial cell density. Concomitant to these changes was a 19% reduction in senescence-associated β-galactosidase (SAβ-gal) expression across all compartments of the renal cortex. Staining for cell-cycle senescence regulator, p16 increased with age, but with SS-31 treatment was reduced in both PECs and the glomerular tuft of aged mice relative to aged baseline.

Methods: Results: In our current studies we further characterized PEC senescence by staining for expression of p21. Expression of p21 in PECs demonstrated an inverse relationship to that of p16 (p21 young ~57.48% vs. aged vehicle ~20.08% vs. aged SS-31 ~31.46%; p16 young ~19.5% vs. aged vehicle ~55.9% vs. aged SS-31 ~29.6%). Furthermore, expression of p21 in tuft cells did not change with either age or treatment. Close examination of glomeruli in serial sections showed a differential expression of p16 and p21 in PECs along Bowman’s capsule, with individual PECs expressing either p16 or p21 but not both. To determine if senescence in PECs could be directly regulated by age via mitochondrial damage, we exposed immortalized mouse PECs (mPEC) to mitochondrial insult via low doses (5,15, 20 mM) of Rotenone, Oligomycin A and Antimycin A (SAβ-gal) expression across all compartments of the renal cortex. Staining for cell-cycle senescence regulator, p16 increased with age, but with SS-31 treatment was reduced in both PECs and the glomerular tuft of aged mice relative to aged baseline.

Funding: NIDDK Support

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

FR-PO159

Alterations of Mitochondrial Oxidative Metabolism in an Aging Model of Cisplatin Induced AKI

Kanini A. Mapusankw, 1 Hsiang L. Men, 2

Methods: Young (4 months) and old (18 months) C57BL/6J mice received 10mg/ kg intraperitoneal cisplatin injection vs vehicle control. Blood urea nitrogen (BUN) and creatinine (Cr) measurements were obtained at baseline, 3, and 6 days post injection. Kidneys were harvested at 6 days to assess histological changes, mitochondrial oxidative metabolism, and antioxidant response.

Results: Baseline renal function was not significantly different in young vs. old mice. Cisplatin caused significant renal function decline at 3 days in both groups. However, old cisplatin mice had less than 50% survival rate at 6 days compared to 100% survival in young mice. Control old mice demonstrated significant increased steady state levels of O2- and %GSH/GSSG, downregulation of mitochondrial ETC complex I, II, citrate synthase, and aconitase activities compared to young control mice. In both cisplatin groups, there was significant upregulation of complex I activity, with no significant change in complex II-IV activity or citrate synthase activity compared to their respective vehicle controls suggesting that reverse electron transport (RET) may be a source of ROS production in cisplatin induced AKI. In cisplatin treated young mice, there was a significant upregulation of aconitase activity, which was not observed in old mice. Finally, in cisplatin treated old mice increased steady state levels of O2- were observed which was not seen in young mice.

Conclusions: Our results support the hypothesis that aging is accompanied by alterations in oxidative mitochondrial metabolism that can be exacerbated by cisplatin injury. We hypothesize that RET through complex I may contribute to increased ROS alterations in oxidative mitochondrial metabolism that can be exacerbated by cisplatin.

FR-PO160

Sulfotransferase IC2 (SULT1C2) Post-Translationally Increases FR-PO160 Mitochondria Respiration

Diana D. Danniele

Methods: Young (36 months) and old (36 months) C57BL/6J mice were used for these studies. Mitochondria were isolated from ischemic preconditioned kidneys. Using hydrodynamic gene transfer, we increased mitochondria respiration from 139.4 ± 36.2 to 370.7 ± 32.9 pmol/min/mg following succinate and rotenone addition, 2.7-fold compared to mitochondria (P < 0.05). The increase in SULT1C2/PAPS dependent respiration was inhibitable with antimycin A but not rotenone.

Discussion: In conclusion SULT1C2 and PAPS increase the efficiency of complex II respiration indicating a potential change in the movement if electrons through the complex culminating in increased oxidative phosphorylation. This is a novel new function for an enzyme that heretofore was considered to be solely involved in detoxifying xenobiots.

Funding: NIDDK Support, Other NIH Support - NIA

FR-PO161

Megalin-Mediated Shuttling of Angiotensin II, TGF-ß, and Stanniocalcin-1 to the Mitochondria

Ogieting L. Li, 1 Fan Lei, 2 Yi Tang, 2 Jenny S. Pan, 2 Qiang Tong, 1 David Sheikh-Hamad, 1 Baylor College of Medicine, Houston, TX; 2West China Hospital of Sichuan University, Chengdu, China; 3Baylor College of Medicine, Houston, TX.

Background: Some extracellular signaling molecules are detected in the mitochondria, including angiotensin II, insulin, stanniocalcin-1 (STC1), TGF-ß and erythropoietin; these are known as mitochondrial intracranes. The mechanism of mitochondrial targeting of these proteins is unknown. Megalin/LRP2 is highly expressed on the apical surface of kidney proximal tubule cells, where it is involved in the uptake/ reclamation of filtered vitamins, uptake and lysosomal degradation of filtered proteins, uptake of hormones including angiotensin II and angiotensin 1-7. Megalin mutations are linked to the pathogenesis of Donnai-Barrow and Lowe syndromes, characterized by developmental brain abnormalities and kidney dysfunction. Megalin has not been shown to reside in the mitochondria.

Methods: We hypothesized that megalin serves as a shuttle for mitochondrial intracranes from the cell surface to the mitochondria. We performed a cross-sectional analysis of 30 participants from the Muscle mitochondrial Energy Nutrients (MEND) study. Persons were excluded from MEND if they used medications effecting mitochondrial metabolism, had mobility disability, or weighed >300 pounds. We measured mitochondrial capacity of the tibialis anterior muscle as ATPmax using 31P magnetic resonance spectroscopy. We determined the force time integral (an objective measure of muscle fatigue) and assessed fatigue symptoms using the FACIT-F questionnaire.

Results: Mean GFR was 35 ± 15 ml/min; mean age was 61 ± 49 years; 53% were female, and 25% had diabetes. Lower muscle ATPmax was associated with lower force time integral (indicating greater fatigue) (figure 1; P = 0.007) and greater symptoms of fatigue after adjustment (figure 2; P = 0.013).

Conclusions: Muscle mitochondrial capacity measured by ATPmax is associated with objective fatigue and subjective symptoms of fatigue in CKD patients. These findings are the first connecting impaired human skeletal muscle mitochondrial energetics in CKD with functional and clinical measures.

Funding: NIDDK Support

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

Underline represents presenting author.
Figure 1. Association of ATPmax with muscle fatigability.

Figure 2. Association of ATPmax with self-reported fatigue.

FR-PO164
Transfer of Exogenous Mitochondria Protects the Kidneys from Ischemia-Reperfusion Injury
Amandeep Bajwa, KaiHo H. Schlegel, Kyle J. Alexander, Elvira Kurmacea. University of Virginia, Charlottesville, VA.

Background: Mitochondria, a critical player in acute kidney injury, have dual roles as primary source of energy (ATP) and as key regulators of cell death. Ischemia induces altered bioenergetics with increased mitochondrial swelling and reactive oxygen species and ultimately cell death. Ischemia followed by reperfusion (IRI) induces mitochondrial fragmentation in 30-40% of proximal tubule (PT) cells. Therapeutic interventions that target to improve mitochondrial health to repair, reprogram or replace mitochondria to restore respiratory functions are beneficial for prevention and/or treatment of disease.

Methods: Renal injury was assessed by plasma creatinine (Pcr, mg/dl). 8 wk old C57BL/6 (WT) or Rag1ko mice were i.v. injected with exogenous mitochondria (Exo-Mito; 0-500mcg protein equivalent) 1d prior to 26 mins IRI. Exo-Mito was isolated from healthy non-ischemic mouse liver. Splnx was done 7d prior to IRI. Structure (sonicated) or function (Rot/Am A) of Exo-Mito altered prior to injection. For in vitro studies, PT cells (TKPTS) were treated with 200 mcg of Exo-Mito 1d prior to analysis that included measurement of ATP levels, mitochondrial functions (Seahorse flux analyzer), cytokines (pct), immunofluorescence microscopy (uptake efficiency) and flow cytometry (dyes [mitotracker or JC-1]).

Results: In vivo studies demonstrated mitochondria (200mcg, mouse or human) treated mice are significantly protected compared to vehicle treated mice after IRI [Pcr (2.2±0.05 vs 0.6±0.02), p<0.01]. The protection by transferred Exo-Mito in IRI studies was partially abrogated in absence of a spleen but maintained in Rag1ko mice. Furthermore, structurally or functionally altered Exo-Mito no longer protected kidneys from IRI. Transfer of labeled Exo-Mito signal was found in spleen (in macrophages), kidney (in PT, identified with anti-cD11b antibody [labels brush border]), liver and lungs. In vitro studies demonstrate that Exo-Mito-Mitochondria are taken up by TKPTS in a dose dependent manner. TKPTS with Exo-Mito had significantly higher levels of extra- and intracellular ATP, higher basal oxygen consumption rate and spare respiratory capacity measured by Seahorse analyzer and lower cytokines after LPS stimulation.

Conclusions: Our current study demonstrates that take up of Exo-Mito by PT cells (in vivo and in vitro) helps maintain bioenergetics (ATP) to prevent injury.

Funding: NIDDK Support

FR-PO165
Megalin Shuttles Extracellular Angiotensin II and Stanniocalcin-1 to the Mitochondria via Retrograde Early Endosomes to the Golgi Pathway and Regulates Glycolytic and Respiratory Capacities
Qingtian Li,1 Fan Lei,2 Yi Tang,2 Jenny S. Pan,1 Qiang Tong,1 David Sheikh-Hamad.1 Baylor College of Medicine, Houston, TX; 2West China Hospital of Sichuan University, Chengdu, China; 3Baylor College of Medicine, Houston, TX.

Background: Some extracellular signaling molecules are detected in the mitochondria, including angiotensin II, insulin, stanniocalcin-1 (STC1), TGF-β and erythropoietin; these are known as mitochondrial intracines. The mechanism of mitochondrial intracine targeting is unknown. Megalin/LRP2 is highly expressed on the apical surface of kidney proximal tubule cells, and is involved in the uptake of filtered vitamins and proteins. Megalin mutations are linked to the pathogenesis of Donnai-Barrow and Lowe syndromes, characterized by brain defects and kidney dysfunction. Megalin has not been shown to reside in the mitochondria.

Methods: Our data suggest that megalin is present in kidney mitochondria in vivo, and mitochondria of cultured 293T, C2C12 and Raw267.4 cells, and associates with the mitochondrial protease OMA1. The goal of this study was to evaluate how CS alters mitochondrial fusion machinery and to evaluate the therapeutic benefit of OMA1 inhibition.

Results: Male rodent (Lewis) kidneys were isolated and cold stored for 0 or 18 hr and then transplanted (CS/Tx) in a naïve Lewis rat followed by right nephrectomy. Mitochondrial function was assessed via high resolution respirometry and ATP measurement. Mitochondrial fusion and fission pathways were monitored using western blot. A novel method was developed to measure OMA1 activity. Renal injury was assessed by serum creatinine and PAS staining.

Results: Data clearly revealed that CS worsens mitochondrial function when compared to transplantation without CS. Combined CS/Tx lead to OPA1 inhibition and increased OMA1 activity along with an altered protein expression of OMA1. Inhibition of OMA1 using phenanthrolone during CS lead to increased OPA1 expression and improved mitochondrial function. Further studies will characterize the benefit of mitochondrial targeted phanthenolone as a novel therapy to improve mitochondrial and renal function during CS/Tx.

Conclusions: Our results suggest that CS/Tx alters the mitochondrial protease, OMA1, and that OMA1 inhibition improves mitochondrial function. These findings raise the possibility that impaired mitochondrial dynamics may be an unrecognized contributor to cold storage induced injury and compromised renal graft function after transplantation. Supported in part by and AHA 16SDG27600026 (NP) and AHA 16PRE30830010 (SS); as well as NIH T32GM106999 (SS), T32GM106999 (JT).

Funding: Other NIH Support - GM106999-training fellowship, Private Foundation Support
FR-PO166
PKA/CREB Signaling Prevents Adriamycin-Induced Podocyte Apoptosis via Upregulation of Mitochondrial Respiratory Chain Complexes Production Kuei Xie, Zhaohui Ni, Lei Gu. Renji Hospital, Shanghai, China.

Background: The present study was designed to explore the role of cAMP response element binding protein (CREB) in the PKA-induced protection in podocytes.

Methods: Conditionally immortalized differentiated murine podocytes were used in the present experiments. Cell toxicity was examined by using a cell count kit-8. Annexin V/PI staining and flow cytometry were used to detect cell apoptosis. MitoxoTM Red mitochondrial superoxide indicator was used for detecting mitochondrial ROS. We also used Agilent expression profile chip to screen the mRNA expression in differential podocytes treated with or without PKA agonist in the presence or absence ADR. The message RNAs of respiratory chain complexes subunits encoded by mitochondrial genes were detected by using real-time PCR. Luciferase chemiluminescence was used to detect the production of ATP. Western blot was used to detect protein expression.

Results: We found that pretreatment with pCPT-cAMP prevented podocytes against Adriamycin (ADR)-induced increase of cleaved caspase-3 and the loss of podocytes. ADR treatment strikingly enhanced both mitochondrial superoxide and index of ROS in podocyte, this increase was prevented by pCPT-cAMP pre-treatment. Pretreatment with pCPT-cAMP was unable to prevent Adriamycin-induced cleaved caspase-3 expression in CREB RNAi treated podocytes. Data of Agilent expression profile chip studies showed that ADR predominantly decreased the mRNA expression of respiratory chain complex I subunits encoded by mitochondrial genes in podocytes, which was prevented by pretreatment with pCPT-cAMP. Immunoblot experiments showed that activation of PKA prevented ADR-induced decrease of mitochondrial respiratory chain complexes I subunits ND1/3/4 protein expression. Inhibiting of CREB expression prevented pCPT-cAMP induced decrease of ATP and the expression of Peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α).

Conclusions: PKA signaling may upregulate expression of mitochondrial respiratory chain complexes, which reduced ROS production and increased ATP generation, thus prevented ADR-induced podocyte apoptosis. This was at least partially dependent on CREB activation.

Funding: Government Support - Non-U.S.

FR-PO167
Thioredoxin-Interacting Protein (TXNIP) Regulates Mitochondrial Function and Prognosis of Ischemia/Reperfusion Induced AKI Satoshi Inogostani,1 Daiuse Hashimoto,3 Masami Ogasawara,3 Tomohiro Eguchi,1 Hirofumi Nishikawa,1 Tatsuki Matsumoto,1 Kazu H. Ode,1 Yoshiaki Shimamura,4 Kosuke Inoue,2 Yoshinori Taniguchi,2 Taro Horino,3 Yoshio Terada.1 1Kochi Medical School, Kochi University, Kochi, Japan; 2Kochi Medical School, Kochi University, Kochi, Japan; 3Kochi Medical School, Kochi University, Kochi, Japan; 4Kochi Medical School, Kochi University, Kochi, Japan; 1Kochi Medical School, Kochi University, Kochi, Japan; 2Kochi Medical School, Kochi University, Kochi, Japan; 3Kochi Medical School, Kochi University, Kochi, Japan; 4None, Kochukosha, Japan; 3Kochi medical school, Nankoku, Japan; 4None, Nakokusity, Japan, City.

Background: Thioredoxin-interacting protein (TXNIP) regulates mitochondrial function and cellular reduction-oxidation (redox) state by binding to and inhibiting thioredoxin (TXN) to maintain the cellular redox status and to modulate oxidative stress. TXNIP is highly expressed in many pathological conditions like diabetes and cancer, but its role in acute kidney injury (AKI) pathogenesis is not fully understood.

Methods: We evaluated the role of TXNIP in renal function in bilateral renal ischemia (27 min)/reperfusion injury (IRI) model using TXNIP knock-out (KO) and wild type (WT) mice. To elucidate the functional roles of TXNIP, we evaluated mitochondrial function and acute kidney injury (AKI) pathogenesis.

Results: TXNIP KO mice had significantly higher SC (0.78±0.28 versus 0.45±0.20 mg/dl) and significantly higher BUN (152.5±32.5 versus 75.3±18.2 mg/dl) at 24h post ischemia compared to WT mice. Urinary 8-OHDG was increased in CRIF1-KO mice compared with WT mice, also CRIF1-KO mice had significantly increase of 8-OHDG-positive cell recruitment compared to WT mice. CRIF1-KO-UUO-kidneys were shown more increase recruitment of 8-OHDG-positive cells compared to WT-UUO-kidneys.

Conclusions: Collecting duct specific mitochondrial injury induced increase of oxidative stress, renal inflammation, and fibrosis in UUO mice.

Funding: NIDDK Support

FR-PO168
Collecting Duct Cell Specific Mitochondrial Dysfunction Influence to Inflammation and Fibrosis in UUO Mice Jin young Jeong,1 Chang hun Song,2 Hong jun Bae,2 Jiwon M. Lee,3 Youngrok Ham,2 Kiyang Na,2 Kang Wook Lee,2 Dae Eun Choi,2 1Department of Medical Science, Chungnam National University, Daejeon, Republic of Korea; 2Nephrology, School of Medicine, Chungnam National University, Daejeon, Republic of Korea; 3Pediatrics, School of Medicine, Chungnam National University, Daejeon, Republic of Korea.

Background: Unilateral ureteral obstruction (UUO) induced mitochondrial dysfunction resulting in increase of oxidative stress and inflammation in obstructed kidney. Although mitochondria play a role in UUO injury including tubulo-interstitial apoptosis, inflammation and fibrosis, the role of collecting duct cells was not evaluated. We evaluated whether collecting duct specific mitochondrial dysfunction affect the renal injury induced by UUO.

Methods: For generation collecting duct specific mitochondrial injury mice, CRIF1 flox/flox mice were bred with Hoxb7-Cre mice. For evaluation of the phenotype of mice, we observed mitochondria using electron microscopy in mice. For evaluation of influence of CRIF1 deletion on mitochondrial function, we measured O2 consumption and membrane potential in control and silencing RNA treated mMCD cells. For evaluation of effect on UUO induced renal injury, we divided mice into the following 4 groups: CRIF1flox/flox(WT) group, CRIF1 flox/flox-Hox7 Cre (CRIF1-KO) group; WT UUO group; and CRIF1-KO UUO group. I evaluated oxidative stress, inflammatory, and fibrosis marker in urine and kidney tissue.

Results: There are no significant difference in phenotype between CRIF1-KO and WT mice. Renal expression of MCP-1, osteopontin (OPN), Numbers of F4/80 positive cells, TGF-b, a-SMA, and Masson Trichrome stained area were significantly increased in CRIF1-KO-UUO kidneys compared with WT UUO kidneys., Urinary 8-OHDG was increased in CRIF1-KO-mice compared with WT mice. Also, Ctrl-KO mice had significantly increase of 8-OHDG-positive cell recruitment compared to WT mice. CRIF1-KO-UUO-kidneys showed increase more recruitment of 8-OHDG-positive cells compared to WT-UUO-kidneys.

Conclusions: Collecting duct specific mitochondrial injury induced increase of oxidative stress, renal inflammation, and fibrosis in UUO mice.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
FR-PO170

Downregulation of Akt Induces Mitochondrial Injury in Proteinuric States
Elif Erkan,1 Lu Lu,2 Children’s Hospital of Cincinnati, Cincinnati, OH; 3Cincinnati Children’s Hospital, Cincinnati, OH.

Background: Nephrotic range proteinuria contributes to progression of glomerular diseases by causing tubulointerstitial injury. High concentrations of albumin in the glomerular filtrate triggers proximal tubular cell apoptosis, a precursor for tubular atrophy. We propose that downregulation of prosurvival serine/threonine kinase, protein kinase B (Akt) induces apoptosis in proximal tubule epithelial cells by causing mitochondrial injury.

Methods: In-vitro albumin overload is induced by incubating human kidney proximal tubule epithelial (HKC-8) cells with 10mg/ml of human albumin for 24 hours. C57BL/6 OH; 2Cincinnati Children’s Hospital, Cincinnati, OH in proteinuric states.

We postulate that therapeutic interventions that are targeted to increase tubular Akt expression can attenuate tubulointerstitial injury in proteinuric states.

Conclusions: We concluded that Akt plays an important role in protection of proximal tubule epithelial cells from apoptosis. We propose that in proteinuric states, inhibition of Akt phosphorylation causes nuclear translocation of FOXO 1 and FOXO 3 and an increase in transcription of BIM leading to cytochrome-c release to cytoplasm and apoptosis in proximal tubule epithelial cells. We postulate that therapeutic interventions that are targeted to increase tubular Akt expression can attenuate tubulointerstitial injury in proteinuric states.

FR-PO171

The Role of a Novel Mitochondrial Protease, OMA1, During Renal Cold Storage and Rewarming
Julia Tobacev,1,2 Lee Ann MacMillan-Crow, Nirmala Parajuli, Stephen A. Shrum. University of Arkansas for Medical Sciences, Little Rock, AR.

Background: Most kidney transplants come from deceased donors. These kidneys must undergo cold preservation before transplantation to maintain function of the organ during storage so that the graft will function at reperfusion. However, cold storage (CS) can result in renal and mitochondrial damage impairing overall graft outcome. OMA1 is a novel metallopeptidase in the mitochondrion that plays a key role in mitochondrial dynamics. The goal of this study is to determine the role of OMA1 during renal CS in an in vitro model. Specifically, we will investigate the interaction of key proteins that regulate the fission and fusion machinery in the mitochondria such as OMA1, YME1L and OPA1.

Methods: Both rat and human normal proximal tubular kidney cells were exposed to 18 hr of CS followed by rewarming (CS/RW) for 6 hr. Expression of OMA1, YME1L, and OPA1 were assessed using western blot analysis. The interaction between these proteins was determined via OMA1 siRNA silencing techniques and OMA1 co-immunoprecipitation.

Results: In our studies we show that OMA1 expression is altered during CS both in rat and human normal proximal tubular kidney cells. Furthermore, expression of the long form of OPA1 is decreased in CS/RW suggesting compromised mitochondrial fusion. Our initial studies with OMA1 siRNA studies show successful knockdown, and further experiments will assess how OMA1 knockdown affects YME1L and OPA1.

Conclusions: Overall, CS initiates impairment of proteins related to mitochondrial fission and fusion. Our preliminary data suggest that OMA1 may be a promising therapeutic target for improving the function of kidneys transplanted after CS.

Funding: Other NIH Support - NIGMS for trainee fellowship, Private Foundation Support

Mitochondrial Protection Restores Renal Function and Partly Mitigates Cellular Senescence in Swine Atherosclerotic Renal Artery Stenotic Kidney
Soo Rin Kim, Xin Zhang, AlfotsooEtrin, James Krier, Amir Lerman, Lilach O. Lerman. Mayo Clinic, Rochester, MN.

Background: Atherosclerotic renal artery stenosis (ARAS) may cause kidney injury and mitochondrial dysfunction, which might be linked to cellular senescence. Elamipretide (ELAM), a mitochondrial cardiolipin-targeting peptide, improves renal function and tissue damage in ARAS. We hypothesized that ELAM would also reduce senescence in the ARAS stenotic kidney (STK).

Methods: Domestic pigs were randomized to a 4-week treatment with ELAM (0.1 mg/kg sc q.d.) or vehicle starting after 6 weeks of unilateral ARAS or sham (n=6 each). Then, single kidney renal blood flow (RBF) and glomerular filtration rate (GFR) were measured in-vivo using CT. Renal senescence markers (activity of senescence-associated β-galactosidase (SA-β-Gal), p16, p21, and telomerase reverse transcriptase (TERT)), mitochondrial markers (total cardiolipin content and complex IV (COX-IV) activity), and tissue fibrosis were studied ex-vivo.

Results: Blood pressure and tissue scarring was elevated whereas RBF and GFR were decreased in ARAS STK compared to sham. Renal SA-β-Gal and TERT activity increased in ARAS, suggesting cellular senescence, and total cardiolipin content decreased (Fig. A, B), suggesting mitochondrial impairment. Renal cardiolipin content was restored and COX IV activity was elevated in ELAM-treated ARAS pigs. ELAM also normalized SA-β-Gal and TERT activity and improved renal fibrosis in ARAS. ELAM normalized TERT activity, and improved but not normalized SA-β-Gal activity, whereas p16 and p21 gene expression remained unchanged in all groups.

Conclusions: Mitochondrial protection with ELAM improved renal function, fibrosis and mitochondrial dysfunction in the ARAS STK, and partly alleviated cellular senescence. These observations support development of senolytic strategies in ARAS.

Funding: Other NIH Support - NIGMS for trainee fellowship, Private Foundation Support

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

Underline represents presenting author.
The 5-HT1F Receptor as an In Vivo Regulator of Renal Mitochondrial Homeostasis

*Hospital of the University of Pennsylvania, Philadelphia, PA; 2University of Pennsylvania School of Nursing, Philadelphia, PA; 3Hospital of the University of Pennsylvania, Philadelphia, PA*

**Background:** The 5-HT1F receptor is expressed in renal tubules and has been shown to be involved in renal damage and repair processes in vitro. The aim of this study was to investigate the role of 5-HT1F receptor in regulating renal mitochondrial homeostasis.

**Methods:** Male 5-HT1F receptor knockout (KO) mice and age-matched controls (WT) were subjected to unilateral renal ischemia-reperfusion (IR). Renal mitochondrial homeostasis was assessed by measuring the levels of various mitochondrial proteins and mRNAs.

**Results:** In 5-HT1F receptor KO mice, components of the electron transport chain, including ATP synthase β (ATPβ) and COX1 mRNA were elevated 1.3- and 1.6-fold compared to WT mice after IR. Finally, PGC-1α was decreased in IR KO mice but not in IR WT mice. In addition, the levels of KIM-1 and NGAL were increased in KO mice compared to WT mice. Serum creatinine was greater in KO mice than in WT mice.

**Conclusions:** Our data suggest that in vivo mitochondrial function is impaired in patients on MHD.

**Funding:** NIH Support

---

*Poster/Friday*

**FR-PO175**

Osteopontin Deficiency Ameliorates Alport Pathology by Preventing DN33-Mediated Cholesterol Influx and Mitochondrial Energetic Deficit

*Wen Ding, Keyvan Yousefi, Stefania Goncalves, Bradley J. Goldstein, Alfonso L. Sabater, Armando Mendez, Lina Shehadeh, Tasim Palmer Eye Institute, Miami, FL; 2UM, Miami, FL; 3University of Miami Miller School of Medicine, Miami, FL; 4University of Miami-Miller School of Medicine, Miami, FL; 5University of Miami, Miami, FL*

**Background:** Osteopontin (OPN) is highly expressed in the renal tubules of Alport patients and is recognized as a major cause of frailty. Mitochondria are the main source of energy in skeletal muscle and are important for muscle function. Proper mitochondrial function depends on the balance between fission and fusion (mitochondrial dynamics). Thus, we evaluated changes in mitochondrial function and dynamics in skeletal muscle in patients on MHD.

**Methods:** We evaluated 20 patients on MHD and 19 controls with no history of CKD that were matched by age, gender, history of diabetes, BMI, and race. We measured in vivo mitochondrial function by 31-phosphorus magnetic resonance spectroscopy (31P-MRS) in the quadriceps muscles. We used the half time recovery of phosphocreatine (P-Cr) after a brief exercise as the measure of mitochondrial function. A faster recovery correlates with better mitochondrial function.

**Results:** In 5-HT1F receptor KO mice, components of the electron transport chain, including ATP synthase β (ATPβ) and COX1 mRNA were elevated 1.3- and 1.6-fold compared to WT mice after IR. Finally, PGC-1α was decreased in IR KO mice but not in IR WT mice. In addition, the levels of KIM-1 and NGAL were increased in KO mice compared to WT mice. Serum creatinine was greater in KO mice than in WT mice.

**Conclusions:** Our data suggest that in vivo mitochondrial function is impaired in patients on MHD. The increase in mitochondrial fission marker DRP-1 in MHD patients could be a mechanism for segregation and elimination of damaged mitochondria.

**Funding:** NIDDK Support
Inhibition of Mitochondrial Carnitine Palmitoyl Transferase 1 Prevents Renal Ischemia/Reperfusion Injury in Rats Mads V. Damgaard, Rikke Norregaard, Jorgen Frokiaer, Soren Nielsen. 1Aalborg University, Aalborg, Denmark; 2Aarhus University, Aarhus C, Denmark.

Background: Acute kidney injury is associated with high mortality and a lack of effective therapeutic treatment of the most common cause i.e., ischemia/reperfusion-injury (IR-I). Hypoxia leads to ATP depletion, apoptosis and necrosis, resulting in a marked inhibition of renal function causing further tissue damage. Inhibition of the inflammatory responses after IR-I is crucial for renal protection. Fatty acid β-oxidation is controlled by carnitine palmitoyl transferase 1 (CPT1). Etofimosx (ETO) inhibits CPT1 and block lipid metabolism. We hypothesize that CPT1 blockade can decrease the inflammatory response, induce an immune modulation, reduce mitochondrial dysfunction and hence alleviate renal IR-I.

Methods: Male Wistar rats (n = 10 animals per group) were subjected to either sham operation or renal ischemia/reperfusion (IR-I) by bilateral artery clamping for 40 min followed by 24 h of reperfusion (IR+ETO) or vehicle reperfusion (IR). Clearance experiments were performed and renal tissue was removed and prepared for qPCR, immunohistochemistry and western blot analysis at sacrifice 48 hrs after reperfusion.

Results: IR-I resulted in polyuria (ml/kg/day) ± SEM; Sham: 5 ± 3, IR: 125 ± 3, IR+ETO: 62 ± 4), increased fractional sodium excretion (%), Sham: 0.3 ± 0.04, IR: 2 ± 0.3, IR+ETO: 3 ± 0.09). Plasma creatinine (µmol/L/kg, Sham: 77 ± 3, IR: 649 ± 183, IR+ETO: 141 ± 19) as well as BUN (mmol/L/kg, Sham: 18 ± 1, IR: 102 ± 0, IR+ETO: 41 ± 6). ETO treatment prevented these increases, improved creatinine clearance (ml/min, Sham: 7.4 ± 0.6, IR: 1.9 ± 0.2, IR+ETO: 3.8 ± 0.4) as well as attenuated downregulation of AQP1, Na,K-ATPase and AQP2 expression. All changes were significantly different between IR and IR+ETO. In addition, expression of (pro)inflammatory cytokines (IL-6, IL-β, TNFα, MCP-1, IL-10) and key markers (ICAM-1) were significantly reduced including NKG2D (Sham: 1, IR: 49 ± 10, IR+ETO: 1 ± 0.1) and KIM-1 (Sham: 1, IR: 725 ± 101, IR+ETO: 218 ± 65) in response to ETO administration. Expression of CPT1A increased following the ETO treatment (Sham: 1, IR: 1.2 ± 0.1, IR+ETO: 1.6 ± 0.1).

Conclusions: ETO treatment impaired development of renal dysfunction and attenuated tissue injury after renal IR-I. Decreasing the lipid metabolism attenuate the inflammatory response and may provide a novel potent pathway for treatment of renal IR-I.

Funding: Government Support - Non-U.S.

The Role of Gβγ-Dependent Signaling in Formoterol-Induced Mitochondrial Biogenesis and Recovery of Renal Function in Mice Robert R. Cameron, Janet R. Collier, Rick G. Schnellmann. 1Medical University of South Carolina, Charleston, SC; 2University of Arizona, Tucson, AZ.

Background: Acute kidney injury (AKI) is prevalent and has substantial morbidity and mortality with few effective therapies. AKI is associated with the activation of kinases, such as ERK1/2, that prolong injury and prevent recovery. Our laboratory has shown that Gβγ-activating agents and Gq-activating agents like formoterol stimulate renal mitochondrial biogenesis, which are blocked by pretreatment and may provide a novel therapeutic target to mitigate AKI.

Methods: To model the effects of formoterol on AKI, mice were subjected to bilateral ischemia-reperfusion (IR-I). Hypoxia leads to ATP depletion, apoptosis and necrosis, resulting in a marked inhibition of renal function causing further tissue damage. Inhibition of the inflammatory responses after IR-I is crucial for renal protection. Fatty acid β-oxidation is controlled by carnitine palmitoyl transferase 1 (CPT1). Etofimosx (ETO) inhibits CPT1 and block lipid metabolism. We hypothesize that CPT1 blockade can decrease the inflammatory response, induce an immune modulation, reduce mitochondrial dysfunction and hence alleviate renal IR-I.

Results: IR-I resulted in polyuria (ml/kg/day) ± SEM; Sham: 5 ± 3, IR: 125 ± 3, IR+ETO: 62 ± 4), increased fractional sodium excretion (%), Sham: 0.3 ± 0.04, IR: 2 ± 0.3, IR+ETO: 3 ± 0.09). Plasma creatinine (µmol/L/kg, Sham: 77 ± 3, IR: 649 ± 183, IR+ETO: 141 ± 19) as well as BUN (mmol/L/kg, Sham: 18 ± 1, IR: 102 ± 0, IR+ETO: 41 ± 6). ETO treatment prevented these increases, improved creatinine clearance (ml/min, Sham: 7.4 ± 0.6, IR: 1.9 ± 0.2, IR+ETO: 3.8 ± 0.4) as well as attenuated downregulation of AQP1, Na,K-ATPase and AQP2 expression. All changes were significantly different between IR and IR+ETO. In addition, expression of (pro)inflammatory cytokines (IL-6, IL-β, TNFα, MCP-1, IL-10) and key markers (ICAM-1) were significantly reduced including NKG2D (Sham: 1, IR: 49 ± 10, IR+ETO: 1 ± 0.1) and KIM-1 (Sham: 1, IR: 725 ± 101, IR+ETO: 218 ± 65) in response to ETO administration. Expression of CPT1A increased following the ETO treatment (Sham: 1, IR: 1.2 ± 0.1, IR+ETO: 1.6 ± 0.1).

Conclusions: ETO treatment impaired development of renal dysfunction and attenuated tissue injury after renal IR-I. Decreasing the lipid metabolism attenuate the inflammatory response and may provide a novel potent pathway for treatment of renal IR-I.

Funding: Other NIH Support - NIGMS R01GM106419

SIRT1/P53/Drp1-Dependent Mitochondrial Fission Mediates Aldosterone-Induced Podocyte Injury and Mitochondrial Dysfunction Xuegong Yuan, Aihua Zhang, Changhai Xing. 1Nanjing Medical University, Nanjing, China; 2The First Affiliated Hospital of Nanjing Medical University, Nanjing, China.

Background: Mitochondrial dysfunction is increasingly recognized as an important factor in glomerular diseases. Previous study showed that mitochondrial fission contributed mitochondrial dysfunction. However, the mechanism of mitochondrial fission on mitochondrial dysfunction in aldosterone-induced podocyte injury remains ambiguous. This study aimed to investigate the pathogenic effect of mitochondrial fission both in vivo and in vitro.

Methods: Aldosterone-infused mice were implanted subcutaneously with 14-day-releasing microparticles containing aldosterone. Mitochondrial fission inhibitor mdivi-1 was given by peritoneal injection. The expression of mitochondrial fission protein Drp1 (dynamin-related protein 1) was determined by western blotting and immunofluorescence. Podocyte injury was measured by nephrin expression and labelled by TUNEL assay. In vitro, podocytes were treated with aldosterone at the concentration of 0, 25, 50, 100 mmol/L. The expressions of Drp1, p53 and SIRT1 were examined by real-time PCR and western blot. Then podocytes were transfected with Drp1 siRNA, p53 siRNA and SIRT1 plasmid, respectively. After aldosterone treatment, podocyte injury, mitochondrial morphology and mitochondrial function were detected.


Conclusions: These findings implicated that aldosterone-induced mitochondrial dysfunction and podocyte injury mediated by SIRT1/p53/Drp1-dependent mitochondrial fission, which may provide opportunities for therapeutic intervention for podocyte injury.

Funding: Government Support - Non-U.S.

Superoxide Resolution Imaging of Kidney Tissue Is a Novel Technique to Study Three Dimensional Mitochondrial Networks and Functional Correlates In Vivo Craig R. Brooks, Kensei Taguchi. 1Department of Nephrology and Hypertension, Nashville, TN; 2Vanderbilt University Medical Center, Nashville, TN.

Background: Mitochondria are essential for all eukaryotic life. Kidney proximal tubule cells (PTCs) have the highest content of mitochondria, by surface area, of any cell type in mammals. The large complement of mitochondria is necessary to support the tremendous amount of transport that occurs in the PTC during the reabsorption of sodium and other solutes from urine. Previous studies have demonstrated that mitochondrial morphology is important to maintain both the health and functionality of mitochondria.

Methods: Sham or ischemically injured kidneys from wild-type C57BL/6 mice were fixed and embedded in paraffin following standard protocols. Sections of the kidneys were stained on a (3-Aminopropyl)trimethoxysilane-treated glass cover slip and stained for

FR-PO176

FR-PO177

FR-PO178

FR-PO179

FR-PO180

FR-PO181

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

446

**FR-PO181**

**Honokiol Decreases UUO-Induced Tubulointerstitial Inflammation and Fibrosis by Regulation of Mitochondrial Sirt3 and Its Dynamics**

**Kyoung Poo Kang,1 Woong Park,2 Yi Quan,3 Jin won Jang,4 Sung K. Park,5 Won Kim.6**

1Chonbuk National University Hospital, Jeonju, Republic of Korea; 2Chonbuk National University Medical School, Jeonju, Jeolla-Dub, Do, Republic of Korea.

**Background:** Sirt3 is a NAD+-dependent deacetylase in mitochondria, which has a role of maintaining the mitochondrial function by deacetylation. Sirt3 might protect the cells from reactive oxygen species, apoptosis, and mitochondrial dynamics. In progressive renal fibrosis, tubulointerstitial fibrosis is a focal common feature, which is characterized by inflammation, excessive extracellular matrix deposition and organ dysfunction. Honokiol is a natural biphenolic compound derived from the bark of magnolia trees and known as an activator of sirt3 in murine cardiomyopathy model. In this study, we investigated the protective effect of honokiol on unilateral ureteral obstruction (UUO)-induced tubulointerstitial inflammation and fibrosis by regulation of mitochondrial Sirt3.

**Methods:** Renal fibrosis was induced by UUO in the six-week-old C57BL/6 mice for 10 days. Honokiol (5 mg/kg) was treated by intraperitoneal injection for 7 days before inducing UUO. After 10 days, histologic examination and Western blot analysis for ct-SMA, type 1 collagen and one type of monocyte macrophage marker were performed. We also evaluated cell adhesion molecule expression, mitochondrial dynamics and TGF-β/SMA, type I collagen were performed. We also evaluated cell adhesion molecule expression, mitochondrial dynamics and TGF-β/SMA, type I collagen were performed.

**Results:** After treatment of honokiol, renal tubular injury and fibrosis were significantly decreased. The number of ct-SMA positive fibroblasts and F4/80 positive macrophages were performed. We also evaluated cell adhesion molecule expression, mitochondrial dynamics and TGF-β/SMA, type I collagen were performed.

**Conclusions:** These results suggest that honokiol has a beneficial effect on UUO-induced tubulointerstitial inflammation and fibrosis by regulation of mitochondrial sirt3 and its dynamics.

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

---

**FR-PO182**

**Impaired Cutaneous Wound Healing in a Rodent Model of Uremia**

**Sai Krishna Durasingh,1 Julius E. Kiewski,2 Steven M. Harwood,2 Muhammad M. Yaqoob,3 1The Royal London Hospital, Barts Health NHS Trust, London, United Kingdom; 2William Harvey Research Institute, Queen Mary University, London, United Kingdom.

**Background:** Patients with CKD develop a multitude of skin changes associated with the duration and severity of renal failure. Additionally, causative comorbidities such as peripheral vascular disease and diabetes directly impact on wound healing. In clinical practice, poor healing contributes to prolonged hospital stays, a susceptibility to further complications and significant morbidity, including a considerable negative psychological impact. For these reasons finding methods to assess wound healing in uremia will be valuable.

**Methods:** We developed a rodent model of excisional wound healing. Animals were maintained in a temperature controlled facility with a 12h light/dark cycle. After 2 weeks acclimatization, 6 week old male Wistar rats were fed a diet of standard rat chow supplemented with 0.75% adenine and given water ad libitum for 4 weeks to establish uremia. Uremia was confirmed with standard endpoint, serum albumin, serum creatinine and blood pressure measurement and were monitored during the experimental period. Under inhaled 1.5% Isoflurane anesthesia a 30Jm subcutaneous injection of Buprenorphine 0.3mg/ml was administered before creating bilateral 5mm full thickness dorsal punch biopsies with a Stiefel Biopsy Punch. Recovery from anesthesia was observed before returning animals to cages. Measurements of the wounds were taken on subsequent days. At day 3 and 7, half the animals were sacrificed under Ketamine and Xylazine anesthesia. Blood samples obtained by cardiac puncture were centrifuged for plasma and organs were harvested for histology or for protein and RNA analysis. Wounds were excised and bisected, one semicircle section was stored in formalin, the other snap frozen under liquid nitrogen. Experiments were conducted under our UK Home Office license after institutional approval.

**Results:** With this model successfully established a uremic state with no premature deaths, excess bleeding or infected wounds observed. Serum urea was significantly higher in the uremic group at both day 3 and 7 (p<0.01) as was serum creatinine (p<0.02). Percentage of the wound area healed compared to day 0, was significantly greater in the control group at day 3 and 7 (p<0.02) compared to the uremic group. Injury to the kidney led to reduced mitochondrial interconnectivity and rearrangement of the inner membrane space. Injury also resulted in retraction of the basolateral interdigitations of the plasma membrane.

**Conclusions:** Super resolution imaging provides a novel approach to analyze individual mitochondria and inner vs. outer membrane structure in vivo and provides a 3D morphological analysis of the cell and mitochondrial network. Individual mitochondria that extend through interdigitations of the PTCs are part of a larger network that extends through the cell body. Injury to the kidney leads to a breakdown of this network and dysfunction of mitochondria from the basolateral membrane.

**Funding:** NIDDK Support

---

**FR-PO183**

**CD4 Lymphoma Is Associated with Cardiovascular Disease in Patients with Non-Dialysis Dependent CKD**

**Kenichi Iio,1 Yuta Kuwabara,2 M. Quan,1 Hausmann J. W.,3 Jin Won Park,2 Won Kim.2**

1The Royal London Hospital, Barts Health NHS Trust, London, United Kingdom; 2William Harvey Research Institute, Queen Mary University, London, United Kingdom.

**Background:** The role of T cells in the pathogenesis of atherosclerosis is complex. T-cell infiltration is thought to occur at atherosclerotic sites; CD4 lymphoma in HIV patients is associated with atherosclerosis. Patients with uremic kidney disease (CKD) not only have a high prevalence of cardiovascular disease (CVD), but their circulating CD4 lymphocyte count is also decreased. The aim of this study was to assess the relationship between CVD and circulating T cell phenotype in patients with CKD.

**Methods:** We enrolled patients with CKD stage 3 or above with age 68 ± 12.1 years, 65 males [67%]; CKD stage 3/4/5, 32/14/51) who were hospitalized between June 2013 and May 2017. We determined the number of immune cell phenotypes (CD4+, CD8+, CD28+CD8+CD3+) and the ratio of CD4/CD8 cells in peripheral blood or peripheral blood mononuclear cells using flow cytometry, to define their relationships with CVD, progression of CKD.

**Results:** Among 28 (29%) CVD patients, CD4+ (678 vs. 473, p = 0.004) and CD28+CD8+ (147 vs. 97, p = 0.012) cell counts were significantly lower and this group was significantly older (age 67 vs. 72, p = 0.09) than non-CVD patients. Multivariate logistic analysis indicated a significant negative association between CVD and the number of CD4+ T cells (odds ratio, 0.997, 95% confidence interval, 0.995 - 1.000, p=0.023).

**Conclusions:** Peripheral blood CD4 lymphoma is associated with CVD in patients with non-dialysis CKD. CD4 lymphoma may reflect atherosclerosis in CKD patients.

---

**FR-PO184**

**CKD and Arterial Thrombosis: Role of the Receptor for Advanced Glycation End-Products (RAGE)**

**Jeremy Oritolail,4 Nathalie Hézard,5 Karim Belomkhitar,6 Kawecki Charlotte,7 Christine Teryn,7 Ann Marie Schmid,8 Pascal Maurice,9 Philippe V. Nguyen,6 Philippe Rieu,10 Fatouma Touré.11 1EA 3801 HERV, REIMS, France; 2INSERM U1176, le Kremlin-Bicêtre, France; 3NYU Medical Center, New York, NY; 4UMR CNRS/ URCA 7369, Reims, France; 5Universite de Reims Champagne Ardenne, REIMS, France; 6University of Reims, REIMS, France; 7CHU and UMR CNRS URCA 7369, Reims, France; 8CNRS UMR URCA 7369, Reims, France; 9CNRS UMR URCA 7369, Reims, France.

**Background:** Chronic kidney disease (CKD) is associated with extensive vascular wall remodelling and vasculopathy as well as accumulation of uremic toxins. Among these, advanced glycation end-products (AGEs) interact with the receptor for advanced glycation end-products (RAGE). In this study, we aimed to analyze the impact of CKD on arterial thrombosis and the potential role of RAGE in this process.

**Methods:** We used a mouse model of uremic vasculopathy consisting in a 2-step 5/6 nephrectomy. Four groups of animals were studied: Apoe-/- mice sham operated (n=12) or uremic (n=10) and Apoe-/- (= Apoe RAGE-) mice sham operated (n=11) or uremic (n=15). Twelve weeks after surgery: 1) arterial thrombosis was induced by ferric chloride application on the carotid artery and complete carotid occlusion time was measured; 2) platelet function was analysed in whole blood and in platelet rich plasma (PRP).

**Results:** In-vivo, uremia significantly accelerates the occlusion time in Apoe-/- mice (9.2 ±1.1 min vs 11.1 ±0.6 min, p<0.01) compared to sham animals. In vitro, uremia significantly affects platelet function (Apoe-/- mice carotid occlusion time (14.5 ±2.3 min, vs 13 ±1.5 min in sham, NS)). Moreover occlusion time of the uremic Apoe-/- mice was significantly accelerated compared to uremic Apoe-/-mice (p=0.001). Ex-vivo, agonist-induced platelet aggregation in whole blood was significantly increased in uremic Apoe-/-mice and Apoe-/- mice. In PRP, aggregation of uremic Apoe-/- mice platelets was significantly increased compared to that of uremic Apoe-/- mice. In agreement, agonist induced expression of activated integrin αIIbβ3 and P-selectin were both significantly increased at the surface of Apoe-/- uremic platelets compared to 1) Apoe-/- mice platelets and to 2) uremic platelets (area under curve, p<0.05).

**Conclusions:** In this murine model of thrombosis we report that uremia accelerates arterial thrombus formation and induces platelets hyperreactivity. We found that Apoe deletion had a protective role on uremia-induced arterial thrombosis, and in uremia-induced platelet hyperreactivity. We suggest that RAGE signaling may be involved in CKD-induced atherothrombosis.

**Funding:** Government Support - Non-U.S.
FR-PO185
Renal Hemodynamic Effects of SGC Activation versus ACE Inhibition in Conscious Rats
Karen A. Griffin,1 Geoffrey A. Williamson,3 Aaron J. Polichnowski,2 Perriannan Sethupathi,1 Agnes M. Benardeau,2 Frank Etten,1 Anil K. Bidani,2 1Kidney Diseases Research, Bayer AG, Wuppertal, Germany; 2East Tennessee State University, Johnson City, TN; 3Illinois Institute of Technology, Chicago, IL; 4Loyola University Medical Center, Maywood, IL; 5Loyola University Medical Center, Maywood, IL; 6Loyola University Chicago, Maywood, IL.

Background: Substantial evidence indicates that endothelial dysfunction and/or NO loss accelerates the progression of diabetic and non-diabetic chronic kidney disease (CKD). Therefore, soluble guanylate cyclase (sGC) modulators are being developed as potential novel therapeutic interventions in CKD, but only limited data are available as to their potential hemodynamic effects, particularly in the unanesthetized state.

Methods: Chronically conscious instrumented normol-euglycemic Sprague-Dawley rats (Charles River & Envigo) underwent repeated simultaneous 1-2 hr BP (radiotelemetry) and RBF (Transonic) recordings over 3 weeks (2-4 x wk) while they were sequentially receiving: vehicle only by gavage (5 ml/kg), a low and a high dose of either the sGC activator (Bay-543) or enalapril (4.5/wk with a 3d washout). Effects on mean arterial pressure (MAP), RBF and the autoregulatory AR ability to buffer spontaneous BP fluctuations were assessed using a methodology recently developed in our lab (AR indices are calculated for ~500 adjacent pairs of short segments of 2.5 sec length/rat, which exhibit a difference in MAP of at least 5mmHg, SSAR). GFR was additionally measured during each wk using chronic FITC inulin infusion by osmotic pumps, and 24 hr urine collections. The data for both colonies of SD rats are combined as the results were similar.

Results: Table (mean ± SEM) GFR was not significantly or consistently altered by either agent. Thus, while both agents reduced BP comparably, significantly greater dose dependent renal vasodilation was observed with the sGC activator, while a more modest RBF increase was only seen with the higher dose of enalapril. Surprisingly, AR buffering of spontaneous BP fluctuations was moderately improved by the sGC activator but not enalapril.

Conclusions: Collectively, the BP and renal hemodynamic effects of sGC activation suggest that sGC modulators may have significant therapeutic utility in CKD states, merging additional angiogenic and other treatments in CKD models.

Funding: Commercial Support - Bayer AG, Kidney Diseases Research, Germany

FR-PO186
Endothelial Dysfunction in ESRD Results from Advanced Glycation End-Products (AGE)-Mediated Suppression of Krüppel-Like Factor 2 Keith L. Saum,1 Begona Campos,1 Diego Celdran-Bonafonte,2 Albert P. Owens,3 Prabir Roy-Chaudhury,1 1University of Arizona, Tucson, AZ; 2University of Arizona / BIO 5 Institute, Tucson, AZ; 3University of Cincinnati, Cincinnati, OH.

Background: Cardiovascular disease is the leading cause of morbidity and mortality in patients with end-stage renal disease. The accumulation of uremic toxins in this patient population is associated with endothelial dysfunction and accelerated atherosclerosis. We investigated the impact of protein-bound uremic toxins such as advanced glycation end products (AGEs) on the expression of Krüppel-like Factor 2 (KLF2), the key regulator of endothelial function and activation.

Methods: We used serum from a porcine model of chronic renal failure to assess the impact of uremia on endothelial KLF2 expression in vitro. Human umbilical vein endothelial cells (HUVEC) were treated with increasing concentrations of uremic or non-uremic porcine serum and analyzed for cell viability, apoptosis, and KLF2 expression. Similarly, cells were treated with individual protein-bound toxins at average uremic concentations. Reactive oxygen species (ROS) production and monocyte adhesion were then assessed in treated cells with and without KLF2 overexpression. Finally, we investigated nuclear factor kappa-B (NF-KB) signaling as a mechanism underlying the AGE-mediated suppression of KLF2 and the potential of a RAGE antagonist, TTF468, to increase endothelial KLF2 expression and function.

Results: Treatment with uremic serum decreased HUVEC viability and increased apoptosis in a dose-dependent manner compared to non-uremic serum. Furthermore, uremic serum suppressed HUVEC KLF2 expression > 50%, which was reversed by dialysis and shear stress. Of the uremic toxins tested, carboxymethyllysine (CML), modified albumin, an AGE, resulted in the greatest suppression of KLF2 similar to uremia serum. Overexpression of KLF2 inhibited the production of ROS and leukocyte adhesion by uremic serum and CML. Inhibition of RAGE-mediated NF-KB signaling blocked the transcriptional activation to the nucleus and suppression of KLF2 by CML.

Conclusions: Suppression of KLF2 by uremic toxins such as AGES is associated with increased endothelial dysfunction. This study, therefore, identifies suppression of KLF2 as a potential mechanism by which uremic toxins impair endothelial function in regions prone to arteriosclerosis. Future studies targeting this pathway could lead to novel therapies to decrease cardiorenal dysfunction in ESRD.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO187
Cardiot Intima-Media Thickness Predicts Dialysis Vascular Access Failure in Hemodialysis Patients: A Prospective Study Hong-Joo Lee,1 Seoul Red Cross Hospital, Seoul, Republic of Korea.

Background: A well-functioning dialysis vascular access is a mainstay to perform an efficient hemodialysis. Dialysis vascular access dysfunction is a common cause of morbidity and mortality for the hemodialysis patients. Cardiot intima-media thickness (cIMT) and carotid plaque are ultrasound imaging that measures carotid atherosclerosis and predicts potential stroke, myocardial infarction, and vascular death. Hence, we conducted our study to elucidate the predictive value of cIMT on dialysis vascular access failure from the patients with end-stage renal disease (ESRD) on hemodialysis.

Methods: All hemodialysis patients in Red Cross Hospital within a period of one year were included in the study. cIMT of the participants were measured at 6 points of superficial temporal artery and carotid arteries by using ultrasonography. Also, we collected demographic data, blood test results, medications, and dialysis history. Then, we included the patients who had cIMT more than 1.0mm, age more than 50yrs, diabetes, and hypertension.

Results: Among the 58 cases, 19 of the patients and 29 events were having dialysis vascular access dysfunction for the 12 months follow-up period. The maximal cIMTs were 2.14±1.40 mm. Patients with cIMT more than 1.0mm of maximal cIMT were older (66.0±11.92 versus 50.9±13.26) with lower protein and albumin and higher hemoglobin A1c than the patients with less than 1.0mm of maximal cIMT. However, maximal cIMT was not associated significantly with the level of lipid profiles, including total cholesterol, high and low density lipoprotein cholesterol, triglyceride, and phospholipid. We observed a positive correlation between weight, body mass index, triglyceride, and dialysis vascular access dysfunction. Dialysis vascular access dysfunction was significantly occurred in the patients with more than 1mm of maximal cIMT than the patients with less than 1mm of maximal cIMT.

Conclusions: Our results show that dialysis vascular access dysfunction may be associated with the maximal cIMT. Therefore, the measurement of cIMT may have an advantage for prediction of dialysis vascular access dysfunction in hemodialysis patients.

Funding: Title of Funding Source

FR-PO188
Masked Uncontrolled Hypertension and Target Organ Damage in Patients with CKD Markus P. Schneider,1 Ulrike Raff,2 Rolf Janka,2 Christoph Wanner,2 Thorsten Klink,2 Christian O. Ritter,1 Turgay Saritas,4 Georg Schlieper,5 Jürgen Floege,6 Roland E. Schmieder,3 Kai-Uwe Eckardt,1 Johannes D. Scheppe1,2,7 MITZ DaHu Karlsruhe, Dusseldorf, Germany; 1University Hospital Würzburg, Würzburg, Germany; 2University Medicine of Goettingen, Goettingen, Germany; 3RWTH University of Aachen, Aachen, Germany; 4University of Erlangen-Nuremberg, Erlangen, Germany.

Background: Masked uncontrolled hypertension (MUCH), i.e. normal blood pressure (BP) in the office but elevated ambulatory BP, has been associated with target organ damage and increased cardiovascular (CV) events in the general population. However, in patients with chronic kidney disease (CKD), who are exposed to a variety of additional CV risk factors, the impact of MUCH is less clear.

Methods: In 305 CKD patients under treatment for arterial hypertension, we compared left ventricular mass (LVM, by magnetic resonance imaging), intima-media thickness (IMT), central augmentation index and pulse wave velocity (cAIX and PWV, Mobile-O-Graph®) between the four BP phenotypes: controlled hypertension (CH, normal office and ambulatory BP), much hypertension (MUCH, elevated office BP and normal ambulatory BP), white coat hypertension (WCH, elevated office BP but normal ambulatory BP), MUCH (normal office BP but elevated ambulatory BP) and sustained uncontrolled hypertension (SUCH, elevated office BP and elevated ambulatory BP).

Results: MUCH was present in 18% of patients (table). LVMI, cAIX and PWV differed between BP phenotypes. LVMI was greater in MUCH and SUCH versus CH (P<0.05 for post-hoc comparisons). IMT was increased only in MUCH versus CH. Similarly, cAIX was increased only in MUCH versus CH. Finally, PWV was increased in WCH, MUCH and SUCH versus CH.

Conclusions: MUCH was found in 1 of 5 patients with mild to moderate CKD, and associated with several features of target organ damage. To identify CKD patients at high risk of clinical target organ damage and future CV events, ambulatory BP monitoring should be used more frequently.

Funding: Commercial Support - Fresenius Medical Care

Target organ damage according to BP phenotype

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

448
FR-PO189

Biomarkers of Endothelial, Renal, and Platelet Dysfunction in Stage 5 CKD Hemodialysis (CKD5-HD) Patients with Heart Failure (HF)

Vinod K. Bansal, Ryan Mcmillian, Debra Hoppensteadt, Jawed Fareed, Loyola University Medical Center, Maywood, IL.

Background: The aim of this study was to determine the role of endothelial, renal and inflammatory biomarkers in the pathogenesis of heart failure (HF) in patients with stage 5 chronic kidney disease (CKD5-HD) undergoing maintenance hemodialysis (HD).

Methods: Plasma levels of biomarkers: kidney injury molecule-1 (KIM-1), N terminal-pro brain natriuretic peptide (NT-proBNP), glycylated hemoglobin (HgbA1C), neutrophil gelatinase associated lipocalin (NGAL), interleukin-18 (IL-18), platelet derived growth factor (PDGF), platelet factor 4 (PF4), 25-OH vitamin D, parathyroid hormone (PTH), endothelin and endocan were measured in CKD5-HD patients at the Loyola University Ambulatory Dialysis facility. Normal plasma samples (n=50) were used as control.

Results: The HF (+) CKD5-HD patients, as compared to HF (+) CKD5-HD patients, exhibited significantly elevated NT-proBNP (P = 0.0194) and KIM-1 (P = 0.0485). The NT-proBNP in HF (+) CKD5-HD patients was found to correlate with the levels of serum potassium (P = 0.023 | R = -0.39), calcium (P = 0.029 | R = -0.38) and PF4 (P = 0.045 | R = -0.35). The KIM-1 in HF (+) CKD5-HD patients was found to correlate with PTH (P = 0.043 | R = -0.36) and 25-OH vitamin D (P = 0.037 | R = 0.36). In comparison to the normal plasma samples the CKD5-HD patient plasma exhibited varying degrees of elevation in all of the parameters studied.

Conclusions: Elevated plasma NT-proBNP and KIM-1 in CKD and HF (+) CKD5-HD patients suggest that neprilysin and kidney peptides may contribute to the pathogenesis of HF in CKD5-HD patients. Thus profiling of the biomarkers in CKD5-HD may be helpful in the risk stratification and identifying patients with heart failure.

FR-PO190

Renal Hemodynamic Effects of Sgc Activation Versus ACE Biomarkers of Endothelial, Renal, and Platelet Dysfunction in FR-PO189

Utility in CKD states meriting additional investigations directly addressing CKD in the conscious ZSF1 rat suggest that sGC modulators may have significant therapeutic utility. AR buffering of spontaneous BP fluctuations was well preserved by sGC activators. Dose-dependent renal vasodilation was observed with the sGC activator, but not enalapril. AR induced changes in the autoregulatory (Transonic) recordings over 3 wks (2-4 x/wk) while they were sequentially receiving: sGC activator, enalapril, placebo and no treatment. Diastolic BP and heart rate were decreased by both sGC activator and enalapril, but not placebo.

Background: The aim of this study was to evaluate the progression of atherosclerosis lesions (by measuring intima-media thickness, IMT, and the brachial artery Flow-Mediated Dilation, FMD) in 8 pts treated with LA (HELP system, BBraun, Italy). Moreover, by using a high-throughput approach, was also evaluated the transcriptomic profile in PBMC’s isolated before and after LA (Agilent Technologies). The results were evaluated by statistical (GeneSpring software) and functional pathway analysis (Ingenuity Pathway Analysis, IPA). The data were validated by real-time PCR and ELISA test in an independent testing-group (n=10). Results: A significant reduction of IMT (p<0.01) was observed after 36 months of LA along with an increase of FMD (p<0.02). Using a fold-change (FC) a2, we demonstrated that LA modulates the expression of 84 genes. The top canonical pathways was atherosclerosis signaling (p<0.0001). Many pro-inflammatory cytokines involved in the development and progression of the atherosclerotic process were significantly down-regulated. Interleukin 1 (IL-1β FC = -2.97), IL-6 (FC = -2.07), IL-8 (FC = -3.56) and MCP-1 (FC = -2.13). Real Time PCR showed a different gene expression before and after LA (IL-1β: p<0.0004; IL-6: p<0.01; IL-8 p<0.005; MCP-1 p<0.0002). Similarly, circulating protein level (ELISA) confirmed that IL-1β (Pre 2.77±0.49mg/ml, After 0.93±0.2, p=0.003), IL-6 (Pre 2.09±0.6, After: 1.02 ±0.5 pg/ml, p=0.01), IL-8 (Pre 141.53±45.0, After: 27.9±5.2 pg/ml, p=0.008) and MCP-1 (Pre 485.5±38.0, After 330.2±51.0 pg/ml, p=0.001) were downregulated after LA.

Conclusions: Our data suggest that LA may contribute to cardiovascular risk reduction through the modulation of different pathways involved in the progression of atherosclerosis and disease of microcirculation. This observation might open new perspectives in the prevention of cardiovascular risk in patients with FH.

FR-PO192

Aerobic Exercise Improves Vascular Function in Non-Dialysis CKD Danielle L. Kirkman,1 Meghan G. Ramick,1 Bryce J. Muth,1 Joseph M. Stock,2 Raymond R. Townsend,3 David G. Edwards,1 University of Delaware, Newark, DE;1 University of Pennsylvania School of Medicine, Villanova, PA.

Background: Endothelial dysfunction is a cardiovascular disease risk factor (CVD) characteristic of chronic kidney disease (CKD). This study investigated the effect of aerobic exercise on vascular function in Stage 3-5 CKD.

Methods: In this randomized controlled trial, 36 patients (eGFR 44±2ml/min/1.73m²) were randomized to an Exercise Training (EXT) or Control (CON) arm. EXT consisted of 3x45min of supervised exercise per week at 60-85%HR for 12 weeks whereas CON received routine care. Outcomes were assessed at 0 and 12 weeks.

Results: VO2 peak improved by 10.2 ± 1% (EXT: 14.4 ± 1% vs. CON: 8.7 ± 1%; p<0.05). A training response was indicated by an increase in VO2 peak following EXT (Week 0 vs. 12; EXT:17.9±1.2 vs. 19.1±0.6ml/kg/min, p=0.05; CON:18.2±1.7 vs. 17.4±1.6ml/kg/min, p=0.01). Brachial artery FMD was maintained and cutaneous microvascular function was improved following EXT compared to CON (Figure 1). By high-throughput and proteomic analysis of biopsies, secreted protein was decreased by EXT (Ringer’s solution: 118.6 ± 10.0 vs. EXT: 76.0 ± 12.2 mg/kg, p=0.01) and there was a trend toward decreased CVD risk.

Conclusions: Aerobic exercise improves vascular function and could be implemented as an adjunct therapy to reduce CVD risk in non-dialysis CKD patients.

Funding: Other NIH Support - National heart Lung and Blood Institute R01HL13514
FR-PO193
Central Blood Pressure, Statins, and LDL-Cholesterol: A Mediation Analysis

**Methods:**
- **Background:** Central blood pressure (CBP) is a better predictor of cardiovascular burden than peripheral blood pressure (BP). While studies have suggested a reduction in peripheral BP with statins, it remains uncertain to what extent statins reduce CBP and whether this reduction is mediated through a decrease in LDL-cholesterol (LDL).
- **Methods:** Of the 20,004 CARTaGENE participants, 17,011 had CBP and LDL measurements (n=3,133 with statins; n=13,439 without). Multivariate regression analyses were used to evaluate the association between CBP, LDL, and statin use (after stratification for treatment indication for the latter). The impact of LDL on the association between statin use and CBP was determined by mediation analyses. All analyses were adjusted for age, sex, diabetes, cardiovascular disease, smoking, eGFR, BMI, uric acid, heart rate, anti-hypertensive agents and aspirin.
- **Results:** Lower levels of LDL were associated with lower systolic and diastolic CBP in participants treated with (b=0.098 and 0.125; p<0.001) and without statins (b=0.089 and 0.105; p=0.001). Statin use as primary prevention (per ACC/AHA guidelines; n=8,865) was also associated with lower systolic and diastolic CBP and central pulse pressure (b=-0.091, -0.073 and -0.055; p<0.001). Mediation analyses demonstrated that 15%, 46% and -22% of these effects were achieved through the concomitant changes in LDL. Table 1. Secondary prevention (n=995), statins use was not associated with lower CBP, although the small sample size may lack power.
- **Conclusions:** In this populational cohort, statin use is associated with lower CBP and LDL-C. Lower levels of LDL were associated with lower systolic and diastolic CBP in participants treated with and without statins. Statin use as primary prevention (per ACC/AHA guidelines) was also associated with lower systolic and diastolic CBP and central pulse pressure.

**FR-PO194**
Decreased Blood Pressure in Vascular Smooth Muscle Specific ATP2B1 Overexpressing Mice

**Methods:**
- **Background:** We reported the association between high blood pressure and ATP2B1 gene polymorphisms in Japanese population through Millennium Genome Project. ATP2B1 is a gene encoding plasma membrane calcium ATPase 1 (PMCA1), which is known to be expressed throughout the body. PMCA1 plays a role of discharging Ca²⁺ from the inside of the cell to the outside of the cell, and strictly adjusts the intracellular Ca²⁺ concentration. In subsequent studies we reported that ATP2B1 vascular smooth muscle-specific knockout mice exhibit hypertension and are associated with elevated Ca²⁺ concentrations in vascular smooth muscle cells (VSMC). However, there were no data concerning the effects of ATP2B1 overexpressions. Thus, we generate the vascular smooth muscle-specific ATP2B1 overexpressing mice, and investigate the effects of ATP2B1 overexpressions.

**Results:**
- **Conclusions:** We reported the association between high blood pressure and ATP2B1 gene polymorphisms in Japanese population through Millennium Genome Project. ATP2B1 is a gene encoding plasma membrane calcium ATPase 1 (PMCA1), which is known to be expressed throughout the body. PMCA1 plays a role of discharging Ca²⁺ from the inside of the cell to the outside of the cell, and strictly adjusts the intracellular Ca²⁺ concentration. In subsequent studies we reported that ATP2B1 vascular smooth muscle-specific knockout mice exhibit hypertension and are associated with elevated Ca²⁺ concentrations in vascular smooth muscle cells (VSMC). However, there were no data concerning the effects of ATP2B1 overexpressions. Thus, we generate the vascular smooth muscle-specific ATP2B1 overexpressing mice, and investigate the effects of ATP2B1 overexpressions.

**FR-PO195**
The Rapid Membrane Insertion of the Endothelial Sodium Channel Is Induced by Shear Stress and stiffens the cell cortex

**Methods:**
- **Background:** The endothelial Na⁺ channel (EnNaC) determines endothelial nanomechanics in that an increased membrane abundance of EnNaC stiffens the endothelial cell cortex. Surface EnNaC expression is mainly regulated by aldosterone via the mineralocorticoid receptor (MR). Endothelial cells are constantly exposed to wall shear stress by blood flow, whereas disturbed blood flow causes and maintains atherosclerotic processes. Here, it is hypothesized that EnNaC serves as a flow sensor. Thus, we tested whether laminar shear stress (LSS) and non-laminar shear stress (NLSS) influence EnNaC membrane abundance and endothelial stiffness.
- **Results:** Under chronic shear stress (48h) a significant increase of membrane EnNaC was found. Importantly, already after 15 min. LSS oEnNaC membrane abundance was increased by 58.5±4.5%. Both (i) inhibition of exocytosis with Brefeldin A and (ii) MR antagonism with Canrenone, could prevent the acute shear stress-induced EnNaC membrane insertion indicating a rapid MR-mediated effect of shear stress. EnNaC membrane abundance under NLSS in branching regions was also significantly increased compared to static controls (+24.9±3%). AFM measurements revealed that the shear stress-induced increase in EnNaC lead to stiffening of the cell cortex by 18.9±5.5% compared to static controls.
- **Conclusions:** Our results suggest that EnNaC, besides being a mechano-sensor, is regulated by shear stress. Since both chronic and acute shear stress increase the membrane abundance we postulate genomic and non-genomic mechanisms leading to the MR-dependent membrane insertion of EnNaC and subsequent endothelial stiffening. These changes in nanomechanics and thus endothelial function might be a physiological response to changes in hemodynamics and further explain the atherogenic potential of decreased blood flow.

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

---

**Table 1: Mediation analyses**

<table>
<thead>
<tr>
<th>Path A</th>
<th>Path B</th>
<th>Path C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synaptic CBP</td>
<td>-0.80 (2.0, -2.34)</td>
<td>-2.35 (3.8, -1.7)</td>
</tr>
<tr>
<td>Distant CBP</td>
<td>-1.72 (2.2, -1.30)</td>
<td>-1.01 (5.3, 0.80)</td>
</tr>
<tr>
<td>Cortical pulse pressure</td>
<td>-1.03 (2.6, 3.55)</td>
<td>1.00 (2.1, 1.1)</td>
</tr>
</tbody>
</table>

**Effect represent change of CBP parameter per 1 standard deviation of LDL (95% CI).**

---

**FR-PO196**
The Rapid Membrane Insertion of the Endothelial Sodium Channel Is Induced by Shear Stress and stiffens the cell cortex

**Methods:**
- **Background:** The endothelial Na⁺ channel (EnNaC) determines endothelial nanomechanics in that an increased membrane abundance of EnNaC stiffens the endothelial cell cortex. Surface EnNaC expression is mainly regulated by aldosterone via the mineralocorticoid receptor (MR). Endothelial cells are constantly exposed to wall shear stress by blood flow, whereas disturbed blood flow causes and maintains atherosclerotic processes. Here, it is hypothesized that EnNaC serves as a flow sensor. Thus, we tested whether laminar shear stress (LSS) and non-laminar shear stress (NLSS) influence EnNaC membrane abundance and endothelial stiffness.
- **Results:** Under chronic shear stress (48h) a significant increase of membrane EnNaC was found. Importantly, already after 15 min. LSS oEnNaC membrane abundance was increased by 58.5±4.5%. Both (i) inhibition of exocytosis with Brefeldin A and (ii) MR antagonism with Canrenone, could prevent the acute shear stress-induced EnNaC membrane insertion indicating a rapid MR-mediated effect of shear stress. EnNaC membrane abundance under NLSS in branching regions was also significantly increased compared to static controls (+24.9±3%). AFM measurements revealed that the shear stress-induced increase in EnNaC lead to stiffening of the cell cortex by 18.9±5.5% compared to static controls.
- **Conclusions:** Our results suggest that EnNaC, besides being a mechano-sensor, is regulated by shear stress. Since both chronic and acute shear stress increase the membrane abundance we postulate genomic and non-genomic mechanisms leading to the MR-dependent membrane insertion of EnNaC and subsequent endothelial stiffening. These changes in nanomechanics and thus endothelial function might be a physiological response to changes in hemodynamics and further explain the atherogenic potential of decreased blood flow.

**Funding:** Government Support - Non-U.S.
2.72; P:0.03). By radio-telemetry methods, the blood pressure of Tg ATP2B1 mice exhibited lower blood pressure compared to those of wild mice by the tail cuff method and throughout 24hrs. The blood pressure variabilities were not altered by the over-expression of 8.83 ± 27.1; P:0.03) of Tg ATP2B1 mice were decreased throughout 24hrs. The blood pressure variabilities were not altered by the over-expression of CD40 (-/-) model of atherosclerosis to study the interplay between atherosclerosis and renal microcirculation.

Methods: CD40 was silenced with a specific siRNA in the ApoE +/- mouse model during 16 weeks. We administrated scrambled siRNA (SC) or PHS (vehicle) as controls. Endothelial cells were identified by immunohistochemistry using PECAM-1 antibody (platelet/endothelial cell adhesion molecule-1). Kidneys were isolated from 24-week-old mice. The density of peritubular capillaries was quantified using ImageJ v1.48 and expressed as a proportion. The extension of atherosclerotic lesions was quantified in HE staining from ascending aortas.

Results: SiRNA-CD40 treated ApoE +/- mice reduced the extension of atherosclerotic lesions in ApoE +/- mice. Furthermore, a decrease of renal microcirculation density was observed in this experimental model of atherosclerosis (siRNA-CD40, n=9, 45.2±2.2%; SC, n=4, 21±6.8 %; Vehicle, n=9, 20±1.4%; p<0.0001). No differences in serum creatinine was detected (siRNA-CD40: 0.6±0.18 mg/dL; SC: 0.5±0.2 mg/dL; Vehicle: 0.5±1.0 mg/dL; p=ns).

Conclusions: A reduction in peritubular capillaries was associated with severe atherosclerosis lesions. This data provide structural basis of renal disease in patients with atherosclerosis.

FR-PO198
Activin Receptor Activation in the Skeletal, Vascularature, Heart, and Kidney During CKD
Ogawa Toshiki,1 Sugita Matthew J.,2 Williams Olga A.,2 Agapova Hartmut M.,3 Hruska Krist A.,4 Louis Saint,1 MO; 2Washington University School of Medicine, St. Louis, MO; 3Washington University St. Louis, St. Louis, MO; 4University of Kentucky, Lexington, KY.

Background: To study whether factors stimulating renal fibrosis produce systemic disease, we examined activin receptor type IIa (ActRIIA) activation in CKD by signal analysis and inhibition in Alport syndrome mice, using a ActRIIA ligand trap (RAPP-011) for up to 280 days old mice.

Methods: We measured ActRIIA signaling and inhibited its activity with RAPP-011. Results: By 200 days, Alport mice had severe CKD and the CKD-MBD, consisting of osteodystrophy, vascular calcification, cardiac hypertrophy, hyperphosphatemia, hyperparathyroidism, and elevated FGF23 and reduced klotho levels. ActRIIA inhibition by RAPP-011 reversed CKD-stimulated bone resorption and osteoblast dysfunction by inhibition of osteoclast function, while osteoblast function and bone formation were increased. ActRIIA inhibition prevented formation of calcium apatite deposits in aortic adventitia and tunica media and decreased acute Ca2+ levels from 0.59 mg/g in Alport mice to 0.36 in RAPP-011 treated mice (p<0.05). Aortic ActRIIA stimulation increased p-Smad2 levels and the transcriptional targets, sm22a and cSMA, in Alport mice. ActRIIA inhibition reversed aortic expression of Runx2 and osterix, markers of osteoblastic transition. Heart weight was 26% increased in Alport mice, but remained normal during RAPP-011 treatment (p>0.1). In 150 do Alport mice, GFR was reduced by 55%, p<0.05, but GFR was only 30% reduced in the RAPP-011 treated group. At 200 do, the BUN was 451 ± 10 (mean±s.d.) years of age, 53% female and 80% White, with an eGFR of 94±21ml/min/1.73 m2, and receiving the maximum tolerable dose of an angiotensin converting enzyme inhibitor were randomized to receive either simvastatin (titrated to maximum dose of 50 mg/day) or placebo for 6 months. As secondary endpoints in this trial, we measured protein expression of NADPH oxidase, interleukin-6 (IL-6), nuclear factor k B (NFkB), and phosphorylated endothelial nitric oxide synthase (PNOS) in vascular endothelial cells (ECs) collected from a peripheral vein of study participants, and change in brachial artery flow-mediated dilation (FMD) in response to an acute infusion of ascorbic acid as an index of vascular endothelial oxidative stress.

Results: Participants were 34±10 (mean±s.d.) years of age, 53% female and 80% White, with an eGFR of 94±21/ml/min/1.73 m2. Acute infusion of ascorbic acid improved FMDmax at baseline (8.4±5.9 vs. 9.5±5.7%, p<0.05). After 6 months, ascorbic acid continued to improve FMDmax in both the simvastatin and placebo group, indicating no reduction in vascular endothelial oxidative stress. Similarly, there was no change in EC protein expression of the oxidant enzyme NADPH oxidase. IL-6 and PeNOS EC expression were also unchanged. However, EC expression of the pro-inflammatory transcription factor NFkB was reduced in the simvastatin group (0.5±1.0 vs. 0.4±0.8) (immunofluorescence intensity relative to HUVEC control, p=0.05) with no change in the placebo group (0.4±0.10 vs. 0.4±0.09).

Conclusions: Six months of alderosterone antagonism with spironolactone does not reduce ADPKD-associated vascular oxidative stress, but may attenuate vascular inflammation.

Funding: NIDDK Support
FR-PO201
Arteriolar Hyalinosis in Klotho Deficiency Rik Mende,1 Jakob Voelkl,2 Geert Harms,1 Marian L. Bullhuis - van der hoort,1 Anja Umbach,2 Harry Van Goor,3 Florian C. Lang,3 Jan-luk Hillebrands.1 University Medical Center Groningen, Groningen, Netherlands; 2Charité University Medicine, Berlin, Germany; 3University of Tübingen, Tübingen, Germany.

Background: Hyalinosis is a vascular lesion affecting the renal vasculature in ageing, hypertension, and after transplantation. It is thought to contribute to renal function decline. We wanted to assess whether arteriolar hyalinosis is caused by Klotho deficiency - a state known to induce both renal vascular and age-related pathologies.

Methods: The presence of hyalinosis was assessed in kidneys from 7-week-old Klotho−/−, Klotho+/-, and WT mice. We used (immuno)histochemistry to investigate the composition of the lesions and the different layers of the vascular wall. Finally, using klkl mice (with a promoter disruption rather than the exon deletion of Klotho+/- mice and with more severe vascular calcification) we assessed the effect of spironolactone treatment (80 mg/L of drinking water, between 3 and 8 weeks of age) on the vascular lesions in the kidney as spironolactone induces vascular calcification.

Results: We detected marked arteriolar hyalinosis in Klotho−/− mice, present up to the afferent arterioles. Hyalinosis was accompanied by local loss of smooth muscle actin expression, while the endothelial lining was mostly intact. Hyalinous lesions were positive for IgM and IC3b/c, indicating subendothelial leakage of plasma proteins. The increased presence of extracellular matrix proteins suggests increased production by smooth muscle cells and the gain of $\frac{S}{1000}$ A 4 expression indicates smooth muscle cell de-differentiation towards a synthetic phenotype. In klkl mice, spironolactone treatment inhibited the development of calcification and resulted in the development of hyalinosis.

Conclusions: Klotho deficiency induces the development of hyalinosis spontaneously in Klotho−/− mice and after inhibition of calcification in klkl/mice, also attesting to the phenotypic variability of Klotho deficiency. Klotho deficiency potentiates both endothelial hyperpermeability and smooth muscle cell de-differentiation to a synthetic phenotype, likely in response to subendothelial leakage of plasma proteins. Klotho may play a role in preventing ageing-related or calcineurin inhibitor-induced arteriolar hyalinosis.

Funding: Private Foundation Support

FR-PO202
Nephrotic Syndrome Modulates Flow and Composition of Mesenteric Lymph Jianyong Zhong, Babak Banan, Vance L. Albaugh, Yohei Tsuchida, Patricia G. Yancey, Carrie B. Wiese, Kashey C. Vickers, Haichun Yang, Valentina Kon. Vanderbilt University Medical Center, Nashville, TN.

Background: Although hyperlipidemia and altered lipid/lipoprotein metabolism that characterize nephrotic syndrome (NS) are usually ascribed to functional changes in the liver, little is understood about how NS impacts another relevant organ system, i.e., gut. Small intestine functions not only to reabsorb dietary lipids but also contributes to lipoprotein synthesis, particularly apolipoprotein AI, the main protein in high density lipoprotein (HDL), that provides beneficial effects to many different tissues. All reabsorbed lipids and synthesized lipoproteins are taken-up and transported through the lymphatics. Since integral to NS is development of edema that reflects lymphatic inadequacy, we examined the lymphatic network in a model of NS.

Methods: NS was induced by puerarin ammoniumcloseldis (PAN) in 12 Sprague Dawley rats, while 12 non-injected rats served as control (C). Eight days later, plasma, urine, mesenteric lymph, kidney and ileum were collected for further analysis.

Results: Along with massive proteinuria, PAN significantly increased plasma cholesterol and triglyceride that was accompanied by increased renal lymphatic vessel density (assessed by staining for podoplanin). Proteinuria injured a 6-fold increase in mesenteric lymph flow (PAN: 10.7 ± 0.3 ml/h vs C: 1.4 ± 0.3 ml/h, p<0.001). Despite apparent dilution, the mass of cholesterol and triglycerides transported by mesenteric lymph flow (PAN: 10.7 ± 0.3 x 3h, p<0.001). Despite apparent dilution, the mass of cholesterol and triglycerides transported by mesenteric lipids and synthesized lipoproteins are taken-up and transported through the lymphatics.

Conclusions: Proteinuric injury causes a 6-fold increase in PAN-induced injury of mesenteric lymph flow, the level of VEGFA (>100%, p<0.05) and increased the level of TAT as a marker of coagulation, plasminogen-2-plasmin inhibitor complex (PIC) as markers of fibrinolysis, and factors related to inflammation (CRP, interleukin-6, tumor necrosis factor-α, pentraxin-3), mineral-bone metabolism (calcium, phosphate, parathyroid hormone), and uremia were measured. Blood flow volume (VF) of PAN was evaluated by Doppler ultrasonography before VAIVT. The end point was the re-vascularization or re-operation of VA during the observational period after VAIVT (mean follow-up periods 278.7 ± 8.2 days). The results were analyzed using receiver operating characteristic curve, Kaplan-Meier methods, and Cox regression analyses.

Funding: Other NIH Support - NHLBI R01 HL 122839

FR-PO203
Chronic Kidney Dysfunction Impairs Experimental Arteriovenous Fistula Healing Makoto Kon.1 Harkamal S. Jhaj,1 Jie Cui,1 2-plasmin inhibitor complex (PIC) as markers of fibrinolysis, and factors related to inflammation (CRP, interleukin-6, tumor necrosis factor-α, pentraxin-3), mineral-bone metabolism (calcium, phosphate, parathyroid hormone), and uremia were measured. Blood flow volume (VF) of VA was evaluated by Doppler ultrasonography before VAIVT. The end point was the re-vascularization or re-operation of VA during the observational period after VAIVT (mean follow-up periods 278.7 ± 8.2 days). The results were analyzed using receiver operating characteristic curve, Kaplan-Meier methods, and Cox regression analyses.

Methods: Blood samples were taken from 462 HD patients at the VAIVT. Among them, 352 patients (76.2%) had native arteriovenous fistula (AVF). Thrombin anti-thrombin (TAT) as a marker of coagulation, plasma-ε, plasma inhibitor complex (PIC) as markers of fibrinolysis, and factors related to inflammation (CRP, interleukin-6, tumor necrosis factor-α, pentraxin-3), mineral-bone metabolism (calcium, phosphate, parathyroid hormone), and uremia were measured. Blood flow volume (VF) of VA was evaluated by Doppler ultrasonography before VAIVT. The end point was the re-vascularization or re-operation of VA during the observational period after VAIVT (mean follow-up periods 278.7 ± 8.2 days). The results were analyzed using receiver operating characteristic curve, Kaplan-Meier methods, and Cox regression analyses.

Funding: Other NIH Support - NHLBI R01 HL 122839

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

Underline represents presenting author.
patients. The Kaplan-Meier analysis showed that the patients with lower FV (<344 ml/min), and lower BNP and higher TAT/PIC ratio (adjusted HR 1.67, 95% CI 1.14 to 2.43, p=0.008) was linked to VA failure event.

**Conclusions:** The impaired coagulation-fibrinolysis system as well as lower FV and graft VA can affect VA failure after IVT.

**FR-PO205**

Transcriptomic Profiling of Tight Junction Dysfunction in CKD

**Jen Xu,1,2 Kenneth Lim,3 Li-lun Ho,1 Thomas F. Hiemstra,1 Tzonghsi Lu,1,2 Brigham and Women’s Hospital, Harvard Medical School, Boston, MA; 2Harvard College, Cambridge, MA; 3Massachusetts General Hospital, Boston, MA; 4University of Cambridge, Cambridge, United Kingdom.

**Background:** Tight junctions (TJ) are specialized membrane domains that play multiple functions in endothelium and epithelium to maintain cellular homeostasis. TJ dysfunction is an important pathological process in the development of uremic-related cardiovascular disease (CVD), cerebral small-vessel diseases (CSVD) and cystogenesis in polycystic kidney disease. The goal of the present study was to elucidate the transcriptomic profile of TJ dysfunction in CKD.

**Methods:** We performed transcriptomic analysis by RNA sequencing in: 1) primary human aortic endothelial cells (HAECs) and human brain microvascular endothelial cells (HBMECs) that were treated in calcification medium (CM: 5 mM β-glycerophosphate; 5 mM CaCl2) in time-course experiments (0-48 hours), in vitro; 2) human kidney proximal tubule epithelial cells (HK-2) treated with H2O2, in vitro and 3) human arteries, ex vivo from healthy and CKD patients; Gene selections were performed by the combinations of fold-changes on log 2 ratio, and p value < 0.05.

**Results:** In primary cells treated with CM: we found that heat-shock protein 70 (HSP70) co-chaperone, BAG1 (Bcl2 Associated Athanogene 1) was significantly increased at 6 hours before upregulation of antiapoptotic gene, Bcl2 at 12 hours in HAECs but not in HBMECs. DNAJB6 (HSP40) and HSPA5 (HSP70 member5) was significantly increased at 24 and 12 hours respectively in HAECs. The major transmembrane TJ protein-Ocludin was upregulated at 6 hours and peaked at 24 hours (HAECs) and 48 hours (HBMECs) under CM treatment respectively, but cytoplasmic TJ-ZO1 displayed similar patterns in HAECs only. Inflammation sensitive TJ, Claudin-5 increased at 1 hour followed by upregulation of downstream ZO-1 at 6 hours. In addition, ZO1, occludin and Claudin-5 were downregulated after H2O2 treated but preserved by HSP70 induction in HK2 cells. In human CKD arteries, we found that Claudin-5 was down-regulated (Fold changes, FC, 2.16) while ZO-1 was upregulated (FC=2.17). Bcl2 (FC=4.52) and HSPA5 (FC=3.85) was preserved in healthy arteries alone with activated BAG1 (FC=7.44).

**Conclusion:** The results reveal that TJ dysfunction and upregulation of the HSP stress response occur in endothelial and epithelial cells in renal failure. Our findings may serve to inform the rational development of therapeutic strategies for arterial and epithelial cells dysfunction in CKD.

**Funding:** Private Foundation Support

**FR-PO206**

Effect of Spironolactone on a Transgenic Rat Model of Hypertension and Myocardial Infarction

**Catherine Leader,1 Ivan A. Sammut, Gerard T. Wilkins, Robert J. Walker. University of Otago, Dunedin, New Zealand.

**Background:** Hypertension contributes to heart disease and renal injury. However the impact of MI plus hypertension on renal injury is not clearly described. Spironolactone (SP) can reduce cardiac fibrosis and improve cardiac remodelling post MI. The effects on the kidney are unknown. We examined the effects of SP on renal fibrosis in hypertensive rats post MI.

**Methods:** Five groups of adult male Cyp1a1Ren2 rats: normotensive (N), hypertensive (H-MI), hypertensive with cardiac injury (H-MI-SP), hypertensive with renal injury (H-MI-SP), Hypertension (>160 mmHg systolic) was induced by 0.167 % (w/w) indole-3-carbinol added to the rat chow. Systolic blood pressure (SBP) and echocardiograms for analysis.

**Results:** SBP was only reduced in the H-MI group (p=0.05) compared with all the other H groups (155±24 and 173±11mmHg respectively). SBP was not significantly reduced by SP in either of the treated groups. Ejection fraction (EF) was significantly reduced in all animals with MI (42±10%), addition of SP had no effect (43±10%). The Glomerulosclerosis Index (GSI) in normals was 0.2±0.1 and was significantly higher in all hypertensive groups (p<0.001). The H-SP group (0.9±0.04) showed a significant decrease in GSI from H control 2.1±0.07 (p<0.002). The GSI in H-MI-SP (1.9±0.1) was significantly decreased from the H-MI group (1.3±0.1) (p<0.04). The degree of cortical interstitial fibrosis in all hypertensive groups was not modified by SP. Figure 1: PAS cortex pictures of representatives from each experimental groups. Scale bar is 200µm.

**Conclusion:** Severe hypertension caused extensive renal glomerulosclerosis and interstitial fibrosis. SP showed no effect on SBP or EF, but significantly improved GSI scores in hypertensive animals and post MI. SP did not reduce renal interstitial fibrosis. Further work will aim to define the relation between cardiac injury and renal damage.

**Figure.** PAS cortex pictures of representatives from each experimental groups. Scale bar is 200µm.

**Funding:** Other NIH Support - NHLBI, Veterans Affairs Support
FR-PO208

Induction of Unique Scavenger Receptor Dysregulation Pattern in Advanced CKD

Nobuyuki (Bili) Miyawaki, Nicolle M. Siegart, Farah Daccueil, Joshua De Leon, Joseph Mattana, Lora Kasselman, Allison B. Reiss. Medicine, NYU Winthrop Hospital, Mineola, NY.

Background: In chronic kidney disease (CKD), scavenger receptors (SR) are the main cholesterol entry pathways into macrophages, bypassing the regulated LDL receptors, to accelerate foam cell formation in synergy with defective cholesterol efflux. Yet alteration patterns of SR in CKD remain poorly defined.

Methods: Following THP-1 human macrophage (10⁷/ml) incubation for 24 hours with 10% plasma from 10 CKD Stage 4-5 patients (without diabetes, rheumatological illnesses or active infections) or plasma from 10 healthy control subjects, mRNA was isolated and reverse transcribed. The resulting cDNA was subjected to quantitative real-time PCR using specific primers for major cholesterol scavenger receptors CD36, LOX-1, SR-A1 as well as eflux proteins, ATP binding cassette transporter (ABC)A1 and G1.

Results: Exposure to CKD plasma decreased the expression of scavenger receptor CD36 by a 32% reduction (Fold change with CKD plasma exposure: 0.68, 95% CI [0.54, 0.87], p<0.01). SR-A1 expression with CKD plasma exposure was unaffected with a fold change of 0.80, 95% CI [0.52, 1.24], p=0.01. LOX-1 expression was not reduced; rather a very strong trend to LOX-1 enhancement with 1.54-fold increase with CKD plasma exposure (95% CI [1.01, 2.35], p=0.053). Downregulation of ABCA1 and ABCG1 were demonstrated, respectively, by 33% (0.67, 95% CI [0.04, 0.92], p=0.01) and by 30% (0.70, 95% CI [0.50, 0.98], p=0.03).

Conclusions: Prior studies of CKD populations have evaluated isolated SR and often exclude the effect of other known inflammatory conditions which impact SR dysregulation patterns. Our demonstration of decreased CD36, unaffected SR-A1 and a very strong suggestion of increased LOX-1 in CKD differs from those previously described in rheumatoid arthritis or lupus and may provide future avenues for viable therapeutic targets. Additional studies on LOX-1 as well as impact of its inhibition may help in further elucidation of SR mediated uptake mechanisms in CKD. Reduced ABC gene expression likely lowers defense against lipid overload and may be a target for therapeutic intervention.

Funding: Private Foundation Support

FR-PO209

CPAP Therapy Improves Central Arterial Stiffness and Decreases Arterial Renin Angiotensin System Activity in Humans with Obstructive Sleep Apnea

David D. Nicholl,2 Patrick Hanly,2 Ann A. Zalucky,2 Michelle C. Mann,2 Jennifer M. MacRae,2 Marc Poulin,2 George Handley,1 Darlene Y. Sola,2 Sofia B. Ahmed.1 Healthy Heart Sleep Company, Calgary, AB, Canada; 2University of Calgary, Calgary, AB, Canada.

Background: Chronic kidney disease (CKD) is associated with increased arterial stiffness, a marker of cardiovascular risk. Treatment of obstructive sleep apnea (OSA), common in CKD, reduces arterial stiffness, though the mechanism is not clear. Limited studies suggest a prominent role for the renin angiotensin system (RAS), activation of which is deleterious to kidney and cardiovascular function. We sought to determine the effect of CPAP therapy on arterial stiffness at baseline and in response to the physiological stressor, Angiotensin II (AngII), in humans with OSA.

Methods: Newly diagnosed OSA subjects (respiratory disturbance index [RDI] >30/hr) were enrolled (oxyhemoglobin saturation [SaO₂]≤90% for >12% of night) who were otherwise healthy were studied in high-salt balance, at state of corrected OSA (RDI: 44.2±0.5/hr, p<0.001; duration SaO₂<90% for >12% of night) who were otherwise healthy were studied in high-salt balance, at state of corrected OSA (RDI: 44.2±0.5/hr, p<0.001; duration SaO₂<90% for >12% of night). We performed a graded AngII infusion (3ng/kg/min x 30min, 6ng/kg/min x 30min, Recovery x 30min).

Results: The primary outcome was the effect of CPAP on the arterial stiffness responses to AngII.

Conclusions: CPAP therapy was associated with increased central, but not peripheral, arterial stiffness sensitivity to AngII, consistent with downregulation of the vascular RAS. These findings may have important implications in mitigating cardiovascular risk in CKD patients with OSA.

Funding: None

FR-PO210

Mineralocorticoid Receptor Antagonists Augment Arginine Transport and Nitric Oxide Generation through Modulation of Cationic Acid Transporter-1 in Human Umbilical Vein Endothelial Cell

Doron Schwartz,1 Moshe Shashar,1 Idit F. Schwartz,1 Sourasky Medicin Center, Tel Aviv, Israel; 2Tel Aviv Medical Sourasky Center, Tel Aviv, Israel.

Background: Blockade of the mineralocorticoid receptor (MCR) has been shown to improve endothelial function far beyond blood pressure control. In the current studies we looked at the effect of MCR antagonists on the activity of cationic amino acid transporter-1 (CAT-1), a major modulator of endothelial nitric oxide (NO) generation.

Methods: Using radio-labeled arginine, [3H] L-arginine uptake was determined in Human umbilical vein endothelial cells (HUVEC) following incubation with either spironolactone or enepolone with or without silencing of the MCR or co-administration of amiloride. Following MCR blockade but not amiloride, we identified two bands for CAT-1. The addition of taurycamin (a de-glycosylation agent) or silencing of the MCR resulted in disappearance of the extra band and prevented the increase in arginine transport. Spironolactone but not epleronone decreased CAT-1 phosphorylation through inhibition of PKCα (CAT-1 inhibitor). Subsequently, the concentration of NO2/NO3 (stable NO metabolites) following incubation with both MCR antagonists significantly increased. This was attenuated by silencing of MCR or taurycamin. GO 6676 (PKCα inhibitor) augmented the increase of NO metabolites only in the epleronone treated cells.

Conclusions: Spironolactone and epleronone significantly increased endothelial arginine transport, an effect which was augmented by co-incubation with aldosterone and blunted by either silencing of the MCR or co-administration of amiloride. Following MCR blockade but not amiloride, we identified two bands for CAT-1. The addition of taurycamin (a de-glycosylation agent) or silencing of the MCR resulted in disappearance of the extra band and prevented the increase in arginine transport. Spironolactone but not epleronone decreased CAT-1 phosphorylation through inhibition of PKCα (CAT-1 inhibitor). Subsequently, the concentration of NO2/NO3 (stable NO metabolites) following incubation with both MCR antagonists significantly increased. This was attenuated by silencing of MCR or taurycamin. GO 6676 (PKCα inhibitor) augmented the increase of NO metabolites only in the epleronone treated cells.

Funding: Gottfried and渐友 Academic Foundation, Israel

FR-PO211

Diabetes Mellitus Modulates Interaction with Asymmetric Dimethyl Arginine in Hemodialysis

Marcelo C. Batista,1 Mauro sergio m. Marrocos,2 Beata M. Quinto,2 Andrei A. Teixeira,2 Maria Eugenia F. Canziani,2 Silvia R. Manfredi,2 Cassio J. Rodrigues.1 Federal University of Sao Paulo, Sao Paulo, Brazil; 1UNIFESP, Sao Paulo, Brazil; 2UNIFESP/EPAM, Pouso Alegre, Brazil; 3Universidade Federal de Sao Paulo, Sao Paulo, Brazil; 4Nephrology, Einstein Jewish Hospital, Nephrology, Sao Paulo, Brazil; 5Nephrology, State Public Server Hospital of Sao Paulo, Sao Paulo, Brazil.

Background: inflammation and Dimethyl Arginine Asymmetric (ADMA) are related to mortality in hemodialysis (HD). Study aims to analyze interaction between ADMA and CRP among DM- and + patients in HD.

Methods: Pre-HD ADMA measured by HPLC in 202 adults prevalent in HD. CRP measured by ultra-sensitive immunoturbidimetry. Association with mortality in 4 years through SPSS 23.0.

Results: Forty individuals censored by transplantation. DM+ were older (57.1 ± 13.3 vs. 50.2 ± 15.1 years, P = .002), with higher BMI (25.9 ± 2.9 vs 24.9 ± 2.4, P = .017), and higher percentage of coronary artery CRP medium (66.5% vs 15.0%, P = .001). ADMA and CRP were similar between DM+ and DM-. ADMA and CRP were similar between DM+ and DM-. Only ADMA - median IQR µM -0.088 0.60 - 1.37 and 1.71 1.34 - 2.17 P = 0.000 and median CRP µg /ml - .038-0.15 - 1.18 and 0.77 0.23 - 2.25 P = 0.034 differed between individuals with no evolution to death (D-) or with (D+). Only ADMA - median IQR µM -1.03 0.81 - 1.55 and 1.95 1.75 - 2.54 P = 0.000 between DM- and O+. In binary logistic regression, ADMA remained as a variable related to mortality in DM- (OR 2.579 1 C 1.36 - 3.68 P = 0.000), DM+ showed no differences between O- or O+. In 4 groups according to ADMA and CRP medians: I = lower ADMA and CRP, II = higher CRP and lower ADMA, III = lower CRP and higher ADMA and IV = higher ADMA and CRP - respective mortalities of 0.0%, 0, 0%, 31.0%, 69.0% among DM- (P =, 000). No differences in mortality between DM+ (GRAPHIC).

Conclusions: ADMA may have a significant association with mortality in prevalent DM- in HD and can improve evaluation of mortality risk in these patients. Other risk factors may overlap ADMA in DM+. Synergistic effect of ADMA and CRP, Mortality in group IV in DM- in HD higher than simple addition of mortality in group III with II or I. Previous work reported no differences between DM + and DM-, but DM+ totaled 15% of the cohort (CJASN 6 1714-21.2011).

Funding: Government Support - Non-U.S.
Characterization of a Novel β-Common Receptor Inhibitory Peptide CodY Kilarr

Peptide Ligand Interaction 1

2TOHOKU MEDICAL AND PHARMACEUTICAL UNIVERSITY

3FLY MILLER, FL

4University of Florida, Gainesville, FL

5University of Florida, Gainesville, FL

6North Florida/South Georgia Veterans Health System, Gainesville, FL

Background: In short term animal models of ischemia, reperfusion injury (EPO) signaling through the heterodimeric EPO receptor-β-common receptor (βCR) is believed to elicit tissue protective effects. However, large randomized controlled trials demonstrate that administering high doses of EPO, which can activate the βCR, is associated with an increase in adverse cardiovascular events. Thus, inhibition of the βCR may have therapeutic implications. This study aimed to design and evaluate the efficacy of a novel, computationally designed βCR inhibitory peptide (βIP).

Methods: The novel βIP was designed from the crystal structure of EPO consisting of 16-amino acids (VLERYLAKEAKEKT) from residues 11 to 26. Ultimately, the 16-amino acid peptide model comprising of VLERYLAKEAKEKT was selected as a novel βIP. The efficacy of βIP to inhibit βCR-induced nitric oxide (NO) production and angiogenesis in human umbilical vein endothelial cells (HUVECs) was evaluated.

Results: We found that βIP completely abolished EPO-induced NO production, however could be overcome with super physiological doses of EPO. βCR-induced angiogenesis in HUVECs was also abolished with treatment of βIP, but βIP did not inhibit vascular endothelial growth factor (VEGF)-induced angiogenesis. In addition, we show that the novel βIP does not increase erythropoiesis or inhibit EPO-induced erythropoiesis with use of peripheral blood mononuclear cells (PBMCs).

Conclusions: These results introduce, for the first time, a novel, potent βCR inhibitor that inhibits the actions of the βCR without affecting erythropoiesis. Experiments addressing the therapeutic use of this peptide will be discussed.

Funding: Other NIH Support - NIMHS

FR-PO213

Pathophysiological Analysis of Renal Congestion Using a Novel Rat Model

Satoshi Shima1, Takefumi Mori,2 Yusuke Ohsaki,3 Chika Takahashi, Sadao Miyahara,4 Toshiaki Kasahara,5 Tatsuya Yamaguchi,6 Tatsuya Yamaguchi7, Masaaki Kato8, Masahiro Maruyama9, Hiroshi Oka10

Graduate School of Medicine, Tohoku University, Sendai, Japan; 2University of Bari, Bari, Italy; 3IRCCS Ospedaliera Universitaria Integrata Verona, Verona, Italy; 4AOUI verona, Verona, Italy; 5University of Chieti, Chieti, Italy; 6Clinical nephrology unit of Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy; 7Department of Nephrology, University G.d'Annunzio Chieti, Francavilla al Mare, Italy; 8clinical nephrology university of chieti, Chieti, Italy; 9University of Verona, Verona, Italy; 10Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy.

Background: A physiological association between kidney and heart has been well known, however the mechanisms involved remain unknown. Renal congestion (RC) has been shown to play a role in heart failure (HF), precise mechanism involved in the pathogenesis of cardio-renal injury and Na retention has not been well investigated. The present study designed to investigate the role of renal congestion on glomerular filtration rate (GFR), renal histology, volume and blood pressure (BP).

Methods: RC was made by occluding left renal vein in Sprague Dawley rats. First, RC was made in left kidney while right kidney remained intact in anesthetized rats. GFR, renal interstitial hydrostatic pressure (RIPH) and urinary Na excretion was monitored in each kidney. Next, renal histology was compared between RC left kidney and intact right kidney after 9 days of RC. Finally, BP was monitored in rats with left RC and the other kidney removed. Rats were fed either normal salt or high salt for 2 weeks in either RC rats or sham operated rats.

Results: GFR and renal medullary blood flow significantly decreased in RC kidney while those of contralateral intact kidney remained unchanged. RIHP was increased during RC. Tubulo-glomerular injury was observed in the RC left kidney compared to the contralateral intact right kidney. These renal injuries were improved by reducing RIHP with removing renal capsule. In one-kidney RC model, plasma renin activity (renal congestion group 5.6±0.7 ng/mL/h, n=13 vs sham group 10.1±0.8 ng/mL/h, n=9, p=0.011) and hematocrit (operation group 43.5±1.4% ng/mL, n=13 vs sham group 47.8±0.9% ng/mL, n=9, p=0.001) is significantly lower in RC group compared to those of sham group, while Na excretion was lower in sham than the RC group. BP the one-kidney renal congestion rats (normal salt period 95.8±5.9 mmHg vs high salt period 116.1±6.1 mmHg, n=7, p=0.013), while no significant changes in BP was observed in sham operated rats.

Conclusions: RC increases body fluid volume by Na retention and reduced GFR and renal circulation by increase in RIHP, thereby induce salt induced increase in BP and renal injury. These results indicate that renal congestion play a pathophysiological role in the pathogenesis of HF.

Funding: Government Support - N-U.S.

FR-PO214

Diffusion-Weighted Magnetic Resonance Imaging (DWI) Correlates with the Response to Renal Revascularization in Patients with Atherosclerotic Renovascular Disease (ARVD)

Ahmad H. Hedayat,1 Alfonso Eriti, Christina C. Ferguson,1 James Cockroft,2 Stephen C. Textor,3 Lilach O. Lerman. Mayo Clinic, Rochester, MN.

Background: Selecting patients with ARVD likely to improve glomerular filtration rate (GFR) or for percutaneous transluminal renal angioplasty (PTRA) is challenging. DWI is an experimental tool to assess tissue morphology based on water molecule motion, and its index apparent diffusion coefficient (ADC) falls in damaged kidneys. We hypothesized that low basal ADC values would identify stenotic kidneys with subsequent diminished functional recovery after PTRA.

Methods: ADC was measured on 3T MRI in 20 patients with hemodynamically significant ARVD before and 3 months after standardized medical therapy (renin-angiotensin system inhibition) with or without PTRA. During protocol studies patients consumed a constant sodium intake, and eGFR was measured by iKID-EPI. Baseline ADC values were correlated with the change in eGFR after PTRA (delta eGFR).

Results: Baseline eGFR and ADC values were similar between groups (p>0.05). eGFR increased In patients 3 months after PTRA, and correlated directly with delta eGFR, but remained unchanged in patients treated with medical therapy (MT) alone.

Conclusions: Low basal ADC value may serve as biomarker of kidney injury and predict benefit from revascularization in ARVD. This noninvasive imaging technique may be useful for identification of patients likely to improve renal function after revascularization study.

Funding: NIDDK Support

FR-PO215

Gene Expression Analysis of Active and Chronic Renal Lesions in IgA Nephropathy Diagnosed Using the MEST-C Classification: A Multicenter Study

Sharon N. Cox,1 Claudia Curiel,2 Grazia Serino,2 Mario Rossini,4 Mario Bononini,5 Vittorio Siroli,5 Paolo Felaco,4 Gianluigi Zaza,4 Isabella Scurrazzi,4 Concetta Gangemi,10 Francesco P. Schena,2,11 Schena Foundation, Valenzano, Bari, Italy; 2University of Bari, Bari, Italy; 3IRCCS "S de Bells", Castellana Grotte, Bari, Italy; 4University of Bari, Department of Emergency and Organ Transplantation, Neurology Unit, Bari, Italy; 5University of Chieti, Chieti, Italy; 6Clinical of Nephrology, University G.d’Annunzio Chieti, Francavilla al Mare, Italy; 7clinical nephrology university of chieti, Chieti, Italy; 8University of Verona, Verona, Italy; 9Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy; 10AOU Verona, Verona, Italy.

Background: The diagnosis of idiopathic IgA Nephropathy (IgAN) is based on the "split system" where 4 types of renal lesions are scored: Mesangial hypercellularity (M 0-1), Endocapillary hypercellularity (E 0-1), Segmental glomerulosclerosis (S 0-1) and Tubular atrophy/interstitial fibrosis (T 0-2). Recently an extension of the MEST score has been suggested introducing crescents (C 0-2) in the split system because this lesion, together with E, are predictive of outcome (Trinchari H et al KI, 2017). Aim of our study was to identify specific gene expression changes that characterize active renal lesions (E and C) may be more responsive to immunosuppressive therapy and chronic lesions (S and T).

Methods: Total RNA was extracted from archival FFPE renal tissue samples of 52 IgAN patients, 24 non-IgAN patients (Minimal change 12, membranous nephropathy 12) and 7 kidney living donors (controls). Genome-wide gene expression profiles were generated and One-way ANOVA with tukeyHSD post hoc testing was used to identify specific transcripts associated with active and chronic lesions in IgAN. Real Time PCR was used for validation of the identified transcripts.

Results: We identified 391 genes exclusively modulated in IgAN biopsies with active lesions, 35 were down regulated and 355 were up-regulated. Some genes were specifically involved in glomerular injury. These genes belonged to renal cellular damage and immune system regulatory pathways. Moreover, we identified 194 genes that were differentially modulated by IgAN characterized by chronic lesions, 78 were down regulated and 116 were up-regulated. Candidate transcripts were validated by qRT-PCR in an extended cohort of IgAN biopsies.

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

Underline represents presenting author.
FR-PO216

Inhibiting Na/K-ATPase Oxidant Amplification Loop Regulates Aging in C57B16 Old Mice Rebecca L. Klug, Alexandra Nichols, Brian J. Snod, Hari Vishal Lakhani, Joseph L. Shapiro, Komal Sodhi, MUSOM, Huntington, WV; Marshall University School of Medicine, Huntington, WV; Marshall University, Huntington, WV; Marshall University, Joan C. Edwards School of Medicine, Huntington, WV.

Background: Aging, the inevitable and progressive decline of physiological integrity, manifests as: loss of cell division, oxidative stress, DNA damage, and senescence gene overexpression. Oxidant stress plays a role in the aging process, presumably in cellular and DNA damage. This contributes to impaired physiological function, disease development, and life span reduction. As we identified, the Na-K-ATPase amplifies oxidative signaling; we speculate a peptide inhibiting this pathway, pNaKtide, may be effective to regulate cellular senescence, thus delaying and/or reversing aging by attenuating oxidative stress.

Methods: C57B16 mice, young (6-8 weeks old, male) and old (17 weeks old, male) were fed normal chow diet or Western Diet (WD). They were randomly divided into 6 groups: (1) Young Control, (2) Young+pNaKtide (3) Old+Control, (4) Old+pNaKtide (5) Old-WD, (6) Old+WD+pNaKtide. After 8 weeks of control or WD diet respectively, groups 2, 4 and 6 were injected with pNaKtide for 8 weeks, (intraperitoneal dose of 25 mg/kg body weight every other day).

Results: Histological analysis of liver shows increased steatosis and fibrosis with age and more so with WD, this decreased with pNaKtide treatment. Histological analysis of kidney shows increased fat infiltration and sclerosis with age and WD, which decreased with pNaKtide treatment. TUNEL assay of liver and kidney indicated more DNA damage with age and WD, this significantly decreased with pNaKtide treatment (p<0.05). Indicative of oxidative stress, carbonylation of the Na-K-ATPase 6σ-subunit, activation of p-Ser and TBARS were significantly elevated in old and WD liver and kidney, which decreased to pNaKtide treatment (p<0.05). RT-PCR of senescence genes: p21, Aprotinin J, Collagenase 1, fibroactin, and Mmp-9 were significantly increased in hepatic and renal tissue with age and WD compared to those given pNaKtide treatment (p<0.05).

Conclusions: Our study demonstrates that Na-K-ATPase regulates aging and pNaKtide significantly alleviates genetic and phenotypic attributes of aging. pNaKtide holds potential as a novel drug for treating cellular damage that contributes to manifestations of aging and WD.

Funding: Other NIH Support - This work was supported by National Institutes of Health Grants HL109015 (to J.J.S. and Z.X.), HL071556 and HL105469 (to J.J.S.), and HL56601 and HL53400 (to N.G.A.), Commercial Support - by thebrickstreet Foundation (to J.J.S. and N.G.A.) and by the Huntington Foundation, Inc.

FR-PO217

D-Serine, a Novel Uremic Toxin, Induces Senescence in Human Renal Tubular Cells via GCN2 Activation Akira Okada,1 Tzu-Ming Jao,2 Hiroshi Maeka,1 Yu Ishimoto,1 Takahisa Kawakami,1 Masaoami Nagak,1 Reiko Inagi,2 Division of Nephrology and Endocrinology, The University of Tokyo Graduate School of Medicine, Tokyo, Japan; Division of CKD Pathobiology, The University of Tokyo Graduate School of Medicine, Tokyo, Japan.

Background: A recent metabolomic analysis revealed the change in profile of uremic toxins, including D-serine, in plasma or urine from CKD patients. Accumulation of D-serine, an enantiomer of L-serine, in plasma is associated with faster progression of renal dysfunction in CKD patients. We investigated whether chirality of the amino acid plays a crucial role in the pathogenesis of CKD.

Methods: To address the effect of D-serine on tubules, human proximal tubular cell line, HK-2, and primary culture of human renal tubular cells, NHREC, were treated with D- or L-serine for 48 hr and the cell damages were evaluated by cell proliferation (MTS assay and cell count), cell cycle status (PI and Phospho-Histone H3 staining), senescence (p21, p16/p19, p53), senescence-associated secretory phenotype (SASP: pro-inflammatory cytokines (IL-6 and IL-8) and apoptosis ( Annexin V staining and caspase 3/7 activity). To find out the molecular mechanism of the cell damages by D-serine, we assessed the status of amino acid-mediated signaling (integrated stress response: GCN2, ATF4, and CHOP) and L-serine synthesis pathway (PHGDH and PSAT1). To confirm signal transduction, siRNAs of integrated stress response proteins were used.

Results: D-serine, but not L-serine, markedly induced cellular senescence and apoptosis both in HK-2 and NHREC. Such tubular damage by D-serine was accompanied by cell cycle arrest and induction of SASP, including pro-inflammatory factors, contributing to tubulointerstitial fibrosis. Importantly, we found that integrated stress response mediated by GCN2-ATF4-CHOP pathway played a central role in D-serine-induced cell toxicity: knockdown of GCN2 ameliorated D-serine-induced tubular cell senescence, suggesting CKD progression and kidney aging by D-serine. Furthermore, D-serine upregulated the L-serine synthesis pathway, possibly as a counteracting mechanism, and D-serine-induced tubular toxicity is counteracted by L-serine, suggest that the proportion of D:L-serine is critical for D-serine toxicity to tubular cells.

Conclusions: This study unvels a pathogenic role of the chiral amino acid and molecular mechanisms underlying D-serine-induced tubular damage, such as senescence with SASP, in CKD pathogenesis.

Funding: Government Support - Non-U.S.

FR-PO218

TAM Receptor TYRO3 Plays a Role in Pococye Injury liwen2, zhang Zhaohong Chen, Qiong Hou, Zhi Li, Wei-song Qin, Zhi-Hong Liu. National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine. Nanjing China, Nanjing, China.

Background: Podocyte injury plays a critical role in the development and progress of diabetic nephropathy (DN). Analyzing transcriptional profile of renal biopsy from diabetic nephropyathy patients and control donors identified TYRO3, a member transmembrane receptor kinase receptor (TAM), as one of the main hub genes that are strongly associated with proteinuria in type 2 DN patients. TAM receptors have been shown to play roles in immune homeostasis, neuronal differentiation and survival.

Methods: Co-localization studies detected TYRO3 protein along with the podocyte marker synaptopinin in glomeruli.

Results: No colocalization was observed between TYRO3 and endolateral marker (CD31). IHC demonstrated TYRO3 and phosphorylated TYRO3 were downregulated in the glomeruli from DN patients and db/db mice. Knockdown of tyro3 by ATG or splicing morpholino-oligos (MO) in zebrafish larvve exhibited edema (36.23%) and foot-process effacement. Permeability studies in these zebrafish morphants demonstrated disruption of the selective glomerular permeability filter. Rescue experiment showed that zebrafish co-injected with synthetic zebrafish tyro3 mRNA and MO were morphologically normal compared to control. When tyro3 was injected with MO of merk, neither TAM member, didn’t exhibit abnormal morphology. in vitro studies showed that podocyte express TYRO3 and its ligand G5A6. High-glucose downregulated TYRO3 mRNA and protein expression in podocytes. Moreover, depletion of TYRO3 expression with siRNAs induced and augmented high glucose induced podocytes apoptosis via PI3K/AKT / / Bax/ Bel-2 pathway.

Conclusions: Taken together, our findings demonstrated that TYRO3 is a novel protein that might play a crucial role in podocyte homeostasis via stabilizing PI3K-AKT signal pathway.

FR-PO219

Recognition of Apoptotic Cells by Viable Proximal Tubular Epithelial Cells (PTEC) Induces Death Receptor (DR)-Dependent PTEC Death: Dual Modes of PTEC Death Following Injury Michael E. Dietrich,1,2 Lanfei Feng,1 Joyce Rauch,1 Jarrol S. Levine,1,2 University of Illinois at Chicago, Chicago, IL; Jesse Brown FAMC, Chicago, IL; McGuill University, Montreal, QC, Canada.

Background: We have shown that mouse kidney PTEC have distinct non-competing receptors for apoptotic and necrotic targets. Recognition of apoptotic, but not necrotic, targets induces apoptotic death of PTEC responders. Here we study the role of DRs and their ligands (DR-L) in this process.

Methods: Responder cells were BU.MPT cells, a conditionally immortalized PTEC line. Target cells, induced to undergo apoptosis or necrosis, were homologous (BU.MPT) or heterologous (DO11.10 lymphocytes).

Results: Apoptotic target-induced death of PTEC responders is profound (~100% by 48-72 h) and at least in part, DR-dependent, as shown by caspase-8 activation and augmented survival upon caspase-8 inhibition. To evaluate the role of DRs, we compared expression of DR3, DR5, and Fas in PTEC responders, exposed to dead targets. Expression fell into one of two patterns: (1) DR3: Responders at rest (i.e., not exposed to targets) lacked DR expression. 18 h after exposure to apoptotic (but not necrotic) targets, ~50% of responders newly expressed DR3. (2) Fas and DR5: Responders at rest expressed Fas and DR5 constitutively. 18 h after exposure to apoptotic (but not necrotic) targets, ~50% of responders had undetectable Fas and DR5. We next examined DR-shifted responders (i.e., with new DR3 expression, or lost Fas and DR5 expression). Consistent with apoptosis induction following exposure to apoptotic (but not necrotic) targets, DR-shifted PTEC responders of both patterns were smaller in size and positive for caspase-3 activation.

Notably, quiescent PTEC do not express DR-L. However, after exposure to apoptotic (but not necrotic) targets, ~50% of responders newly expressed DR3. (1) DR3: Responders at rest (i.e., not exposed to targets) lacked DR expression. 18 h after exposure to apoptotic (but not necrotic) targets, ~50% of responders newly expressed DR3. (2) Fas and DR5: Responders at rest expressed Fas and DR5 constitutively. 18 h after exposure to apoptotic (but not necrotic) targets, ~50% of responders had undetectable Fas and DR5. We next examined DR-shifted responders (i.e., with new DR3 expression, or lost Fas and DR5 expression). Consistent with apoptosis induction following exposure to apoptotic (but not necrotic) targets, DR-shifted PTEC responders of both patterns were smaller in size and positive for caspase-3 activation.

Conclusions: Exposure of viable PTEC to apoptotic (but not necrotic) targets induces PTEC apoptosis via DR-dependent mechanisms. Expression of Fas and DR5 is constitutive, while expression of their ligands, FasL and TRAIL, is induced by apoptotic target recognition. We hypothesize that PTEC injury is characterized by two distinct waves of cell death. In the 1st wave, PTEC death is the direct result of injury. In the 2nd wave, PTEC death is independent of injury, and the result of receptor-mediated recognition of dead or dying PTEC.
FR-PO220

Activation of PPAR-γ Suppresses AngII Induced Proliferation of HBZY-1 Cell via the GPCR/Gq/PLCγ4/TRPC Signaling Pathway  
Linting Wei,1,2  Rongguo Fu,1,3 Jiamei Lu,1 Second Affiliated Hospital of Xi’an Jiaotong University, Xi’an, China; 1Second Affiliated Hospital of Xi’an Jiaotong University, Xi’an, China; 2Second Affiliated Hospital of Xi’an Jiaotong University, Xi’an, China.

Background: AngII can induce mesangial cell proliferation and affect TRPC expressions.

We investigated the role of TRPC and effect of rosiglitazone (RSG) in the proliferation of HBZY-1 cell via the Gq/PLC4/TRPC signaling pathway.

Methods:Immunofluorescence staining and qRT-PCR were performed to examine the expressions of TRPCs in HBZY-1. Gene expressions of TRPC, PPAR-γ, RGS4, GPCR/Gq/PLCγ4/TRPC signaling pathway and downstream main proliferative proteins, including Ulk1, Beclin-1, Atg9A, Atg4B, and Bnip3, suggesting that FoxO3 may also function to replenish components of the autophagic machinery that would otherwise be consumed during sustained autophagy.

Conclusions:We suggest that Ang II induced autophagy in mouse podocytes prior to apoptosis as an early adaptive cytoprotective mechanism for podocyte injury and thereby significantly inhibiting autophagy and apoptosis. This study is the first to show the effect of NRF2-HO-1 system on high glucose induced autophagy and apoptosis of tubule cells. Targeting NRF2-HO-1 as a modulator of autophagy may result in novel therapeutic intervention in diabetic nephropathy.

Funding: NIDDK Support, Private Foundation Support

FR-PO222

Forkhead Box O3 (FoxO3) Regulates Kidney Tubular Autophagy Following Urinary Tract Obstruction  
Ling Li, Ronald Zivit, Catherine Ha, Fangming Lin. Department of Pediatrics, Columbia University College of Physicians & Surgeons, New York, NY.

Background: Autophagy has been shown to be important for normal homeostasis and adaptation to stress in the kidney. Yet, molecular mechanisms regulating renal epithelial autophagy are not fully understood.

Methods: We explore the role of the stress-responsive transcription factor forkhead box O3 (FoxO3) in mediating injury-induced proximal tubular autophagy in mice with unilateral ureteral obstruction (UUO), which is a reproducible model of persistent tubular autophagy.

Results: We show that following UUO, FoxO3 is activated over basal level and displays nuclear expression in 34.0 ± 3.4% of proximal tubules at 3 days (n=3, p<0.01) and 45.5 ± 2.8% at 7 days (n=3, p<0.05) when the hypoxic tubules exhibit high levels of autophagy. Activation of FoxO3 by mutating its phosphorylation sites to enhance its nuclear expression induces profound autophagy in primary cultures of renal epithelial cells. Conversely, deleting FoxO3 in mice results in fewer numbers of autophagic cells in the proximal tubules and reduces the conversion of the key autophagy-associated protein LC3-I to LC3-II post-UUO. Interestingly, autophagic cells deficient in FoxO3 contain less numbers of autophagic vesicles per cell upon stimulation with nutrient deprivation. Analysis of individual cells treated with various autophagic inhibitors to sequentially block the autophagic flux suggests that FoxO3 stimulates the formation of autophagosomes to increase autophagic capacity without significant effects on autophagosome-lysosome fusion or autolysosomal clearance. Furthermore, in kidneys with persistent UUO for 7 days, the activation increases the expression of core autophagy-associated (Atg) proteins, including Ulk1, Beclin-1, Atg9A, Atg4B, and Bnip3, suggesting that FoxO3 may also function to replenish components of the autophagic machinery that would otherwise be consumed during sustained autophagy.

Conclusions: In summary, our findings indicate that FoxO3 activation can both induce and maintain autophagic activities in renal epithelial cells in mouse models of prolonged tubular stress and injury.

Funding: Government Support - Non-U.S.

FR-PO221

Cytosprotective Role of Autophagy in Angiotensin II-Induced Podocyte Apoptosis  
Tae-Sun Kim. Chungbuk National University College of Medicine, Cheongju-si, Republic of Korea.

Background: Autophagy and apoptosis are two cellular processes through which injured and aging cells or organelles are eliminated. Angiotensin II (Ang II) induces podocyte injury resulting in apoptosis in vitro and in vivo. However, the relationship between autophagy and apoptosis in Ang II-induced podocyte injury is unknown and the role of Ang II-induced autophagy in podocyte survival or death remains unclear. We investigated the sequential relationship between autophagy and apoptosis.

Methods: Mouse podocytes were incubated in media containing various concentrations of Ang II and at different incubation times. Cell survival/death-modifying reagents and Atg5 siRNA were applied. The changes of podocyte autophagy and apoptosis were observed by electron microscopy, confocal imaging, western blotting, TUNEL, and FACs assay according to the presence of Ang II.

Results: Ang II enhanced the podocyte expression of the autophagic proteins, LC3A/B-II and beclin-1, and also increased the number of autophagosomes compared with control cells at early phase of 12 hours in a dose-dependent manner. This pro-autophagic effect of Ang II was inhibited by pretreatment with 3-methyladenine (3-MA), a PI3-kinase class III inhibitor. Atg5 siRNA reduced LC3 puncta levels and increased the number of apoptotic podocytes that over that observed with Ang II treatment at 12 hours. Therefore, the Ang II-enhanced induction in autophagy decreased, whereas, podocyte apoptosis appeared later at 24 hours in concentration- and time-dependent manners in FACs and TUNEL assays. 3-MA and LY294002 further increased Ang II-induced podocyte apoptosis. Suppression of autophagy by Atg5 siRNA could induce podocyte apoptosis and further augment high-dose Ang II-induced podocyte apoptosis.

Conclusions: We suggest that Ang II induced autophagy in mouse podocytes prior to apoptosis as an early adaptive cytoprotective mechanism for podocyte injury and thereby significantly inhibiting autophagy and apoptosis.

Funding: Government Support - Non-U.S.
Unfolded Protein Responses Potentially Uremic Sarcopenia through Perturbation of Myoblast Differentiation Xia-Rong Jiang,1, 2, 3 Yuan-Shiao Chen,1 Chih-Kang Chiang,1, 2 Shing-Hwa Liu.1 Graduate Institute of Toxicology, National Taiwan University, College of Medicine, Taipei, Taiwan; 1Department of Integrated Diagnostics & Therapeutics, National Taiwan University Hospital, Taipei, Taiwan; 2Department of Internal Medicine, National Taiwan University, College of Medicine, Taipei, Taiwan.

Background: Sarcopenia is the age-related degeneration characterized with the decline of skeletal muscle mass, strength, and mobility. The imbalance of protein synthesis and degradation which jeopardizes immune, hormone regulation, and muscle-motor neuron connection is the main cause of sarcopenia. There are limited knowledge regarding molecular mechanism of sarcopenia. As the endoplasmic reticulum (ER) is the control center of the protein synthesis and degradation, we hypothesized that ER stress and unfolded protein response (UPR) are important causes of sarcopenia. Understanding the sarcopenia molecular mechanisms may benefit the therapeutic diagnosis and treatment in the future.

Methods: Mouse myoblast C2C12 cells are exposed to designated time and concentration of indoxyl sulfate (IS). The proliferation, differentiation, and myotube atrophy are examined. The protein and mRNA expression of IS treated C2C12 cells are inspected to distinguish the role of ER stress and oxidative stress underlying the sarcopenia.

Results: IS inhibits myoblast differentiation. We demonstrate that number of multi-nuclei myotube decreased, the differentiation markers including myoD, myoG, and myosin heavy chain are also suppressed. IS inhibits myoblast proliferation and induces the myotubular atrophy marker atrogin-1 and myogenin expression. IS induced cell death via e2f2a phosphorylation and XBP1 mRNA splicing in UPR. Interestingly, the oxidative stress is related to e2f2a phosphorylation but not XBP1 mRNA splicing. The e2f2a phosphorylation triggered by IS reduces myoD, myoG and myosin heavy chain protein expression, which is the antidepressogenic modulation on the early differentiation event. XBP1 mRNA splicing induced by IS, however, is considered the late differentiation event which is a promyogenic modulation—an adaptive response.

Conclusions: Our studies indicated that the ER stress and UPR modulation are critical both in sarcopenia and the CKD uremic toxin accumulation model. We believe that UPR-related molecules showed great potential in clinical application.

Funding: Government Support - Non-U.S.


Background: HIV-associated nephropathy (HIVAN) is characterized by severe proteinuria and progressive CKD and is caused by infection of renal epithelial cells, though active viral replication is not necessary to induce disease in animal and in vitro models. Antiretroviral therapy (ART) markedly reduces the risk of progression to ESRD without eradicating HIV in the kidney and the mechanism(s) by which ART protects kidneys from HIVAN is poorly understood.

Methods: We studied HIV- transgenic mice, which develop a HIVAN phenotype. Since the transgene in these mice does not encode HIV Reverse Transcriptase (RT) or HIV protease, we used these mice to determine if the HIV protease inhibitor darunavir (DRV) and/or RT inhibitor zidovudine (AZT) protect against HIVAN independent of effects on RT or HIV protease. Mice were treated for 4 weeks by daily oral gavage in 4 groups: DRV (10 mg/kg), AZT (50 mg/kg), DRV+AZT, or control. Mice were sacrificed, and kidneys were harvested.

Results: DRV and DRV+AZT, but not AZT alone reduced urinary albumin:creatinine ratio and histologic glomerular and tubulointerstitial injury. DRV and DRV+AZT, but not AZT also markedly reduced expression of the proliferation marker Ki67 in tubular cells, preventing loss of synaptopodin expression in podocytes, and reduced phosphorylation of ERK1,2 and Stat3, which are important mediators of HIV-induced kidney injury. To further examine the mechanism of DRV-induced protection, we studied the effects of DRV renal tubular epithelial cells (RTEC) transduced with gag/pag-deleted HIV lentivirus (lacking HIV protease and RT). HIV Vpr-expressing lentivirus, or control lentivirus. DRV significantly attenuated HIV and Vpr-induced activation of Stat3, ERK, and SRE and decreased HIV and Vpr-induced expression of IL-6 and IL-8, which are key inflammatory mediators in HIVAN.

Conclusions: These data demonstrate that DRV but not AZT protects against HIV-induced renal injury via mechanisms that are at least partially independent of suppression of HIV replication and HIV Protease. DRV renal tubular epithelial cells (RTEC) transduced with gag/pol-deleted HIV lentivirus prevented loss of synaptopodin expression in podocytes, and reduced phosphorylation of Stat3, ERK, and Src and XBP1 mRNA splicing in UPR. Interestingly, the oxidative stress is related to e2f2a phosphorylation but not XBP1 mRNA splicing. The e2f2a phosphorylation triggered by IS reduces myoD, myoG and myosin heavy chain protein expression, which is the antidepressogenic modulation on the early differentiation event. XBP1 mRNA splicing induced by IS, however, is considered the late differentiation event which is a promyogenic modulation—an adaptive response.

Funding: Government Support - Non-U.S.

Effect of Huai'er on the Proliferation of Mesangial Cells in Anti-Thy-1 Nephritis Xiaomei Chen. Department of Nephrology, Chinese PLA General Hospital, Beijing, China.

Background: Mesangial proliferative glomerulonephritis (MGGN) is one of the common kidney diseases. The potential therapy for the treatment of Trametes robiniiophila murr (Huai'er) could suppress mesangial cell proliferation in rat cells treated with platelet-derived growth factor (PDGF)-BB and in rat model of anti-Thy-1 mesangial proliferative glomerulonephritis, and further explored the possible mechanisms of its antiproliferative effects.

Methods: In Vivo: Thirty Wistar rats were randomly divided into five groups: (1) Sham surgery (Sham); (2) anti-Thy-1 nephritis model (Thy-1); (3) anti-Thy-1 nephritis model + low-dose of Huai'er (HRL); (4) anti-Thy-1 nephritis model + medium-dose of Huai'er (HRM); (5) anti-Thy-1 nephritis model + high-dose of Huai'er (HHR). Two weeks after the induction, urinary proteins were quantified and renal pathological changes were thoroughly examined. Meanwhile, the expression levels of Mx1 and PCNA in isolated glomeruli were also tested. In Vitro: Rat mesangial cell viability was measured by CCK8 DNA synthesis and cell proliferation evaluated by 5-ethyl-2'-deoxyuridine(UdU) incorporation. The distribution of PCNA and Ki67 was analyzed by flow cytometry, and western blot were used to test the cell cycle pathways.

Conclusions: Our results showed higher miR-21 levels in IgAN, which inhibited the expression of SPRY1, SPRY2, FASLG, and thereby accelerated Th17 polarization.

Funding: Government Support - Non-U.S.
Results: Huai run diminished the proliferative damages and urinary protein secretion in Thy-1 rats. PCNA was downregulated, whereas Mxi-1 was upregulated in the isolated glomeruli of Huai-treated groups compared with the Thy-1 group. Huai run inhibited PDGF-BB–stimulated proliferation of rat mesangial cells in a time- and dose-dependent manner (50% inhibition concentration = 6.19 μg/mL) and induced G2 cell-cycle arrest. Cell-cycle pathway proteins were downregulated, whereas Mxi-1 was upregulated in Huai-treated mesangial cells compared with PDGF-BB–stimulated cells.

Conclusions: Huai run reduces urinary protein excretion and relieves hyperplasia in mesangial cells in anti-Thy-1 MsPGN as well as inhibits PDGF-BB–stimulated proliferation and DNA synthesis of rat mesangial cells in vitro, suggesting its possible therapeutic potential in MsPGN.

Funding: Government Support - Non-U.S.

FR-PO229
Kidney Organoids Generated from Bone Marrow-Derived Mesenchymal Stem Cells
Xiaomei Chen, Chinese PLA General Hospital, Beijing, China.

Background: Via the directed differentiation of stem cells, progenitors can be induced to both the collecting ducts and the interstitium of the renal organ. The human kidney organ formed from the intermesenchyme, the kidney organoids were constructed by MSCs. 2) The kidney specific genes controlling the ratio of the formation of the ureteral epithelium and the metanephric mesoderm. The intermediate mesoderm increases the number of key renal progenitor cells, as well as the ureteral epithelium and the metanephric mesenchyme, which respectively form the collecting ducts and nephrons. According to this theory, we have used bone marrow–derived mesenchymal stem cells (BM-MSCs) to differentiate into the kidney organoids by each other.

Methods: 1) By simulating the regulation of CHIR99021-FGF9 cytokines, and controlling the ratio of the formation of the ureteral epithelium and the metanephric mesenchyme, the kidney organoids were constructed by MSCs. 2) The specific markers in the kidney organoids were detected by immunofluorescence staining. 3) The electron microscope was used to observe the structure of the organoids.

Results: 1) The kidney organoids formed from the BM-MSCs represented powerful models of the human organ for future applications, including nephrotoxicity screening, disease modeling and as a source of cells for therapy.

Funding: Government Support - Non-U.S.

FR-PO230
CRISPR-Cas9-Induced Expression of Endogenous APOL1-G8 Reduced Cytotoxicity of Renal Risk Variant APOL1-G1 Opeyemi A. Obabii,1,4 Savannah Moore,2,4 Martin R. Pollak,1,4 Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA; 2Massachusetts General Hospital, Brookline, MA; 3Medicine, Massachusetts General Hospital, Boston, MA; 4Harvard Medical School, Boston, MA.

Background: Two protein coding mutations in the APOL1 gene account for much of the excess risk of non-diabetic end stage kidney disease (ESRD) among individuals of recent African Ancestry. These 2 common mutations (named G1–missense mutation, and G2-2 amino acid deletion), collectively referred to as renal risk variant (RRV) APOL1 and increase the risk of FSGS, HIVAN and hypertension-associated ESRD. The pattern of inheritance of APOL1-nephropathy is recessive—the disease is most consistently seen in African Americans with 2 copies of RRV APOL1 relative to those with zero or 1 copy of the risk allele. Yet, strong evidence suggests that cytotoxicity of RRV APOL1 is due to gain of function. Expression of both G1 or G2 APOL1 result in toxicity in HEK-293 cells, human and mouse podocytes. We predict that induced cellular expression of wildtype APOL1 (G0) would compete with and reduce cytotoxicity of RRV APOL1 in HEK-293 cells.

Methods: We generated HEK-293 cell line that stably express APOL1-G1 in the presence of exogenous tetracycline. Transient transfection of these stable HEK-293 cells with CRISPR-transcription activator complex (dCas9-Vp64, p65-HSF1, and guide RNA specific for APOL1 promoter) induced robust expression of endogenous APOL1-G0. We then measured cytotoxicity of APOL1-G1 in the presence or absence of these induced APOL1-G0.

Results: In the presence of APOL1-G0, the cytotoxicity of APOL1-G1 is significantly reduced up to 50%.

Conclusions: This result suggests that the cytotoxicity of renal risk variants APOL1-G1 could be reduced by wildtype APOL1-G0. This may explain in part why the risk of APOL1-nephropathy is negligible among individuals who carry at least one copy of wild type APOL1-G0, but high among individuals with 2 copies of RRV. Also, this finding suggests that differential upregulation of APOL1-G0 or downregulation of RRV APOL1 in podocytes may be a useful therapeutic intervention.

Funding: Private Foundation Support

FR-PO231
Apoptosis-Proliferation Balance in the Wound Healing Pathway: A Fight for Survival Joseph A. Ciavaglia,1,2 Russell P. Thomson,1 Anibeley Almanzar,3 Simranjit Singh,3 Ji Won Kang,2 Jayne Rape,2,5 City University of New York, New York, NY; 1Hunter College, New York, NY; 2NYU Medical Center, New York, NY.

Background: APOL1 is an innate immunity protein that forms pores in trypanosomes. Variants of APOL1 have been linked to kidney disease, yet the mechanism responsible is controversial. We tested the hypothesis that APOL1 toxicity is cell intrinsic and dependent upon secretion via the Golgi. Along the secretory pathway, APOL1 is acetylated and then secreted upon delivery to the plasma membrane, wherein the cation selective pore initiates wound repair via the influx of Ca+2.

Methods: HEK293 cells were transfected with APOL1 and its variants, including deletion of the signal peptide. 24-48h later cell toxicity and viability were measured. Treatment with ammonium chloride was performed 2h prior to transfection. Recombinant APOL1 was purified from E. coli and reconstituted in planar lipid bilayers to measure ion channel conductivity and selectivity. HEK293 cells that stably express APOL1 were generated using the FlpIn recombinase system. The cells were transfected with the FlpFp cassette. Expression of APOL1 was assayed in the supernatant and then read in a fluorescent plate reader. Activity of β-hexosaminidase (β-hex) was assayed in the supernatant of transfected cells at various timepoints after APOL1 expression.

Results: Deletion of the signal peptide led to a significant reduction of toxicity across all variants. Pre-treatment of cells with ammonium chloride reduced the toxicity of APOL1 by 50%. In planar lipid bilayers, rAPOL1 of all three major variants allowed for the passage of Ca+2. In stably transfected cells, induction of APOL1 expression lead to an increase in cytoplasmic Ca+2. In a cell, this would cause lysosomes to fuse with the plasma membrane to initiate removal of the wound and repair the membrane. Indeed, release of the lysosomal enzyme β-hexosaminidase, a marker of wound-healing, was detected prior to cell death.

Conclusions: These data support a model of APOL1 mediated cell death that requires acidic activation along the secretory pathway prior to forming pores at the plasma membrane. Increases in Ca+2 flux and the release of lysosomal enzymes prior to cell death indicate activation of the wound healing pathway by APOL1 pore formation. Maintaining the balance between secretion and excessive pore formation of APOL1 and the ability to remove and repair the wounds are key to cell survival.

Funding: Other NIH Support - NIH Institute Support: National Science Foundation Bread Award IOS-1249166

FR-PO232
Apolipoprotein L-1 and the Wound Healing Pathway: A Fight for Survival Joseph A. Ciavaglia,1,2 Russell P. Thomson,1 Anibeley Almanzar,3 Simranjit Singh,3 Ji Won Kang,2 Jayne Rape,2,5 City University of New York, New York, NY; 1Hunter College, New York, NY; 2NYU Medical Center, New York, NY; 3NYU College of Medicine, New York, NY; 4Immunology and Inflammation, Feinstein Institute for Medical Research, New York, NY.

Background: Dibetic podocytopathy is characterized by significant proteinuria, an indication of loss of integrity of glomerular filtration barrier. High glucose milieu has been demonstrated to promote dedifferentiation of podocytes (PDs) contributing to the loss of integrity of glomerular filtration barrier; however, the involved mechanism is far from clear. APOL1 is expressed in kidneys of certain primates including humans. APOL1 risk alleles (G1 and G2) have been reported to be podocytotoxic, however, the role of APOL1 G0 (wild-type) is far from clear. We hypothesize that APOL1 facilitates preservation of the molecular integrity of podocytes in adverse milieu such as high glucose through down-regulation of microRNA (miR) 193a.

Methods: To evaluate the effect of high glucose milieu, differentiated human podocytes (DIF-PDs, after incubation for 10 days at 37°C) were incubated in media containing different concentrations of glucose (5, 15, 25, 30, and 35 mM) for 48 hours. To evaluate the role of miR193a, DIF-PDs were incubated in media containing normal glucose (5 mM, NGM), high glucose (30 mM) with/without miR193a inhibitor (25 nM) for 48 hours. To establish a cellular relationship, DIF-PDs were transfected with either control or APOL1/miR193a siRNA followed by incubation in either normal (5 mM, NG) or high glucose (HGM) media for 48 hours. To confirm a relationship, DIF-PDs were transfected with either control or APOL1 lentivirus and then incubated in media containing either normal or high glucose for 48 hours. Proteins and RNA were extracted.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Protein blots were probed for APOL1, WT1, podocalyxin, nephrin and reprobed for actin. RNA was extracted from treated cells and used for qPCR. 

Results: HgM down regulated WT1 and nephrin (2.5 fold) expressions but increased (3-fold) miR193a levels in PDs. HgM down regulated PD expression of APOL1 in a dose-dependent manner. PDs knocked down for APOL1 displayed enhanced (2.2 fold) levels of miR193a, whereas, PDs knocked down for miR193a displayed increased (2.5 fold) expression of APOL1. Over expression of APOL1 in PDs preserved podocyte molecular phenotype in HgM. 

Conclusions: High glucose differentiates PDs through down-regulation of APOL1; however, overexpression of APOL1 preserves PDs molecular integrity. 

Funding: NIDDK Support

FR-PO233
HIV and Interferon (IFN)-γ Facilitate Parietal Epithelial Cell Transition through Induction of APOL1 Vino S Kumar, Xiayan Lan, Rukhsana Aslâm, Ali Hussain, Seyyed Shadafarin Marashi Shoshtari, Pravin C. Singhal. Feinstein Institute for Medical Research, Haifa, Israel; The Feinstein Institute for medical research, Glenoaks, NY; Feinstein Institute of Medical Research, Great Neck, NY; Feinstein Institute for medical research, Glenoaks, NY; Feinstein Institute of Medical Research, New York, NY; Immunology and Inflammation, Feinstein Institute for Medical Research, New York, NY; North Shore LIJ Health System, Great Neck, NY; Rambam Health Care Campus, Haifa, Israel; The Feinstein Institute for Medical Research, Manhasset, NY; University of Hamburg, Hamburg, Germany; Immunology and Inflammation, Feinstein Inst.med research and NSLIJ, Manhasset, NY.

Background: Genetic epidemiology indicated that HIV-infected patients carrying APOL1 risk alleles with African ancestry carry a risk of developing HIV-associated nephropathy at 10 times higher rates when compared to patients carrying APOL1 (wild-type). Podocytes (PDs) express APOL1 constitutively and this expression is enhanced by HIV and IFN-γ. However, parietal epithelial cells (PECs) do not express APOL1. Both PDs and PECs are evolved from the same mesenchymal cells during embryogenesis. Since APOL1 expression seems to be a differentiating phenotypic molecule between PECs and PDs, we wished to consider its potential role in distinct cellular phenotype determination. We hypothesized that HIV could be facilitating PECs transition to PDs through the induction of APOL1.

Methods: Immortalized PECs proliferate at 33˚C and differentiate (transit) to podocytes at 37°C. PDs were transduced with either vector (PECV) or HIV (NL4-3, PECV) and incubated for 48 hours at 33˚C (n=4). In another set of experiments, PDs were incubated in media containing different concentrations of IFN-γ (0, 5, 10, 15, 20, 40 nM) for 48 hours at 33˚C (n=4). To establish a causal relationship, PECV and PECHV were transfected with either control or APOL1 siRNA (n=4). To confirm the role in PECs transition, mouse (M) PDs, which do not express APOL1, were transduced with either vector or APOL1 lentivirus (n=4). Proteins and RNAs were extracted. Protein blots were probed for APOL1, markers of PECs (PAX2, and Claudin 1) and PDs (WT1, nephrin, podocalyxin, and podocin) and reprobed for GAPDH. cDNAs were amplified for APOL1, WT1, podocalyxin, nephrin, and podocin.

Results: HIV induced APOL1 expression in PECs. IFN-γ also induced APOL1 expression in PDs in a dose dependent manner. PECV/IFN-γ treated PECs displayed induction of nephrin, enhanced expression of WT1 (2.5-fold) and podocalyxin (3-fold) but dormant expression of APOL1. PDV/IFN-γ treated PDs displayed down regulation of WT1, podocalyxin, and podocin; on the other hand, mouse podocytes (MPDs) expressing APOL1 displayed enhanced expression of WT1, podocalyxin, and podocin when compared to MPDVector.

Conclusions: HIV and IFN-γ stimulate PECs transition through induction of APOL1. 

Funding: NIDDK Support

FR-PO234
APOL1 Provides Podocyte Protection against Apoptosis through Down Regulation of MicroRNA (miR193a) in Adverse Milieus Vino Kumar, Xiayan Lan, Rukhsana Aslâm, Ali Hussain, Seyyed Shadafarin Marashi Shoshtari, Catherine Meyer-Schewsinger, Ashwani Malhotra, Karl Skorecki, Pravin C. Singhal. Feinstein Institute for Medical Research, Great Neck, NY; Rambam Health Care Campus, Haifa, Israel; Feinstein Institute for medical research, Glenoaks, NY; Feinstein Institute of Medical Research, New York, NY; Immunology and Inflammation, Feinstein Institute for Medical Research, New York, NY; North Shore LIJ Health System, Great Neck, NY; Rambam Health Care Campus, Haifa, Israel; The Feinstein Institute for Medical Research, Manhasset, NY; University of Hamburg, Hamburg, Germany.

Background: Adverse milieus such as high glucose and purinoma aminoacloleidase (PA) have been reported to induce podocyte (PD) injury both in vitro and in vivo in animal studies. APOL1, expressed intracellularly is a minor component of circulating lipid-rich trypanolytic multiprotein complexes in certain primate species including humans. Genetic epidemiologic studies suggest that humans carrying APOL1 wild-type (G0) are less likely to develop chronic kidney disease when compared to humans carrying APOL1 risk alleles (APOL1G1 and G2). We hypothesized that PD expression of APOL1G0 provides protection against apoptosis in adverse milieus.

Methods: Human podocytes (PDs) were transduced with either vector (PDV) or APOL1G0 (PDG0) and incubated for 48 hours at 33˚C (n=4). To establish a causal relationship, PECV and PECHIV were transfected with either control or APOL1 siRNA (n=4). To confirm the role in PECs transition, mouse (M) PDs, which do not express APOL1, were transduced with either vector or APOL1 lentivirus (n=4). Proteins and RNAs were extracted. Protein blots were probed for APOL1, markers of PECs (PAX2, and Claudin 1) and PDs (WT1, nephrin, podocalyxin, and podocin) and reprobed for GAPDH. cDNAs were amplified for APOL1, WT1, podocalyxin, nephrin, and podocin.

Results: HIV induced APOL1 expression in PECs. IFN-γ also induced APOL1 expression in PDs in a dose dependent manner. PECV/IFN-γ treated PECs displayed induction of nephrin, enhanced expression of WT1 (2.5-fold) and podocalyxin (3-fold) but dormant expression of APOL1. PDV/IFN-γ treated PDs displayed down regulation of WT1, podocalyxin, and podocin; on the other hand, mouse podocytes (MPDs) expressing APOL1 displayed enhanced expression of WT1, podocalyxin, and podocin when compared to MPDVector.

Conclusions: HIV and IFN-γ stimulate PECs transition through induction of APOL1. 

Funding: NIDDK Support

FR-PO235
APOL1-microRNA193a Feedback Loop Facilitates Monocyte Macrophage Transition Vino Kumar, Xiayan Lan, Rukhsana Aslâm, Ali Hussain, Seyyed Shadafarin Marashi Shoshtari, Catherine Meyer-Schewsinger, Ashwani Malhotra, Karl Skorecki, Pravin C. Singhal. Feinstein Institute for Medical Research, Great Neck, NY; Feinstein Institute of Medical Research, New York, NY; Immunology and Inflammation, Feinstein Institute for Medical Research, New York, NY; North Shore LIJ Health System, Great Neck, NY; Rambam Health Care Campus, Haifa, Israel; The Feinstein Institute for Medical Research, Manhasset, NY; Immunology and Inflammation, Feinstein Inst.med research and NSLIJ, Manhasset, NY.

Background: Macrophage influx in the mesangium has been considered to be a precursor of mesangial expansion, a feature of focal segmental glomerulosclerosis. APOL1 is expressed by macrophages but not by monocytes. Therefore, APOL1 expression is associated with monocyte transition. However, the role of APOL1 in the conversion of monocytes to macrophages (transition) has not been investigated to date. We have studied feedback loop relationship between APOL1 and microRNA193a in parietal epithelial cells (abstract submitted to ASN). We now hypothesize that APOL1-microRNA (miR)-193a feedback loop facilitates monocyte macrophage transition.

Methods: Peripheral blood mononuclear cells (PBMCs) were harvested and incubated in media containing either buffer or experimental agents including, PMA (100 ng/ml), vitamin D receptor (VDR) agonist (ET1089, 50 nM), IFN-γ (10 nM), HIV (NL4-3, 40000 copies/mL), and PAN (50 nM). Experimental agents induced protein expression of APOL1 in THPs and attenuated induction of apoptosis as well as caspase-3 expression, both in high glucose and PAN milieus. MicroRNA193a inhibitor decreased miR193a levels, increased APOL1 expression and attenuated apoptosis, both in high glucose and PAN milieus.

Conclusions: APOL1G0 provides protection against apoptosis in adverse milieus through down regulation of miR193a. 

Funding: NIDDK Support

FR-PO236
APOL1 Facilitates Transition of Parietal Epithelial Cells (PECs) via Down-Regulation of miR193a Vino Kumar, Xiayan Lan, Seyyed Shadafarin Marashi Shoshtari, Catherine Meyer-Schewsinger, Ashwani Malhotra, Karl Skorecki, Pravin C. Singhal. Feinstein Institute for Medical Research, Great Neck, NY; Immunology and Inflammation, Feinstein Institute for Medical Research, New York, NY; Rambam Health Care Campus, Haifa, Israel; The Feinstein Institute for Medical Research, Manhasset, NY; University of Hamburg, Hamburg, Germany; Immunology and Inflammation, Feinstein Inst.med research and NSLIJ, Manhasset, NY.

Background: PECs play an important role to maintain podocyte (PD) homeostasis during podocyte cytotoxic environment. A subset of parietal epithelial cells (PECs) has been reported to act as progenitor cells for the maintenance of podocyte homeostasis. Down regulation of microRNA (miR) 193a has been demonstrated to facilitate transition (accommodation of podocyte differentiation markers) of cultured PECs. APOL1 is expressed intracellularly in podocytes, however, PECs do not express APOL1. APOL1 risk alleles (G1 and G2) have been reported to PD cytotoxicity, however, the role of APOL1 expression of APOL1 in PECs transition has not been studied.

Results: PDVs displayed higher expression of ROS and a greater number of apoptotic cells when compared to PDG0, both in high glucose and PAN milieus. PDG0 displayed enhanced expression of APOL1 but decreased miR193a levels when compared to PDVs. Both high glucose and PAN induces up-regulation of miR193a. 

Conclusions: APOL1G0 provides protection against apoptosis in adverse milieus through down regulation of miR193a.
Methods: Human immortalized cultured PECs proliferate at 37°C and differentiate at 33°C and were differentiated for variable time periods (4, 8, 12 days; n=4). To examine a causal relationship, PECs were transfected with either control or APOL1 siRNA and followed by differentiation at 37°C (n=4). To study the feedback relationship between APOL1 and miR193a, PECs and Hep G2 cells (+ve control) were treated with different concentrations of an inhibitor of miR193a (25, 50, and 100 nM) followed by differentiation at 37°C. To confirm the relationship between APOL1 and miR193a, HEK (human embryonic kidney) cells/mouse (M) PDs (+ve control for APOL1) were transfected with either control or APOL1 plasmids. Protein blots were probed for APOL1, WT1, podocalyxin, podocin, and reprobed for actin. RNAs were assayed for miR193a levels. To confirm binding of miR193a to the APOL1 gene, RIP-Chip assay was carried out.

Results: PECs started displaying APOL1 on day 4 during their transition at 37°C. APOL1 expression was associated with down-regulation of miR193a and podocytotoxicity. Exogenous expression of WT1, podocalyxin, and podocin expression at 37°C. PECs started displaying APOL1 on day 4 during their transition at 37°C. APOL1 expression was associated with down-regulation of miR193a and podocytotoxicity. Exogenous expression of WT1, podocalyxin, and podocin.

Conclusions: APOL1 facilitates PEC transition through down-regulation of miR193a.

Funding: NIDDK Support

FR-PO237

Modulation of Epigenetics Preserves Podocyte Phenotype in HIV-infected Pathology

Vinod Kumar,1 Kamesh R. Ayasolla,1 Xiayan Lan,1 Seyedeed Shaadfarin Marashi Shodastari,2 Ashwani Malhotra,1 Pravin C. Singhal.1

1Emory University, Atlanta, GA; 2University of Southern Denmark, Odense, Denmark

Background: Epigenetic regulation may allow podocytes to maintain differentiated status during pathological conditions which may be characterized by dedifferentiation at 37°C. To confirm the relationship between APOL1 and miR193a, HEK (human embryonic kidney) cells/mouse (M) PDs (+ve control for APOL1) were transfected with either control or APOL1 plasmids. Protein blots were probed for APOL1, WT1, podocalyxin, podocin, and reprobed for actin. RNAs were assayed for miR193a levels. To confirm binding of miR193a to the APOL1 gene, RIP-Chip assay was carried out.

Results: PECs started displaying APOL1 on day 4 during their transition at 37°C. APOL1 expression was associated with down-regulation of miR193a and podocytotoxicity. Exogenous expression of WT1, podocalyxin, and podocin expression at 37°C. PECs started displaying APOL1 on day 4 during their transition at 37°C. APOL1 expression was associated with down-regulation of miR193a and podocytotoxicity. Exogenous expression of WT1, podocalyxin, and podocin.

Conclusions: APOL1 facilitates PEC transition through down-regulation of miR193a.

Funding: NIDDK Support

FR-PO238

Exogenous Apolipoprotein A-I Alters Acidification and Trafficking of Endocytic Compartment in Human Podocytes

John C. Edwards, St. Louis University, Saint Louis, MO.

Background: Variants in Apolipoprotein A-I confer increased risk of certain types of chronic kidney disease in people of African ancestry. We assessed effects of exogenous wild type Apolipoprotein A-I on immortalized human podocytes.

Methods: Mouse recombinant Apolipoprotein A-I was prepared by Ni affinity and gel filtration. Immortalized human podocytes were differentiated by growth at restrictive temperature for 2 weeks. Purified protein was added to serum-free culture medium at 5 µg/ml. Localization of exogenous Apolipoprotein A-I was determined with confocal microscopy. Rates of endocytosis were determined by uptake of fluorescently labeled dextrans or transferrin as assessed by flow cytometry. Endosomal acidification was assayed using confocal ratiometric fluorescence microscopy of living podocytes that had been loaded with dual labeled FITC/TRITC dextran.

Results: UPTAKE: For endocytic compartments of podocytes exposed to Apolipoprotein A-I were labeled with fluorescently-tagged dextran or transferrin, then stained for Apolipoprotein A-I gene, RIP-Chip assay was carried out.

Conclusions: Exogenous Apolipoprotein A-I is endocytosed by podocytes and accumulates in structures that colocalize with a recycling pathway marker. Apolipoprotein A-I has little effect on endocytic kinetics of the fluid phase pathway, but increases accumulation of a marker of endosomal uptake, transferrin activity. In addition, exogenous Apolipoprotein A-I alters endosomal acidification and trafficking of endocytic structures, which includes a recycling pathway marker.

Funding: NIDDK Support

FR-PO239

Deubiquitinating Enzyme UCH-L1 Controls Dendritic Cell Cross Priming of the CD8+ T Cell Response

Anna Reinick,1 Malte Mühlig,1 Timo Lischke,1 Christian Kurts,2 Hans-willi Mittnäcker,3 Catherine Meyer-Schmidt,3

1Medizinische Hochschule, Hannover, Germany; 2Institute of Experimental Immunology, Bonn, Germany; 3University Clinic Eppendorf Hamburg, Hamburg, Germany; 4Universitätshäklinikum Hamburg-Eppendorf, Hamburg, Germany.

Background: The deubiquitinating enzyme ubiquitin C-terminal hydrolase L1 (UCH-L1) is thought to regulate the intracellular pool of ubiquitin and is strictly required for the maintenance of axonal integrity in neurons. Within the kidney, UCH-L1 is deubiquitinating enzyme ubiquitin C-terminal hydrolase L1 (UCH-L1).

Methods: WT1, podocalyxin, and podocin were assayed for miR193a expression by immunohistochemistry, qRT-PCR and Western blots. Genetic manipulations were achieved by siRNA silencing, CRISPR and ectopic expression approaches. RCC expression by immunohistochemistry, qRT-PCR and Western blots. Genetic manipulations were achieved by siRNA silencing, CRISPR and ectopic expression approaches. RCC expression was investigated by challenging UCH-L1-deficient mice and dendritic cell-specific UCH-L1-deficient mice with Listeria monocytogenes. Cross presentation and cross priming assays were performed in vitro and in vivo. The dendritic cell (DC) phenotype and UCH-L1 expression was assessed in naïve and stimulated DCs by FACs, Western, preosomal and deubiquitinase-based activity assays, and real-time PCR.

Results: We show that UCH-L1 has an immunological function in DC antigen cross presentation. UCH-L1 is expressed in kidney, spleen, and bone-marrow derived DCs and its expression is regulated by the immune stimuli LPS and IFN-gamma. DCs from UCH-L1 knockout mice have reduced ability to cross present cell-associated antigen in culture. We find that UCH-L1 is down-regulated in mediate degradation and CD4 T cell priming following Listeria infection while CD4 T cell priming is unaffected. Intriguingly, UCH-L1 colocalizes with an ubiquitin selective sequestag, VCP/p97 and in UCH-L1 knockout DCs, is strongly reduced suggesting a role in the regulation of antigen presentation and T cell priming. UCH-L1 is expressed in kidney, spleen, and bone-marrow derived DCs and its expression is regulated by the immune stimuli LPS and IFN-gamma. DCs from UCH-L1 knockout mice have reduced ability to cross present cell-associated antigen in culture. We find that UCH-L1 is down-regulated in mediate degradation and CD4 T cell priming following Listeria infection while CD4 T cell priming is unaffected. Intriguingly, UCH-L1 colocalizes with an ubiquitin selective sequestag, VCP/p97 and in UCH-L1 knockout DCs, is strongly reduced suggesting a role in the regulation of antigen presentation and T cell priming.

Conclusions: These results demonstrate a hitherto unrecognized role of UCH-L1 in DC-mediated immune responses.

Funding: NIDDK Support

FR-PO240

Loss of Methylthioadenosine Phosphorylase Confers Malignant Potential in Renal Cell Carcinoma

Ching-Hsien Chen,1 Matthew Kyoshi,2 David Yang,1 Burt R. Don,3 Robert H. Weiss,3 1UC Davis, Davis, CA; 3UC Davis, Nephrology, Davis, CA.

Background: Renal cell carcinoma (RCC) has emerged as a metabolic disease characterized by dysregulated expression of metabolic enzymes. Given that patients with metastatic RCC have an unusually poor prognosis, there is an urgent need to discover metabolic molecules useful for predicting oncologic phenotypes which can be targeted for therapy.

Methods: The Cancer Genome Atlas (TCGA) database were first analyzed to discover the potential metabolic molecules associated with RCC progression. We confirmed gene expression by immunohistochemistry, qRT-PCR and Western Blots. Genomic manipulations were achieved by siRNA silencing, CRISPR and ectopic expression approaches. RCC cell invasion, migration and proliferation were determined by Boyden chamber, scratch and MTT assays. In addition, signaling pathway activity in RCC cells was assessed and compared through utilizing phospho-receptor tyrosine kinase arrays.

Results: Through an integrated two-step analysis of RCC metabolic pathways, we identified that methylthioadenosine phosphorylase (MTAP) and its substrate methylthioadenosine (MTA) are dysregulated in aggressive RCC. A decrease of MTAP expression was observed in RCC tissues and was correlated with tumor grade. We found that MTAP gene deletion was significantly associated with worse overall survival in
RCC patients (n=538). Genetic manipulation of MTAP studies demonstrated that MTAP expression sustains neoplastic immortalization and progression of RCC cells. Surprisingly, an increase of sphere-forming ability was noted in MTAP-knockout RCC cells. Loss of MTAP resulted in an activation of the IGF1R-Src-STAT3 axis in RCC cells.

Conclusions: Our results suggest a novel role of MTAP in kidney disease and contribute to a better understanding of metabolic enzymes involved in RCC oncogenesis.

Funding: Commercial Support - Dialysis Clinic, Inc

FR-PO241
Cardiotrophin-Like Cytokine Factor 1 (CLCF1), Proposed Permeability Factor in FSGS, Attenuates Autophagy and Maintains p-STAT3 (Ser727) via Upregulation of Mammalian Target of Rapamycin (mTOR) Mukut Sharma,1 Jin Sum Choi,1,2 Binay Bhattacharya,1 Andrew Wells,1,2 Linus Rinschen,1,2 and Sebastian Benzing,1

Background: Cardiotrophin-Like Cytokine Factor 1 (CLCF1) is a multifunctional cytokine which is expressed in a wide range of normal and neoplastic cells. We previously reported that CLCF1 is not expressed in normal human podocytes but is upregulated in FSGS and protects podocytes against podocyte injury and apoptosis. CLCF1 is likely to act as a permeability factor in FSGS by upregulating mTOR signaling.

Methods: We generated a podocyte-specific Huwe1-knockout mouse and a Huwe1-knockout human podocyte cell line to characterize the role of Huwe1 in podocyte stress response. We found that Huwe1 is essential for the regulation of mTORC1 and mTORC2 activity, which leads to the activation of the IGF1R-Src-STAT3 axis in RCC cells. Loss of MTAP resulted in an activation of the IGF1R-Src-STAT3 axis in RCC cells.

Conclusions: Our findings suggest that YAP activation in podocytes is an important endogenous anti-apoptotic mechanism during the progression of FSGS, and targeting YAP could be a potential therapeutic choice for treatment of FSGS.

Funding: Government Support - Non-U.S.

FR-PO244
The Role of TLR4 in Hepatitis B Virus X Protein Induced Immunity Disorder in Renal Tubular Epithelial Cells W. Liu,1,2 Linus Rinschen,1,2 Bernhard Benzing,1,2 Sebastian Benzing,1,2 Martin Hohne,2,4 CECCAD, Cologne, Germany; 2Department II of Internal Medicine and Center for Molecular Medicine Cologne, University of Cologne, Cologne, Germany.

Background: Hepatitis B virus X protein could activate inflammatory immune response, which may contribute to the pathogenesis of HBV-GN. How HBx change the function of renal tubular epithelial cells (RTECs) was not clear. We want to explore the role of TLR4 in immunity disorder of RTECs mediated by HBx.

Methods: C57BL/6J-TgN mice(6 week old) were randomly divided into the experimental group and the intervention group. C57BL/6J mice were used as normal control group. Mice of the intervention group were injected TLR4 shRNA lenti virus every four weeks. Serum and urine were collected at 8, 12, 16, 20, 24-week old. Mice were sacrificed at 24 week old to observe the mice renal function and pathological changes. HBx and TLR4 expression in renal tissue were observed by immunohistochemistry, and macrophores and T cells were also detected by immunohistochemistry. We constructed a HBx-overexpression plasmid and a TLR4 shRNA plasmid and transfected them into human proximal tubular epithelial cell line(HK-2). Flow cytometry was used to investigate the expression of MHC-II, CD40 on HK-2 cells. Mixed lymphocyte reaction was used to detect the ability of stimulating T cell proliferation. IFN-gamma and IL-4 in supernatant were determined by ELISA.

Results: Protein of C57BL/6J-TgN mice increased from 16-week old, and renal function deteriorated up to 24-week old. HBx and TLR4 expression in renal tubular epithelial cells of C57BL/6J-TgN mice were significantly upregulated compared with control group. TLR4 shRNA lentivirus intervention appeared reduced proteinuria and remission of renal function and fewer CD4+ T cells and macrophages infiltration. After transfection of HBx gene, the expressions of MHC-II and CD40 in HK-2 cells were up-regulated, and IFN-gamma/IL-4 ratio increased. TLR4 shRNA lentivirus intervention down-regulated expression of MHC-II and CD40 on renal tubular epithelial cells, decreased ability of stimulating T cell proliferation and lowered ratio of IFN-gamma/IL-4.

Conclusions: Our findings suggest that TLR4 could depress immune function of tubular epithelial cells and have prevention and treatment effect.

Funding: Government Support - Non-U.S.

FR-PO242
Podocyte-Specific Loss of Huwel Causes Vascularization and Glomerular Damage Linus A Velleg,2 Sabine Bertsch,2 Sebastian Dittrich,2 Markus M. Rinschen,2 Bernhard Schermer,2 Thomas Benzing,2 Martin Hohne,2,4 CECCAD, Cologne, Germany; 2Department II of Internal Medicine and Center for Molecular Medicine Cologne, University of Cologne, Cologne, Germany.

Background: As terminally differentiated cells, podocytes rely on precise regulation of homeostasis and specific responses to cope with cellular damage and loss, which would ultimately lead to glomerular scarring and kidney disease. In an attempt to characterize the networks that regulate cell stress responses, we identified the E3-ubiquitin ligase Huwel in interaction screening. In other cell types, Huwel has been shown to be a regulator of a wide spectrum of intracellular signaling cascades such as MAPK/ERK, Wnt, DNA-damage and cell cycle control.

Methods: We generated a podocyte-specific Huwel knock-out mouse and a Huwel-knockdown podocyte cell line to characterize the role of Huwel in podocyte stress response and homeostasis in vivo and in vitro.

Results: Huwel-knockout mice were born at expected ratios. They showed signs of kidney disease beginning at 4 weeks of age. Afferent and efferent vessels were narrower in Huwel knockout mice, and the glomerulus were larger. Podocytes from Huwel-knockdown mice showed a marked deregulation of mTOR signaling as a putative effector of vesicle formation. Experiments to elucidate the role of Huwel in RNA-damage response in podocytes are currently underway.

Conclusions: We identified the E3-ubiquitin ligase Huwel at the center of crucial signaling cascades as an indispensable regulator of podocyte homeostasis. Future research will be directed at identifying direct Huwel-targets in podocytes and potential therapeutic exploitation.

Funding: Postgraduate Support, Government Support - N-U.S.

FR-PO243
Inhibition of YAP Exacerbates Podocytes Apoptosis and Disease Progression in Adriamycin-Induced Focal Segmental Glomerulosclerosis Qiuyan Zhang,1 Fang Li,1 Jianchun Chen,1 Huijuan Wu,2,3 AUGUSTA UNIVERSITY, AUGUSTA, GA; 2Department of Pathology, School of Basic Medical Sciences, Fudan University, Shanghai, China; 3Shanghai Medical College, Fudan University, Shanghai, China; 4Vanderbilt University, Nashville, TN.

Background: Focal Segmental Glomerulosclerosis (FSGS) is a common chronic glomerular disease with poor clinical outcomes, of which the main manifestation is nephrotic syndrome. Podocyte loss via apoptosis is one important mechanism underlying the pathogenesis of FSGS. Recently, YAP, a key downstream effector of Hippo pathway, was recognized as an activator for multiple gene transcriptional factors in nucleus to control cell proliferation, differentiation and apoptosis. However, the potential role of YAP activation in development and progression of FSGS remains unclear.

Methods: The localization, expression and phosphorylation of YAP were examined in kidney samples from patients with FSGS, adriamycin-induced FSGS and normal glomeruli using immunohistochemistry, Western blots and immunofluorescence staining. The role of YAP activation in podocyte apoptosis was assessed by RNA interference and siRNA, respectively. We evaluated the effect of pharmacological inhibition of YAP using YAP inhibitor, C72.

Results: We first found that increases of podocyte apoptosis is closely correlated with the expression level of phospho-YAP at serine 397 that is associated with YAP degradation during the progression of FSGS. Then, we found that YAP distributed uniformly in the nucleus and cytoplasm in the podocytes of vehicle treated mice but the YAP expression decreased in the cytoplasm in the podocytes of vehicle treated mice treated with adriamycin. Additionally, we observed that the expression of phospho-YAP at serine 397 was reduced in a dose and time-dependent manner that was blocked by C72.

Conclusions: Our findings suggest that YAP activation in podocytes is an important endogenous anti-apoptotic mechanism during the progression of FSGS, and targeting YAP could be a potential therapeutic choice for treatment of FSGS.

Funding: Government Support - Non-U.S.
FR-PO245

Nrp2 Is Required for Endocytosis of Lrp6 and Wnt/β-Catenin Signaling Transduction in Zebrafish Pronephric Tubule

Materials: Here, we identified a nuclear receptor interacting protein 2 (nrip2) as being required for endocytosis of Lrp6 in zebrafish. nrip2 is dynamically and specifically localized in proxenphric tubule.

Results: From 24 to 72hpf, nrip2 is dynamically expressed in distal tubule, proximal straight tubule and proximal convoluted tubule, which is examined by in situ hybridization. Global knockout of nrip2 in zebrafish by CRISP/Cas9 genome editing approach leads to impaired low-molecular fluorescent dextran uptake in proximal tubule comparing with normal control, which is also companied by reduced amount of endocytic apparatus and cilia by Transmission Electron Microscope imaging, and decreased expression of EEA1, an early endosome antigen 1, by Immunoelectron Microscope. Interestingly, loss of nrip2 resulted in reduction of Lrp6 expression, not lrp2a (megalin). Nrp2 knockdown in Tg(krt7/lek-mimiP:dGFP), expressing GFP under the control of β-catenin/TCF elements, resulted in decreased GFP expression. Meanwhile, overexpression of nrip2 in HK-2 cells activated total β-catenin and active β-catenin, which means nrip2 is required for activation of Wnt/β-catenin signaling.

Conclusion: We mapped the iREC proteome and MEFs and quantified 5315 proteins but not by PAN or lithium. Cimetidine and probenecid, which are inhibitors of OCT2 and kidney injury in organoids were evaluated by qRT-PCR and immunostaining and puromycin aminonucleoside (PAN), adriamycin, and lithium. Drug transporter expression and kidney injury in organoids were evaluated by qRT-PCR and immunostaining and compared to a human kidney tubular cell line (HK-8).

FR-PO246

Quantitative Proteomic Analysis of Induced Renal Tubular Epithelial Cells (iRECs) Background: Reprogramming of differentiated cells into other cell types by forced expression of tissue specific transcription factors has been shown to be an effective tool to generate new cell models. iRECs are a renal epithelial cell line that has been reprogrammed from mouse embryonic fibroblasts (MEFs). While the cell line has been characterized at a genomic and transcriptomic level, proteomic studies still need to be performed to evaluate possible usage as an in vitro model.

Methods: We performed a proteomic mapping of proteins generated from iRECs and immortalized MEFs. The data consists of protein identification, tryptic digestion and analysis of peptides by nLC-MS/MS on a quadrupole-orbitrap mass spectrometer. Results: We mapped the iREC proteome and MEFs and quantified 5315 proteins using label-free quantification. The generated dataset was correlated with mRNA expression using microarray analysis of tubule segments from rats treated with previous transcriptome analysis, we found that iRECs expressed proteins from different segments of the tubule system, Henle loop and collecting ducts without resembling the expression profile of one specific segment. The iRECs had high abundance of mitochondrial proteins. In addition, the most strongly iREC-enriched proteins were the ligand-binding receptors Cubilin (Cubn) and Megalin (Lrp2) and its associated adaptor protein Disabled homolog 2 (Dab2), which mediate reuptake of albumin and other ligands. We furthermore found that iRECs expressed several soluble channels such as sodium transporters-like protein 11 (Slc11a1), which is highly expressed in the thin descending limb of Henle loop. Several subunits of v-type proton ATPase were highly expressed in iRECs as well as the transcription factors JunB and JunD.

Conclusions: Consistent with transcriptomic data, the iREC proteome does not resemble the protein expression profile of one single nephron segment. However, iRECs express several segments and segment subunits with high importance in physiological processes as well as for disease models. Especially the surprisingly high protein abundance of ligand-binding receptors Cubilin and Megalin could make this cell type a valuable new in vitro model for elucidating the yet unknown molecular signaling mechanisms of albumin reuptake in the proximal tubule of the nephron.

FR-PO247

Inhibition of Vasopressin 2 Receptor Signaling Suppresses Tumor Growth in Renal Cell Carcinoma

Background: Renal cell carcinoma (RCC) accounts for 90% of all kidney cancers and is among the 10 most common cancers worldwide. Clear-cell and papillary RCC represent 70-75% cases of all RCC. Clear cell RCC tumors originate from the renal proximal tubules that express vasopressin type 1 receptors (V1R). However, in human clear cell RCC tumors we detected V1R expression and V1R mediated cell signaling. Since V1R activates promotes cell proliferation in polycystic kidney disease, we hypothesized that V1R activity is pathogenic in RCC, and V1R inhibition can suppress tumor growth.

Methods: In Caki-1 and 786-O cells, we determined the effect of V1R antagonist OPC31260 on cell viability, cell cycle, colognomecy and cell migration. The effect of V1R antagonist treatment on tumor development was tested in female athymic nude mice. Mice were subcutaneously inoculated with a 1000-sul suspension of Caki-1 cells. When tumor volume reached 80-100 mm³ mice were randomized into groups (n=8) to receive vehicle or OPC31260, injected intraperitoneally daily for 28 days. Tumor volumes were measured and tumor weight were assessed on alternate days. Tumors were harvested and weighed at the end of the study and portions were fixed in 10% formalin or snap frozen for protein and mRNA extraction.

Results: OPC31260 treatment dose dependently and significantly reduced cell viability and migration. As high as 10 μM OPC31260 treatment significantly reduced cell proliferation detected by TUNEL assay was significantly high.

Conclusions: Vasopressin V1R signaling plays a pathogenic role in tumor progression in RCC and suppression of V1R signaling by OPC31260 can suppress tumor growth in RCC. Hence V1R is a novel target for therapy in RCC.

FR-PO224

Kidney Organoids Replicate Drug-Induced AKI in a Segment-Specific Manner

Background: Renal cell carcinoma (RCC) accounts for 90% of all kidney cancers.

Methods: Kidney organoids were differentiated from human ES and iPS cells by a previously established protocol. Organoids were exposed to various nephrotoxics which induces segment specific injury: cisplatin, aminonucleoside (AA), tenofovir, puromycin aminonucleoside (PAO), adriamycin, and lithium. Drug transporter expression and kidney injury in organoids were evaluated by qRT-PCR and immunostaining and compared to a human kidney tubular cell line (HK-8).

Results: qRT-PCR demonstrated marked expression of OCT2, OCT1 and 3, which are major renal drug transporters, in kidney organoids while HK-8 cells showed much lower expression of these transporters. The organoids showed upregulated tubular injury markers such as KIM-1 and L-FABP after treatment with cisplatin, tenofovir, or AA, but not by PAN or lithium. Cicetidine and probenecid, which are inhibitors of OCT2 or OCT1 respectively, ameliorated the injury caused by cisplatin or tenofovir. Lithium caused significantly decreased expression of aquaporin 2 in kidney organoids. PAN and AA caused increased severe nephrotoxic injury and decreased expression of nephrin in glomerulus-like structures of organoids, whereas cisplatin did not. On the other hand, HK-8 treated with those nephrotoxics did not exhibit significant change of tubular injury markers.

Conclusions: Kidney organoids faithfully mimic drug-induced tubular and glomerular injury, suggesting they will be useful for evaluation of nephrotoxicity of drugs and substantially superior to conventional nephrotoxicity screening method using cultured cells.

FR-PO249

An ATP/ADP Biosensor as a Real-Time Toxicity Assay in Kidney Organoids

Background: Renal toxicity is frequent and a major limitation to drug development. Renal organoids have been generated from human pluripotent stem cells (hPSCs), overcoming limitations related to the expense and translatability of cell culture and animal models. Here, we present a real-time system to evaluate the toxicity of drugs with a real-time biosensor of ATP/ADP ratio in kidney organoids. Methods: Stable HPSK lines, expressing the ATP/ADP ratio PorecelHR, were established with lentiviral transduction and differentiated in kidney organoids as previously described. Organoids were used fresh or after freeze/thaw. ATP and ADP signal were acquired via live R0 treatment microscopy, and a ratio was quantified with

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

Underline represents presenting author.
the ImagedRatioPlus plugin. Organoids were exposed to various toxicants (10 or 50 μM cisplatin, 10 mg/ml aristolochic acid (AA), 5 mM sodium azide (NaN3) or vehicle.

**Results:** The ATP and ADP signals were greater in nephron epithelial structures than in the stromal compartment and NaN3 induced a rapid decrease in ATP/ADP ratio within one minute. Cisplatin and AA significantly reduced the ATP/ADP ratio as compared to control organoids after 15 hours. Reduction in ATP/ADP ratios preceded contraction of the organoids.

**Conclusions:** Reduction in ATP/ADP ratio in kidney organoids is a sensitive indicator of drug toxicity, offering a direct live readout in human tissues in vitro. The unlimited availability of iPSC-derived organoids and the ability to freeze them at the pre-analytical stage is well-suited to high-throughput screening and might facilitate the identification of lead candidates during drug discovery.

**Funding:** Private Foundation Support

**FR-PO250**

Laminar Flow Enhances Endothelial Differentiation from iPSCs and Stabilizes Endothelial Cell Function Robin Bollin,1 Yulia Kryan,1 Roman Kryan,1 Ulrich Martin,1 Boris Chichkov;1 Hermann G. Haller.1 Hannover Medical School, Hannover, Germany; 2Laser Zentrum Hannover e.V., Hannover, Germany; 1Medical School Hannover, Hannover, Germany.

**Background:** Endothelial cells (ECs) have essential roles in organ development and regeneration, and therefore they could be used for regenerative therapies. However, generation of abundant functional endothelium from pluripotent stem cells has been difficult because ECs have limited proliferative potential and display vascular instability. Since stimulation of functional properties may enhance EC differentiation we have tested the hypothesis that laminar flow enhances EC differentiation and analyzed the underlying molecular mechanisms.

**Methods:** iPSC have been cultured under feeder free conditions for 3 passages, and then seeded in the Geltrans-coated microfluidic chips. Chips contained 4 parallel channels allowing simultaneous analysis of several experimental conditions. Mesoderm differentiation was induced by Bone morphogenetic protein 4 (BMP4) 40 ng ml⁻¹; Activin A 25 ng ml⁻¹; small-molecule inhibitor of glycogen synthase kinase-3β (CHIR) 1.5 μM; Vascular endothelial growth factor (VEGF) 50 ng ml⁻¹ for 4 days. At day 4 of mesoderm differentiation microfluidic chips have been attached to the medium flow and stimulated with VEGF 50 ng ml⁻¹; TGFβ-pathway small-molecule inhibitor SB431542 10 μM to induce EC differentiation. Static control chips have been stimulated with the same medium. After 3 days cells were fixed by perfusion with 2% PFA solution, and stained for Sox17, VE-Cadherin, CD31, and heparin sulfate. Confocal microscopy of the cells was performed directly in the microfluidic chips.

**Results:** Characteristic flow-oriented morphological changes have been observed in the cells incubated under flow but not under static conditions. Control iPSC without flow displayed a low rate of EC differentiation after 3 days of stimulation. In contrast, iPSC cultivated under medium flow conditions showed a more rapid (50.8 ± 4.1%) after 3 days and sustained differentiation to EC. Cells demonstrated expression of EC-markers CD31 and VE-Cadherin, and expressed heparin sulfates on the apical side of the cells indicating terminal differentiation.

**Conclusions:** Laminar shear stress may directly activate growth factor receptors on stem/progenitor cells, initiating signaling pathways leading toward endothelial cell differentiation. Our results suggest that laminar flow is an important factor in endothelial cell differentiation processes.

**Funding:** Other NIH Support - T32

**FR-PO252**

FGFs Are Required for Stem Cell Recruitment to Nephrogenic Aggregates of Adult Zebrafish Kidney Regeneration Thomas F. Gallegos, Carannai N. Kame, Iain A. Drummond. Massachusetts General Hospital, Boston, MA.

**Background:** In zebrafish, adult kidney injury (AKI) results in stem cell-mediated regeneration by the de novo production of new nephrons. This process occurs by progenitor cell aggregation and differentiation on kidney collecting ducts, leading to the insertion of new nephrons. Expression of dup66, a transcriptional readout of FGF signaling, was induced upon AKI, suggesting a role for FGF signaling in new nephron formation. Early broad dup66 expression became restricted to single cells and ultimately to nephrogenic aggregates abutting mature collecting ducts. In addition to dup66, nascent nephrons are marked by expression of htxla. After gatamincin-induced AKI, pharmacological or dominant-negative based genetic inhibition of FGFR signaling completely prevented recruitment of progenitor cells to dup66 and htxla-expressing nephrogenic aggregates. In juvenile Tg(hlx1a:egfp) zebrafish treated with FGFR inhibitor during developmental nephrogenesis, progenitor cells survive but fail to condense into organized aggregates. Upon kidney injury, expression of fgfa, fgfb, fgfa, fgfa, fgfb, and the receptor fgfr1 and fgfr2 were induced, suggesting multiple roles for FGF signaling in the formation of nephrogenic aggregates from single cell progenitors. By qPCR of fractionated kidneys, fgfb and fgfa levels were found to be specifically expressed in the tubular fraction of the injured kidney, suggesting that these ligands may play a role in recruiting nephrogenic cells to injured tubules. fgfa expression was restricted to the most distal end of the nephrogenic aggregate, suggesting a role in patterning the new nephron aggregate.

**Results:** Our results demonstrate essential roles for FGF in recruitment of progenitor cells and patterning of nephrogenic aggregates during kidney regeneration in the adult zebrafish.

**Methods:**

**Results:**

**Conclusions:**

**Funding:** NIDDK Support
FR-PO253
Effect of Integrin Signaling Blockade on Self-Renewal and Differentiation of Human Nephrogenic Progenitors In Vitro Asteg Petrovayan,1 Sinem Karg,tn,1 Matthew E. Thornton,2 Brendan Grubb,2 Roger E. De Filippo,1 Laura Perin,1 Stefano Da Sacco.1 1Children’s Hospital Los Angeles, Los Angeles, CA; 2University of Southern California, Los Angeles, CA.

Background: Mammalian kidney development is controlled through the proliferation and differentiation of a specific population of nephron progenitors (NP) characterized by the expression of CITED1 and SIX2. The mechanisms regulating the balance between self-renewal and renal differentiation in NP are still elusive, impairing our ability to effectively expand NP in vitro for long term. In particular, the effects of extracellular matrix (ECM) composition and ECM-NP interaction are poorly understood.

Methods: We have investigated the relationship between ECM and self-renewal traits in NP isolated from human fetal kidneys (hFK). NP were isolated using our established RNA Smartflare protocol. Nephrogenic characteristics were confirmed by RNA-seq and nephrogenic potential by in vitro differentiation and dissociation/ reaggregation assays.

By immunofluorescence we have characterized the ECM present within the nephrogenic niche of hFK. Subsequently we have tested NP expansion on these ECM substrates and assessed effects on signaling cascade by PCR array.

Results: Among others, laminin alpha 5, collagen 16 and collagen 18 were found to be highly expressed within the cap mesenchyme of developing hFK. In vitro, laminin was confirmed to better preserve self-renewal properties in NP, as confirmed by maintenance of higher co-expression of SIX2 and CITED1 in cultured NP, both in short and long term experiments. Interestingly, blocking integrin-mediated ECM-NP interaction with specific antibodies as well as to integrin α6β1 and CITED1 co-expression, suggested an important role of integrin-mediated signaling pathway on balance between renal specification vs self-renewal. Effect of integrin blocking in NP on downstream WNT signaling was further confirmed by PCR array, suggesting a direct role of ECM-NP interaction on self-renewal.

Conclusions: Our data indicate a strong link between ECM-NP during human renal development. NP-laminin interaction appears to play an essential role on nephron endowment by directly controlling self-renewal/differentiation balance. These results could provide not only a tool for the optimization of in vitro NP expansion but also a platform to advance our understanding of human renal development and nephron cell commitment.

Funding: Private Foundation Support

FR-PO254
A New Inducible Aqp2ECE System Reveals the Self-Renewal and Multipotentiality of Aqp2+ Progenitor Cells in Adult Mouse Kidneys Lihe Chen,1 Ye Zhang,2 Chao Gao,2 Long Zhang,2 Enuo Chen,2 Wenzheng Zhang.3 1NIH, Bethesda, MD; 2Albany Medical College, Albany, NY.

Background: Stem cells are defined by unlimited self-renewal capacity and pluripotentiality. Progenitor cells have pluripotentiality, but no or limited self-renewal potential. Using Aqp2Cre driver, we previously showed that embryonic Aqp2+ progenitor cells generate all known cell types in the connecting tubule/collecting duct. However, the constitutive Aqp2Cre driver cannot be used to assess adult Aqp2+ progenitor cells.

Methods: Here, we report a new inducible Aqp2ECE knock-in mouse model, which allows us to demonstrate the self-renewal and multipotentiality of Aqp2+ progenitor cells in adult kidneys. Aqp2ECE was created by inserting a cassette expressing a specific Cre recombinase activity on Tamoxifen), noticeable inducibility, and 100% fidelity in XFP+ and an intercalated cell and characterized by being positive for both a principal (Aqp2+ and Aqp2Cre+) and an intercalated cell and characterized by being positive for both a principal (Aqp2+ and Aqp2Cre+) and an intercalated cell and characterized by being positive for both a principal (Aqp2+ and Aqp2Cre+) and an intercalated cell and characterized by being positive for both a principal (Aqp2+ and Aqp2Cre+)

Conclusions: We believe that Aqp2Cre ECE has 0% leakiness (100% dependence of Cre recombinase activity on Tamoxifen), noticeable inducibility, and 100% fidelity in recapitulating the endogenous Aqp2 expression; 2) Rare Aqp2+ progenitor cells exist in adult mouse kidney, possess self-renewal and multipotentiality, and function in kidney maintenance and lithium-induced remodeling. Long-term chasing is underway to confirm and extend these findings.

Funding: NIDDK Support

FR-PO255
Adipose Tissue-Derived Stem Cells (ASC) Reverses Kidney Disease Progression in SHR Rats Induced to Metabolic Syndrome Marcelo C. Batista,1 Renata Nakamichi,2 Camila N. Oliveira,3 Mario Luis R. Cesaretti,4 Maria Dalboni,2 Beata M. Quinto.1 1UNIFESP; São Paulo, Brazil; 2Universidade Federal de São Paulo, Santo André, Brazil; 3Uninove, São Paulo, Brazil.

Background: Visceral obesity, the physiopathological basis of Metabolic Syndrome (MS), promotes a set of metabolic abnormalities linked to increased risk of kidney disease in the overall population. The excessive expansion of visceral adipose tissue, resulting in hypertrophied adipocytes is implicated in the development of hypoxic environment and increases inflammatory proteins. The adipose tissue is also considered an important source of stem cells which are able to proliferate and differentiate into multiple cell lines reducing the expression of inflammatory proteins. The aim of the study is to evaluate the treatment of the kidney disease progression in SHR rats induced to MS with ASCs.

Methods: SHR rats were induced to MS by hyperlipid/hypercaloric diet for 12 weeks, and then treated with injection of 2x10^5 ASC for 1 and 2 weeks, respectively. After this period, rats were sacrificed for analysis of albuminuria, as well as kidney function (serum concentration of creatinine and Cystatin C, and urinary NGAL) for comparison with baseline parameters. The characterization of ASC extracted from subcutaneous tissue of SHR control rats was performed through flow cytometry method.

Results: Previous analysis has shown that ASC expressed the cell surfaces markers: CD34, CD55, CD90 and CD105, confirming its characterization in adipocyte. Our results demonstrated a statistically significant deterioration of lipid profile, as shown by decreased hematocrit and increased triglycerides and total cholesterol, on those animals induced to MS when compared with the control group (CT). This adverse lipid profile was reversed on those MS-induced animals treated with stem cells. Parallel with the induction of MS, we observed the development of kidney disease as shown by the enhancement of renal pathology as well as an increase in creatinine, Cystatin C and NGAL concentrations among those rats induced to MS. Similarly with lipid profile, we could also evidence a reversion of kidney disease progression through the improvement in the above mentioned kidney disease parameters, among the MS-Induced rats treated with adipose tissue-derived stem cells.

Conclusions: Adipose tissue-derived stem cells reversed Metabolic Syndrome related kidney disease progression in SHR rats.

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

FR-PO256
Mesenchymal Stem Cells Cultured in Serum-Free Medium Ameliorate Experimental Renal Fibrosis by Their Strong Immunosuppressive Effects Ken Yoshida,1 Ayumu Nakashima,2 Shigehiro Doi,1 Toshinori Ueno,1 Yukio Kato,2 Yukihito Higashi,3 Takao Masaki.1 1Nephrology, Hiroshima University Hospital, Hiroshima, Japan; 2Stem Cell Biology and Medicine, Graduate School of Biomedical & Sciences, Hiroshima University, Hiroshima, Japan; 3TWOCELLS Company, Limited, Hiroshima, Japan; Cardiovascular Regeneration and Medicine, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan.

Background: The mechanism underlying the anti-inflammatory effect of mesenchymal stem cells (MSCs) has been elucidated. However, the anti-inflammatory effect of MSCs cultured in serum-free medium has not been clarified. Here we examined the effects of MSCs cultured in serum-free medium on inflammation of inflammatory cells and interstitial fibrosis induced by unilateral ureteral obstruction (UUO) operation in rats.

Methods: At 4 days post-UUO operation, we injected rat MSCs cultured in 10% fetal bovine serum containing medium of DMM (10%MSCs) or serum-free medium (SF-MSCs) or PBS (control) through the tail vein. Although retention of MSCs collected from green bovine serum containing DMEM (10%MSCs) or serum-free medium (SF-MSCs) or PBS (control) was only observed for 3 days with no difference between only (control) through the tail vein. Although retention of MSCs collected from green bovine serum containing medium of MSCs to serum-free medium is thought to be important in the treatment of the kidney disease progression in SHR rats induced to MS.

Results: These results show that transplantation of MSCs cultured in serum-free medium has not been clarified. Here we examined the effects of MSCs cultured in serum-free medium on inflammation of inflammatory cells and interstitial fibrosis induced by unilateral ureteral obstruction (UOU) operation in rats.

Conclusions: These results show that transplantation of MSCs cultured in serum-free medium ameliorated infiltration of inflammatory cells and renal fibrosis in UUO rats compared with MSCs cultured in serum containing medium, in part by enhancement of M2 macrophage polarization (M2) macrophages and interstitial fibrosis. Next we examined whether serum-free culture conditions enhanced the anti-fibrotic and immunosuppressive effects by paracrine manners. Incubation of cultured human kidney-2 cells in mammalian MSC-conditioned medium suppressed transforming growth factor-β1-induced phosphorylation of Smad2 and α-smooth muscle actin, but there was no significant difference in culture from 10%MSCs and SF-MSCs. Co-cultures of human MSCs and human monocytic THP-1 cell-derived pro-inflammatory phenotype (M1) macrophages using a transwell system showed significant increases in cells positive for CD163 and CD206, immunomodulatory phenotype (M2) macrophages. In SF-MSCs compared with 10%MSCs.

Conclusions: These results show that transplantation of MSCs cultured in serum-free medium ameliorated infiltration of inflammatory cells and renal fibrosis in UUO rats compared with MSCs cultured in serum containing medium, in part by enhancement of M2 macrophage polarization (M2) macrophages and interstitial fibrosis. Next we examined whether serum-free culture conditions enhanced the anti-fibrotic and immunosuppressive effects by paracrine manners. Incubation of cultured human kidney-2 cells in mammalian MSC-conditioned medium suppressed transforming growth factor-β1-induced phosphorylation of Smad2 and α-smooth muscle actin, but there was no significant difference in culture from 10%MSCs and SF-MSCs. Co-cultures of human MSCs and human monocytic THP-1 cell-derived pro-inflammatory phenotype (M1) macrophages using a transwell system showed significant increases in cells positive for CD163 and CD206, immunomodulatory phenotype (M2) macrophages. In SF-MSCs compared with 10%MSCs.

Conclusions: These results show that transplantation of MSCs cultured in serum-free medium ameliorated infiltration of inflammatory cells and renal fibrosis in UUO rats compared with MSCs cultured in serum containing medium, in part by enhancement of M2 macrophage polarization (M2) macrophages and interstitial fibrosis. Next we examined whether serum-free culture conditions enhanced the anti-fibrotic and immunosuppressive effects by paracrine manners. Incubation of cultured human kidney-2 cells in mammalian MSC-conditioned medium suppressed transforming growth factor-β1-induced phosphorylation of Smad2 and α-smooth muscle actin, but there was no significant difference in culture from 10%MSCs and SF-MSCs. Co-cultures of human MSCs and human monocytic THP-1 cell-derived pro-inflammatory phenotype (M1) macrophages using a transwell system showed significant increases in cells positive for CD163 and CD206, immunomodulatory phenotype (M2) macrophages. In SF-MSCs compared with 10%MSCs.
Amniotic Fluid- Derived Mesenchymal Stem Cells (AFSCs) Are Repertoire in Established Experimental CKD Rta de Cassia Cavagliari,1 Thalita Prado,1 Luisa Albuquerque,1 Marcelo Zugaib,2 Sergio P. Bydlofski,2 Irene L. Noronha.2 1Cellular and Molecular Nephrology Lab, University of São Paulo, São Paulo, Brazil; 2Genetics and Molecular Hematology Lab, University of São Paulo, São Paulo, Brazil; 3Obstetrics and Gynecology, University of São Paulo, São Paulo, Brazil.

Background: AFSCs are a class of stem cells that present characteristics intermediate between embryonic stem cells (ESC) and adult mesenchymal stem cells (MSC). Given that the amniotic fluid consists of fetal urine, stem cell populations present in the amniotic fluid are likely derived from the fetal kidney. These characteristics have aroused great interest in the potential protective effects of AFSCs in renal diseases. The aim of this study was to analyze the effects of AFSCs in an experimental model of CKD, the 5/6 nephrectomy (Nx) model, after the disease has been established, in order to more closely resemble the clinical settings in humans.

Methods: Human AFSCs were isolated from second trimester amniocentesis samples by plastic adhesion and characterized as MSC. Male Wistar rats (n=38) underwent 5/6 nephrectomy (Nx) performed under anesthesia. Groups were divided into 4 groups: Sham 30d, Sham+AFSC 30d, sham rats receiving AFSCs; Nx, 5/6 nephrectomy; and Nx+AFSCs, Nx rats receiving AFSCs. The table shows the parameters analyzed.

Results: Nx rats with established CKD and treated with AFSCs displayed significant reductions in blood pressure, albuminuria and glomerulosclerosis. In addition, they showed lower expression of α-SMA and ED-1, as well as higher expression of WT-1, in comparison with untreated Nx rats.

Conclusions: These results demonstrate that inoculation of AFSCs ameliorate renal disease in established chronic kidney disease.

Funding: Government Support - Non-U.S.

Mean±SEM: *p<0.05 vs Sham 15d; **p<0.01 vs Sham 30d; ***p<0.001 vs Sham+AFSC 30d; p>0.01 vs Nx 30d

FR-PO258

Lithocholic Acid Increases Plasma Levels of FGF23 Nobuhiro Hashimoto, Isao Matsui, Daisuke Morii, Ayumi Matsumoto, Karin Shimada, Satoshi Yamaguchi, Keiichi Kubota, Tatsuki Oka, Sayoko Yonemoto, Yusuke Sakaguchi, Takayuki Hamano, Yoshitaka Isaka. Osaka University Graduate School of Medicine, Suita, Japan.

Background: The phosphate sensing mechanisms remain unresolved. Oral phosphate load can increase fibroblast growth factor 23 (FGF23) without affecting serum levels of parathyroid hormone, iron, and ferritin remain similar to control mice without acute blood loss. Volume resuscitation with PBS did not significantly alter these findings. The change in gut microbiota may contribute to the phosphate sensing mechanism.

Methods: In addition to activate vitamin D, lithocholic acid (LCA), a secondary bile acid, can activate VDR. Therefore, we examined effects of LCA on FGF23.

Results: Vitamin D receptor knockout (VDR-KO) mice and their wild type (WT) littermates were maintained on rescue diet (20% lactose, 2% Ca, 1.25% P). Mice fed with diet containing 0.2% cholic acid (CA), chenodeoxycholic acid (CDCA), deoxycholic acid (DCA), or lithocholic acid (LCA) were analyzed. Effects of bile acids in vitro were analyzed by using UMR106 cells. Gut flora of phosphate loaded mice were analyzed by PCR.

Methods: We found that acute blood loss leads to an increase in plasma cFGF23 levels in bled animals was accompanied by increased plasma cFGF23 levels at 6 hours. Administration of erythropoietin led to an acute increase in plasma cFGF23 levels similar to that observed in acute blood loss. Fgf23 mRNA expression was increased 20-fold in bone marrow, but not in bone, of bled versus control mice, suggesting bone marrow as a key source of elevated plasma FGF23 levels following acute blood loss. To extend these findings to humans, we measured plasma FGF23 levels in 131 critically ill patients admitted to the intensive care unit to assess the association with number of blood transfusions as an indicator of acute blood loss.

Conclusions: We conclude that FGF23 production is rapidly increased after acute blood loss, and that erythropoietin may be the mediator of this increase. Thus, erythropoietin may represent a novel physiologic regulator of FGF23 production.

Funding: NIDDK Support, Private Foundation Support
Ratios of Parathyroid Hormone, Fibroblast Growth Factor 23, and 1,25-Dihydroxyvitamin D and Cardiovascular Events
Adeera Levin, Ognjenka Djurdjev, Mila Tang, Claudia Zierold, Frank A. Blocki, Fabrizio Bonelli, Myles S. Wolf
Background: Abnormal calcium homeostasis in patients with CKD may impact vascular health. Ratios of parathyroid hormone (PTH(1-84)), fibroblast growth factor 23 (FGF23) and 1,25-dihydroxyvitamin D (1,25(OH)2D) may provide insight into risk of cardiovascular events (CVE).

Methods: We examined data from CanPREDDICT, a prospective CKD pan-Canadian cohort from 2008-2013, followed biannually for 5yrs, with adjudicated outcomes. PTH(1-84), intact FGF23 and 1,25(OH)2D were evaluated at baseline using precise new assays (DiaSorin Inc), on the LIASON XL analyzer. We used Cox proportional hazards to examine composite renal events (CRE) defined by need for renal replacement therapy or dialysis, and/or composite vascular events (CVE) defined by non-fatal MI, non-fatal stroke, ischemic heart disease events, heart failure, or CVE death. We evaluated HRs for age, sex, diabetes and CVE history, BP, weight, eGFR, ACR, Alb, PO4, Ca, Hgb, K+ (baseline), and Pi levels, assessed renal function and measured FGF23 mRNA expression in vitro. Univariate and multivariate adjusted HRs were calculated per one standard deviation increments using natural log-transformed variables where appropriate.

Results: The study cohort included 1784 pts with a median follow-up of 41 months; mean age of 68yrs; 62% males; and mean eGFR of 28 ml/min/1.73m2 (19% <20ml/min, 42% 20-29ml/min and 39% 30-45ml/min). There were 429 (24%) CRE. Higher PTH(1-84) and FGF23 levels, and lower 1,25(OH)2D may be protective against CRE. The ratio of these may offer better insights than any one value alone. Further study of individual and combinations of biomarker levels is needed.

Funding: Commercial Support - DiaSorin Inc

FR-PO261
Ratios of Parathyroid Hormone, Fibroblast Growth Factor 23, and 1,25-Dihydroxyvitamin D and CKD Progression
Adeera Levin, Ognjenka Djurdjev, Mila Tang, Claudia Zierold, Fabrizio Bonelli, Myles S. Wolf
Background: Patients with CKD experience variable rates of progression. Ratios of PTH(1-84), fibroblast growth factor 23 (FGF23) and 1,25-dihydroxyvitamin D (1,25(OH)2D) describing relative values of important hormonal systems and renal tubular function that provide insight into risk of CKD progression.

Methods: We examined data from CanPREDDICT, a prospective CKD pan-Canadian cohort from 2008-2013, followed biannually for 5yrs, with adjudicated outcomes. PTH(1-84), intact FGF23 and 1,25(OH)2D were evaluated at baseline using precise new assays (DiaSorin Inc), on the LIASON XL analyzer. We used Cox proportional hazards to examine composite renal events (CRE) defined by need for renal replacement therapy or dialysis, and/or composite vascular events (CVE) defined by non-fatal MI, non-fatal stroke, ischemic heart disease events, heart failure, or CVE death. We evaluated HRs for age, sex, diabetes and CVE history, BP, weight, eGFR, ACR, Alb, PO4, Ca, Hgb and K+ (base). Univariate and multivariate adjusted HRs were calculated per one standard deviation increments using natural log-transformed variables where appropriate.

Results: There were 429 (24%) CRE. Higher PTH(1-84) and FGF23 predict higher risk of CRE, higher levels of 1,25(OH)2D may be protective against CRE. The ratio of these may offer better insights than any one value alone. Further study of individual and combinations of biomarker levels is needed.

Funding: Commercial Support - DiaSorin Inc

FR-PO262
Ratios of Parathyroid Hormone, Fibroblast Growth Factor 23, and 1,25-Dihydroxyvitamin D and Cardiovascular Events
Adeera Levin, Ognjenka Djurdjev, Mila Tang, Claudia Zierold, Frank A. Blocki, Fabrizio Bonelli, Myles S. Wolf
Background: Abnormal calcium homeostasis in patients with CKD may impact vascular health. Ratios of parathyroid hormone (PTH(1-84)), fibroblast growth factor 23 (FGF23) and 1,25-dihydroxyvitamin D (1,25(OH)2D) may provide insight into imbalances in the system and its relation to cardiovascular events (CVE).

Methods: We examined data from CanPREDDICT, a prospective CKD pan-Canadian cohort from 2008-2013, followed biannually for 5yrs, with adjudicated outcomes. PTH(1-84), intact FGF23 and 1,25(OH)2D were evaluated at baseline using precise new assays (DiaSorin Inc), on the LIASON XL analyzer. We used Cox proportional hazards to examine adjudicated CVE, adjusted for age, sex, diabetes and CVE history, BP, weight, eGFR, ACR, Alb, PO4, Ca, Hgb and K+ (base). Univariate and multivariate adjusted HRs were calculated per one standard deviation increments using natural log-transformed variables where appropriate.

Results: The study cohort included 1784 pts with a median follow-up of 41 months; mean age of 68yrs; 62% males; and mean eGFR of 28 ml/min/1.73m2 (19% <20ml/min, 42% 20-29ml/min and 39% 30-45ml/min). There were 429 (24%) CRE. Higher PTH(1-84) and FGF23 predict higher risk of CRE, higher levels of 1,25(OH)2D may be protective against CRE. The ratio of these may offer better insights than any one value alone. Further study of individual and combinations of biomarker levels is needed.

Funding: Commercial Support - DiaSorin Inc

FR-PO263
Increased FGF23 Production in CKD: Is Associated with Altered Osteocyte Development and Bone Mineralization
Corey Dussold, Samantha Neuburg, Ying Liu, Jian Feng, Xueyan Wang, Valentin David, Myles S. Wolf, Aline Martin, Northwestern University, Chicago, IL; Texas A&M-Baylor College of Dentistry, Dallas, TX; Duke University, Durham, NC.
Background: Fibroblast growth factor (FGF)-23 is a hormone produced by osteocytes that regulates phosphate (Pi) homeostasis. Chronic kidney disease mineral and bone disease (CKD-MBD) leads to alterations of mineral and bone metabolism, including elevation of circulating FGF23 levels that is associated with increased risk of cardiovascular mortality. The mechanism of increased FGF23 in CKD is poorly understood and the impact of the CKD on osteocyte development and maturation has not been described. We tested the hypothesis that CKD induces changes in osteocyte morphology that result in altered osteocyte network, bone mineralization and mineral metabolism.

Methods: Using 3D-microtomography, acid-etched scanning electron microscopy, whole bone FITC staining and Imaris modelisation, we studied the bone and osteocyte phenotype of 9-week-old Col4a3-/- mice with advanced CKD and wild-type (WT) littermates. We assessed in vitro matrix mineralization by alizarin red S (ARS) staining and osteoblast differentiation by alkaline phosphatase (ALP) staining of WT and Col4a3-/- isolated primary osteoblasts (BMSCs). In parallel, we measured serum FGF23 and Pi levels, assessed renal function and measured FGF23 mRNA expression in vitro and in vivo.

Results: Renal function was dramatically impaired in Col4a3-/- mice (BUN: 100±12 vs 18±1 mg/dL) and we observed a 15-fold increase in bone FGF23 mRNA expression, a 70-fold increase in serum FGF23 and a 50% increase in serum Pi levels (p<0.05 vs. WT). Col4a3-/- mice displayed a 5% decrease in bone mineral density (BMD) and a 14% decrease in bone mineral content (BMC) in the cortical area compared to WT. The bone mass was 10% lower in Col4a3-/- mice compared to WT. The cortical area showed an 80% reduction in number and length of the dendritic processes (p<0.05 vs. WT). In vitro, Col4a3-/- BMSCs maintained intrinsically abnormalities in activity and mineralization (~40% ALP activity and ARS; p<0.05 vs. WT).

Conclusions: Our data show that impaired osteocyte morphology and function is associated with defective bone mineralization and FGF23 overproduction in CKD. Whether impaired osteocyte morphology is a cause of FGF23 overproduction and whether rescue of the bone mineralization and osteocyte morphology defects could prevent FGF23 elevation in CKD requires further investigation.

Funding: NIDDK Support

FR-PO264
Effects of Repeated Ferric Carboxymaltose on Phosphate and FGF23 Levels
Rupal Mehta, Alex Hodakowski, Xuan Cai, Myles S. Wolf, Tamara Isakova
Background: Treatment of iron deficiency anemia (IDA) with a single dose of ferric carboxymaltose (FCM) reduces FGF23 (eFGF23) levels, but paradoxically increases levels of biologically intact FGF23 (FGF23), which results in hypophosphatemia. Although clinical trials of single doses of FCM reported high rates of reversible hypophosphatemia of unknown clinical significance, numerous reports have emerged of prolonged hypophosphatemia with severe skeletal complications in patients who received repeated doses of FCM. No studies reported on the effects of repeated FCM dosing on phosphate and FGF23 levels.

Methods: We are conducting a longitudinal observational study of individuals who are receiving two doses of FCM for treatment of their IDA. We aim to test the following hypotheses: 1) repeated FCM dosing will be associated with prolonged increases in
Effects of Iron Sucrose on Fibroblast Growth Factor 23 (FGF23) Levels in Iron-Deficient Patients with CKD and Heart Failure (HF) — Rupal Mehta,1 Alex Hodakowski,1 Xuan Cai,1 Myles S. Wolf,1 Tamara Isakovia2 — Duke University, Durham, NC;2 Feinberg School of Medicine, Northwestern University, Chicago, IL;3 Northwestern University, Feinberg School of Medicine, Chicago, IL.

Background: Iron deficiency (ID) is a potent stimulus for increased FGF23 production. In healthy individuals with ID, upregulated FGF23 production is matched by FGF23 cleavage resulting in elevated c-terminal FGF23 (cFGF23) but normal intact FGF23 (iFGF23) levels. We hypothesize that FGF23 cleavage is impaired in CKD and HF and that the resultant imbalance between production and relatively decreased FGF23 cleavage contributes to the known elevation of iFGF23 levels in CKD and HF. Furthermore, if FGF23 cleavage is impaired in CKD and HF, we hypothesize that correction of ID in CKD and HF will lower both c- and iFGF23 levels unlike healthy individuals with normal cleavage in whom iron treatment only lowers cFGF23.

Methods: We recruited 18 individuals with ID anaemia with CKD and HF to investigate the effects of 5 weekly doses of iron sucrose on c- and iFGF23 levels. ID anaemia was defined as hemoglobin <12 g/dl and transferrin saturation (TSAT) <20%, or a hemoglobin <12 g/dl with a ferritin <100 mg/dl and TSAT <30%. Measurements were taken at baseline, prior to each iron dose, after 5 weeks, and 3 months later.

Results: Baseline laboratory values were as follows: mean eGFR was 36 ± 18 ml/min/1.73m², median ferritin was 44.0 (interquartile range [IQR] 22, 44 mg/dl), median TSAT 8% (IQR 8-19), median cFGF23 335 (IQR 158-480) RU/ml, and median iFGF23 147 (IQR 81-267) pg/dl. Baseline c- and iFGF23 strongly correlated (Spearmann Correlation Coefficient 0.71, p value < 0.001). After 5 weeks, median cFGF23 was 142 (IQR 90-433) RU/ml with a mean decrease of -118 Ru/ml (-135 Ru/ml). Median iFGF23 correlated with age, BAP, and walking speed. The stepwise regression analyses revealed that serum phosphorus, calcium, and TSAT were the only independent predictors of FGF23 (standardized regression coefficients were 0.620, 0.442, and 0.381, respectively, R²=0.762, p<0.001). There was no significant relationship between FGF23 and serum creatinine.

Conclusions: FGF23 production can be independently associated with BM as well as calcium and phosphate in MHD patients.

FR-PO267
Cardiac Fibroblast Growth Factor 23 Is Induced by Activated Renin-Angiotensin-Aldosterone System and Promotes the Pro-Fibrotic Crosstalk between Cardiac Myocytes and Fibroblasts — Maren Leifheit-Nesler,1 Felix Kirkhoff,2 Julia Nespor,2 Beatrice Richter,4 Joerg Heinike,1 Dieter Haffner,5 Hannover Medical School, Hannover, Germany;1 Hannover Medical School, Hannover, Germany;3 Hannover Medical School, Hannover, Germany;4 University of Alabama at Birmingham, Birmingham, AL.

Background: FGF23 is a circulating factor that plays an critical role in the regulation of phosphate and vitamin D. In MHD patients, an increase in FGF23 can lead to the development of cardiovascular complications. FGF23 is produced by mature osteoblasts and osteocytes; however, the relationship between bone and FGF23 productions remains poorly understood. We investigated whether bone content is related with FGF23 levels in MHD patients.

Methods: MHD patients with dialysis vintage at least 3 months (n=107) were enrolled in this study. Serum concentration of intact FGF23 (ELISA, Kainos) and the factors related to mineral bone disorders (calcium, phosphorus, bone-type ALP [BAP], 1,25(OH)2 vitamin D [calcirol], 25(OH) vitamin D), inflammation (high-sensitivity CRP, interleukin-6, tumor necrosis factor-α), uremia (creatinine, p-cresol, indoxyl-sulfate, pentosidine) were measured. Walking speed, anthropometric parameters (body mass index, grip strength), bioelectrical impedance analysis (fat mass, body water volume) using inBody, and advanced body composition parameters (bone mineral content [BMC], bone mineral density [BMD], muscle mass) using Hoelogic QDR Discovery were assessed.

Results: MHD patients recruited in this study showed mean age of 66.1±1.1 years, mean dialysis vintage 88.3±8.5 months, and median of serum FGF23 of 2100 (541 to 5825 pg/ml). Log-transformed FGF23 levels were associated with body weight, muscle mass, BMC, BMD, grip strength, serum calcium, phosphates, creatinine, and negatively linked with age, BAP, and walking speed. The stepwise regression analyses revealed that serum phosphorus, calcium, and BMC were the independent predictors of FGF23 (standardized regression coefficients were 0.620, 0.442, and 0.381, respectively, R²=0.762, p<0.001). There was no significant relationship between FGF23 and serum creatinine.

Conclusions: FGF23 production can be independently associated with BMC as well as calcium and phosphate in MHD patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
angiotensin-aldosterone system (RAAS), strongly induced FGFR3 in cardiac myocytes to directly promote fibrotic and hypertrophic response.

Conclusions: In conclusion, stimulation with active RAAS components induces FGFR3 expression in cardiac myocytes, which in turn stimulates the pro-fibrotic crosstalk between cardiac myocytes and fibroblasts.

FR-PO268

Effect of Dietary Sodium and Phosphorus Intake on Fibroblast Growth Factor-23 in Patients with Diabetic Nephropathy

Background: Many clinical studies have demonstrated that serum fibroblast growth factor-23 (FGF23) levels are significantly associated with left ventricular hypertrophy (LVH). Although LVH is frequently observed in hypertensive patients, no experimental and clinical data have proved that FGF23 induces LVH in these patients. A previous study showed that subjects with high serum FGF23 levels may lead to hypertension in the future. Thus, the association between FGF23, hypertension, and LVH is very complex and remains unknown. We therefore study the change in serum and intracardiac FGF23 during the progression of hypertension using spontaneously hypertensive rats (SHR).

Methods: We used male SHRs (HT group) and Wistar Kyoto rats (WKY) as a control group in the present study. At 10 weeks, urinary and blood biochemical analyses and blood pressure measurements were performed for these rats. At 18 weeks, the rats were sacrificed, and urinary and blood biochemical analyses and real-time PCR were performed in the two groups.

Results: At baseline, serum calcium, phosphate, and FGF23 levels were comparable between the two groups. Although serum creatinine levels were also comparable, blood pressure, urinary excretion of albumin, and serum NT-proBNP levels were significantly elevated in the HT group compared to the control group. At 18 weeks, relative heart weight and serum NT-proBNP levels were significantly higher in the HT group. In addition, serum calcium and phosphate levels were significantly lower and serum FGF23 levels were significantly higher in the HT group than in the control group. Further analysis showed that mRNA expression of FGF23 in the heart was significantly increased in the HT group than in the control group. Both serum FGF23 levels (r=0.63, p<0.05) and intracardiac mRNA expression of FGF23 (r=0.79, p<0.05) were significantly correlated with relative heart weight.

Conclusions: During the progression of hypertensive, serum FGF23 levels were elevated and LVH progressed. Although it is not known whether change in FGF23 in cardiac myocytes, which in turn stimulates the pro-fibrotic crosstalk between cardiac myocytes and fibroblasts.

FR-PO269

Effect of Dietary Sodium and Phosphorus Intake on Fibroblast Growth Factor-23 in Patients with Diabetic Nephropathy

Background: The background of this study is that dietary sodium and phosphorus and plasma FGF23 levels is not well-studied in advance of diabetic nephropathy. However, this association in CKD patients is unclear. FGF23 levels have been associated with increased risk of mortality. It has been suggested but not proved that long-term management of hyperphosphatemia is required to achieve sufficient reductions in FGF23 levels. Initiation of hemodialysis leads to a marked removal of phosphate from the body and resultant reductions in PTH levels, but the effect of hemodialysis initiation on FGF23 has not been clearly demonstrated.

Methods: We conducted a prospective observational study of twenty patients initiating hemodialysis. We followed up over five days with four hemodialysis sessions. We did not change the prescription of vitamin D receptor activators, phosphate binders, or cinacalcet during the study period. We measured biochemical parameters of mineral metabolism including FGF23 pre and post each hemodialysis session, a total of 8 times.

Results: Serum full-length FGF23 levels were measured using a chemiluminescent enzyme immunoassay (Kyowa Medex, Co., Ltd) and soluble Klotho levels were measured using an enzyme linked immunosorbent assay (Immuno-Biological Laboratories, Co., Ltd). At baseline, serum levels were as follows: phosphorus, 5.6 ± 1.9 mg/dl; intact PTH, 297 ± 107 pg/ml. Initiation of hemodialysis led to a progressive reduction in serum phosphorus, intact PTH, and FGF23 levels (median percent changes from baseline to the start of the 4th hemodialysis session were −32%, −48%, and −43%, respectively). Prescription of vitamin D receptor activators did not modify the effect of hemodialysis initiation on FGF23 levels. There was no meaningful change in soluble Klotho levels.

Conclusions: FGF23 levels decrease drastically after initiation of hemodialysis. A markedly reduced removal of phosphate by hemodialysis initiation could suppress the production of FGFR3 by osteocytes. Our findings suggest a critical role of phosphorus retention in markedly elevated FGFR3 and support the importance of serum phosphorus management for suppressing FGF23 production, which may have diverse toxic effects.

FR-PO270

Effect of Treatment of Metabolic Acidosis on Fibroblast Growth Factor-23 in Patients with CKD

Background: The background of this study is that dietary sodium and phosphorus and plasma FGF23 levels is not well-studied in advance of CKD. We conducted a study to test the hypothesis that treatment with oral sodium bicarbonate in patients with CKD and metabolic acidosis reduces intact FGF23 (iFGF23) levels.

Methods: We performed a prospective, randomized, open-label, 14-week crossover study of 20 patients with stage 3-4 CKD (eGFR 15-44 ml/min/1.73m²) and metabolic acidosis (serum bicarbonate level of <22 and >16 mEq/L). Subjects were randomly assigned to start with treatment or control. Each period was 6 weeks in duration with a 2-week washout period in between. Patients were treated with oral sodium bicarbonate at a dosage of 300 mg/kg/day of sodium bicarbonate.

Results: The mean (SD) age and eGFR was 58.5 ± 12.8 years and 24.6 ± 1.1 ml/min/1.73m², respectively, if iFGF23 increased significantly during the treatment period (p=0.008) and not during the control period (p=0.68). When we compared iFGF23 between the treatment and the control periods, there was a trend towards significance (p=0.065). Serum phosphorus increased significantly during the treatment period but not in the control group. There was no increase in phosphorus between the groups (p=0.388). There was no significant change in serum parathyroid hormone or kidney function in either group.

Conclusions: Treatment of metabolic acidosis with sodium bicarbonate in CKD increases serum phosphorus and iFGF23. The mechanism of these observations is unexplained and further studies are needed to confirm these results.

Funding: NIDDK Support, Other NIH Support - NHLBI
**FR-PO272**

**Oxygen Consumption Is the Major Determinant of Klotho Release by the Kidney**

**Daniela Picciotto,1,3 Giacomo Garibotto,1,3 Samantha Milanesi,4 Abitha Murugavel,6,3 Francesca Viazzi,5,3 Daniela Verzola,2 DIMI, Genoa University, Genoa, Italy; 1University of Genoa Di.M.I. Nephrology, Genoa, Italy; 3Clinica nefrologica, Dialisi, Trapianto, Ospedale Policlinico San Martino, Genoa, Italy; 4University of Genoa, Genoa, Italy; 5University of Genova, Genova, Italy; 6University of Genova, Genova, Italy.

**Background:** Plasma levels of soluble αKlotho (sKlotho), an anti-aging protein which serves as the co-factor for FGF23, progressively decline along with CKD progression. However, our knowledge of the sites and mechanisms which regulate circulating sKlotho is still incomplete.

**Methods:** To explore the role of the kidney and of the extra-renal sites on the metabolic handling of sKlotho, we measured sKlotho levels in venous effluents from different organs, including the kidney, the splanchnic organs and lung, as well as in arterial blood, in a cohort of patients (n=20, 10M/10F, age 56-82 yr, BMI 25±1 Kg/m², eGFR 63±4 ml/min/1.73 m² range 23-98 ml/min), undergoing a right-sided cardiac catheterization.

**Results:** Mean arterial sKlotho was 202±26 pg/ml. Renal vein sKlotho concentrations were remarkably higher (by ~8 %, p<0.05) than the corresponding arterial values, indicating that plasma sKlotho increases substantially after a single pass across the kidney. The fractional enrichment (FE) of sKlotho across the kidney was similar (8±6 vs. 9±4 %, respectively) in patients with normal renal function (n=11) and in patients with GFR<60 ml/min (n=9, eGFR 39±3 ml/min). sKlotho level in the liver vein was lower (by 23±6 %, p<0.05) than the arterial one in patients with GFR<60 ml/min. Arterial sKlotho levels were almost identical to pulmonary artery values. In all subjects, at univariate analysis, fractional enrichment (FE) of sKlotho across the kidney was directly related to the fractional extraction of oxygen (r=0.412, p<0.05), and inversely, to plasma sodium (r=0.434, p<0.05) and uric acid (r=0.357, p<0.06) but not to eGFR, hemoglobin and phosphate levels. At multivariate analysis, the fractional extraction of oxygen across the kidney was the only determinant of sKlotho FE.

**Conclusions:** Our data show that the human kidney is the only site for sKlotho production in the body, while splanchnic organs may participate to sKlotho removal. Oxygen uptake by the kidney is the major determinant of sKlotho production by the human kidney, suggesting a role for hypoxemia on reducing the availability of sKlotho to the systemic circulation. Besides providing a better understanding of physiology of αKlotho metabolism, the data reported in this study could be useful to understand the alterations in αKlotho that are observed in CKD and many systemic and organ diseases.

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

**FR-PO273**

**The Effect and Possible Mechanism of Klotho on the Expression of Fibroblastic Growth Factor 23 (FGF23) Secreted by Osteoblast-Like UMR-106 Cells**

**Huijuan Mao, Lulu Ma. First Affiliated Hospital of Nanjing Medical University, Nanjing, China.

**Background:** To investigate the effect and possible mechanism of Klotho on the expression of FGF23, progressively declined along with CKD progression. However, our knowledge of the sites and mechanisms which regulate circulating sKlotho is still incomplete.

**Methods:** UMR-106 cells were divided into 5 groups and cultured for 72 h: (1) control group,(2)β-glycerophosphate(β-GP) group,(3)β-GP+Klotho group,(4)β-GP+LiCl group,(5)β-GP+Klotho+LiCl group, and then the expression of FGF23, P-GSK-3β and GSK-3β protein was measured by Western blotting. The levels of mRNA of FGF23 and c-myc were determined by RT-PCR.

**Results:** 1. β-GP induced the increase of expression of FGF23 mRNA and protein. Compared with β-GP group, FGF23 mRNA and protein expression was downregulated after treating with Klotho(Figure 1).2. β-GP induced the increase of expression of P-GSK-3β and c-myc mRNA.Compared with β-GP group, P-GSK-3β and GSK-3β protein was measured by Western blotting. The levels of mRNA of FGF23 and c-myc were downregulated after treating with Klotho(Figure 2).3. The expression of FGF23, P-GSK-3β and GSK-3β and c-myc mRNA were upregulated when treated with LiCl(Figure 1 and 2).

**Conclusions:** Klotho down-regulates the expression of FGF23 induced by hyperphosphate in osteoblast-like UMR-106 cells via Wnt/β-catenin pathway.

**Funding:** Government Support - Non-U.S.
Biochemical determinations of 25D, 1,25D, 24,25D and DBP were measured at baseline in patients aged 65.8 (20.6, 71.0) years (n = 35) and HV aged 41.0 (29.0, 62.0) years (n = 7). To test this possibility, we assessed vitamin D catabolism after a single ergocalciferol administration. Vitamin D deficiency is highly prevalent in dialysis patients and D vitamin metabolites may reduce serum 25(OH)D and 1,25(OH)2D levels. To test this, concentrations of both 1,25D3 and 24,25D3 correlated strongly with 25D3 (R2 = 0.4558 and R2 = 0.493, respectively). In contrast, the correlations between 25D3 and 1,25D3, and between 25D3 and 24,25D3, in HD were weaker (R2 = 0.1285 and R2 = 0.4654, respectively).

Methods: All patients ingested a single oral dose of 50,000 IU ergocalciferol, HD patients aged 65.8 (20.6, 71.0) years (n = 35) and HV aged 41.0 (29.0, 62.0) years (n = 7). Biochemical determinations of 25D, 1,25D, 24,25D and DBP were measured at baseline and 2-5 days after D2 ingestion. Biochemical markers at baseline and post-therapy were compared.

Results: Concentrations of 25D3 increased after D2 in both HD and HV (average increases of +14.5 ng/mL [95% CI 9.5-29.4] and +21.2 [95% CI 14.6-29.8], respectively). Although average pre-treatment 25D3 concentrations were significantly higher in HD compared to HV (21.2 ng/mL [95% CI 14.6-29.8] vs. 14.5 ng/mL [95% CI 9.5-29.4]), p<0.05, concentrations of 24,25D3 were lower in HD (5.5 ng/mL [95% CI 3.5-15.6] vs. 14.5 ng/mL [95% CI 9.5-29.4], p<0.05). Average concentrations of 1,25D3 was also lower in HD (4.7 pg/mL [95% CI 2.8-8.4] vs. 54.1 pg/mL [95% CI 47.7-69.2], p<0.05). Amongst HV, concentrations of 25D3 decreased on average by -0.6 ng/mL [95% CI -3.9 to -0.2] after vitamin D administration, and 1,25D3 decreased by -10.6 pg/mL [95% CI -20.2 to -0.5), whereas there was no significant decrease in 24,25D3. Amongst HD, no significant changes in 25D3, 24,25D3, or 1,25D3 were seen. Amongst HV, concentrations of both 1,25D3 and 24,25D3 correlated strongly with 25D3 (R2 = 0.4558 and R2 = 0.493, respectively). In contrast, the correlations between 25D3 and 1,25D3, and between 25D3 and 24,25D3, in HD were weaker (R2 = 0.1285 and R2 = 0.4654, respectively).

Conclusions: CKD is associated with higher 25D3, but lower 24,25D3 and 1,25D3 concentrations, and 1,25 levels are more closely associated with 24,25D3 than with 25D3 in ESKD. Feedback regulation of both 1,25D3 and 24,25D3 by PTH and/or FGF23 in HD warrants further investigation.

Funding: NIDDK Support, Private Foundation Support

FR-PO275
The Relation of the 24,25 to 25-Hydroxyvitamin D Ratio with Bone Density and Fracture Risk in Older Adults: The Cardiovascular Health Study
Charles Ginsberg,1 Ronit Katz,1 Ian H. de Boer,2 Bryan R. Kestenbaum,2 Michel Chonchol,3 Michael Shlipak,1,2 Mark J. Sarnak,4 Andrew N. Hoofnagle,5 Dena E. Rifkin,6 Franav S. Garmirelli,7 Joachim H. Ik.8 University of Anschutz Medical Center, Aurora, CO;1University of Washington, Seattle, WA;2San Francisco VA Medical Center, San Francisco, CA;3Tufts Medical Center, Boston, MA;4University of Washington, Seattle, WA;5University of California, San Diego, San Diego, CA;6University of California, San Francisco, San Francisco, CA.

Background: Serum 25-hydroxyvitamin D [25(OH)D] concentrations may not optimally indicate vitamin D receptor (VDR) activity. Catabolism of 25(OH)D to 24,25-dihydroxyvitamin D [24,25(OH)2D] is stimulated by active 1,25-dihydroxyvitamin D. Thus, higher concentrations of 24,25(OH)2D and a higher ratio of 24,25(OH)2D to 25(OH)D (the vitamin D metabolite ratio [VMR]) may provide additional information on receptor activity. We compared the strength of associations of these markers with serum PTH concentrations, hip bone mineral density (BMD), and incident hip fracture among community-living older participants in the Cardiovascular Health Study (CHS).

Methods: We conducted a case-cohort study of 1116 CHS participants with over sampling for fracture outcomes. We used multiple linear regression to assess associations of 25(OH)D, 24,25(OH)2D, and VMR with PTH and hip BMD in the random cohort. We used a Cox proportional hazards model to estimate the association of each marker with incident fracture in the complete case-cohort population.

Results: Mean age was 78, 60% were female, and mean eGFR was 64 +/-16 ml/min/1.73m2. Serum 25(OH)D, 24,25(OH)2D, and VMR were each associated with PTH; the sizes of these associations were statistically indistinguishable. Higher serum 24,25(OH)2D3 concentrations, but not 25(OH)D3 or VMR, were associated with greater hip BMD. There were 289 hip fractures during 8.4 years mean follow-up. Serum concentrations of 24,25(OH)2D3 and VMR but not 25(OH)D3 were associated with incident fracture (Table).

Conclusions: Lower 24,25(OH)2D concentrations and VMR but not 25(OH)D concentrations were associated with hip fracture risk in community-living older adults.

Funding: NIDDK Support, Other NIH Support - NIH Loan Repayment Program, NHLBI, NINDS, National Institute on Aging, Private Foundation Support

Association of Vitamin D Measures with Incident Hip Fracture

Data for model adjusted for age, sex, race, season of measurements, site of measurement BMI, eGFR, serum calcium, phosphate and FGF-23.

FR-PO276
International Serum 25-OH-Vitamin D Measurement, Levels, and Treatment among Patients with CKD in Everyday Nephrology Practice; Results from CKDopps Sophie Liabot,4 Keith McCullough,5 Ronald L. Pisoni,5 Yvonne Meier,5 Jarcy Zee,5 Helmut Reichel,1 Per Petters-Filho,6 Friedrich K. Port,1 Bruce M. Robinson,4 Ziad Massy,4 Nephrological Center, Villingen-Schwenningen, Germany;5Vigor Pharma Ltd, Glattbrugg, Switzerland;6Ambrose Pare University Hospital, Bouldinge Billancourt Paris cedex, France;7Arbor Research Collaborative for Health, Ann Arbor, AL;8CHU Amiens, Amiens, France;9Pontificia Universidade Catolica do Parana, Curitiba, Brazil.

Background: CKD progression is linked to a decrease in 25 hydroxycholecalciferol (25(OH)D) with implications for secondary hyperparathyroidism. While the optimal
The Impact of CKD on Analytical Performance of 25 Vitamin D Assays

Hanna Karla A. Guypayss2, Machad2, Carolina S. Martins2, Vanda Jorgetti2, Rosilene M. Elias3, Rosa M. Moyses4,1 Universidade Nove de Julho, São Paulo, Brazil; 3Nephrology, Universidade de São Paulo, São Paulo, Brazil.

Background: Current guidelines recommend evaluation of 25 vitamin D (25vitD) status and therapy when serum levels are below 30 ng/ml. Significant differences among some assays have been described. However, the impact of renal disease on these differences has never been measured until now. In our study, the assay for 25vitD measurement was changed from Diasorin® to Beckman Coulter Unicel DXI 8000®, which gave us the opportunity to evaluate the impact of the assay in the levels of 25vitD in CKD patients.

Methods: We obtained data from 540 patients [122 with eGFR > 90 ml/min (normal renal function); 138 with 30-60 ml/min (CKD3); 124 with 15-29 ml/min (CKD4) and 156 on dialysis (CKD5D)] in which serum 25vitD was measured with both assays with a time difference of 6 months.

Results: The median of serum 25vitD increased [23 (19-29) vs. 29 (22-37) ng/ml; p<0.0001], but could not be explained by seasonal differences, as the second measurement was done at wintertime. 25vitD increased in patients with CKD 3, 4 and 5D, but not in individuals with normal renal function. Indeed, the more advanced the CKD, the higher the median increase [5 ng/ml (9-3.4) in normal renal function; 3.5 ng/ml (2.8-1.1) in CKD3; 3 ng/ml (1.3-9) CKD4; and 8 ng/ml (1.1-15) in CKD5D; p<0.0001]. The prevalence of 25vitD insufficiency increased from 49 to 62% in the entire population and from 44 to 57% only in CKD patients (p = 0.001 and 0.0001, respectively).

Conclusions: Our findings confirm the disagreement between 25vitD assays, showing higher levels with Beckman Coulter Unicel DXI 8000®, which is more marked in CKD patients, suggesting that non-active fragments usually found in this population might be recognized as intact 25vitD. This technical problem will certainly affect hypovitaminosis D diagnosis and also therapy in CKD patients.

Funding: Government Support - Non-U.S.
VDR Deficiency Induces the Parathyroid Glands Lesions via NFκB Pathway Activation in Uremic Patients

**Jing Mao**, Minmin Zhang, Li Ni, Mengqing Wang, Jing Chen. Huashan Hospital, Fudan University, Shanghai, China.

**Background:** Secondary hyperparathyroidism (SHPT) is one of the most common complications in CKD-MBD, but its pathogenesis remains unknown. Recent studies showed that 1,25D suppressed Nuclear Factor-κB (NFκB) activation to suppress tumor hyperplasia. Therefore, whether VDR deficiency induce the tumor-like hyperplasia of parathyroid gland (PTG) via the NFκB pathway activation in uremic patients.

**Methods:** PTG samples were collected from parathyroidectomy surgery of 10 uremic patients who failed to medical treatment with approval of the Ethics Committee on Human Research at Huashan Hospital. Immunohistochemistry and Western blot detected the expression of VDR, pp65 and PCNA in diffuse and nodular hyperplastic PTG. In vitro, freshly excised PTG tissues were minced into 1mm3 fragments and incubated with 1,25D (0μM, 1μM, 10μM, 100μM) and PDTC (0μM, 2μM, 20μM, 200μM) for 24 hours. ELISA kit measured the levels of iPTH from supernatant. Real-time PCR measured the mRNA levels of preproPTH, PCNA, VDR and IκBκx. Western blot measured the protein levels of VDR, pp65, pp65 and PCNA.

**Results:** Compared with diffuse hyperplasia, immunohistochemistry results showed that VDR expression was down-regulated by 34.97% (P<0.01), while pp65 and PCNA were up-regulated by 86.51% (P<0.01) and 97.37% (P<0.01) in nodular hyperplastic glands. Western blot confirmed these above. In vitro, 1,25D up-regulated protein and mRNA levels of VDR by 150.62% (P<0.05) and 35.62% (P<0.05), down-regulated protein of CaSR by 67.32% (P<0.01), up-regulated mRNA level of IκBκx by 72.77%, (P<0.01), and down-regulated protein and mRNA levels of PCNA by 42.48% (P<0.05) and 38.49% (P<0.01). These results suggested that 1,25D could activate VDR, inhibit cellular proliferation and inhibit NFκB activation. PDTC did not affect VDR expression, but down-regulated protein level of pp65 by 73.08% (P<0.01), down-regulated protein and mRNA levels of PCNA by 47.39% (P<0.05) and 26.95% (P<0.05). These results suggested that PDTC inhibit NFκB activation and inhibit cellular proliferation, while it had no effect on VDR expression. ELISA results showed that 1,25D and PDTC could both down-regulate iPTH levels by 61.16% (P<0.01) and 49.86% (P<0.01). These results suggested that CaSR and Gcm2 might be involved in the hyperplasia of PTG in uremic patients, the exact mechanism needs further study.

**Conclusions:** Deficiency of VDR and activation of NFκB pathway may be involved in the hyperplasia of PTG in uremic patients, the exact mechanism needs further study.

Severe CKD Environment Affects CaSR Gene Expression and the Cascade of Genes in Parathyroid Glands Even without High Phosphorus Diets

Takuto Uchivama, Ichiro Okido, Sahoko Kamejima, Akio Nakashima, Takashi Yokota. Division of Kidney and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan; Division of Nephrology and Hypertension, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan; Jikei University School of Medicine, Tokyo, Japan; The Jikei University School of Medicine, Tokyo, Japan.

**Background:** Chronic kidney disease (CKD) disrupts mineral homeostasis and its representative pathosis is defined as secondary hyperparathyroidism (SHPT). SHPT occurs during the early course of progressive renal insufficiency, and is associated with mortality and cardiovascular events. Reduction of the calcium-sensing receptor (CaSR) occurs during progressive disease through this process, although the underlying mechanism remains largely unknown.

**Methods:** CKD was induced by 0.75% adenine-containing diet. CKD rats and control rats were maintained for 2 weeks on diets containing 0.7% phosphorus or 1.3% phosphorus. The CaSR mRNA was reduced in CKD rats fed the normal and high phosphorus diets. In a gene expression analysis, TaqMan probes were used to do the PCR. DNA methylation analysis was performed using a restriction digestion and quantitative real-time polymerase chain reactions. CaSR and glial cells missing-2 (Gcm2) promoter, was significantly decreased in CKD NP and CKD HP rats. Consequently, our data suggest that Gcm2 was responsible for the reduction in mRNA and protein levels of CaSR and VDR in PTGs of CKD HP rats.

**Conclusions:** CaSR expression in parathyroid glands was observed in CKD NP and CKD HP rats; however, the DNA hypermethylation was not demonstrated. We then analyzed the Gcm2 gene and its protein expression, as upstream transcription factor of CaSR, and we verified its depression in CKD NP and CKD HP rats. Consequently, our data suggest that Gcm2 was responsible for the reduction in mRNA and protein levels of CaSR and VDR in PTGs of CKD HP rats.
FR-PO284

Interactions of Calcium, Vitamin D, and Kidney Function with Parathyroid Hormone Levels
Rita L. McGill,1 Elaine M. Worcester,2 Jennifer L. Ennis,1 Sangeet Dhillon-Jhuttu,2 Fredric L. Coo,3 Litholink Corporation, Chicago, IL; 1University of Chicago, Chicago, IL.

Background: Parathyroid hormone (PTH) is a crucial factor in regulating calcium homeostasis and bone mineral deposition. Vitamin D and estimated glomerular filtration rate (eGFR) also interact with PTH, and we aimed to better characterize the interplay between these factors.

Methods: Laboratory results performed at LabCorp between April 2011 and February 2014 were assessed, if simultaneous PTH, calcium, vitamin D and eGFR were available. Calcium and vitamin D were categorized, and analyses were stratified for National Kidney Foundation stage of chronic kidney disease (CKD). Percentages of tests in which a PTH>65 was observed were calculated and plotted for each combination of calcium, vitamin D, and eGFR.

Results: Among 126,615 patients, 38% were male and mean age was 65.6 years. Compared to those with the GFR-90, PTH levels were more likely to be abnormal in CKD stages 2 and 3A. Higher vitamin D levels were associated with lower PTH in all patients, and this effect became more prominent with decreasing eGFR. The normal U-shaped relationships between calcium and PTH were distorted in CKD stages 4 and 5.

Conclusions: PTH levels become detectably abnormal even in very early CKD. Repletion of vitamin D to levels of 40 ng/ml or greater reduces PTH in patients with eGFR ≤ 15.

FR-PO285

Kidney and Parathyroid Transplants for Hereditary Hypoparathyroidism: Due to a Calcium Sensing Receptor (CaSR) Mutation Reduced Calcium but Did Not Normalize Serum Calcium Due to a Calcium Sensing Receptor (CaSR) Mutation Reduced Calciuria Percentage of Patients with PTH > 65, by Calcium, Vitamin D, and Chronic Kidney Disease Stage

Percentage of Patients with PTH > 65, by Calcium, Vitamin D, and Chronic Kidney Disease Stage

FR-PO286

TRPC1 Gene Deletion Disturbs Homeostasis of Intracellular Free Calcium ((Ca2+)), Produces Hyperparathyroidism, Hypercalciemia, Hyperphosphatemia, and Increased Bone Mass Due to Renal Ca and P Retention

Bonne Eby,1 Marta Onoprik,2 Marybeth Humphrey,1 Leonidas Tsiskos,1 Kai Lau,1,2 Nephrology, University of Oklahoma Health Sciences Center, Oklahoma City, OK; 3Cell Biology, University of Oklahoma Health Sciences Center, Oklahoma City, OK; 4Rheumatology, University of Oklahoma Health Sciences Center, Oklahoma City, OK; 5Medicine, VA Hospital, Oklahoma City, OK.

Background: Mice deleted of the gene for transient receptor potential canonical channel 1 (TRPC1) have higher PTH (313 vs. 218 pg/ml), hypercalciemia (11.3 vs 10.2 mg %) & hypercalcua (1.2 vs 2.2 mg/dl), indicating TRPC1 deficiency mimics familial hypocalciuric hypercalcemia phenotypes from CaSR inactivating mutations. Micro-CT shows increased tibia bone volumes:volume (11 vs 6%). Their hind limbs were broader (185 vs 151 mg). We now studied the potential mechanisms for other gain of function mutations was identified. Having replaced the CaSR in the kidney and parathyroids with the combined allotraft transplants we presume that renal calcium metabolism has been normalized and the new kidney will be protected from recurrent nephrocalcinosis. The need for supplemental calcium to prevent hypocalcemia suggests that CaSR in other organs (such as bone or gut), has a greater contribution in maintaining serum calcium levels than preventing calcium loss through the kidney.

Funding: Private Foundation Support, Clinical Revenue Support

FR-PO287

Accuracy, Precision, and Stability of the LIAISON 1-84PTH 3rd Generation Assay: Comparison to Existing Intact PTH Assays

Anne Valcour,1 Kevin J. Martin,2 Sudhaker D. Rao,1 Douglass M. Hawkins,3 Frank A. Blocki,4 Claudia Zierold,2 Fabrizio Bonelli,1 Henry Ford Health System, Detroit, Mi; 2LabCorp, Burlington, NC; 3DaSorin Inc., Stillwater, MN; 4Saint Louis University Med Ctr, St. Louis, MO; 5DiaSorin spa, Stillwater, MN.

Background: Over the past few decades, PTH immunoasays have progressed through successive generations resulting in increased specificity and accuracy for detecting circulating PTH. With the introduction of 3rd generation assays, in which the biologically active PTH (1-84) is specifically targeted, the PTH (7-84) and other fragments are not detected. The specific recognition of PTH (1-84) whole molecule allows standardization and calibration with existing standards.

Methods: Samples from patients on hemodialysis, with primary hyperparathyroidism, and apparently healthy subjects were examined in different collection tubes (plasma, serum and EDTA). Samples from patients on hemodialysis, with primary hyperparathyroidism, and apparently healthy subjects were examined in different collection tubes (plasma, serum and EDTA). Samples from patients on hemodialysis, with primary hyperparathyroidism, and apparently healthy subjects were examined in different collection tubes (plasma, serum and EDTA).

Results: Our data support the model that, activated by upstream CaSR signaling, TRPC1 functions as a SOCE channel to control PT [Ca2+]i and regulate PTH secretion. Increased bone mineral accretion in TRPC1 deletion is mediated by greater renal Ca & P retention, the latter likely due to low FGF23 from reduced [Ca2+]i in osteocytes. At similar diet intake, 24 hr urine P is similar (3.5 vs. 4.1 mg/d). Fasting serum P was elevated (7.4 vs. 6.3 mg %) due to concurrently decreased P clearance (48 vs. 67 ml/min).

Conclusions: 1. Our data support the model that, activated by upstream CaSR signaling, TRPC1 functions as a SOCE channel to control PT [Ca2+]i and regulate PTH secretion. 2. Increased bone mineral accretion in TRPC1 deletion is mediated by greater renal Ca & P retention, the latter likely due to low FGF23 from reduced [Ca2+]i in osteocytes. 3. The apparent skeletal PTH resistance is explicable by the hypercalciemia, hyperphosphatemia, & the known impaired osteoclast proliferation, differentiation & function due to loss of TRPC1 functions.

Funding: NIDDK Support, Veterans Affairs Support
Calcification in Experimental CKD

Calcitriol at Therapeutic Doses for SHPT Promotes Vascular Calcification

Calcium homeostasis is important in both health and disease. Vitamin D deficiency in chronic kidney disease (CKD) leads to secondary hyperparathyroidism (SHPT) which can cause cardiovascular disease (CVD) and death.

Methods: Calcium homeostasis was measured in healthy Sprague-Dawley rats and in CKD Sprague-Dawley rats treated with paricalcitol. CKD rats were divided into 4 groups and treated with paricalcitol: 0.20mg/kg/day (n=9), 0.25mg/kg/day (n=9), 0.50mg/kg/day (n=9) and 1.00mg/kg/day (n=9).

Results: Treatment with paricalcitol increased serum calcium in CKD rats (p<0.05). Treatment with 0.20mg/kg/day of paricalcitol was found to be effective in increasing serum calcium to normal levels (p<0.05).

Conclusions: Paricalcitol at therapeutic doses for SHPT has the potential to promote vascular calcification.

Calcium Homeostasis in Human Subjects

Calcium homeostasis was measured in healthy human subjects treated with teriparatide. Subjects were divided into two groups: a low-dose group (n=10) and a high-dose group (n=10). Subjects were treated with teriparatide for 12 months.

Results: Treatment with teriparatide increased serum calcium in all subjects (p<0.05). However, the increase was greater in the high-dose group (p<0.05).

Conclusions: Teriparatide at therapeutic doses for osteoporosis has the potential to promote vascular calcification.

Calcium Homeostasis in Experimental Animals

Calcium homeostasis was measured in healthy Sprague-Dawley rats and in CKD Sprague-Dawley rats treated with paricalcitol. CKD rats were divided into 4 groups and treated with paricalcitol: 0.20mg/kg/day (n=9), 0.25mg/kg/day (n=9), 0.50mg/kg/day (n=9) and 1.00mg/kg/day (n=9).

Results: Treatment with paricalcitol increased serum calcium in CKD rats (p<0.05). Treatment with 0.20mg/kg/day of paricalcitol was found to be effective in increasing serum calcium to normal levels (p<0.05).

Conclusions: Paricalcitol at therapeutic doses for SHPT has the potential to promote vascular calcification.
reductions in PTHa30% and 52.9% subjects achieved PTH<300pg/mL during the study. All subjects received therapy with vitamin D sterols during the study. 94.1% of subjects had ≥1 treatment-emergent AE. The most common AEs were cough, hypertension, upper respiratory tract infection, and vomiting. There were no treatment-related serious AEs, fatal AEs nor AE leading to the discontinuation of CIN.

**Conclusions:** No subject had a Ca value below the threshold for the primary endpoint. Data show a downward trend in PTH from baseline after CIN administration. Safety data were consistent with the known safety profile.

**Funding:** Commercial Support - Amgen Inc

FR-PO292

**A Phase 3, Multicenter, Randomized, Open-Label, Controlled Study to Assess the Efficacy, Safety, and Tolerability of Cinacalcet in Addition to Standard of Care in Pediatric Subjects Ages 6 to 17 Years**

Franz S. Schaefer,1 Dorota Drozd,2 Bruno L. Fouqueray,3 Jan Iles,4 Xiaoie Ma,5 Michelle N. Rheault,6 Constantinos J. Stefanidis,7 Nancy S. Rehfeld,8 Bradley A. Warady,4 9 A. and P. Kyriakou Children’s Hospital Athens, Greece, Athens, Greece; 8Amgen Inc, Thousand Oaks, CA; 4Amgen, Inc, San Bruno, CA; 4Children’s Hospital Boston, Boston, MA; 6None, ZUG, Switzerland; 7The Children’s Mercy Hospital, Kansas City, MO; 3University of Heidelberg, Heidelberg, Germany; 5University of Minnesota, Minneapolis, MN; 9Jagiellonian University Medical College, Krakow, Poland.

**Background:** Standard of care (SoC) for secondary hyperparathyroidism for children on dialysis includes vitamin D sterols, calcium (Ca) supplementation, and phosphate (P) binding agents. Cinacalcet (CIN) has been shown to reduce parathyroid hormone (PTH), Ca, and P. Efficacy and safety data for CIN are limited in the pediatric chronic kidney disease population.

**Methods:** Pediatric subjects ages 6 to<18yrs were randomized 1:1 CIN=SoC=SoC stratified by age (6 to<12 & 12 to<18 yrs) to evaluate the efficacy of CIN=SoC for reducing mean plasma PTH by ≥30% from baseline during the efficacy assessment phase (EAP) wks 17-20. Eligible subjects had 2 consecutive PTH levels≥300pg/mL at entry and albumin corrected Ca (CaAC)≥8.8mg/dL. CIN was administered once daily starting at 0.2mg/kg/day and adjusted once monthly up to 2.5mg/kg/day or 180mg, whichever was lower, based on PTH, CaAC, ionized Ca (iCa), and safety. CIN was held if iCa<8mg/dL or iCa<1mmol/L. Nature, frequency, and severity of adverse events (AEs) were assessed.

**Results:** 22/27 CIN=SoC=SoC (56% boys) and 25/28 SoC (46% boys) randomized subjects received ≥1wks of treatment. Mean age was 12.6yrs with more subjects in the 12 to<18yrs group. The proportion of subjects who achieved PTH reduction ≥30% was not significant: 22.2%(6/27) CIN; 31.0%(8/26) SoC (p=0.42 stratified by age). Mean(SD) duration of exposure to CIN was 112.8(41.0)days with average weight-adjusted daily dose of 0.24mg/kg/day. CIN was held if ≥1 AE during the study with most ≥1 AEs were assessed.

**Conclusions:** Efficacy of CIN was not demonstrated likely due to inadequate exposure. Safety data were consistent with the known safety profile.

**Funding:** Commercial Support - Amgen Inc

FR-PO293

**Demographic Predictors of Mineral and Bone Disorders in the Pediatric Dialysis Population**

Marciana F. Lacerda,1 Melissa Soochoo,2 Elani Streja,3 Keith C. Norris,1 Isibolu B. Salasuy,4 Kamary Kalantar-Zadeh,2,5 UCLA, Los Angeles, CA; 1UCI, Orange, CA.

**Background:** Secondary Hyperparathyroidism in pediatric patients on dialysis results in bone and cardiovascular abnormalities that have major implications on morbidity and mortality in both childhood and adulthood. Therefore, it is important to understand the factors which contribute to and predict perturbations in the markers of mineral and bone disease.

**Methods:** In a sample of 661 children with ESRD we explored predictors of abnormalities in Calcium (Ca), Phosphorous (P04), Alkaline Phosphatase (ALP) and Parathyroid Hormone (PTH) levels within the first 3 months of dialysis using linear regression models adjusted for age, sex, race and ethnicity, disease type, Ca, P04, AP, and medication use.

**Results:** The cohort characteristics are displayed in Table 1. Using age-adjusted norms and K/DOQI-defined goals of PTH values ≥2-10 times the upper limit of normal, we found that Ca, ALP and PTH were most frequently within goal ranges, while P04 was most frequently above goal (Figure 1). Significant predictors of these markers included age which predicted higher PTH, lower ALP and lower Ca; Female gender which predicted lower P04 and lower ALP; Hispanic ethnicity which predicted higher PTH and lower Ca and P04 (Table 2).

**Conclusions:** Non-modifiable demographic factors associate with the markers of MBD. In particular, Black and Hispanic children have higher PTH levels and, in addition, Black children have lower ALP levels. While optimization of CKD-MBD management requires consideration of these observed differences, further studies are needed to assess potential racial/ethnic differences in PTH targets in children on dialysis.

**Funding:** NIDDK Support

FR-PO294

**Mineral and Bone Disorder (MBD) Markers and Management over the First 5 Years after Dialysis Start: Results from the DOPPS**

Angelos Karaboyas,1 Hal Morgenstern,1 Bruce M. Robinson,1 Friedrich K. Port,1 Yvonne Meier,2 Stefan H. Jacobson,3 Masafumi Fukagawa,2 Ronald L. Pisoni.1 Arbor Research Collaborative for Health, Ann Arbor, MI; 2University of Michigan, Ann Arbor, MI; 3Vifor Pharma Ltd, St. Gallen, Switzerland; 4Danderyd Hospital, Stockholm, Sweden; 5Tokai University School of Medicine, Isehara, Japan.

**Background:** Abnormalities in MBD markers - including parathyroid hormone (PTH), serum phosphorous (P), calcium, and 25-hydroxy (OH) vitamin D - in the period immediately following hemodialysis (HD) initiation may increase short- and long-term risk of morbidity and mortality. International and racial variations in MBD markers and treatments have been well-described, but not their trajectories after transition to HD.

**Methods:** Locally weighted regression (LOESS) was used to smooth trends in mean MBD markers and drug prevalence over the first 5 years of HD using 472,930 patient-months from 34,105 patients in phases 4-5 (2009-2015) of the Dialysis Outcomes and Practice Patterns Study (DOPPS).

**Results:** PTH levels were high at HD initiation, especially among black patients in the US. PTH then declined during the first year of HD before increasing in the US and Europe but not in Japan. P levels increased sharply after HD initiation before subsequently declining in Europe but not in the US or Japan. Active vitamin D and cinacalcet prescription increased over 5 years, and was greatest in US black patients. Oral nutritional vitamin D was not prescribed in Japan, but was in Europe (27%) and the US (12%) despite infrequent measurement of 25-OH vitamin D.

**Conclusions:** Variation in PTH at HD initiation by region and race may reflect differences in patient characteristics, pre-HD care, and/or timing of HD initiation. After an initial decline, we observed a rise in PTH with time on HD in US patients, particularly black patients, despite greater prescription of vitamin D and cinacalcet than in other regions. The rapid rise in P immediately following HD initiation may be partially attributable to loss of residual renal function. Future research is needed to study how MBD management before, during, and after the transition to HD can be optimized to improve clinical outcomes.

**Funding:** Commercial Support - Amgen, Kyowa Hakko Kirin, Baxter Healthcare, AstraZeneca, Hexal AG, Janssen, Keryx, Proteon, Relypsa, Roche, Vifor Fresenius Medical Care Renal Pharma, Private Foundation Support, Government Support - Non-U.S.
FR-PO295

Risk Factors for Hungry Bone Syndrome after Parathyroidectomy in CKD Patients on Dialysis
Jorge I. Fonseca-Correa,1 Juan Carlos Ramírez-Sandoval,2 Luis Rojas-Concha,2 Antonio Madrazo-Ibarra,2 Pindaro S. Martínez-Delfín,3 Paola Zinser-Peniche,4 Juan Pablo Pantoya,4 Mauricio Sierra-Salazar,5 David VELAZQUEZ-FERNANDEZ,5 Miguel Herrera-Hernández,5 Ricardo Correa-Rotter,5 Escuela de Medicina, Universidad Panamericana, Mexico City, Mexico; 4Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México city, Mexico; 5Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México City, Mexico; 6Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico, Mexico; 7Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Puebla, Mexico; 8Universidad Nacional de la Nutrición, Mexico City, Mexico; 9Universidad Panamericana, CDMX, Mexico.

Background: Hungry bone syndrome (HBS) is a frequent event after parathyroidectomy (PTx). While risk factors for HBS are well known in primary hyperparathyroidism (HPT), it is unclear whether these risk factors are similar in secondary or tertiary HPT.

Methods: We retrospectively analyzed the risk factors for HBS of a single-center cohort of 68 dialysis patients who underwent PTx. We defined HBS as persistent hypocalcemia (corrected calcium <7.5 mg/dL) lasting >3 days -with or without hypophosphatemia- requiring extended hospital stay for intravenous calcium supplementation. All patients were followed up for one year.

Results: HBS occurred in 36 (53%) patients. In the bivariate analysis, a higher preoperative intact parathyroid hormone (iPTH) (1984±777 vs. 940±581 pg/mL; p<0.001), a higher alkaline phosphatase (ALP) (706 [322-1155] vs. 132 [108-233] IU/L; p<0.001), and older dialysis vintage (4 [3-4] vs. 6 [4-11] years; p=0.049) independently predicted the development of HBS. Peritoneal dialysis (PD) treatment protected against HBS (68% Non-HBS vs. 47% HBS were on PD; p=0.02). Age, weight, preoperative phosphorus, and type of surgery did not predict HBS occurrence. Calcitriol prophylaxis for >2 days, prescribed in 91% of patients with HBS, was not effective to prevent HBS (median dose of 1.25 mcg/day [IQR 0.75-2.25]). When a multivariate analysis was performed only iPTH and ALP remained as predictors of HBS. During the year of follow-up, 4 (6%) patients died and 21 (31%) received a kidney transplant. At one year, patients who developed higher doses of calcium prescription (CaCO3 6.8 gr/day [IQR 3.0-11.8] vs. 1.5 gr/day [IQR 0.3-3.0]) and calcitriol (0.75 mcg/day [IQR 0.5-1.5] vs. 0.25 mcg/ day [IQR 0.0-0.75]) were at higher risk of HBS occurrence. Logistic regression odds ratios and the outcome of 1-year mortality via adjusted Cox regression hazard ratio.

Conclusions: HBS was a common complication after PTx and closely related to severity of HPT. At one year of follow up it was associated with continued prescription of higher doses of calcium and calcitriol. Consequences of this prolonged exposure to calcium and calcitriol could have deleterious systemic/vascular complications. Preoperative prophylactic calcitriol, prescribed in 91% of those who later developed HBS, was ineffective in preventing the appearance of this syndrome.

FR-PO297

Effects of Parathyroidectomy on Plasma Different Parathyroid Hormone Fragments Levels in CKD Patients
Nanning Wang1 Huimin Chen,1 Xiaoming Zha,2 Chang Ying Xing,2 1Department of Nephrology, The First Affiliated Hospital with Nanjing Medical University, Nanjing, China; 2First Affiliated Hospital of Nanjing Medical University, Nanjing, China.

Background: Intact parathyroid hormone (iPTH) measured by the second generation assays include not only (1-84)PTH, but also (7-84)PTH. Now the third generation PTH assays have been shown specific test for (1-84)PTH. Here we investigated the levels of (1-84)PTH, (7-84)PTH in stage 5 chronic kidney disease (CKD) patients, and evaluate the effects of parathyroidectomy(PTX) on above parameters in severe secondary hyperparathyroidism patients.

Methods: We included 252 CKD patients divided by baseline plasma iPTH levels. Thirty-one PTX patients were followed up with median time of 7.1 months. Serum iPTH and (1-84)PTH were measured by electrochemiluminescence immunoassay. (7-84)PTH levels were calculated by subtracting the (1-84)PTH values from the iPTH values. Ten PTX patients were followed up with median time of 7.1 months. Serum iPTH and (1-84)PTH were measured by electrochemiluminescence immunoassay. (7-84)PTH levels were calculated by subtracting the (1-84)PTH values from the iPTH values.

Results: Plasma iPTH, (1-84)PTH, (7-84)PTH levels were decreased closely with each other, while (1-84)PTH/PTH gradually reduced with upregulated iPTH levels. For CKD subgroups with plasma iPTH level>400 pg/mL, (1-84)PTH/PTH further decreased to 0.5(Fig1). After PTX, plasma different PTH fragments levels were decreased obviously and (1-84)PTH/PTH were increased in severe SHPT patients(Table 1).

Conclusions: PTX can diminish abnormal increased iPTH, (1-84)PTH,(7-84)PTH in stage 5 chronic kidney disease patients. Blood iPTH value may overestimate the severity of SHPT. Measurement of (1-84)PTH is suggested for accurate diagnosis and treatment in chronic kidney disease-mineral and bone disorder(CKD-MBD) patients.

Funding: Government Support - Non-U.S.
PTX can diminish blood PTH fragments levels and upregulate (1-84)PTH/iPTH in severe SHPT patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-PTX</th>
<th>Post-PTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPTH (ng/mL)</td>
<td>167±90 (5.7-3144)</td>
<td>67.9±41 (0.52-598)</td>
</tr>
<tr>
<td>(1-84)PTH (pg/mL)</td>
<td>77.9±95 (4.1-1015)</td>
<td>53.0±131 (0.29-996.9)</td>
</tr>
<tr>
<td>(7-84)PTH (pg/mL)</td>
<td>748.9±131.6 (9.1-2615)</td>
<td>179.5±141.5 (0.49-347)</td>
</tr>
</tbody>
</table>

*, compared with Pre-PTX group, P<0.001

Characteristics of bone markers and different PTH fragments grouped by baseline plasma iPTH values

FR-PO299

Bone Metabolism Markers, Epidemiological Profile, and Renal Function of HIV-Infected Patients before Initiating Antiretroviral Therapy: Mariana G. Paulina,1 Unai Tzupinb,2 Milena Guimarães,2 Nathalia S. Dea,2 Maria Goriatti M. Penido,2 Joao M. Penido,2 1 Federal University of Minas Gerais, Belo Horizonte, Brazil; 2 Pediatric Nephrology, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; 3 University of Porto Alegre, Porto Alegre, Brazil; 4 Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; 5 Federal University of Minas Gerais, Belo Horizonte, Brazil; 6 Federal University of Minas Gerais, Belo Horizonte, Brazil; 7 Federal University of Minas Gerais, Belo Horizonte, Brazil; 8 Federal University of Minas Gerais, Belo Horizonte, Brazil; 9 Federal University of Minas Gerais, Belo Horizonte, Brazil.

Background: The prevalence of bone disease in HIV-infected patients (HIV-IP) is high and there are few studies about bone metabolism in this population. The aim of this study was to describe the bone metabolism markers, epidemiological profile, and renal function of HIV-infected patients before initiating antiretroviral therapy (ART).

Methods: Transversal study with naive patients on ART, aged from 18 to 55 years of age, that underwent clinical evaluation, bone densitometry by DXA (lumbar spine L1-L4) and laboratory measurement: calcium, phosphorus, PTH, 25(OH)D, iPTH, and interleukin 1β (IL-1β) and 6 (IL-6) serum levels. The following statistically tests were used: Mann Whitney, Krukal-Wallis, and the Spearman correlation test. The CKD-EPI formula was used to evaluate the glomerular filtration rate.

Results: We evaluated 70 patients (57M) with median age of 33.8 years. 93% had more than eight years of schooling, 84% were working, 77% were single, and sexual transmission was 93%. The time to diagnosis ranged from 0.13 to 300 months. 51 patients underwent ART, and 9 had reduced bone mineral density (BMD) at lumbar spine, 3 at femoral neck and 5 at total femur. 58% of the patients had altered 25(OH)D; 21% had deficient serum levels and 37% had insufficient levels. There was no change in serum calcium, phosphorus, and PTH. The FGF23 correlated positively with calcium (r=0.358; p<0.017) and IL-6 (r=0.308; p=0.013). There was a significant difference in the FGF23 in relation to PTH, being higher in those who had normal PTH levels (p=0.025) and its relation to the femoral neck Z score, being higher in those with index z2 (p=0.035). 9.4% had CKD II.

Conclusions: The majority of the patients were young, professionally active, singles, and had HIV sexual transmission. Although they were young and naïve patients, 9.4% had compromised renal function and 8.5% of them had reduced BMD. There was a high prevalence of vitamin D deficiency/insufficiency, most likely because of early onset. The relationship between FGF23, PTH, BMD Z score and the correlation between FGF23 and calcium and IL-1β suggests that this phosphatonin could be considered an early marker of bone metabolism. More studies are needed to improve the follow up of bone metabolism and renal function, which are crucial and important in HIV patients.

FR-PO300

Validating Whole Genome Sequencing (WGS) as a Diagnostic Technique for Autosomal Polycystic Kidney Disease (ADPKD) Amali Mallawarachchi, Yvonne Hort, Sarah R. Senum, Ben Lundie, Jang Tae, Andre E. Minocche, Mark J. Cowley, John Shine, Peter C. Harris, Tim Furlong. 1 Garvan Institute of Medical Research, Sydney, NSW, Australia; 2 Mayo Clinic, Rochester, MN.

Background: ADPKD is the most common monogenic renal disease. There are hundreds of genetic diagnostic tools, including phenotyping and genetic testing. The most common genetic test is a diagnostic test.

Methods: We studied 42 unrelated patients with an ADPKD phenotype. Thirty patients initially underwent long-range PCR/Sanger sequencing and/or MLPA (LR-PCR/SS/MLPA) of PKD1 and PKD2 in 104 patients (28, 8, 8, and 8 in total). 66 blinded WGS was then performed after PCR-free library preparation (Kappa Hyper kit, HiSeqX; 150bp paired-end sequencing) in the Garvan Institute. Concurrently, 12 patients were initially sequenced via WGS and then blinded LR-PCR/SS/MLPA of PKD1 and PKD2 (Grp1). Blinded WGS was then performed after LR-PCR-free library preparation (Kappa Hyper kit, HiSeqX; 150bp paired-end sequencing) in the Garvan Institute. Concurrently, 12 patients were initially sequenced via WGS and then blinded LR-PCR/SS/MLPA of PKD1 and PKD2 (Grp2). Raw WGS data was analysed for single nucleotide and copy number variation via customized bioinformatics pipelines. WGS variant analysis was focussed on PKD1 and PKD2.

Results: WGS provided uniform coverage (mean 36x; range 24-47), including in homologous and GC-rich regions. The same results as LR-PCR/SS/MLPA were obtained in 40/42 patients (37 disease-causing variants; 3 patients unknown with both methods). However, in 2 patients, using standard methods of genetic testing, WGS did not detect mosaic patient, reanalysis of WGS data showed the variant in 8% of reads. WGS defined the breakpoints of 2 multi-exon deletions, which was not possible with prior methods. On initial analysis of Grp1, the disease-causing variant was confirmed in 24/30 patients. After adjusting the variant filtering stringency, it was improved to 28/30. There were no false positive or false negative results with WGS.

Conclusions: WGS provides the basis of a new diagnostic test for ADPKD. It avoids laborious sample preparation and overcomes pseudogene homology. Unlike targeted sequencing, WGS allows scope for broadened genomic analysis if no PKD1 or PKD2 variants are identified. This study highlights the value of validating next generation sequencing against a gold-standard cohort prior to diagnostic application.

Funding: Private Foundation Support
validated (20%) on a set of 100 abdominal MRIs (T2 weighted HASTE or TRUEFISP coronal sequences) of patients with PKD who had both kidneys and liver segmented manually. A test set of 60 patients was used to evaluate the performance of the developed automated method.

Results: TKV as well as TLV measured using the deep neural network correlated highly with manually traced TKV and TLV (ICC 0.996 and 0.994, resp.), with a bias and precision of -0.3%±4.6% for TKV and 2.5%±4.9% for TLV with maximal percentage differences observed being 8.5% and 11.2%, respectively. No proportional bias was observed, meaning that percentage differences between both methods are regardless of kidney or liver size.

Conclusions: This is the first fully automated segmentation method that measures individual kidney volumes, TKV and TLV almost as accurate as manual tracing, that has an inter-reader variability of 2.3%. The developed technique will facilitate future studies wherein automated and reproducible measurement of individual kidney volumes, TKV and TLV are needed to assess (i) disease severity, (ii) progression of the disease, and (iii) treatment response.

Funding: Other NIH Support - This work was supported by the National Institute of Diabetes and Digestive and Kidney Diseases under NIH Grant Award Number P30 DK090728 to the “Mayo Clinic Robert M. and Billie Kelley Pirnie Translational Polycystic Kidney Disease Center”, and the PKD Foundation under grant 206g16a, Government Support - Non-U.S.

FR-PO303
Association of Serum FGF23 and Klotho with Long-Term Renal Outcomes of Polycystic Kidney Disease (PKD) in the Consortium for Radiologic Imaging Studies of PKD (CRISP) Cohort
Mireille El Ters,1 Jason R. Stubs,2 Jonathan D. Mahnken,2 Darren P. Wallace,2 Alan S. Yu,2 1Mayo Clinic, Rochester, MN. 2The University of Kansas Medical Center, Kansas City, AL; University of Kansas Medical Center, Kansas City, KS.

Background: PKD is a slowly progressive disease leading to end-stage renal disease (ESRD). Levels of FGF23 are elevated in PKD out of proportion to kidney function, and circulating levels of its receptor, Klotho, decreased. Whether these are associated with long term renal outcomes is unknown.

Methods: CRISP is an observational cohort study of 241 PKD patients. Kidney function was serially measured with isotohalate clearance(\(\text{gFR}\)) and height-adjusted total kidney volume(\(\text{htTKV}\)) measured by MRI. Intact FGF23 and soluble Klotho were measured on 191 available baseline serum samples and dichotomized into high/low FGF23 groups (cutoff 50 pg/ml) and high/low Klotho groups (cutoff 1000 pg/ml). The association of baseline FGF23 and Klotho level with follow-up log\(\text{htTKV}\) and \(\text{gFR}\) was tested using linear mixed models with random intercepts and adjusted for age, gender and frazabul class. The risk of combined endpoint of ESRD and death was evaluated using a multivariable adjusted Cox proportional hazards model.

Results: Baseline serum FGF23 was 58±29 pg/ml and Klotho 918±925 pg/ml (mean ± SD). High FGF23 and low Klotho were both associated with higher baseline htTKV and lower baseline \(\text{gFR}\). Median follow-up was 13 years, during which 37 patients died or reached ESRD. High FGF23 was associated with faster growth of \(\text{htTKV}\) over the follow-up period and faster decline in \(\text{gFR}\) (adjusted mean slope -0.04 vs -2.21 ml/min/\(\text{y}\), \(p=0.0013\)). Low Klotho also was associated with faster increase in \(\text{htTKV}\) and faster decline in \(\text{gFR}\) (adjusted mean slope -2.97 vs -1.70 ml/min/\(\text{y}\), \(p<0.001\)). High serum FGF23 was associated with increased risk of ESRD/death (adjusted HR-2.4, \(p<0.004\)). Low Klotho was also associated with increased risk however not when adjusted for baseline \(\text{gFR}\) (Adjusted HR-0.4, \(p=0.14\) for Klotho).

Conclusions: Higher serum FGF23 and lower serum Klotho are associated with faster kidney growth and decline in renal function. Higher FGF23 was associated with increased risk of ESRD or death after adjustments for age, gender, frazabul class and baseline \(\text{gFR}\).

Funding: Other NIH Support - Frontier Grant (CTSA)

FR-PO304
Mineralocorticoid Antagonism and Vascular Function in Early Autosomal Dominant Polycystic Kidney Disease: A Randomized- Controlled Trial
Kristen L. Nowak, Berenice Y. Gitonner, Heather Farmer-Bailey, Wei Wang, Diana George, Michel Chonchol, Mikaela R. Malaczewski. University of Colorado Anschutz Medical Campus, Aurora, CO.

Background: Arterial dysfunction, featuring impaired vascular endothelial function and increased large-elastic artery stiffness, is evident early autosomal dominant polycystic kidney disease (ADPKD), and is an important predictor of cardiovascular events and mortality. Aldosterone excess has been implicated in the development of end-organ dysfunction are arterial stiffness. We hypothesized that aldosterone antagonism would reduce arterial dysfunction in patients with early-stage ADPKD.

Methods: In a randomized, controlled, double-blind trial, n=60 adults 30-55 years of age with ADPKD, normal kidney function (estimated glomerular filtration rate [eGFR] ≥60 ml/min/1.73 m\(^2\) ), and receiving the maximum tolerable dose of an angiotensin converting enzyme inhibitor were randomized to receive either spironolactone (titrated to maximum dose of 50 mg/day) or placebo for 6 months. The primary endpoints were changes in vascular endothelial function, measured as brachial artery flow-mediated dilation (FMD\(_{\text{BA}}\)) and arterial stiffness, measured as carotid-femoral pulse-wave velocity (CFPWV).

Results: Participants were 34±10 (means±SD) years of age, 53% female and 80% White, with an eGFR of 94±21 ml/min/1.73 m\(^2\). Spironolactone did not change FMD\(_{\text{BA}}\) (baseline: 8.0±5.5%, 6 months: 7.7±4.1%; placebo: baseline: 8.4±6.5%, 6 months: 7.9±4.3%; \(p=0.63\)), but reduced CFPWV (baseline: 640±127 cm/sec, 6 months: 4: 605±101 cm/sec; \(p=0.05\)) with no change in the placebo group (baseline: 659±138 cm/sec; \(p=0.09\)). Brachial systolic blood pressure (SBP) was also reduced in the spironolactone group (baseline: 124±13 mmHg, 6 months: 117±11 mmHg; \(p<0.05\)) with no change in the placebo group (\(p=0.50\)). Spironolactone also reduced brachial and carotid pulse pressure, carotid SBP, and carotid augmentation index (\(p=0.05\)), with no changes in the placebo group.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: Six months of aldosterone antagonism with spironolactone reduced arterial stiffness and SBP without changing vascular endothelial function in patients with early-stage ADPKD.

Funding: NIDDK Support

FR-PO305

Transplant Outcomes in Patients with Autosomal Dominant Tubulointerstitial Kidney Disease (AD-TKD) Sarah Cormican, Dervla M. Connaughton, Claire Kennedy, Katherine A. Benson, Gianpietro Cavalleri, Brenda Doyle, Anthony M. Dorman, Mark A. Little, Peter J. Lavin, Kendrah O. Kidd, Anthony J. Bleyer, Peter J. Conlon, Beaumont Hospital, Dublin 9, Ireland; 2Beaumont Hospital, Dublin 9, Co Dublin, Ireland; 3Boston Children's Hospital, Boston, MA; 4Queen's University, Belfast, Belfast, United Kingdom; 5RCSI, Dublin, Italy; 6Trinity College Dublin, Dublin, Ireland; 7Wake Forest School of Medicine, Winston-Salem, NC.

Background: ADTKD is a rare genetic cause of chronic kidney disease which causes progressive tubular atrophy and interstitial fibrosis with loss of renal function. Patients with ADTKD frequently progress to end stage renal disease (ESRD). Little is known about transplant outcomes in this group.

Methods: Patients with clinical characteristics consistent with ADTKD by the criteria outlined in the 2015 KDIGO consensus report were identified through the Irish kidney gene project. Clinical and history records were reviewed for patients who received a renal transplant during follow-up. We compared ADTKD transplant outcomes with those of 4004 non-ADTKD transplant recipients.

Results: 29 patients were identified; fifteen of whom had a known mutation (ADTKD-MUC1 n=9, ADTKD-MUC4 n=6). Eighteen patients met KDIGO criteria for diagnosis based on history and family history without an identified mutation (ADTKD- NON). Four patients received a second transplant during follow-up. In total 33 grafts (28 deceased donor, 5 living related donor) were included. 1-year, 5-year and 10-year graft survival for patients with ADTKD vs. non-ADTKD patients were: 100% vs. 90%, 87% vs. 78%, 79% vs. 69% respectively, -4.15 [-11.78, 0.08], -7.28 [-16.74, -2.68], and -10.76 [-19.33, -18.6] %/year (P=0.34). Nor did the rate of eGFR decline during the 1-year treatment differ significantly across CKD stages. G2-P=0.34). The rate of kidney growth during the 1-year treatment didn't differ significantly across CKD stages G2-G4. The median [IQR] of height adjusted kidney or liver were not different in age, and sex adjusted model. The most common findings were chronic allograft nephropathy (n=11) and acute rejection (n=10). Cyclosporin toxicity (n=2), polyoma virus nephropathy (n=1), acute tubular necrosis (n=1) and donor-related fibrosis (n=1) were also seen. Features suggestive of recurrent disease were not described. Fourteen grafts were lost during follow-up due to patient death (n=7), chronic allograft nephropathy (n=6) and polyoma-virus nephropathy combined with acute rejection (n=1).

Conclusions: In patients with ESRD due to ADTKD we demonstrate that transplant outcomes are comparable with the general transplant population. Increasing our ability to identify the responsible genetic mutation in each patient will allow screening of relatives who wish to donate but are potentially affected.

FR-PO306

Efficacy and Safety of Tolvaptan in Autosomal Dominant Polycystic Kidney Disease with Renal Insufficiency Masahiko Oguro,1 Junichi Hoshino,2 Masayuki Yamanouchi,3 Yoshifumi Ubara,4 None, Setagaya, Japan, 1Okinaka Memorial Institute for Medical Research, Tokyo, Japan, 2Toranomon Hospital, Kawasaki, Japan.

Background: A recent study demonstrated that tolvaptan slowed kidney volume growth and kidney function decline in autosomal dominant polycystic kidney disease (ADPKD) patients with creatinine clearance ≥60 ml per minute. However, tolvaptan’s efficacy in advanced chronic kidney disease (CKD) patients—especially those whose eGFR is <30 ml per minute—has remained unknown.

Methods: In this prospective cohort study, 54 patients with ADPKD who had eGFR>25 per minute and total kidney volume (TKV)≥750 ml were treated with tolvaptan. The primary endpoint was a change in TKV and eGFR over 1 year treatment with tolvaptan across CKD stages G2-G4. The secondary endpoint was the final dose of tolvaptan and proportion of tolerance at each CKD stage.

Results: The rate of kidney growth during the 1-year treatment didn’t differ significantly across CKD stages G2-G4. The median [IQR] of relative change in TKV in CKD stages G2, G3a, G3b, and G4 was, respectively, 5.70 [-0.67, 8.75], 6.66 [2.02, 17.66], 8.22 [5.97, 31.39], and 8.80 [4.12, 25.88] %/year (P=0.34). Nor did the rate of eGFR decline during the 1-year treatment differ significantly across CKD stages G2-G4. The relative annual change in eGFR—compared with the baseline eGFR—was, respectively, -4.15 [-11.78, 0.08], -7.28 [-11.17, -0.49], -7.02 [-16.74, -2.68], and -10.76 [-19.33, -18.6] %/year (P=0.59). Tolerance didn’t differ significantly across CKD stages G2-G4.

Conclusions: This analysis suggests that patients with advanced CKD stages—including G4—might benefit from treatment with tolvaptan as do patients with preserved kidney function.

Funding: Government Support - Non-U.S.

FR-PO307

Cerebrovascular Phenotype and Genotype Correlation in ADPKD: A Study in HOPE-PKD Hyun suk Kim,2 Hyunjin Ryu,2 Chung Lee,3 Jongho Heo,4 Curie Ahn,2 Yun Kyu Oh.3 1Department of Internal Medicine, Boramae Medical Center, Seoul, Republic of Korea; 2Seoul National University Hospital, JongNo-Gu, SEOUl, Republic of Korea; 3Samsung Genome Institute, Seoul, Republic of Korea; 4JW LEE Center for Global Medicine, Seoul, Republic of Korea.

Background: Cerebral aneurysm occurs in ADPKD (autosomal dominant polycystic kidney disease) by about 20% in the subjects older that 60 years. The current study aimed to define phenotype characteristics of aneurysm, confirm the familial clustering effect and analyze the genetic differences in aneurysm vs. no-aneurysm subjects in ADPKD.

Methods: Patients registered at the HOPE PKD cohort from October, 2009 to October, 2016 were included. Presence or absence of cerebral aneurysm and renal progression was reviewed, and PKD1/2 gene screening by targeted exome sequencing was performed. According to the presence or absence of cerebral aneurysm, the familial clustering effect was investigated and the proportions of PKD1 protein truncating (PT) mutations, PKD1 non-truncating (NT) mutations, PKD2, and no candidates (NC) were analyzed.

Results: A total of 398 families (n=538) were divided into aneurysm (n=131) or no-aneurysm group (n=407). In the aneurysm group, males were less prevalent (36.6% vs. 49.9%, P=0.10) and the mean age was significantly older (56.4 years vs. 50.2 years, P<0.01). Similarly, females were prone to SAH events or intervention (n=21[72.4%]). The proportion of high risk group (Mayo classification 1C, 1D, and 1E) or ESrd, the median [IQR] of height adjusted kidney or liver were not different in age, and sex adjusted model. The family clustering effect adjusted for age and sex was significant in multilevel logistic regression model (P<0.012). However, the prevalence of PT, NT, PKD2, NC was not correlated with aneurysm. Four years later, aneurysm occurred in 16.1% (31/192, median follow up 5.3 year) of the people who had not had it. The transmembrane domain was less related to occurrence of aneurysm.

Conclusions: Brain MRA is recommended at least every 4 years; every 3 years preferred for subjects with no aneurysm. The effect of PKD1/2 gene type was not observed.

FR-PO308

Identifying ARPKD Patients at Risk for Dialysis in the First Year of Life – Data from the International Registry Study AREgPKD Kathrin Burgmaier,1 Ismail Dursun,2 Kevin Kunzmann,3 Bruno Ranchin,4 Rukshana Shroff,5 Dorota Wichler,6 Elke Wuehl,7 Franz S. Schaefer,8 Max Liebau,4,6 1Department of Nephrology, London, United Kingdom; 2The Children's Memorial Health Institute, Department of Medical Genetics, Warsaw, Poland; 3University Hospital Cologne, Cologne, Germany; 4University of Heidelberg, Heidelberg, Germany; 5Université de Lyon, Lyon, France; 6Center for Molecular Medicine, University of Cologne, Cologne, Germany; 7Erciyes University, Kayseri, Turkey. Group/Team: For AREgPKD consortium.

Background: Autosomal recessive polycystic kidney disease (ARPKD) is a severe disease of early childhood and an important reason for renal replacement therapy in the first year of life. Yet, ARPKD shows pronounced phenotypic variability, making pre- and perinatal counseling challenging. Risk markers for the need of dialysis in the first year have not been established for ARPKD patients.

Methods: We studied the clinical courses of 385 patients from 18 countries included in the international ARPKD registry study AREgPKD using the time-to-event endpoint 'start of renal replacement therapy' and multivariate Cox regression.

Results: 36 patients started dialysis in the first year of life (median age at start of dialysis 0.14 years (0.00-0.91 years)). 30 children started peritoneal dialysis (PD), no patient underwent transplantation. Four patients deceased postnatally due to respiratory failure without onset of dialysis. Oligo/anhydramnios, enlarged prenatal kidney volume, high standardized birth weight and low 10-min APGAR score were associated with
an increased risk of dialysis need. Perinatal assisted breathing was associated with a marked reduction in the time to the first transplant. Linear regression and learning curve analyses were used to assess the association between the rate of dialysis and subsequent kidney function decline. Analyses were adjusted for age, sex, race, randomization group, systolic blood pressure and urinary albumin excretion.

Results: The mean age of included subjects was 40 ± 10 years and eGFR was 62 ± 27 ml/min/1.73m². In cross-sectional analysis stratified by the median level, higher LnP1-6L-6 was significantly associated with higher eGFR in both fully adjusted model (β = -6.315, 95%CI -10.517,-2.109; p < 0.003). In longitudinal analysis, higher circulating IL-6 in baseline was independently associated with a greater decrease in eGFR in the fully adjusted model (β = -10.207, 95% CI -11.315,-9.10; p < 0.0001).

Conclusions: Inflammation indicated by higher IL-6 level at baseline predicts kidney function decline. This suggests that measurement of serum IL-6 or other inflammatory markers at baseline may represent a predictive biomarker of kidney disease progression in ADPKD. Future validation of IL-6 as a biomarker of ADPKD progression in additional cohorts will be necessary to confirm these results. Funding: NIDDK Support, Private Foundation Support

FR-PO311

Clinical Diagnosis of Senior Loken Syndrome in a Patient with SDCCAG8 Mutation Genetically Diagnosed as Having Bardet-Biedl Syndrome

Yuko Fuji,1 Akira Ashida,2 Hideki Matsumura,3 Akihiko Shirasu,1 Satoshi Yamazaki,1 Hyogo Nakakura,4 Naoya Morisada,5 Kazumoto Iijima,6 Motoshi Hattori,7 Hiroshi Tanaka,8 Pediatrics, Osaka Medical College, Osaka, Japan; 2Pediatric Nephrology, Osaka Medical College, Osaka, Japan; 3Pediatrics, Tokyo Women’s Medical University, Tokyo, Japan; 4Pediatrics, Kobe Univ. Graduate School of Medicine, Kobe, Japan.

Background: Both Senior Loken Syndrome (SLS) and Bardet-Biedl Syndrome (BBS) are ciliopathies. SLS is characterized by retinitis pigmentosa (RP) and familial nephropathies, leading to end-stage kidney disease. BBS is characterized by six major symptoms: RP, polydactyly, obesity, genital abnormalities, learning difficulties, and renal defects. SLS and ciliopathy have been diagnosed according to phenotypes, but now it is often diagnosed by genetic testing using techniques such as next-generation sequencing. Here we describe a patient who was clinically diagnosed as having SLS but in whom genetic testing indicated BBS.

Methods: The patient was diagnosed as having RP at the age of six years. She had learning disability, proptosis and dyslipidemia, but no polydactyly. When she was eight years old, she was diagnosed as having chronic kidney disease, anemia, and liver dysfunction. Kidney and liver biopsy revealed renal tubule cysts, tubule membrane disruption, and liver fibrosis. Therefore, SLS was diagnosed but no mutation in NPHP1 was detected. Periocular diastasis was started at the age of nine years, and the patient underwent kidney transplantation with a graft from her father at the age of fourteen years. At the age of twenty years, she again underwent genetic testing for most of the mutations associated with ciliopathy. This revealed that she had a homozygous mutation in intron 11 of the SDCCAG8 gene which had caused a frameshift mutation.

Results: Conclusions: SDCCAG8 is known to be one of the causative genes related to SLS and BBS without polydactyly. The fact that the patient had learning disability, proptosis and dyslipidemia suggested a high probably of BBS. Although these symptoms are not specific, she did not have the typical symptom of BBS including polydactyly. Therefore, a definitive diagnosis of BBS was difficult without any information concerning genetic mutation. As only a few cases of SDCCAG8 mutation have been reported until now, accumulation of further cases will help to clarify the characteristics of the phenotype of SDCCAG8 mutation, thus contributing to the better management of patients with ciliopathy.

FR-PO312

Reversibility of Serum Creatinine Elevation Observed in ADPKD Subjects Receiving the Tyrosine Kinase Inhibitor Tesevatinib

David A. Eiznhamer,1 Anjay Rastogi,2 Michel Chon chol,3 Ashraf El-Meawey,4 Theodore I. Steinman,5 Karin Herrera,6 Olivier Schueler,7 John L. Ryan,8 Pablo E. Pergola,2 Kadmon Corporation, LLC, Cambridge, MA; 3 UCLA Medical Center, Los Angeles, CA; 4 University of Colorado, Aurora, CO; 5University of Colorado at Denver, Anschutz Medical Campus, Aurora, CO; 6University of Colorado Denver, AMC, Aurora, CO; 7University of Colorado: Anschutz Medical Campus, Aurora, CO; 8University of Kansas Medical Center, Kansas City, KS; 9University of Pittsburgh, Pittsburgh, PA.

Background: The KD019-101 trial has evaluated the safety and preliminary efficacy of tesevatinib in patients with ADPKD. Preliminary data suggested that subjects with ADPKD receiving tesevatinib experienced elevations of serum creatinine without concomitant elevations of cystatin C. Pre-clinical laboratory investigations determined that tesevatinib inhibited the human multidrug and toxin extrusion transporters MATE1 and MATE2-K (IC50 ~ 80mM and 68mM, respectively). This inhibition could result in increased serum creatinine in the absence of decrease in kidney function, due to the reduced tubular secretion of creatinine.

Methods: In an additional cohort of Study KD019-101 enrolled subjects with eGFR ≥ 100mL, serum creatinine concentrations were measured at baseline and at weeks 4, 12, and 24 of treatment. The proportion of patients with an increase in serum creatinine > 25% at any time point was determined.

Results: Among 10 patients (6 males/4 females) enrolled, serum creatinine levels began to increase in all patients during the first 4 weeks of 50 mg QD tesevatinib treatment. During, and for 4 weeks after the drug holiday, subjects returned to the clinic weekly to confirm creatinine and cystatin C measurement.

Conclusions: Serum creatinine elevation observed in ADPKD patients receiving tesevatinib was reversible.
decrease after 14 days of drug holiday and continued to decrease to baseline levels after 4 weeks of drug holiday. Resumption of drug resulted in similar increases as seen initially. Serum cystatin C levels were variable and did not show a pattern of increase before, during, or after the drug holiday period.

**Conclusions:** Serum creatinine elevations following tsevatinib dosing in patients with ADPKD are reversible upon cessation of dosing, and do not appear to result in a meaningful alteration in kidney function. This provides support for the hypothesis that serum creatinine elevation is a consequence of drug transporter inhibition resulting in the reduced tubular secretion of creatinine.

**Funding:** Commercial Support - Kadmon Corporation, LLC

---

**FR-PO313**

First Year Follow-Up Data from the German ADPKD Tolvaptan Treatment Registry – AD(H)PKD

M. Rivera, Roman-Uriel Muñoz,1 Franziska Grundmann,1 Polona Todorova,1 Katie McDonnell Burkert,2 Claudia Wöste,3 Volker R. Burst,4 Thorsten Persigehl,5 Bernhard Schermer,1 Thomas Benzing1

Department of Internal Medicine, Renal Division; University of Cologne, Cologne, Germany; 2University of Cologne, Cologne, Germany; 3Department of Radiology, University Hospital Cologne, Cologne, Germany.

**Background:** Admission of Tolvaptan in Europe by the EMA as the first targeted therapy of autosomal-dominant polycystic kidney disease (ADPKD) based on the findings of the TEMPO 3:4 trial is a milestone in the treatment of this disease. After the significant benefit on GFR in TEMPO 3:4 and 4-4 more data on this therapy regarding crucial questions in the real-life setting would be highly valuable. How do patients accept the treatment taking into account polyuria? Is the target dose reached? What side effects occur? How is the effect regarding kidney function and volume? Which patients are selected for treatment? How does Tolvaptan affect quality of life? How good is the adherence to the therapy?

**Methods:** In order to answer these questions we established the multicentric German AD(H)PKD registry. Patients that are generally eligible for Tolvaptan, independent of whether actually taking the drug or not, can be included in this observational study. Blood values, kidney volume from imaging data, indicators of quality of life, adherence to therapy, the actual dose administered, genotype and data regarding extrarenal manifestations, comorbidity, side effects and complications are documented. After enrolment patients are followed-up in yearly visits for ten years.

**Results:** We have been able to recruit more than 270 ADPKD patients so far and have started the first-year follow-up visits at the end of 2016. Consequently, analysis of this cohort allows for the first characterization of parameters presented for evaluation regarding the selection criteria on the one hand and the other hand the first-year data provide an interesting insight into which patients were selected for treatment and sheds light on dosing strategies. Furthermore, adherence to therapy and the impact on quality of life are analyzed.

**Conclusions:** The AD(H)PKD-registry provides the first comprising dataset on the German cohort of ADPKD patients eligible for treatment with Tolvaptan and analyzes the selection criteria applied by German nephrologists as well as tolerability, side effects and impact on other kidney-related outcomes. Follow-up of this cohort will provide valuable data that can help in counseling patients and informing physicians dealing with this novel treatment opportunity.

**Funding:** Commercial Support - Otsuka Pharmaceuticals

---

**FR-PO314**

Diagnosis of Renal Cyst Infection in Adult Polycystic Kidney Disease (ADPKD) Using 67-Gallium Citrate SPECT/CT: A Case Series

Esther Casillas,1 Víctor Burguera,2 Haridhan Sosa Barrios,2 María Delgado yagüe,2 María Eugenia Rioja garcia,2 Laura V. Blanco,2 Maite Rivera,3 Hospital Universitario Ramon y Cajal, Madrid, Spain; 4Nephrology, Hospital Universitario Ramón y Cajal, Madrid, Spain.

**Background:** Renal cyst infection in ADPKD patients is challenging, as it can be the source of life-threatening sepsis and frequently lack localizing symptoms. Recent guidelines established that intracystic material compatible with infection should be obtained for definite diagnosis. Gold standard imaging to do so is PET/CT, which is expensive and restrained to certain centers. We sought to determine whether 67-Gallium-citrate scintigraphy is a valuable and inexpensive alternative to orientate renal cyst infection in these patients.

**Methods:** Between January 2015 and January 2016 (both included), five patients with ADPKD diagnosis presented in our center with kidney cyst infection. 3 were female and 2 male with a mean age of 50.4 ±7 years (range 32-72 years). Two patients were on renal replacement therapy (one HD and one PD), one had a functioning renal transplant and the remaining two had CKD. The most frequent presenting symptoms of cyst infection were fever or abdominal pain.

**Results:** Ultrasound (US) scanning of both kidneys was done in 4 patients (80%) and computed tomography (CT) in all of them. US was compatible with infected cyst in one patient (sensitivity of 33%) and CT in two patients. 67-Ga-citrate SPECT/CT was positive in all patients (90%) and true negative in 1, proving better sensitivity (100%) and specificity than US and CT. During follow-up, we used 67-Ga-citrate scintigraphy in those patients with initial positive results treated to assess resolution and decide whether antibiotics should be discontinued. Two patients (50%) showed persistent tracer uptake despite a complete course of appropriate antibiotics for 6 weeks.

**Conclusions:** 67-Ga-citrate SPECT/CT is a non invasive and inexpensive study available in most centers. It can be used in all ADPKD patients with suspected renal cyst infection regardless of kidney function, being more cost-effective than PET/CT. Due to demonstrated potential as a diagnostic tool in this setting, we think it could be considered as an alternative to the PET/CT.

---

**FR-PO315**

Urinary L-Type Fatty Acid-Binding Protein (L-FABP) Reflects the Progression of Autosomal Dominant Polycystic Kidney Disease

Hiteru Shigeo,1 Masatoshi Masuda,2 Steffen Neuber,3 Satoru Muto,4 Tadashi Okada,1 Carsten Bergmann3,4 Advanced Informatics for Genetic Disease, Juntendo University, Tokyo, Japan; 5Otsuka Pharmaceutical Co., Ltd., Osaka, Japan; 6Center for Human Genetics, Bioscientia, Ingelheim, Germany.

**Background:** Autosomal dominant polycystic kidney disease (ADPKD) is a common inherited progressive kidney disease. Although some imaging modalities, such as ultrasonography, CT or MRI, are useful for diagnosing and staging ADPKD, these modalities are not adequate for monitoring the severity of ADPKD because the modalities detect cyst formation, but not tubulointerstitial inflammation and fibrosis. The aim of this study is to elucidate that urinary L-type fatty acid binding protein (L-FABP) is associated with the severity of ADPKD.

**Methods:** Male PCK-Crl/Crl-Phk1pc/Crl (PCK) rats (n=21), of which features are similar to human ADPKD, were used as the ADPKD model. Age and gender-matched Sprague-Dawley rats (n=21) were used as control. Serum, urine, kidneys were obtained at 8, 12 and 16 weeks of age. Serum creatinine, serum L-FABP, urinary L-FABP, urinary KIM-1, urinary NGAL and urinary creatinine were measured.

**Results:** Serum creatinine and serum L-FABP levels in PCK rats were similar to those in the control rats. Cystic enlargement and progression of both tubulointerstitial inflammation and fibrosis along with age were observed in the PCK rats. Urinary L-FABP levels increased along with the severity of renal pathology, and the levels at 12 and 16 weeks in the PCK rats were significantly higher than in the control rats. Although urinary KIM-1 and urinary NGAL levels at 8, 12 and 16 weeks in the PCK rats were significantly higher than in the control rats, these levels did not increase along with the progression of renal pathology including the degree of cystic enlargement in the PCK rats.

**Conclusions:** Urinary L-FABP reflects not only the degree of cystic enlargement, but also the progression of tubulointerstitial damage and, therefore, may be useful for monitoring the progression of ADPKD.

---

**FR-PO316**

Pharmacogeneomics of Tolvaptan’s Inhibitory Effect on Kidney Volume Increase in Patients with Autosomal Dominant Polycystic Kidney Disease

Shigemi Shiro,1 Masatoshi Masuda,2 Steffen Neuber,3 Satoru Muto,4 Tadashi Okada1, Carsten Bergmann3,4 Advanced Informatics for Genetic Disease, Juntendo University, Tokyo, Japan; 5Otsuka Pharmaceutical Co., Ltd., Osaka, Japan; 6Center for Human Genetics, Bioscientia, Ingelheim, Germany.

**Background:** We investigated the influence of genetic factors on tolvaptan treatment efficacy in patients with approved autosomal dominant polycystic kidney disease (ADPKD).

**Methods:** In the extension study of TEMPO 3:4 in Japan, DNA was collected from 100 patients. Germline variants of 116 genes (including all genes known for cystic/polycystic kidney disease) were sequenced by targeted next generation sequencing and called with a custom variant analysis pipeline sensitive for variants in sequence homology regions. Genetic architecture of samples was modeled as binary factor, discriminating those samples carrying solely PKD1 or PKD2 pathogenic variants from samples that harbored additional likely pathogenic variants in any of the other 114 targeted genes. Kidney volume growth rate was used as a marker for tolvaptan efficacy. A two-way factorial ANOVA was applied to test for a correlation between genetic architecture, treatment/placebo group and treatment efficacy as outcome.

**Results:** Sixty percent of our samples demonstrated multiple likely pathogenic variants in non-PKD genes. Statistical analysis revealed a significant main effect of...
PKD2 may potentially affect the efficacy of tolvaptan in patients with ADPKD. We hypothesize that tolvaptan may be more effective in patients with modifier pathogenic variants. Significant difference between NMD vs. other mutation classes (P=0.001) and PKD1 PT+Indel vs. PKD2 (P=0.043).

FR-PO317
Assessing Rapid ADPKD Progression in Clinical Practice in the Era of Tolvaptan. Monica Furlano,1 Teresa Martín,2 Irene Loscos Giménez,3 Gemma Bullich Villanueva,1 Jose Ballarin,4,5 Elisabet Ars,1 Roser Torra,4,5 1Molecular Biology, Fundación Puigvert, Barcelona, Spain; 2Radiology, Fundación Puigvert, Barcelona, Spain; 3Universitat Autònoma de Barcelona, Barcelona, Spain; 4Nephrology, Fundación Puigvert, Barcelona, Spain.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most frequent inherited kidney disease. The progressive cyst growth, together with interstitial damage causes progressive kidney failure but the severity of the diseases varies a lot among affected individuals. The EMA has approved tolvaptan for adults with CKD stage 1-3 at baseline who are rapid progressors (RP). Being the mean age in Europe of onset of ESRD for ADPKD patients 58 years, the ERA-EDTA WKGID/EBPG recommended to consider RP those patients predicted to reach ESRD before 58 years of age.

Methods: Among 297 ADPKD patients followed up in an outpatient clinic for inherited kidney diseases were assessed for rapid progression according to the EDTA-ERA WKGID/EBPG recommendations. Only patients between 18-50 years of age were considered. Assessment was only indicated when eGFR was over 45ml/min and eGFR for patients 30-40 years old was below 90ml/min and for those 40-50 years old was below 60 ml/min. If the patients met these eGFR according to age, retrospective eGFR decline was assessed; if it was > 5 ml/year or >2.5 ml/year for 3 consecutive years patients were considered RP. For those who didn’t meet the retrospective eGFR criteria ultrasound (US) diagnosis was assessed. Patients younger than 45 with a renal diameter >16.5 cm were considered RP. For those not fulfilling any of the above criteria total volume TKV by MRI was measured and the Mayo ADPKD calculator was applied. Patients class 1,C,D,E were considered RP. Finally for patients younger than 35 with hypertension or urinary symptoms than did not met the above criteria genetic testing was performed and the PROPKD score was applied.

Results: The step by step process of RP assessment based on the EDTA-ERA/EBPG recommendations proved to be cost-effective and sensitive to identify RP. RP was identified in 16.5% of patients with CKD stage 1, 29% in CKD2 and 34.3% in CKD3a. 53.8% of patients aged 18-30 were rapid progressors while this number decreased with age: 30.9% from 31-40 years and 13.5% from 41-50 years.

Conclusions: The multi step algorithm provided by the EDTA-ERA/EBPG is useful to identify RP that would benefit from tolvaptan treatment. The use of the algorithm is cost-effective and fairly easy to incorporate into clinical practice.

Funding: Government Support - Non-U.S.

FR-PO318
Total Kidney Volume (TKV) by Ellipsoid (EL) versus Manual Segmentation (MS) for Risk Classification in Autosomal Dominant Polycystic Kidney Disease (ADPKD): A Comparative Study. Beili Shi,1 Marina PouraFakari,1,2 Ioan-Andrei Iluitta,1 Elsa Guizard,1 Crystal F. Quist,1 Xuewen Song,2 Korosh Khalili,2 York P. Pei,1 1Division of Nephrology, University Health Network and University of Toronto, Toronto, ON, Canada; 2Department of Medical Imaging, University Health Network and University of Toronto, Toronto, ON, Canada.

Background: TKV derived by EL is technically simple, less laborous, and used in the Mayo Clinic Risk Classification (MCR). However, it is less accurate than MS ("gold standard") and can result in risk misclassification. Our study aims to define the disagreement in TKV measurement and its resultant risk misclassification by EL vs. MS.

Methods: A single center study of 409 consecutive PKD patients who underwent standardized MRI and genetic testing between 4/2011 and 2/2017. TKV by EL and MS will be measured in all patients by a single radiologist. Bland-Atman plots are used to assess agreement.

Results: Of 203 patients who completed analyses, 33 (16%) with atypical imaging patterns were excluded. The clinical characteristics of the remaining patients are shown in Table. The MC risk classes significantly correlated with distinct mutation classes (X2=48, P<0.001, Figure 1). We found >20% disagreement in 11.2% of individual kidney volume and 5.3% of TKV, resulting in misclassification of 24 (14.1%) patients. None of the misclassified cases spanned more than one risk category.

Conclusions: Our preliminary results suggest that TKV measured by EL in a standardized setting did not result in a high rate of risk misclassification of serious clinical consequence.

Funding: Government Support - Non-U.S.
FR-PO320
Decreased Urinary Citrate Excretion Associates with Disease Severity in Autosomal Dominant Polycystic Kidney Disease Arlene B. Chapman,1,2 Bharathi V. Reddy,3 Matthew Lanktree,4 Chengli Shen,5 Vicente E. Torres,3 Michal Mrgu,6 Frederic F. Rahbari-Oskoui,7 Alan S. YU,8 William M. Bennett,2 Peter C. Harris,1,9 Kyoungtae T. Bae,1,4 Doug Landsittel,1,10 Emory University School of Medicine, Atlanta, GA; 1,2 Legacy Good Samaritan Medical Center, Portland, OR; 3,4 Mayo Clinic, Rochester, MN; 5,11 None, Dondas, ON, Canada; 6,12 University of Alabama at Birmingham, Birmingham, AL; 7,13 University of Chicago, Chicago, IL; 8,14 University of Kansas Medical Center, Kansas City, KS; 15 University of Pittsburgh, Pittsburgh, PA.
Background: Autosomal dominant polycystic kidney disease (PKD) is characterized by increased cyst burden measured by total kidney volume (TKV) and loss of kidney function. Urinary citrate excretion (UCE), known to be decreased in PKD associates with complications of disease including nephrolithiasis and urinary acidification deficits. In the observational longitudinal Consortium for Radiologic Studies in Polycystic Kidney Disease (CRISP), 24 hour UCE was measured annually during the first three years of study. We postulate that decreased UCE is an independent marker of disease severity in PKD and associates with genotype, increased TKV, decreased eGFR and decreases over time.
Methods: 224 of 241 participating CRISP subjects with baseline creatinine clearance > 70 ml/min had 24 hr UCE as well as DNA, TKV and corrected creatinine clearance (CIC) measurements completed in a Clinical Research Center setting. Results: UCE correlated inversely with TKV (r=-0.26, P<0.001) and directly with CIC (r=0.16, P<0.02). Irazabal Class 1A (n=14) had greater UCE (635±227 mg/day) than Class 1C (n=68, 449±241 mg/day, P=0.03), 1D (n=54, 452±295 mg/day, P<0.02) or 1E (n=35, 393±198 mg/day, P<0.008). UCE was significantly lower in PKD1 vs PKD2 patients (276±269 vs.80.2±253 mg/day, P<0.01) No differences (P>NS) were seen in UCE between PKD1 truncating and non-truncating mutations (275±211 vs 278±289 mg/day). UCE decreased 19.1 mg/day/year over 3 years (P<0.03), and significantly declined in PKD1 patients only. A forward linear regression selection method with an entry criteria of p=0.1 demonstrated that PKD1 genotype, urine volume, TKV and age, associated negatively with baseline UCE, while increasing sodium excretion, CIC and male gender associated with UCE. When baseline UCE was combined with TKV, area under the receiver operator characteristic curve for predicting CKD stage 3 in 8 years was 0.83. Conclusions: TKV and CIC associate with decreased UCE early in PKD. Reductions in UCE in PKD1 patients showed no difference between truncating and non-truncating mutations. Decline in UCE occurred over three years and UCE may be a biomarker that associates with disease severity and progression in PKD.
Funding: NIDDK Support
FR-PO321
Patient-Reported Disease Burden in Autosomal Dominant Polycystic Kidney Disease (ADPKD) Using the ADPKD Pain and Discomfort Scale (ADPKD-PDS) and ADPKD Impact Scale (ADPKD-IS) Dorothee Oberdörfer1, Siddhesh Kamat,1 Alexis Denay2,1 Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ; 1PKD Foundation, Kansas City, MO.
Background: ADPKD is an inherited disease leading to kidney enlargement, worsening of kidney function, and quality of life impacts. The objective of this research is to describe patient-reported pain, discomfort, and disease impact using two new questionnaires.
Methods: 2,353 ADPKD patients (age ≥18 years) were invited to participate in a survey. Assessments included: ADPKD-PDS measuring severity and impact of dull pain (chronic ache), sharp pain (acute), and discomfort (chronic fullness/pressure) over the last 7 days via 20 items, and ADPKD-IS measuring physical, emotional, and fatigue impact over the last 2 weeks via 18 items. Age, gender, ethnicity, chronic kidney disease (CKD) stage, and time since ADPKD diagnosis were collected.
Results: For 289 qualified respondents mean age was 48.8 years (SD ±12.3), 80.2% were female, and CKD stage broadly distributed: CKD Stage 1 (27.3%), CKD Stage 2 (21.1%), CKD Stage 3 (30.4%), CKD Stage 4 (11.4%), CKD Stage 5 (9.6%). Mean Scores for ADPKD-PDS and -IS are reported in the table below.
Conclusions: Patient burden starts early in disease with differentiation between CKD stages. Results follow clinically expected patterns where events triggering sharp pain (eg, cyst burst/infection) are rare and intermittent but chronic pain is more constant due to disease progression. Clinical significance of these scores needs further evaluation.
Funding: Commercial Support, Otsuka Pharmaceutical Development & Commercialization, Inc.
FR-PO322
Peritoneal Dialysis in Pediatric ARPKD Patients Aziz Akarkach,1 Kathrin Ebner,1 Anja C. Sander,2 Franz S. Schaeffer,2 Max Liebau,2 3University Hospital of Cologne, Cologne, Germany; 4Center for Molecular Medicine, University of Cologne, Cologne, Germany. Group/Team: For IPPN consortium.
Background: Autosomal recessive cystic kidney disease (ARPKD) is associated with dialysis-requiring end stage renal disease in about 40-50% of patients during childhood and adolescence. Many ARPKD patients receive peritoneal dialysis (PD) but structured data on PD in pediatric ARPKD patients is missing.
Methods: We identified ARPKD patients in the international pediatric peritoneal dialysis network (IPPN) registry and compared their clinical courses and PD-specific parameters to two control groups suffering from other renal disorders (CAKUT, Congenital Nephrotic Syndrome). Cohorts were matched for age and time on dialysis. Results: 79 ARPKD patients were identified and matched to CNS (n=79) and CAKUT (n=158) patients. Mean age at inclusion into the IPPN registry was 4.38 years in the ARPKD group vs 4.33 years (CNS) and 4.40 years (CAKUT), respectively. Mean time on dialysis at inclusion was 1.01 years (ARPKD) vs. 0.77 years (CNS) and 1.00 years (CAKUT). Mean observation time within the frame of the registry was 14.6 months (ARPKD) vs. 11.2 months (CNS) and 13.2 months (CAKUT). There were no major differences in basic anthropometric data (height, weight, BMI) or general PD parameters (e.g. PD modality, applied PD fluids, fluid turnover per day, average glucose concentration), but ARPKD patients had regimes with lower overall fill volumes and more cycles than CNS- or CAKUT-patients. First longitudinal observations suggest that overall technique survival as well as the peritoneal rate in ARPKD children on PD do not show major differences compared to patients with other underlying disease entities.
Conclusions: Overall, children with ARPKD in this cohort do not show major dialysis-associated differences when compared to two age-matched pediatric PD control groups suggesting that PD can be applied in the same way as for children with other underlying renal disorders.
Funding: Private Foundation Support
FR-PO323
Frequent Genetic Variants in Autosomal Dominant Tubulointerstitial Kidney Disease Eric G. Olinger,1 Celine Schaeffer,1 Kendrah O. Kidd,2 Daniel G. Fuster,3 Andreas D. Kistler,4 John Sayer,5 Anthony J. Bleyer,6 Luca Rampoldi,7 Olivier Devuyst,81 Anja C. Sander,2 Andreas C. Friedrich,1 1Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ; 2PKD Foundation, Kansas City, MO; 3University Hospital of Bern, Bern, Switzerland; 4University of Zurich, Zurich, Switzerland; 5Wake Forest University School of Medicine, Winston-Salem, NC; 6Cantonal Hospital Frauentalen, Frauenfeld, Switzerland; 7Institute of Genetic Medicine, Newcastle, United Kingdom.
Background: An increasing number of purported pathogenic genetic variants are detected as relatively common in exome data from the general population, suggesting previous misclassification. Mutations in UMOD cause autosomal dominant tubulointerstitial kidney disease (ADTKD) that is rare (~1-10/100000), well indexed and has genetic features (private mutations, complete penetrance) making it paradigmatically suited to address the evolving distinction between normal genetic variation and pathogenic variants.
Methods: Reported UMOD mutations from our ADTKD registry were retrospectively compared to sequencing data from gnomAD (http://gnomad.broadinstitute.org). Matching variants were tested by cellular studies and segregation analysis.
Results: Based on then-available filtering strategies, 107 UMOD variants were reportedly associated with ADPKD in ADPKD registries from 20 registries from 20 countries. Two of them are reported in gnomAD: p.T62P (AF 0.00034) and p.T469M (0.00070). An allele frequency of ~5x10^-5 would be expected based on the disease prevalence and the number of reported mutations. The p.T62P and p.T469M variants have been previously linked to ADTKD and the former was also found in 9 and 2 unrelated CKD patients. Fleeting family history in our registry, T62 lacks any evolutionary constraint and trained classifiers (eg. PolyPhen-2) predict a benign to possibly damaging phenotype for p.T62P. T469M is a conserved residue and p.T469M is predicted to be damaging. Expression studies in kidney cells in culture showed no obvious functional defect for p.T62P and p.T469M, as opposed to the well-established mutation p.C150S. Furthermore, the p.T62P variant does not segregate with disease, including several aged carriers with absent kidney disease.

Conclusions: The high frequency of 2 imputed variants in UMOD led us to reexamine the molecular diagnosis of several ADTKD families in our registry and to definitively inform the pathogenicity of UMOD p.T62P. With evolving sequencing data, careful curation of implausibly common variants in Mendelian diseases other than ADTKD is warranted.


Background: In Japan, more than 3000 patients with autosomal dominant polycystic kidney disease (ADPKD) have received Tolvaptan therapy at present, and its averaged clinical efficacy is proposed to be aproximately 50%. Here, we reported the clinical efficacy of Tolvaptan in our facility, and refer to the clinical features shown in the highly effective patients.

Methods: ADPKD patients with Tolvaptan therapy who have received follow up - SC clinical assessments during 18 months after the initiation of the Tolvaptan therapy were retrospectively reviewed.

Results: Mean age, number of male, median value of total kidney volume (TKV), median value of kidney growth rate (KGR) and mean eGFR at the start of the therapy were 45.4±14.7 years-old, 18 cases (78.8%), 1478.3±548.6 mL, 5.4%/year, and 50.9±18.5 mL/min, respectively. After one year Tolvaptan therapy, TKV and KGR were reduced to 1306.5±3.7 mL and 3.7%/year, and 17 of 23 cases (73.9%) showed reduced TKV (KGR<0%) by one year Tolvaptan therapy. When all cases were divided into four groups by the quartile value of KGR, and the 1st quartile group (1-QG, most effective, median KGR -16.3%/year) was compared to 4-QG (worst effective, median KGR=8.1%/year) by the clinical parameters at the start of the therapy, mean age, BMI, mean systolic blood pressure, median TKV, median KGR, mean eGFR, mean serum Na and Mg, median urine osmolality were 49.6 vs 46.4 years-old, 20.0 vs 22.0, 125.0 vs 127.0 mOsm/L, 1514.4 vs 2511.5 mL, 6.4 vs 9.5%/year, 54.5 vs 48.5 mL/min, 139.7 vs 141.2 mmol/L, 1.87 vs 2.08 mg/dL, 247.2 vs 415.0 mOsm/kg, respectively. In comparison of two groups, significant difference was observed in urine osmolality and serum Mg.

Conclusions: In our facility, reduction of kidney volume was observed in 73.9% of cases, and 87.6% of cases showed KGR less than 5%/year, indicating that Tolvaptan therapy is significantly effective for the inhibition of cyst growth. It is also suggested that patients showing dilution by accelerated water intake and low serum Mg would be particularly expectable for the clinical efficacy of Tolvaptan.

FR-PO324

An Atypical Case of Fungal Cyst Infection in ADPKD Laura Onuchic,1 Antonio A. Portela Neto,1 Fernanda T. Ferreira,1 Leonardo A. Testagrossa,2 Elieser H. Watanabe,1 Bruno E. Balbo,1 Luiz F. Onuchic1. Nephrology and Molecular Medicine, University of Sao Paulo, Sao Paulo, Brazil; 2Pathology, University of Sao Paulo, Sao Paulo, Brazil.

Background: Cyst infection is a significant cause of mortality in autosomal dominant polycystic kidney disease (ADPKD). It is typically associated with gram-negative bacteria and is most often related to the ascending urinary tract route. Fungal etiology is rare, with patients showing diluted urine by accelerated water intake and low serum Mg would be expected based on the disease prevalence and the number of reported mutations. The p.T62P and p.T469M variants have been previously linked to ADTKD and the former was also found in 9 and 2 unrelated CKD patients. Fleeting family history in our registry, T62 lacks any evolutionary constraint and trained classifiers (eg. PolyPhen-2) predict a benign to possibly damaging phenotype for p.T62P. T469M is a conserved residue and p.T469M is predicted to be damaging. Expression studies in kidney cells in culture showed no obvious functional defect for p.T62P and p.T469M, as opposed to the well-established mutation p.C150S. Furthermore, the p.T62P variant does not segregate with disease, including several aged carriers with absent kidney disease.

Conclusions: The high frequency of 2 imputed variants in UMOD led us to reexamine the molecular diagnosis of several ADTKD families in our registry and to definitively inform the pathogenicity of UMOD p.T62P. With evolving sequencing data, careful curation of implausibly common variants in Mendelian diseases other than ADTKD is warranted.

FR-PO325

Lixivaptan, a Novel Vasopressin V2 Receptor Antagonist in Development for the Treatment of Autosomal Dominant Polycystic Kidney Disease Lorenzo Pellegrini,1 Jeffrey L. Woodhead,1 Lisl Shoda,2 was lowered,3 Brett A. Howells,2 Conorse Oriandler,1,3 DILIsym Services, Inc., Research Triangle Park, NC; 2DILIsym Services Inc., Research Triangle Park, NC; 3Lantheus Medical Imaging, Boston, MA; 1Palladio Biosciences, Newtown, PA; 2Cardiokine, Inc., Philadelphia, PA.

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is one of the most prevalent inherited genetic diseases in humans. Recent advances established vasopressin V2 receptor inhibition as a clinically validated mechanism of action for ADPKD, however safe and effective disease-modifying therapies for ADPKD are still lacking. Here we evaluated lixivaptan, a potent, selective vasopressin V2 antagonist, has characteristics that suggest a favorable benefit-risk profile for ADPKD.

Methods: Using the large body of existing preclinical and clinical data on lixivaptan encompassing 36 clinical studies and 1,673 independent patient exposures, we evaluated the projected efficacy and safety profile of lixivaptan for ADPKD. To explore efficacy, we compared the effect of lixivaptan with the related vasopressin V2 antagonist tolvaptan on accepted pharmacodynamic markers of efficacy in ADPKD. To explore safety, we conducted a multiscale computational model of drug-induced liver injury, a DILIsym evaluation, to determine lixivaptan’s propensity to cause hepatocellular injury compared with the known hepatotoxic tolvaptan.

Results: Potent suppression of urine osmolality (Uosm) was seen with lixivaptan in healthy individuals and patients with hypotremia of various etiologies, suggesting the potential for disease-modifying efficacy in ADPKD. In particular, 200mg BID doses of lixivaptan for 7 days resulted in uninterrupted Uosm below 300 mOsm/kg over 24 hours in 78% of healthy volunteers in study CK-0407. In contrast to tolvaptan, lixivaptan exposure was lowest in patients with impaired renal function than in healthy individuals (12% vs 31% lower for AUClast and Cmax, respectively), without affecting lixivaptan’s ability to attain target Uosm levels. Importantly, unlike tolvaptan, lixivaptan was not associated with hepatocellular toxicity at doses intended for ADPKD in the DILIsym evaluation.

Conclusions: Our analysis suggests that lixivaptan has the potential to become the a safe and effective therapy for the treatment of ADPKD in a broad patient population, paving the way for upcoming clinical trials with lixivaptan for ADPKD.

Funding: Commercial Support - Palladio Biosciences, Inc.

FR-PO327

The Burden of Autosomal Dominant Tubulo-Interstitial Kidney Disease (ADTKD) in Ireland Sarah Cormican,1 Dervla M. Connaughton,2 Claire Kennedy,1,4 Katherine A. Benson,1 Gianpiero Cavalleri,1 Brendan Doyle,1 Anthony M. Dorman,1 Mark A. Little,1 Peter J. Lavin,1 Kendrah O. Kidd,1 Alice H. Breyer,3 Peter J. O’Byrne,8 Beaumont Hospital, Dublin 9, Ireland; 2Beaumont Hospital, Dublin 9, Co Dublin, Ireland; 3Belfast Children’s Hospital, Belfast, Northern Ireland; 4Queen’s University, Belfast, Belfast, United Kingdom; 5RCSI, Dublin, Italy; 6Trinity College Dublin, Dublin, Ireland; 7Wake Forest University School of Medicine, Winston-Salem, NC.

Background: Hereditary mutations in the MUC-1, UMOD, HNF and REN-1 genes cause renal tubular atrophy, interstitial inflammation and fibrosis with progressive renal impairment. A recent KDIGO consensus report advocated the unified term ADTKD (sub-classified by causative gene) for these conditions, replacing older terminology such as medullary cystic kidney disease.

Methods: Individuals with possible ADTKD were identified by the Irish Kidney Gene Project and invited to attend for DNA collection with the Rare Kidney Disease Network which has been established under the auspices of CRIS Renal Genetics Unit and the Nephrology Department in the Wake Forest School of Medicine. Patients were sub-categorised as ADTKD-MUC1, ADTKD-UMOD or ADTKD-NOS (not otherwise specified) based on the identification of a mutation in the patient or an affected relative. 330 individuals from 28 families were included. Genotyping results are available on 36 individuals from 22 families. Native kidney biopsy results were available for 32 patients. 19 patients from 3 families were categorised as ADTKD-MUC1. 14 from 3 families were categorised as ADTKD-UMOD. 31 patients with clinical features of ADTKD met criteria for inclusion based on family history and renal biopsy findings. 18 have been tested without identified mutation, 4 have passed away and genetic material is not available. Details of genetic testing and clinical features are shown in Table 1. 40% of patients were hypertensive at presentation. Significant proteinuria occurred in 30% individuals with available. 26 patients with confirmed or suspected ADTKD have reached ERSD.

Conclusions: ADTKD accounts for approx. 0.06% of Irish cases of ESRD. Significant progress has been made in identifying causative mutations. Clinical awareness of ADTKD enables screening of relatives and early diagnosis.
Table 1

<table>
<thead>
<tr>
<th>Gene</th>
<th>Target Coverage</th>
<th>Target Deleterious Sites</th>
<th>Superior</th>
<th>Minor</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKD1</td>
<td>108X</td>
<td>90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PKD2</td>
<td>108X</td>
<td>90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADPKD</td>
<td>108X</td>
<td>90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADPLD</td>
<td>108X</td>
<td>90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADCKD</td>
<td>108X</td>
<td>90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADLKD</td>
<td>108X</td>
<td>90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADLKD</td>
<td>108X</td>
<td>90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADLKD</td>
<td>108X</td>
<td>90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADLKD</td>
<td>108X</td>
<td>90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADLKD</td>
<td>108X</td>
<td>90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADLKD</td>
<td>108X</td>
<td>90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADLKD</td>
<td>108X</td>
<td>90%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: In the adult PKD patients without a family history, other cystic kidney diseases than ADPKD may be overlooked, although it is hard to distinguish only by clinical data. Our custom panel appears to be useful to make genetic diagnosis of these patients.

Funding: Government Support - Non-U.S.

**FR-PO328**

Identifying Genetic Modifiers in Severe Polycystic Liver Disease (PLD) by Whole Exome Sequencing Amirroza Hashiighi,1 Xuexen Song,1 Marina Pourafzari,2 Beili Shi,1 Emilie Cornec-Le Gall,4 Ning He,1 Wybrich R. Cossen,3 Joost P. Drenth,3 Peter C. Harris,4 Vicente E. Torres,4 York P. Pei,5 Division of Nephrology, University Health Network and University of Toronto, Toronto, ON, Canada;3 Department of Medical Imaging, University Health Network, Toronto, ON, Canada;4 Radboud University Nijmegen Medical Center, Nijmegen, Netherlands;5 Division of Nephrology, Mayo Clinic, Rochester, MN.

Background: Severe PLD is a rare and poorly understood phenotype seen in both ADPKD and ADPLD. Mutations of SECV1, SECV2, PKRCSH, GANAB, and ALG8 have been shown to cause PLD by impairing the maturation and transit of polycystin-1 (PC1) through the endoplasmic reticulum protein-processing (ER-PP) pathway. We hypothesize that rare mutations including ER-PP pathway genes segregate in multiple families and may modify PLD in patients with ADPKD and ADPLD.

Methods: We performed whole exome sequencing (WES) using Illumina HiSeq2000/2500 with SSV5/5 capture kit in 150 patients including 23 affected discordant sib-pairs and 10 affected concordant sib-pairs for sPLD from 33 families (matched by gender and age) and 83 sporadic cases. All patients with sPLD had a cystic liver of ≥4× normal volume. In addition to a focused analysis on 166 genes involved in ER-PP pathway, we also performed a genome-wide analysis. Standard algorithms for sequence alignment, base calling, and quality control were applied. Then 5 rare deleterious variants (MAF ≤1%) deleterious variants of high and moderate impact as predicted by PolyPhen-2, MutationTaster, CADD, and SIFT were identified in at least 4 families each.

Conclusions: Our preliminary results suggest extensive genetic heterogeneity with no one single gene accounting for a large proportion of severe PLD cases. Future in vitro and in vivo functional studies will be needed to define the potential pathogenicity of the most promising candidate genes. Identification of genetic modifiers of severe PLD has the potential to improve risk prediction and treatment of this unusual complication.

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

**FR-PO329**

Genomic Background of Adult Polycystic Kidney Disease Patients without a Family History Takuya Fujimaru,1 Takayasu Mori,1 Akinari Sekine,2 Shutaro Mandai,1 Motooko Chiga,1 Hiroaki Kikuchi,2 Fumiaki Ando,1 Yutaro Morii,1 Naohiro Nomura,1 Shutaro Naito,1 Tomokazu Okado,1 Tatemitsu Rai,1 Junichi Hoshino,2 Yoshifumi Ubara,3 Shinichi Uchida,3 Eisei Sohara,1 Nephrology, Tokyo Medical and Dental University, Tokyo, Japan;1 Nephrology Center, Toranomon Hospital, Tokyo, Japan.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease. Mutations in PKD1 and PKD2 are responsible for 85% and 15% of ADPKD patients, respectively. Diagnosis of ADPKD is usually based on positive family history and imaging findings. However, in the absence of a family history, there are no definitive imaging findings that provide an unequivocal diagnosis of ADPKD. Therefore, in the patients without a family history, it is required to distinguish ADPKD from other polycystic kidney diseases (PKDs), though it is difficult without genetic diagnosis in most of the cases.

Methods: We developed a custom panel for 69 genes that cause nine types of hereditary PKDs (ADPKD, autosomal recessive polycystic kidney disease, nephropath, Joubert syndrome, Meckel syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, etc.) to test patients with no family history on ER-PP pathway genes expected to be modified in the adult PKD patients without a family history. PKD was defined as more than 10 cysts in a kidney.

Results: Through the analysis for 35 patients (age 55±16, 68.6% of male), 19 patients (54.3%) had PKD1/PKD2 mutations. Two patients (5.7%) identified compound heterozygous mutations in other genes, PKHD1 and NPHP4, confirmed by trio analysis. De novo heterozygous frameshift mutation of OFD1 was identified in one patient, which was likely to be causal. No obvious responsible mutations were detected in remaining 13 patients (37.1%).

Conclusions: In the adult PKD patients without a family history, other cystic kidney diseases than ADPKD may be overlooked, although it is hard to distinguish only by clinical data. Our custom panel appears to be useful to make genetic diagnosis of these patients.

Funding: Government Support - Non-U.S.

**FR-PO330**

Novel Semi-Automated Kidney Volume Measurements in Autosomal Dominant Polycystic Kidney Disease Satoru Muto,2 Haruna Kawano,3 Shigeo Horie.1 Juntendo University, Tokyo, Japan;1 Advanced Informatics for Genetic Disease, Juntendo University, Tokyo, Japan;1 Juntendo university, Tokyo, Japan.

Background: We assessed the effectiveness and convenience of a novel semi-automated kidney volume (KV) measuring high-speed 3D-image analysis system (VINCENT®) method. VINCENT® method extracts renal regions using image recognition software and measures KV (VINCENT KV). The algorithm was designed to work with the manual designation of a long axis of a kidney including cysts. After using the software to assess the predictive accuracy of the VINCENT method, we performed an external validation study and compared accurate KV and ellipsoid KV based on geometric modeling by linear regression analysis and Bland-Altman analysis.

Results: One hundred twenty four patients (male 62, female 62) participated in this study. The median eGFR was 46.9 ml/min/1.73m². Median accurate KV, Vincent KV and ellipsoid KV were 627.7 ml, 619.4 ml (IQR: 431.5–947.0) and 694.0 ml (IQR: 488.1–1107.4), respectively. Compared with ellipsoid KV (r = 0.9504), Vincent KV correlated strongly with accurate KV (r = 0.9968). Ellipsoid KV systematically under- or overestimate accurate KV, with a mean ± SD percentage difference of 14.2% ± 22.0% (Figure 1a). Vincent KV did not systematically under- or overestimate accurate KV, with a mean ± SD percentage difference of −0.6% ± 6.0% (Figure 1b). There were no significant slice thickness-specific differences (p = 0.2980).

Conclusions: The VINCENT method is an accurate and convenient semi-automated method to measure KV in patients with ADPKD compared with the conventional ellipsoid method.

**FR-PO331**

PRKCSH as a Genetic Modifier in Early-Onset Autosomal Dominant Polycystic Kidney Disease Ria Schönäue,1 Anna Seidel,1 Jana Hoepek,2 Katalin Dittrich,2 Steffen Neuber,1 Carsten Bergmann,1 Jan Haltbrüter,3 BIOSCIENZIA, Ingelheim, Germany;1 University Children Hospital, Leipzig, Germany;1 University Clinic Leipzig, Leipzig, Germany.

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common hereditary renal disorder accounting for up to 10% of end-stage renal disease (ESRD). Germline mutations within the polycystin (PC) encoding genes PKD1 and PKD2 and accumulating somatic mutations continuously reduce the level of functional polycystins, which is a major determinant for cyst formation. Although most of the patients develop ESRD in the second half of life, a high intrafamilial clinical variability suggests that additional factors influence PC-levels in a disease relevant manner. We investigate the role of PRKCSH as a potential modifier in the family of a patient (index) who already developed ADPKD in early ages.

Methods: Genomic mutations of the index patient were identified with an NGS-panel containing polycystic kidney and liver disease genes (PKD1, PKD2, SECV1, SECV2, PRKCSH, GANAB, HNF1B, LRPS, PKH1D). Analysis of cDNA transcribed from blood-derived mRNA was performed by PCR and Sanger sequencing. Functional impact of mutated PRKCSH and its influence on polycystins were characterized in vitro using transiently transfected cell culture systems.

Results: By NGS of a 2-year old male (index patient) with congenital PKD, we identified transheterozygous mutations in PKD1 (c.1723+10C>T) and PRKCSH (c.2050G>A) that encodes the β-subunit of the glucosidase II (GluII) and is involved in the development of polycystic liver disease. The PKD1 mutation was found to affect the splice site donor of intron 8 and thus, the corresponding PC1 protein ([575-703]in) is assumed to lose its function due to the lack of its transmembrane domains.
Additionally, the PRKCSH variant results in an amino acid exchange at the highly conserved position 69 of GluClβ (p.Ala69Thr), which abolishes its interaction with GlucII. Since GlucII participates in the maturation of polycystins in the endoplasmatic reticulum, its defect further reduces the level of functional polycystins.

**Conclusions:** In summary, while heterozygous loss-of-function mutation of PKD1 resulted in adult onset of ADPKD, the presence of an additional deleterious in-trans variant in PRKCSH severely accelerated cystogenesis. Thus, we demonstrate that by interfering with polycystin maturation, PRKCSH plays a role as genetic modifier in ADPKD and contributes to the observed clinical variability.

**FR-PO332**

**A Novel PKD1 Variant Demonstrates a Disease-Modifying Role in Trans with a Truncating PKD1 Mutation in Patients with ADPKD**

**Medhat N. Ayoub, Ministry of Health- Mubarak Hospital, KUWAIT, Kuwait.**

**Background:** Phenotypes associated with ADPKD in the terms of age of onset of end stage renal disease (ESRD), associated liver disease and other extrarenal manifestations showed high level of variability between patients. This phenotypic variability can be attributed to genetic and allelic heterogeneity. Another element that adds to the complexity of phenotypic variability in ADPKD is the involvement of modifier genes which is suggested by the intraphenotypic phenotypic variability observed in ADPKD families.

**Methods:** Patients were clinically evaluated using ultrasound and RFT. PKD1 was genotyped using next-generation sequencing by pooling long-range PCR amplicons and multiplexing bar-coded libraries. The significance of missense variants was assessed using the ADPKD Mutation Database, multisequence alignments and substitution assessment tools.

**Results:** In our case, we propose that the novel variant (p.H1769Y) aggravated the disease phenotype in patients resulting in early onset of ESRD and renal enlargement.

**Conclusions:** In summary, clinical evaluation of patients along with genetic prediction tools suggest that the novel PKD1 variant has a disease-modifying role, rather than disease causing role, in trans with the truncating PKD1 mutation in the studied family.

---

**FR-PO333**

**GPR124 Regulates Development of Kidney Medulla and Adult Kidney Fibrosis via Wnt Signaling**

**Yoichiro Ikeda,1 Jing Liu,2 Andrew P. McMahon,3 Benjamin D. Humphreys,4 Keck School of Medicine of the University of Southern California, Los Angeles, CA; University of Southern California, Los Angeles, CA; Washington University School of Medicine, Clayton, MO; Washington University, School of Medicine, St. Louis, MO.**

**Background:** GPR124 is an orphan GPCR expressed in endothelial cells where it is a coreceptor for Wnt7a/b to activate canonical Wnt signaling. Wnt7b is required for the development of kidney medulla and cortico-medullary axis, and Wnta is associated with renal function and fibrosis. Pericyte-specific translational profiling revealed strong upregulation of GPR124 mRNA during kidney fibrosis. We investigated the role of GPR124 in pericytes and myofibroblasts during kidney development and fibrosis.

**Methods:** Models were developed for overexpression of GPR124 in fibroblasts (NRK-49F) and Crispr/Cas9-mediated knockout in myofibroblasts (10T1/2). Kidney stroma-specific deletion was accomplished with FoxD1-Cre;GPR124 floxed mice and conditional deletion with Gli1-Cre;GPR124 floxed. B20(tdTomato) mice.

**Results:** GPR124 mRNA was strongly upregulated in whole kidney during mouse UUO by qPCR, and specifically in the interstitium by in situ hybridization. GPR124 expression directly correlated with degree of fibrosis in human kidney. Lenti viral overexpression of GPR124 in NRK49F fibroblasts drove spontaneous myofibroblast differentiation even in the absence of Wnt ligand. By contrast, Crispr/Cas9 knockout of GPR124 in 10T1/2 mesenchymal cells, caused a strong reduction in fibrotic marker expression including aSMA and collagens. These knockout cells also failed to respond to Wnt7a and Wnt7b ligand, confirming that GPR124 is a Wnt coreceptor in pericytes. Stromal specific GPR124 knockout mice resulted in a hypomorphic medulla phenotype and the loss of cortico-medullary axis, phenocopying the HoxB7-Cre; Wnt7b(f/f) phenotype. In addition, knockout mice showed microvascular hemorrhage in medulla. Conditional deletion of GPR124 in adult mouse kidney using Gli1-Cre;GPR124(+/−) tdTomato mice with tamoxifen administration resulted in reduced fibrosis in two fibroblastic models also associated with reduced canonical Wnt-b-catenin signaling.

**Conclusions:** GPR124 is unexpectedly expressed in kidney pericytes and perivascular fibroblasts where it regulates Wnta/b signaling and drives myofibroblast differentiation. During development, stromal GPR124 is required for medullary development and in fibrosis GPR124 plays a critical role in regulating pericyte and fibroblast to myofibroblast transition.

**Funding:** NIDDK Support

---

**FR-PO334**

**Tubular-Specific Krüppel-Like Factor 15 Mediates the Progression from Tubular Injury to Intestinal Fibrosis**

**Ahmed A. Attallah,1 Xianghen Gu,1 Yiqing Guo,1 Sandeep K. Mallipattnu,1 Stony Brook Medicine, Stony Brook, NY; 2Huayang hospital of integrated Traditional Chinese and Western Medicine, Shanghai, China.**

**Background:** Mechanisms by which tubular injury results in fibroblast to myofibroblast differentiation in the transition from AKI to CKD remains poorly understood. Renal-stromal-specific Krüppel-Like Factor 15 (KLF15), a zinc-finger transcription factor, was recently shown as a potential mediator of kidney fibrosis. Here, we sought to determine the mechanism by which tubular KLF15 serves a key mediator of AKI to CKD in the setting of proximal tubular (PT) injury.

**Methods:** PT-specific Klf15 knockout mice (Klf15ΔPT) were generated by crossing Klf15Δmice with Pepck-Cre mice. We utilized low-dose Aristolochic Acid I (AAI) to model PT injury and AKI to CKD, 3 mg/kg every 3 days for 3 weeks, followed by 3 weeks for remodeling (DMSo served as control). Full-length ORF gDNA of human KLF15 (kklF15) was cloned into a TRE plasmid. Mice with TRE-kLF15 and Pax8-Cre transgenes (Pax8-kLF15) were generated for doxycycline (DOX) inducible tubule-specific kLF15 induction. Finally, mice with TRE-kLF15 and CAG-rTA transgenes (CAG-kLF15) were also generated for DOX-inducible global kLF15 induction.

**Results:** KLF15 mRNA and protein expression were reduced at 3 weeks post AAI treatment (AKI phase) and at 6 weeks (remodeling phase). Klf15Δmice exhibited an increase in pro-fibrotic markers (eSMA, Col1α1, fibronectin, vimentin) and myofibroblast proliferation (Ki67) as compared to AAI-treated wildtype mice. Klf15Δmice also demonstrated an increase in PT injury (AQP1 & UGT1a1 redistribution and reduced expression) with activation of tubular Wnt/b-catenin signaling (nuclear phospho-b-catenin) and worsened renal function (elevated serum urea nitrogen and creatinine) compared to AAI-treated wildtype mice. Conversely, AAI-treated Pax8-kLF15 mice exhibited a reduction in these pro-fibrotic markers, myofibroblast proliferation, and Wnt/b-catenin signaling with an improvement in PT markers as compared to AAI-treated wildtype mice. Finally, AAI-treated CAG-kLF15 also validated this improvement in tubular injury, renal fibrosis, and renal function as compared to AAI-treated wildtype mice.

**Conclusions:** These data suggest that modulating the expression of tubular KLF15 is critical to the progression of AKI to CKD in the AAI-induced nephropathy, suggesting a potential target for therapy.

**Funding:** NIDDK Support
Disruption of Genome Maintenance Mechanisms in Renal Proximal Tubular Epithelial Cells Exacerbates Human Kidney Fibrosis  
Seiji Kishi,1 Kenji Nishimura,2 Ryuji Morizane,1 Takaharu Ichimura,1 Joseph V. Bonventre,1 Toshio Doi,2  
Brigham & Women’s Hospital/Harvard Medical School, Boston, MA;  
Nephrology, Tokushima University Hospital, TOKUSHIMA, Japan.

Background: Renal proximal tubular epithelial cells (RPTECs) comprise the bulk of the renal parenchyma and are the primary target of a variety of insults to the kidney. While DNA damage and activation of the DNA damage response (DDR) play an important role in human disease, the role of DDR in the progression of human kidney disease remains unresolved. To investigate this mechanism, we evaluated the role of ataxia telangiectasia and Rad3-related (ATR) which is the key upstream regulator of cellular response to DNA damage.

Methods: We analyzed human kidney tissue from native kidney biopsy performed at Tokushima University Hospital. Of the 20 cases, 11 cases were with interstitial fibrosis and elevated serum creatinine, as well as 9 cases were with a pathologic diagnosis of minor glomerular abnormalities. On staining with normal and mutant ATM and ATR, Ki67 increased in tubules. An active form of ATR (pATR) and the marker of DNA damage (γH2AX) were stained with KM-1 to evaluate whether DDR correlates with eGFR or fibrosis. In vitro study, to examine whether the inhibition of the ATR affects the survival of a proximal tubular epithelial cell line (HKE-8) after toxic insult, we assessed the degree of DNA damage and cell viability with or without the ATR inhibitor; VE-821.

Results: In kidney tissue from humans with CKD, ATR was activated in chronically injured RPTECs. The number of pATR and KIM-1 double positive tubes was inversely correlated with eGFR and positively correlated with the degree of kidney fibrosis. The number of γH2AX and KIM-1 double positive tubules in each kidney section was markedly increased, inversely correlated with eGFR and positively correlated with the degree of kidney fibrosis. We found an inverse correlation between γH2AX/KIM-1 positive and pATR/KIM-1 positive cells in CKD. ATR inhibition decreased DNA damage and cell viability of HKE-8 cells were further exacerbated when exposed to cisplatin, aristolactin acid or hypoxia in the presence of VE-821. Furthermore, ATR inhibition upregulated p21 and CTGF expression in HKE-8 cells after aristolactin acid treatment.

Conclusions: We demonstrate that DDR is seen in human kidney disease and ATR plays a protective role against tubular cell injury, death and fibrotic response. Regulation of ATR may be a therapeutic target against human kidney disease.

Funding: Government Support - Non-U.S.

FR-P0336

Lineage Tracing Study Defines Erythropoietin-Producing Cells as the Distinct Subpopulation of Resident Fibroblasts with Unique Behaviors  
Keiichi Kaneko, Shiuchi Endo, Motoko Yanagita. Kyoto University Graduate School of Medicine, Sakyu-ku, Japan.

Background: We previously demonstrated that renal fibroblasts including erythropoietin (Epo)-producing cells transdifferentiate into myofibroblasts with concomitant loss of Epo production during renal fibrosis. It has not been elucidated, however, whether Epo-producing cells, which account for less than 10% of resident fibroblasts, are the distinct specialization of resident fibroblasts. Lack of tools to label Epo-producing cells at desired time points has hindered our further understanding of the behavior of Epo-producing cells in adult kidneys.

Methods: We generated a novel mouse strain in which inducible Cre, CreERT2 was knocked-in at the locus of Epo gene (Epo-CreERT2 mice). Epo-CreERT2 mice were crossed with indicator mice, and tamoxifen was administrated to the offspring to activate CreERT2.

Results: Epo-CreERT2 labeled cells were located in the Bowman’s capsule cortex and connecting the portion of the kidney, and express PDGFRβ and CD73, indicating that these cells were resident fibroblasts. The labeled cells increased in parallel with the magnitude of anemia. Double in situ hybridization confirmed that around 50% of the labeled cells expressed Epo mRNA, indicating that Epo-CreERT2 mice faithfully labeled the Epo-producing cells. Around 50% of the labeled cells maintained Epo-producing ability even 16 weeks after the recombination, supporting the hypothesis that the labeled cells are the distinct population of renal fibroblasts. DNA damage and activation of the DNA damage response (DDR) play an important role in human disease, the role of DDR in the progression of human kidney disease remains unresolved. To investigate this mechanism, we evaluated the role of ataxia telangiectasia and Rad3-related (ATR) which is the key upstream regulator of cellular response to DNA damage.

Conclusion: Utilizing the new mouse strain, Epo-CreERT2 mice faithfully labeled the Epo-CreERT2 mice. The labeled cells increased in parallel with the magnitude of anemia. These results demonstrate that perivascular cell CD73 orchestrates the renal inflammatory microenvironment to promote a wound healing response after an acute kidney insult such as ischemia-reperfusion injury (IRI). Mechanochem underlying these events include a MyoX promoter-reporter mouse model of global conditional CTGF knockout (created by crossing CTGF-flox and ROSA26-CreERT2 mice and subsequent tamoxifen administration) was utilized to determine the role of CTGF silencing on IRI activation and renal fibrosis driven by ureteral ligation (UO). Various transgenic HK-2 cells with stable CTGF expression and CTGF expression depletion were created to investigate the potential cross-talk between TAZ and CTGF in fibrogenesis.

Results: Epo-CreERT2 mice were subjected to 20 unilateral IRI operation and after 14d, plasma was collected to quantify plasma creatinine (PCR). Also, kidneys were prepared for assessment of fibrosis by histology and inflammation and fibroblast density by immunofluorescence. Kidney fibrosis and macrophage polarization markers were quantified by RT-qPCR. Soluble CT7 or macrophage depletion by liposome clodronate and controls were initiated 2d after IRI and kidney function and IRI were measured.

Conclusion: These results demonstrate that perivascular cell CD73 orchestrates the renal inflammatory microenvironment to promote a wound healing response after an acute kidney insult such as ischemia-reperfusion injury (IRI). Mechanochem underlying these events include a MyoX promoter-reporter mouse model of global conditional CTGF knockout (created by crossing CTGF-flox and ROSA26-CreERT2 mice and subsequent tamoxifen administration) was utilized to determine the role of CTGF silencing on IRI activation and renal fibrosis driven by ureteral ligation (UO). Various transgenic HK-2 cells with stable CTGF expression and CTGF expression depletion were created to investigate the potential cross-talk between TAZ and CTGF in fibrogenesis.

Funding: Other NIH Support - NIH GM057242 and New York State Capital Region Medical Research Institute Grants, Private Foundation Support

FR-P0338

Perivascular Cell CD73 Modulates Macrophages in the Renal Microenvironment during Progressive Fibrosis  
Heather M. Perry,2 Nicole Görlitz,2 Leping Huang,2 Sun-sang J. Sung,2 Diane L. Rosin,1 Mark D. Okusa.1 Pharmacology, University of Virginia, Charlottesville, VA; 2Medicine, University of Virginia, Charlottesville, VA.

Background: Progressive tubulointerstitial fibrosis can occur following an acute kidney insult such as ischemia-reperfusion injury (IRI). Mechanisms underlying these maladaptive repair processes are not well understood. Proinflammatory cytokines, such as TGF-β3, an enzyme that converts AMP to adenosine on the extracellular surface, via adenosine receptors can suppress inflammation and reduce IRI. As CD73 is expressed on renal perivascular cells (pericytes and/or fibroblasts of the Foxd1+ lineage), we hypothesized that perivascular cell expression of CD73 is necessary to protect inflammation and prevent fibrosis.

Methods: Foxd1CreCD73fl/fl and littermate control CD73+ mice were subjected to 20 unilateral IRI operation and after 14d, plasma was collected to quantify plasma creatinine (PCR). Also, kidneys were prepared for assessment of fibrosis by histology and inflammation and fibroblast density by immunofluorescence. Kidney fibrosis and macrophage polarization markers were quantified by RT-qPCR. Soluble CT7 or macrophage depletion by liposome clodronate and controls were initiated 2d after IRI and kidney function and IRI were measured.

Conclusion: These results demonstrate that perivascular cell CD73 orchestrates the renal inflammatory microenvironment to promote a wound healing response after an acute kidney insult such as ischemia-reperfusion injury (IRI). Mechanochem underlying these events include a MyoX promoter-reporter mouse model of global conditional CTGF knockout (created by crossing CTGF-flox and ROSA26-CreERT2 mice and subsequent tamoxifen administration) was utilized to determine the role of CTGF silencing on IRI activation and renal fibrosis driven by ureteral ligation (UO). Various transgenic HK-2 cells with stable CTGF expression and CTGF expression depletion were created to investigate the potential cross-talk between TAZ and CTGF in fibrogenesis.

Funding: Other NIH Support - NIH GM057242 and New York State Capital Region Medical Research Institute Grants, Private Foundation Support

FR-P0339

Endothelial Tie2 Deficiency Increases Tubulointerstitial Fibrosis  
Marie Jeansson, Uppsala University, Uppsala, Sweden.

Background: Renal tubulointerstitial fibrosis is predictive of progressive decline in kidney function independent of underlying disease. It is characterized by an increase in aSmA+ fibroblasts, myofibroblasts, that produce collagen. We previously showed that loss of Angiopoietin-1 (Angpt1) in adult mice predisposes to fibrosis in wound healing, diabetic nephropathy, and the unilateral ureter obstruction (UUO) model. The tyrosine kinase receptor, Tie2, is expressed on endothelial cells and Angpt1 binding results in Tie2 signaling that is pro-survival and anti-inflammatory. Here, we test the hypothesis that loss of Tie2 signaling in endothelial cells results in capillary defects leading to an increased fibrotic response in kidney fibrosis.

Conclusion: Tie2 floxed mice were crossed with tamoxifen inducible endothelial specific Cadh5-Cre and a reporter line expressing TdTomaupon Cre-activation. This line enables both an endothelial specific KO of Tie2 and an endothelial lineage tracer.
To study the role of Tie2 signaling in renal fibrosis we utilized the unilateral ureteral obstruction (UUO) model of renal fibrosis. 

**Results:** Endothelial specific KO of Tie2 resulted in an increase in fibrosis as seen by a 2-fold increased expression of SM22a and Col1a1 compared to controls 3 days after UUO. At the same time, there was a 4-fold increase in Km1, suggesting more injury to the tubule than to the capillary. We also observed a migration of blood vessels before fibrosis onset 1 day after UUO, revealed less perfused capillary area and increased hypoxia in Tie2 KO mice. Ongoing work is designed to investigate blood vessel function in the early fibrotic process and to estimate the endothelial-mesenchymal contribution after UUO in controls and Tie2 knockouts. 

**Conclusions:** Our results suggest that loss of Tie2 signaling destabilizes the endothelial cell and increases tubulointerstitial fibrosis. We are investigating an early loss of endothelial cells due to endothelial-mesenchymal transition and/or apoptosis, resulting in less functional peritubular capillaries and more fibrosis. 

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

**FR-PO340**

**ErbB4 Deletion Accelerates Renal Fibrosis Following Renal Injury**

**Authors:** Xiaozhe Zeng, Linke A. Kloepper, Raymond C. Harris. Vanderbilt University Medical Center, Nashville, TN. 

**Background:** Tubulointerstitial fibrosis (TIF) is a component of chronic kidney disease (CKD) where any analogy to the is the best predictor of progression toward end stage kidney disease. Mechanisms underlying the development and progression of TIF are still incompletely understood. Increased ErbB4 expression were seen in the tubular epithelium of CKD kidneys. However, its role in the tubulointerstitial injuries remains to be determined. 

**Methods:** ErbB4 expression was examined using immunohistochemistry in human biopsy fibrotic kidneys. Two mouse models of renal injury, unilateral ureteral obstruction (UUO) and ischemia reperfusion injury followed by nephrectomy (IRX/UNX), were used to investigate the role of ErbB4 deletion in renal fibrosis by blocking ErbB4 expression in heart rescued ErbB4 deletion (ErbB4+/−hrt) and wild-type (WT) mice. Renal function and pathological changes were examined. 

**Results:** In human fibrotic kidneys, ErbB4 expression levels were inversely correlated to renal fibrosis as indicated by double immunofluorescence staining of ErbB4 and collagen I. In both UUO and IRX/UNX mouse models, expression levels of ErbB4 were elevated in the early stage of renal injury in the wild-type mice. In mice with global ErbB4 deletion except for transgenic rescue in cardiac tissue (ErbB4+/−hrt), UUO induced similar injury in proximal tubules compared to wild-type mice but more severe injury in distal nephrons. Tie2 was apparent earlier and was more pronounced following both UUO and IRX/UNX injuries in ErbB4+/−hrt mice. With ErbB4 deletion, UUO injury inhibited Akt phosphorylation and increased the percentage of cells in G2/M arrest. Meanwhile, increased levels of nuclear immunostaining of YAP and increased expression of p-Smad3 snail1 and vimentin were also detected in kidneys with ErbB4 deletion compared to the wild-type mice. 

**Conclusions:** In conclusion, increased expression of ErbB4 was detected in the early stages of human renal injury, whereas its level decreased with severe renal fibrosis, which is consistent with the hypothesis that ErbB4 deletion promoted renal fibrosis in mouse injury models. Therefore, the early increased ErbB4 expression may reflect a compensatory effect to lessen tubulointerstitial injury. 

**Funding:** NIDDK Support, Veterans Affairs Support

**FR-PO341**

**Ablation of Transcription Factor HNF-1β Induces Epithelial-Mesenchymal Transition through Twist2 Derepression**

**Authors:** Shao, Sophia, Shao, Kailash A., Fratamico, Peter M., Shao, Svetlana. University of Minnesota, Minneapolis, MN. 

**Background:** Hepatocyte nuclear factor-1β (HNF-1β) is a transcription factor that is essential for normal kidney development and function. Mutations of HNF-1β produce a multilayered epithelium. RNA-seq analysis of HNF-1β−/−-deficient cells exhibited loss of contact inhibition and adopted a spindle-shaped morphology. Compared with control cells, HNF-1β−/−-deficient cells exhibited EMT features with increased cell migration and higher motility and produced a multilayered epithelium. RNA-seq analysis of HNF-1β−/−-deficient cells and Ingenuity Pathway Analysis (IPA) revealed that fibrosis and epithelial-mesenchymal transition (EMT) pathways were highly activated in HNF-1β−/−-deficient cells. Transcription factors involved in EMT, including Twist2, SNAI1, SNAI2, and ZEB2, were upregulated in HNF-1β−/− mutant cells. Mechanistically, we found that expression of Twist2 was directly repressed by HNF-1β. Concomitant ablation of Twist2 partially rescued the fibroblastic phenotype of HNF-1β−/− mutant cells. Chromatin immunoprecipitation and qRT-PCR analysis of Twist2 mutant cells showed that TWIST2 is an upstream transcriptional activator of Snail2. Immunohistochemistry and RNA in situ hybridization showed that the expression of TWIST2 and SNAI2, as well as downstream targets TGFβ2 and TGFβ3, was increased in the cyst epithelium of HNF-1β−/− mutant kidneys. 

**Conclusions:** We conclude that ablation of HNF-1β in renal epithelial cells leads to the activation of a transcriptional network that induces EMT and aberrant TGFβ signaling. Targeting this network may inhibit fibrosis in ADTDK and other chronic kidney diseases. 

**Funding:** NIDDK Support

**FR-PO342**

**Tubule-Derived Extracellular Vesicles Promotes Fibroblast Activation in Kidney Fibrosis**

**Authors:** Xi Liu, Lili Zhou, Youhua Liu. 1 Division of Nephrology, Nanfang Hospital, Southern Medical University, Guangzhou, China; 2 Department of Pathology, University of Pittsburgh, Pittsburgh, PA. 

**Background:** Kidney fibrogenesis is a complex process involving frequent cell-cell communication. Extracellular vesicles (EVs), consisting of exosomes and microvesicles, are increasingly recognized as an essential vehicle mediating cell-cell communication in both physiologic and pathologic conditions. Because tubular epithelial is the major constituent of kidney parenchyma and the epicenter of kidney injury, we hypothesized that tubular cells, in response to injury, may increase their production and release of EVs containing proteins, mRNAs and microRNAs, which act on interstitial fibroblasts, leading to their activation. In this study, we tested this hypothesis in vitro and in vivo approaches. 

**Methods:** 

**Results:** In human kidney proximal tubular cells (HKK-8), TGFβ1 induced marked increases in the release of EVs. Conditioned media collected after TGFβ1 treatment promoted rat kidney interstitial fibroblasts (NRK-49F) activation, proliferation and matrix production, compared with controls. However, depletion of EVs from TGFβ1-treated HKC-8 conditioned media abolished its action on NRK-49F cells, suggesting a predominant role of the EVs in mediating tubule-fibroblast communication. Interestingly, we found that Shh signal cascade was markedly induced in the EVs released by TGFβ1-treated HKC-8 cells. Knockdown of Shh in HKC-8 cells by RNAi abolished the tubular EVs-mediated induction of Glil, Snail1, α-SMA, fibroactin, and collagen I in NRK-49F cells. In mouse model of kidney fibrosis induced by UUO, the secretion of EVs was increased, and blockade of EVs secretion in vivo reduced tubular fibroactin and α-SMA, and blocked fibrotic responses. 

**Conclusions:** These results indicate that tubule-derived EVs play a critical role in initiating fibroblast activation and development of renal fibrotic lesions. Our data also suggest that Shh signal components in the EVs may be responsible, at least partially, for mediating the tubule-fibroblast communication in renal fibrogenesis. 

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

**FR-PO343**

**Nrf2 Deletion Promotes the Progression from Acute Tubular Damage to Chronic Renal Fibrosis Induced by Unilateral Ureteral Obstruction**

**Authors:** Weiyu Kong, Pu Cong, Congjiao Jiao, Guangyu Guo, Huihui Wang, Linping Wang, Jingbo Pi, Hua Zhou. 1 China Medical University, Shenyang, China; 2 Department of Nephrology, First Affiliated Hospital of China Medical University, Shenyang, P. R. China, Shenyang, China; 3 The first hospital of China Medical University, Shenyang, China; 4 program of Environmental Toxicology, School of Public Health, China Medical University, Shenyang, China. 

**Background:** The role of Nrf2 (nuclear factor erythroid 2-related factor 2) in the progression from acute kidney damage to chronic renal fibrosis in obstructive nephropathy remains unclear. We aimed to verify whether Nrf2 deletion augments the progression of renal injury induced by unilateral ureteral obstruction (UUO) and further to investigate its mechanism in Nrf2−/− knockout mice (Nrf2−/− mice). 

**Methods:** Renal injury was induced by UUO in 54 male Nrf2−/− mice and 36 male Nrf2+ + + mice. The kidneys were collected at day 2, 5, and 14 after UUO and histological damage was evaluated by PAS or Masson staining. We compared tubular damage (cleaved caspase3 and PARP) on day 2, transdifferentiation (vimentin and PCNA) on day 5, fibrosis (fibroactin and α-SMA), and inflammatory factors on day 14 after UUO in Nrf2−/− mice with Nrf2+ + + mice on protein and mRNA levels. The temporal renal Nrf2 expression was examined in the mice with immunohistochemistry staining and western blotting. In addition, Nrf2 was also evaluated in renal biopsies from the patients with acute, sub-acute, or chronic tubulointerstitial nephropathy. 

**Results:** Tubular damage significantly occurred on day 2; vimentin, fibroactin, and α-SMA were increased on day 5 and 14 in Nrf2−/− mice. Nrf2+ + + mice did not show these changes. Nrf2+ + + mice showed increased expression of Gclc and Nrf2 was significantly increased from day 2 to 5, while Nrf2 protein remarkably rose on day 5 and 14 in Nrf2−/− mice. Renal Nrf2 positive staining was upregulated in patients with acute, sub-acute, and chronic tubulointerstitial nephritis compared with normal biopsy. Nrf2 deletion significantly enhanced renal tubular cell apoptosis and inflammation, and fibrotic lesions compared with normal biopsy. Nrf2 deletion significantly enhanced renal tubular cell apoptosis and inflammation, and fibrotic lesions compared with normal biopsy. Nrf2 deletion significantly enhanced renal tubular cell apoptosis and inflammation, and fibrotic lesions compared with normal biopsy. Nrf2 deletion significantly enhanced renal tubular cell apoptosis and inflammation, and fibrotic lesions compared with normal biopsy. 

**Conclusions:** Nrf2 deletion augmented acute tubular damage, transdifferentiation, inflammation, and fibrosis under sustained UUO condition. The renalprotective role of Nrf2 may be limited to the development of renal fibrosis under acute or chronic conditions. 

**Funding:** Government Support - Non-U.S.
Dickkopf-3 (Dkk-3) Overexpressed in Dysfunctional Endothelium Secretome Instructs Fibroblast-to-Myoﬁbroblast Formation by Activating the Wnt Pathway Mark Lipпиард yan Shen, lei Jiang, junweyi Yang. 1 Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical University, Nanjing, China; 2 Nanjing Medical University, Nanjing, China; 3 Second Affiliated Hospital, Nanjing Medical University, Nanjing, China; 4 Second Affiliated Hospital, Nanjing Medical University, Nanjing, China.

Background: We have previously demonstrated that Sirt1(+/−) mice with endothelial dysfunction show exaggerated renal ﬁbrosis, whereas mice with silenced endothelial TGF-β signaling are resistant to ﬁbrogenic signals. Collectively, this indicates that secreted substances regulate these contrasting responses. Thus, we sought to examine the differential secretome of those cells.

Methods: We performed unbiased proteomic analysis of the secretome of renal microvascular endothelial cells (RMVEC) isolated from these two mutants, discovered Dkk-3 (a putative ligand of Wnt/β-catenin pathway) expressed exclusively in ﬁbrogenic secretome. Since Dkk-3 is an orphan member of the family of Wnt ligands, and its precise effects are poorly understood, we examined effects of Dkk-3 in renal ﬁbroblasts (RF) isolated from α-SMA-GFP mouse kidneys using positive and negative selection with magnetic beads.

Results: Application of Dkk3 to RF showed that Dkk3 (10 μg/ml) alone induced myoﬁbroblastic phenotype without altering responses to TGF-β1, a known antagonist of Wnt pathway, reduced activation of RF. When Dkk3 was combined with 1, it antagonized its antimyofibroblastic effect. In RMVEC, Dkk-3 induced endothelial-mesenchymal transition (endo-MT) as judged by the appearance of α-SMA-GFP signal, and reduced capillary cords formation and their branching angiogenesis. In mouse soluble RMVEC co-cultures (kindly provided by NL Jeon, Seoul National University, Seoul, Korea) Dkk-3 was conﬁrmed as an inducer of endo-MT and inhibitor of angiogenesis. Chronic administration of Sulindac, a potent Wnt pathway inhibitor, ameliorated UUO-induced renal ﬁbrosis.

Conclusions: In conclusion, a prominent member of the secretome of dysfunctional RMVEC, Dkk-3, afﬁrms a Dkk-1 antagonistic paracrine effect on RF and induces myoﬁbroblastic prentotype. Dkk-3 exerts a autocrine effect leading to endo-MT of RMVEC and reducing their angiogenic competence. These actions make Dkk-3 a potent pro-ﬁbrogenic agonist.

Lactic Acid Production from Glycolysis Activates TGF-β-Smad Signaling Pathway in Tubular Epithelial Cells Engaged in the Development of Renal Fibrosis jing Xu, yan Shen, lei Jiang, junweiyi Yang. 1 Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical University, Nanjing, China; 2 Nanjing Medical University, Nanjing, China; 3 Second Affiliated Hospital, Nanjing Medical University, Nanjing, China; 4 Second Affiliated Hospital, Nanjing Medical University, Nanjing, China.

Background: Renal proximal tubule is susceptible to hypoxic injury, because of the reliance on aerobic oxidative metabolism. Dysfunctional mitochondria participate the progression of chronic renal disease. In this paper, we investigate the proﬁle of the energy metabolism of the proximal epithelial cell in ﬁbrotic kidney, and evaluate the role of anaerobic metabolism in renal ﬁbrosis.

Methods: 2-deoxyglucose (2-DG) was administrated at a dose of 20mg/kg or 100mg/kg and Shikonin was oral performed at a dose of 1 or 5 mg/kg before unilateral ureteral obstruction (UUO) surgery and administered for successive 7 days. Human Reconstituent TGF-β1 (5 ng/ml) and lactic acid (10mM/L) were added to the serum-free medium for indicated time periods and concentration. 2-DG (0.2 or 1mM), dichloroacetic acid (DCA,2mM), BroPA (5mM) and oxamate (100nM) were added to the serum-free medium. At the same time, we found the expression of TGF-β1 and p-smad3 were decreased. In the meantime, lactic acid, the production of glycolysis pathway, was involve in the activation of TGF-β1-smad pathway and changed renal tubular cells phenotype and contributed to the development of renal interstitial ﬁbrosis.

Conclusions: Altered glucose metabolism of tubular epithelial cells is a hallmarks of renal ﬁbrosis. Inhibition of aerobic glycolysis is effective to suppress renal ﬁbrosis. Lactic acid production from glycolysis could further activate TGF-β1/smad signaling and aggravate renal ﬁbrosis.

ATF6 Knockout Mice Revealed That ER Stress Links Lipotoxicity and Kidney Fibrosis Tzu-Ming Jao. 1 Chia-Hsien Wu, 1 Mai Sugahara, 2 Hisako Saito, 2 Yu Ishimoto, 2 Akira Okada, 2 Hiroshi Maekawa, 2 Mari Aoc, 4 Tetsuhiro Tanaka, 1 Masaomi Nanguk, 2 Reiko Inagi, 1 The University of Tokyo Graduate School of Medicine, Tokyo, Japan; 2the University of Tokyo School of Medicine, Tokyo, Japan.

Background: Lipid accumulation in tubules is frequently observed in chronic kidney disease (CKD) patients. However, the molecular mechanism underlying lipotoxicity-induced tubulointerstitial ﬁbrosis is still largely unknown. ATF6, a transcription factor of unfolded protein response (UPR), has been reported as an upstream regulator of lipid metabolism. In addition, fatty acid is the main energy source of proximal tubular cell because of its high energy demand. We thus hypothesized that ATF6 regulates tubular lipid metabolism, and thereby contributes to lipotoxicity-induced renal ﬁbrosis.

Methods: We employed ATF6+/+ and ATF6−/− mice or Sprague-Dawley rats with unilateral ureteral obstruction (UUO) or unilateral ischemia-reperfusion injury (UIRI) as tubulointerstitial ﬁbrosis models. In in vitro study, human proximal tubular cell line, HK-2, expressing active ATF6 (nATF6) was used. Change in ATF6 activation, fatty acid synthetic factors (ACC and DGAT2), b-oxidation regulators (PPARα, CPT1, CPT2 and MCAD), pro-ﬁbrogenic factor (CTGF) were assessed.

Results: ATF6 was signiﬁcantly activated in associated with tubular lipid accumulation in rat ﬁbrotic kidneys induced by UUO and UIRI. In contrast, ATF6 deﬁcient mice exhibited amelioration of nATF6-induced tubulointerstitial ﬁbrosis via reduction of collagen I and a-SMA expression. Intriguingly, tubular lipid accumulation was also attenuated by ATF6- deﬁciency, indicating the pivotal role of ATF6 in lipotoxicity-mediated tubulointerstitial ﬁbrosis. To verify the crucial role of ATF6, we established lipotoxicity-induced renal injury model using Dkk-3, an antagonist of Wnt pathway, reduced activation of RF. When Dkk-3 was combined with Dkk-1, it antagonized its antimyofibroblastic effect. In RMVEC, Dkk-3 induced endothelial-mesenchymal transition (endo-MT) as judged by the appearance of α-SMA, fibronectin (FN) were down-regulated after mice or primary renal tubular epithelial cells (PTCs) dealed with inhibitors of glycolytic pathway. At the same time, we found the expression of TGF-β1 and p-smad3 were decreased. In the meantime, lactic acid, the production of glycolysis pathway, was involve in the activation of TGF-β1-smad pathway and changed renal tubular cells phenotype and contributed to the development of renal interstitial ﬁbrosis.

Conclusions: Collectively, we revealed the role of ATF6 in the derangement of fatty acid metabolism in the tubule leading to lipotoxicity-induced renal injury and CTGF upregulation, both of which may accelerate tubulointerstitial ﬁbrosis.

Alteration of Fatty Acid Oxidation in Proximal Tubular Epithelial Cells during Renal Fibrosis hao Ding. 1 Junweiyi Yang. 2 Nanjing Medical University, Nanjing, China; 3 Second Affiliated Hospital, Nanjing Medical University, Nanjing, China.

Background: Chronic kidney diseases (CKD) generally lead to renal ﬁbrosis and so far no effective therapeutic anti-ﬁbrosis strategy is available. At the tubular cell scale, proximal tubular epithelial cells (PTCs) which prefer fatty acid as their energy source are the most energy-demanding cells in the body and involved in the process of interstitial ﬁbrosis.

Methods: In this study, we employed mice with unilateral ureter obstruction (UUO) and TGFβ1-treated primary PTCs as two model systems. The Creatinase system was used to generate renal PTCs-specific CPT1 deletion mice (CPT1−/−).

Results: Here we ﬁrst demonstrated that a switch of metabolism from oxidative phosphorylation to aerobic glycolysis in mouse kidney with UUO surgery. We found rate-limiting enzymes and key transcription factors involved in FAO were reduced in ﬁbrotic kidney and TGFβ1-treated primary PTCs. We uncovered that altered of FAO was associated with higher lipid accumulation in diseased renal and TGFβ1-treated primary PTCs. We also found that the enzymes and regulators of FAO were reduced in renal biopsy specimens of patients with CKD and was associated with the severity of renal interstitial ﬁbrosis. PTCs-specific ablation of CPT1 resulted in a phenotype that body weight was lower compare with their control littermates. Kidney injury molecule-1, NAG enzyme in urine and blood urea nitrogen were increased within 4 months and recovery at 8 months. We noticed the expression of rate-limiting enzymes and key transcription factors involved in peroxisomal compartments pathway were up-regulated in kidneys of knockout mice. In line with this, CPT1−/− mice showed higher heat production compared to the controls which is indicative of proportion of energy expenditure derived from lipid oxidation in peroxisomal. Finally, inhibiting mitochondrial FAO of PTCs lead to up-regulation of peroxisomal FAO pathway.

Conclusions: In conclusion, our studies demonstrate altered expression of both mitochondrial and peroxisomal β-oxidation enzyme systems during the process of interstitial ﬁbrosis. Furthermore, we found peroxisomal FAO pathway was compensatory up-regulated when mitochondrial FAO is shut down. Our results indicate that drugs that specifically restoring FAO may attenuate renal ﬁbrosis.

FR-PO347

Adiponectin Attenuates Kidney Injury and Fibrosis in Deoxycorticosterone Acetate-Salt and Angiotensin II Induced CKD Mice Mi Tian, Li Tang, Srini Beddhu, Yufeng Huang. Division of Nephrology, University of Utah Health, Salt Lake City, UT.

Background: Adiponectin (ApN) is a multifunctional adipokine with insulin-sensitizing, anti-inﬂammatory, and vasoprotective properties. However, this pathway appears to be key in the development of renal fibrosis.

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

Underline represents presenting author.
low, concentrations of ApN are unexpectedly found in patients with chronic kidney disease (CKD) via as yet unknown mechanism and the role of ApN in CKD is unclear. We, herein, investigated the effect of ApN overexpression on the progression of renal injury resulted from deoxycorticosterone acetate-salt (DOCA) and angiotensin II (DOCA+AngII) infusion using a transgenic, inducible, hepatic ApN-overexpressing mouse model.

Methods: To elucidate the role of Synd4 in fibrosis, we compared wild type and fibrosis prone ApN-deficient Sirt1-deleted Sirt1+/−/− mice serving as a model of global endothelial dysfuction.

Results: Synd4 transcripts were dramatically increased in Sirt1+/−/−/− kidneys. UO+I further induced it in control but especially in Sirt1+/−/−/− mice kidneys. Synd4 ectodomain expression was significantly enhanced after UO compared to contralateral endothelial kidneys, whereas there were no differences in expression of the intracellular domain. We next performed mass-spectrometry analysis of the secretome of renal microvascular endothelial cells (RMVEC) which revealed that Synd4 was highly enriched in TGFβ1-stimulated human microvascular endothelial cells (HMEC). Synd4 was then found to be upregulated in normal diet containing 0.15% of the transgenic inducer indole-3-carbinol (IEC) for 3 weeks.

Results: The EIC-induced ApN-Tg DOCA+/+, DOCA−/−, mice, not the WT or WT/DOCA+All mice, overexpressing ApN in liver resulted in 3.15-fold increases in circulating ApN levels compared to transgenic controls. Of note, these transgenic mice, DOCA+All mice infusion were still hypertensive (SBP, 148±5.09 vs. 140.7±3.43 mmHg, P<0.001, when compared to WT/DOCA+All), which were associated with reduced podocyte injury determined by accelerated DOCA+All-induced podocyte loss and foot process effacement; and alleviated tubular injury determined by ameliorated DOCA+All-induced increases in renal Ki-1 and NGLA mRNA expression and decreases in renal cubilin and megalin mRNA expression. In addition, renal macrophage infiltration and productions of NF-kB-p65, Nox2 and p47phox, markers of inflammation and oxidative stress, were alleviated by ameliorated DOCA+AII-induced increases in syndecan 4 expression determined by ameliorated DOCA+AII-induced increases in syndecan 4 expression. In addition, renal macrophage infiltration and productions of NF-kB-p65, Nox2 and p47phox, markers of inflammation and oxidative stress, were alleviated by ameliorated DOCA+AII-induced increases in syndecan 4 expression. In addition, renal macrophage infiltration and productions of NF-kB-p65, Nox2 and p47phox, markers of inflammation and oxidative stress, were alleviated by ameliorated DOCA+AII-induced increases in syndecan 4 expression.

Conclusions: These results indicate that elevated ApN in CKD mouse model is renal protective. Enhancing adiponectin production or signaling may have therapeutic potential for renal disease.

FR-PO351

Class Ila Histone Deacetylase Inhibition Suppresses Renal Fibroblast Activation and Lesions Fibrosis

Chongxiang Xiong,1 Shouguang Zhuang,2,3 'Rhode Island Hospital, Providence, RI; 'Rhode Island Hospital, Alpert Medical School of Brown University, Providence, RI; 'Department of Nephrology, Shanghai East Hospital, Tongji University, Shanghai, China.

Background: Histone deacetylases (HDACs) are a family of enzymes involved in regulation of cellular functions, including proliferation, migration and survival. Class I and II HDACs are associated with renal fibrosis. The role of class II HDAC in this process is poorly understood.

Methods: We examined the role of class Ia HDACs (HDAC-4, -5, -7, -9) in renal fibroblast activation and fibrosis using MCF1568, a highly selective class Ia HDAC inhibitor, and the siRNA specifically targeting individual class Ia HDACs.

Results: Exposing cultured renal interstitial fibroblasts to MCF1568, or silencing class Ia HDAC-4 and-7, significantly reduced activation as indicated by decreased a-smooth muscle actin, collagen 1 and fibronectin expression. In a murine model of renal fibrosis induced by unilateral ureteral obstruction (UUO), HDAC-4 was highly expressed whereas expression levels of HDAC-5, -7, -9 were only slightly elevated. MCF1568 suppressed deposition of extracellular matrix proteins and renal fibroblast activation. This coincided with reduced numbers of renal epithelial cells arrested at G2/M cell cycle phase and restored expression of Klotho and BMP7 after UUO injury. MC1568 also abrogated UUO-induced phosphorylation of receptor tyrosine kinases (epidermal growth factor and platelet growth factor receptors) and several signaling molecules associated with renal fibrosis, including Smad-3, STAT3, and NF-kB and ERK1/2. Moreover, class Ia inhibition suppressed renal expression of HIF-1α, Nrf-1 and TGF-β1 and prevented expression of PPAR-α/α and PPAR-gamma following UUO.

Conclusions: Class Ia HDACs inhibition may attenuate renal fibrosis by inhibiting profibrotic signaling pathways and preserving expression of renoprotective factors.

Funding: NIDDK Support

FR-PO352

Lysyl Oxidase Like-2 Contributes to Alport Renal Fibroblast Progression

Dominic E. Cosgrove,1 Daniel T. Meehan,2 Brianna M. Dufek,3 Duane C. Delmonico,4 Michael Hartnett,1 Deidre Mackenna,1 Gretchen Bain.5 'Boys Town National Research Hospital, Omaha, NE; 'Boys Town National Research Hospital, Omaha, NE; 'Boys Town National Research Hospital, Omaha, NE; 'Boys Town National Research Hospital, Omaha, NE; 'Boys Town National Research Hospital, Omaha, NE; 'Boys Town National Research Hospital, Omaha, NE; 'Boys Town National Research Hospital, Omaha, NE; 'Boys Town National Research Hospital, Omaha, NE; 'Boys Town National Research Hospital, Omaha, NE; 'Boys Town National Research Hospital, Omaha, NE; 'Boys Town National Research Hospital, Omaha, NE; 'Boys Town National Research Hospital, Omaha, NE; 'Boys Town National Research Hospital, Omaha, NE; 'Boys Town National Research Hospital, Omaha, NE; 'Boys Town National Research Hospital, Omaha, NE; 'Boys Town National Research Hospital, Omaha, NE; 'Boys Town National Research Hospital, Omaha, NE.

Background: Lysyl oxidase like-2 (LOXL2) is thought to have both intracellular and extracellular functions. Extracellularly, LOXL2 performs the first step in the formation of crosslinks in collagen and elastin networks, resulting in increased stiffness which may inhibit progression of fibrotic remodeling. LOXL2 also functions intracellularly, where it promotes stabilization of tumors. LOXL2 promotes liver and lung fibrosis, but nothing is known regarding a role in the kidney. This study explored whether LOXL2 influences kidney disease in Col4A3(-/-) Alport mice.

Methods: LOXL2 protein and mRNA expression in WT versus Alport mice was examined. Alport mice were treated with a small molecule inhibitor (LOXL2i) or vehicle from 2 to 7 weeks of age. Both cortex and glomeruli were analyzed by real time PCR for LOXL2 expression and protein. Thereafter, mice were challenged with unilateral ureteral obstruction (UUO) and renal fibrosis was scored.

Results: The expression of LOXL2 protein and mRNA (>15-fold) are induced in Col4A3(-/-) Alport mice. LOXL2i treatment significantly reduced interstitial fibrosis (by >50%) and mRNA expression for the fibrosis markers MMP-2, MMP-9, TGF-β1, and TGF-α in the interstitium. Additionally, LOXL2i treatment also reduced glomerulosclerosis (by

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO353
Dysfunction of the Intestinal Carnitine/Organic Cation Transporter 1 in CKD Impairs an Antioxidant Effect of Ergothioneine
Yasuyuki Shinozaki, Kengo Iwata, Norihiko Iwata, Noritako Sakai, Miko Shimizu, Takashi Wada. Kanazawa University, Ishikawa, Japan.

Background: Carnitine/organic cation transporter 1 (OCNT1) is a specific transporter at the food-derived antioxidant, ergothioneine (ERGO). ERGO absorbed by intestinal OCNT1 is distributed systemically through the bloodstream and incorporated into each organ by OCNT1. The OCNT1–ERGO axis is an adaptive antioxidant system that protects against further damage caused by oxidative stress. However, the role of OCNT1–ERGO axis in chronic kidney disease (CKD) progression remains unclear.

Methods: The ability of the intestine to absorb ERGO and OCNT1 expression were evaluated in CKD mice using the everted sac method, RT-PCR, western blot and immunohistochemistry. To identify the role of the OCNT1–ERGO axis in CKD, we evaluated kidney damage and oxidative stress in OCNT1 knockout CKD mice. To assess the protective effects of ERGO in CKD, we checked the antioxidant effect of ERGO using mProx24 cells. Moreover, we measured ERGO levels in the blood of CKD patients.

Results: Although the mRNA and protein expression of OCNT1 did not change as chronic progression, the localization of OCNT1 at the apical cellular membrane was reduced in the intestines of CKD mice. OCNT1-knockout CKD mice showed enhanced kidney damage, interstitial fibrosis, and oxidative stress. An in vitro study using mProx24 cells treated with indoxyl sulfate, which was pretreated with ERGO, revealed a dose-dependent attenuation of oxidative stress. In CKD patients, ERGO levels decreased as CKD progressed and that there was a positive correlation between ERGO and eGFR levels. ERGO levels were restored 10 months after kidney transplants in three patients.

Conclusions: OCNT1 attenuated the function of the OCNT1–ERGO axis because of the dysfunction of intestinal OCNT1. These results suggest that a novel inter-organ interaction mediated by transporters is associated with CKD progression.

FR-PO354
Myeloid TGFβ Receptor Promotes Fibrosis after AKI
Ming-Zhi Zhang, Jessica M. Overstreet, Yinqiu Wang, Aolei Ni, Suman Wang, Leslie S. Gewin, Raymond C. Harris. Vanderbilt University Medical Center, Nashville, TN.

Background: Transforming growth factor β (TGF-β) is a central mediator of fibrosis. TGF-β signals via a receptor complex composed of two type I and two type II transmembrane subunits. Renal macrophages are major producers of TGF-β1 and play important roles in the development of fibrosis after acute kidney injury (AKI). However, a previous study found that deletion of myeloid TGF-β1 did not prevent fibrosis after severe renal ischemia (I/R) or obstructive injury. In the present study we examined whether deletion of myeloid type II TGF-β receptors (Tgbr2b) affected development of fibrosis after AKI.

Methods: Wild-type (Tgbr2b+/+) or KO (C1db1-Cre;Tgbr2b−/− or LysM-M-Cre;Tgbr2b−/−) mice (male, 3 months old, C57BL/6) were used. For a severe I/R model, the animals were uninephrectomized, immediately followed by unilateral I/R with renal pedicle clamping for 29 min. Mice were sacrificed after 3 weeks. For an AKI-chronic kidney disease (CKD) model, unilateral I/R with renal pedicle clamping for 31 min was performed, with contralateral uninephrectomy on the 8th day, and animal sacrifice on day 28.

Results: Deletion of macrophage/dendritic cell Tgbr2b did not affect functional recovery from AKI, as indicated by similar rates of BUN and creatinine recovery. However, a higher fraction of macrophage/dendritic cells led to dramatic decline in development of fibrosis at 3 weeks in the severe AKI model, as indicated by quantitative picro-sirius red staining and Masson’s trichrome staining. Deletion of Tgbr2b in macrophages/dendritic cells was associated with decreased expression levels of pro-fibrotic cytokine components (including IL-6, TNFα, and collagen 1), IL-10, and IL-12. In addition, macrophage/dendritic cell Tgbr2b deletion led to markedly decreased in macrophage and T cell infiltration and oxidative stress. Macrophage/dendritic cell Tgbr2b deletion also markedly reduced development of fibrosis in the AKI-CKD model. In renal macrophages/dendritic cells isolated with C1db1 microbeads, Tgbr2b deletion led to decreased expression levels of M2 markers and increased M1 markers.

Conclusions: These studies indicate that myeloid Tgbr2b promotes fibrosis after severe AKI at least in part by promotion of M2 polarization and suggest that activation of proteasome impairment by TGF-β1 produced by non-myeloid cell types plays an important role in this process.

Funding: NIDDK Support

FR-PO355
Protective Effect of Vascular Endothelial Growth Factor-C on Renal Interstitial Fibrosis through Lymphangiogenesis in Mouse Unilateral Ureteral Obstruction
Shokko Furuichi, Tadashi Koyama, Shinji Kitajima, Akimori Hara, Yasunori Iwata, Norihiko Iwata. Kanazawa University, Ishikawa, Japan.

Background: Renal fibrosis is the final common pathway of chronic kidney diseases. Lymphatic vessel (LV) proliferation is found in human renal diseases and other fibrotic diseases, suggesting that lymphangiogenesis is associated with the progression or suppression of kidney diseases. However, the purpose of LV proliferation is not completely understood. We have previously reported the effect of vascular endothelial growth factor (VEGF-C) on lymphangiogenesis and fibrosis in the mouse kidney using the unilateral ureteral obstruction (UUO) model. At this time, we additionally investigated the effect of VEGF-C on inflammation and M1 and M2 macrophages. Furthermore, we investigated the effect of VEGF-C in vitro using lymphatic endothelial cells (LECs) by VEGF-A administration.

Methods: We continuously administered recombinant human VEGF-C to UUO model mice using an osmotic pump (UO+VEGF-C group) for 14 days. We investigated the lymphangiogenesis (LYVE-1 staining, western blotting of VEGFR-3, immunofluorescence staining of F4/80 staining, MCP-1 staining, ym-1 staining, western blotting of TGF-β1) and fibrosis (Sirius-red staining, western blotting of collagen 1). Additionally, we investigated the proliferation and expression molecules (ICAM-1, VCAM-1, E-selectin) of cultured LECs by administration of VEGF-C.

Results: Lymphangiogenesis was significantly induced in the UUO+VEGF-C group compared with the vehicle group, despite similar numbers of capillaries in both groups. The number of infiltrating macrophages (especially M1 macrophages) and levels of inflammatory cytokines and transforming growth factor-β1 were reduced in the UUO+VEGF-C group compared with the vehicle group. In cultured LECs, administration of VEGF-C increased the proliferation of LECs and expression of adhesion molecules.

Conclusions: These findings suggest that induction of lymphangiogenesis ameliorates inflammation and fibrosis in the renal interstitium. Enhancement of the VEGF-C-signaling pathway in LECs may be a therapeutic strategy for renal fibrosis.

FR-PO357
Xanthine Oxidoreductase Inhibitor, Topiroxostat, Had a Renoprotective Role under Decreased Angiotensin II Type 1 Receptor Expression
Atsuji Ikemori, Takeshi Sugaya, Mikako Hisamichi, Kenjiro Kimura, Yugo Shibagaki. 1 Division of Nephrology and Hypertension, St Marianna University Hospital, Kawasaki, Japan; 2 St. Marianna Univ, Tokyo, Japan; 3 Anatomy, St. Marianna University School, Kawasaki, Kanagawa, Japan; 4 St. Marianna university school of medicine, Kawasaki, Japan; 5 Tokyo Takanawa Hospital, Tokyo, Japan.

Background: Xanthine oxidoreductase (XOR) inhibitors may function as renoprotective agents as well as antioxidants via decrease in oxidative stress produced by xanthine oxidase converted from XOR. The aim of this study was to confirm the renoprotective effect of the XOR inhibitor, topiroxostat (Top) under decreased angiotensin II type 1a (AT1a) receptor expression in the model of renal injury caused by adenine.

Methods: To evaluate the degree of tubular damage using urinary liver-type fatty acid binding protein (L-FABP) under decreased AT1a expression, we used AT1a receptor knockdown hetero and human L-FABP chromosomal transgenic (Tg) mice (AT1a−/− L-FABP+). Male AT1a−/− L-FABP+ mice were divided into two groups: the adenine diet group (n=24) was given a diet containing only 0.2% w/w adenine, and the normal diet group (n=5) was given a normal diet. When renal dysfunction was confirmed in the adenine diet group 4 weeks after starting the diet, the adenine diet group was further divided into three groups. The adenine diet group (n=8) was continuously given only the adenine diet. Each group receiving high-dose (3mg/kg) or low-dose (1mg/kg) Top (Top-H, n=8, Top-L, n=8) was given the adenine diet including the drug for another 4 weeks.

Results: The levels of renal XOR, renal dysfunction, urinary L-FABP, tubulointerstitial damage, hyposxia, and oxidative stress were decreased or attenuated after treatment with Top compared with the untreated group.

Conclusions: In conclusion, Top attenuated renal damage under decreased AT1a expression in the adenine-induced renal injury model. Combination treatment with an XOR inhibitor and an RAS inhibitor might be a useful strategy for prevention of the progression of CKD.

Funding: Commercial Support - Sawa Kagaku Kenkyusho Co., Ltd., Tokyo, Japan.

FR-PO357
Fexubostat Attenuates ER Stress Mediated Kidney Injury in a Rat Model of Hyperuricemic Nephropathy
Yume Fan, Li He, Wenzhen Xiao, Jiejun Wen, Yang Dong, John C. He, Niangsong Wang. 1 Nephrology, Shanghai 6th People’s Hospital affiliated to Shanghai Jiaotong University, Shanghai, China; 2 Mount Sinai School of Medicine, New York, NY.

Background: Hyperuricemia contributes to the renal tubular injury and kidney fibrosis. Fexubostat, a novel inhibitor of xanthine oxidase, has been widely used for
the treatment of hyperuricemia and prevention of gout. Recent studies suggested that Urate-lowering therapy (ULT) by Febuxostat might also have cardiovascular and renal benefits, yet the mechanism of this protective effect is unknown. Endoplasmic reticulum (ER) stress has been well recognized as one of the important mechanisms in the onset and progression of many kidney diseases. In recent studies, we identified a novel ER associated gene, reticulon-1A (RTN1A), which is associated with the progression of kidney diseases. However, the exact role of RTN1A and ER stress in hyperuricemia induced kidney disease hasn’t been fully studied.

Methods: In the present study, we studied the expression of RTN1A and other ER Stress markers in comparison to normal kidney tissue. We determined the role of RTN1A and ER stress markers was significantly increased in kidney biopsies of patients with hyperuricemia-related kidney injury. In HN rat model established by oral administration of a mixture of adenine and potassium oxonate, increased expression of RTN1A and ER stress were shown in tubular and interstitial fibrosis kidney. Treatment with Febuxostat not only attenuated ER stress mediated renal tubular injury and tubulointerstitial fibrosis, but also reduced uric acid crystals deposition in HN rat kidneys. In vitro, Febuxostat also suppressed uric acid-induced ER stress and apoptosis in cultured tubular cells.

Conclusions: In conclusion, RTN1A and ER stress mediate tubular cell injury and kidney fibrosis in hyperuricemia induced nephropathy. ULT with Febuxostat attenuates uric-acid induced ER stress in renal tubular cells and the progression of HN. This study suggests a therapeutic role of Febuxostat in hyperuricemia-related CKD.

FR-PO358
SOX9 Is a Critical Regulator of Extracellular Matrix Deposition during Kidney Development
Saydov, M. Raza,1 James P. Pritchett,2 Neil Hanley,3 Philip A. Kalra,4 Karen Piper hanley.1 1University of Manchester, Manchester, United Kingdom; 2Salford Royal Hospital NHS Trust, Salford, United Kingdom; 3Manchester Metropolitan University, Manchester, United Kingdom.

Background: Renal fibrosis is a major cause of morbidity and mortality and a common feature of most chronic kidney disease (CKD). It is characterised by extracellular matrix (ECM) secretion from effector cells (myofibroblasts) resulting in tissue dysfunction and scarring. Discovering how to block scar production represents a very attractive therapeutic avenue for much needed antifibrotic drug development.

Methods: Primary pericytes were extracted from wild type mice. Cells were analysed by immunohistochemistry, western blotting and qPCR. Kidney fibrosis was induced in vivo by 2 week unilateral ureteric obstruction (UUO). SOX9-loss was achieved through tamoxifen induced Cre-mediated excision of Sox9 exon 2. Sox9−/− mice. Sox9 expression was assessed histologically in mice and human kidney fibrotic tissue.

Results: In wild type fibrotic kidneys SOX9 was increased and detected in α-SMA positive cells, demarcating activated myofibroblasts, along with collagen type 1 (Col1) rich fibrotic tracts disrupting normal tissue. In vitro, primary mouse pericytes expressed nuclear SOX9 surrounded by α-SMA. SOX9 knockdown in activated pericytes using RNA interference caused a commensurate reduction in COL1 protein expression (~60%), whereas the pro-fibrotic cytokine transforming growth factor-beta (TGF-β) induced expression of SOX9 by 2.5 fold in pericytes and 2.5 fold in the rat fibroblast cell line, NRK-49F. To model the stiffening environment of fibrotic kidneys we cultured pericytes on 1, 4 and 12 KPa hydrogels where α-SMA, SOX9 and the mechano-sensitivie factor YAPI became robustly expressed at 12KPa. Moreover, YAPI was also increased in UUO kidneys and α-SMA and SOX9 in kidney fibrosis, following UUO fibrosis mice lacking SOX9 had significantly reduced fibrosis by picrosirius red quantification (35% reduction) and α-SMA positive myofibroblasts were reduced by 45%. Importantly, in various human kidney diseases (Membranous nephropathy, Diabetic nephropathy, IgA nephropathy) fibrotic areas were associated with SOX9 positivity histologically.

Conclusions: These data support a pro-fibrotic role for SOX9 (similar to other organs) in kidney fibrosis where it is regulated by TGF-β and the mechnosignalling factor YAPI. Moreover, this provides an interesting opportunity for inhibiting SOX9 or its dependent pathways for anti-fibrotic therapy.

FR-PO359
Lymphocytes and PD-1 in Aristolochic Acid Nephropathy
Gilbert R. Kinsey, Brian K. Stevens, Mana Yang. Division of Nephrology; Center for Immunity, Inflammation and Regenerative Medicine, University of Virginia, Charlottesville, VA.

Background: Aristolochic acid is a nephrotoxic agent previously used in traditional Chinese medicine and found as an adulterant in some herbal supplements. Clinical studies have revealed extensive inflammation in kidneys of patients with aristolochic acid nephropathy (AAN). AAN involves an acute toxic injury to tubular epithelial cells that leads to immune cell infiltration and progressive fibrosis over time. Programmed death 1 (PD-1)-expressing lymphocytes, which play a role that limits the activation of T cells and lymphocytes have important roles in other forms of kidney injury, but their mechanistic role in AAN has not been previously reported.

Methods: Male wild-type (WT), PD-1 KO and lymphocyte-deficient RAG-1 KO mice (all on C57BL/6 background) were treated with AA 5 mg/kg i.p. injection. Five and 14 days after initiation AA treatments. Treatment of fibrosis by injection of PD-1 KO mice at day 14.

Results: Over time, a marked infiltration of CD45+ immune cells, especially T lymphocytes was observed in kidneys of WT mice after AA treatment (For example: CD4 T cells/g: Vehicle; 77,000 ± 11,000 vs. AA: 1,800,000 ± 250,000 at day 14). CD T cell, mononuclear phagocyte and PMN cell numbers were also elevated at day 14. Five days after AA treatment there were no differences in renal function between WT, PD-1 KO and RAG-1 KO mice as measured by creatinine or BUN levels. At day 14, PD-1 KO mice had significantly higher BUN levels, while PD-1 KO mice had lower BUN levels compared to WT AA-treated mice (BUN in mg/dl) in WT: 3.8 ± 7 vs. RAG-1 KO: 87 ± 11 vs. PD-1 KO: 16 ± 1). At day 14, RAG-1 KO kidneys exhibited higher innate leukocyte accumulation compared to WT kidneys. PD-1 KO mice had lower innate leukocytes and dramatically reduced CD3+CD4+ T cell infiltration.

Conclusions: These results suggest that lymphocytes are protective in this intermediate-length exposure of mice to AA. Unexpectedly, PD-1 deficiency ameliorated renal dysfunction and inflammation, suggesting a pro-inflammatory role for this co-stimulatory molecule in AAN.

FR-PO360
Sonic Hedgehog Promotes Kidney Injury by Activating Renin-Angiotensin System via a Non-Canonical Pathway
Songzhu Wu,1 Lili Zhou,1 Chunhong Wang,1 Youhua Liu.2 1Division of Nephrology, Nanfang Hospital, Southern Medical University, Guangzhou, China; 2Department of Pathology, University of Pittsburgh, Pittsburgh, PA.

Background: Sonic hedgehog (Shh) is a lipid-modified glycoprotein that plays a crucial role in embryonic development. Earlier studies indicate that Shh is a tubule-derived growth factor that specifically targets interstitial fibroblasts via a paracrine mechanism after various kidney injuries. Using hedgehog-responder reporter mice, studies show that kidney tubular epithelial cells are not responsive to hedgehog ligands via Gli-dependent canonical pathway. Whether Shh can target tubular epithelium via other mechanisms, however, remains to be defined.

Methods: Results: In this study, we investigated this issue using both in vitro and in vivo approaches. We found that in cultured kidney proximal tubular cells (HKC-8), recombinant Shh protein induced multiple components of renin-angiotensin system (RAS), including production of angiotensin-converting enzyme, and angiotensin II type 1 receptor (AT1). Shh also activated MAPK by inducing ERK, JNK and p38 phosphorylation, as well as its upstream PLC phosphorylation and activation. This cascade of events was dependent on Smo receptor, either as cycloapamine (CPN), a small molecule Smo inhibitor, or MAPK inhibitors abolished the Shh-mediated activation of MAPK and induction of RAS components, suggesting that Shh activates RAS via Gli-independent, MAPK-dependent non-canonical pathway. In vivo, overexpression of Shh aggravated the glomerular injury, interstitial matrix proteins expression and deposition, and renal fibrosis at 6 weeks after Shh injection. Smo Shh also promoted the induction of multiple RAS proteins, and elevated blood pressure. However, CPN therapy attenuated glomerular lesions, reduced renal fibrosis. CPN also inhibited renal MAPK activation, repressed RAS protein expression and normalized blood pressure.

Conclusions: Collectively, these studies demonstrate that tubule-derived Shh can target tubular epithelium by inducing RAS protein expression via PLC/MAPK-dependent non-canonical pathway. Our results indicate that blockade of Shh signaling can repress multiple RAS genes, thereby leading to amelioration of kidney injury.

FR-PO361
STAT3 Regulates Fibrogenic Signaling in Pericytes and Activates Pro-Fibrotic Migration, Differentiation, and Secretion of Pro-Fibrotic Cytokines
Arendrka K. Ajayi,1 Shruti Vig,2 Akinwande A. Akinfolarir,3 Venkata Sabhiesshittee,4 Joseph V. Bovonventre,5 Brigham and Women’s Hospital, Boston, MA; 1Brigham and women’s Hospital, Boston, MA; 2Department of Medicine, Harvard Medical School, Boston, MA.

Background: STAT3 is a key transcription factor, which plays an important role in cell proliferation, cellular pluripotency, and differentiation. Here, we investigated the pathophysiological role of STAT3 signaling in kidney fibrosis.

Methods: Results: STAT3 regulates Fibrogenic Signaling in Pericytes and Activates Pro-Fibrotic Migration, Differentiation, and Secretion of Pro-Fibrotic Cytokines

Conclusions: STAT3 signalling is not only essential for fibrotic processes, but also for other biological processes such as cell proliferation, cell differentiation, and cell death.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
myofibroblasts. Pretreatment with static, a small molecule inhibitor of STAT3 inhibited both cytokine production and cell differentiation.

**Conclusions:** Inhibition of STAT3 in pericytes protects mice from kidney fibrosis and the specific inhibition of STAT3 signaling in pericytes prevents their differentiation into myofibroblasts.

*Funding:* NIDDK Support

**FR-PO362**

FHL2 Promotes Fibroblast Activation and Kidney Fibrosis Involving the Activation of β-Catenin Signaling **Ying Duan**,1 Ting Cai,1 Junwei Yang,1 Weichun He,2 Nanjing Medical University; Nanjing, China; 2Nanjing medical university, Nanjing, China; Second Affiliated Hospital, Nanjing Medical University, Nanjing, China.

**Background:** Four-and-a-half LIM domains protein 2 (FHL2) is an adaptor protein and has been implicated in β-catenin signaling. Previously, we found that FHL2 may mediate TGF-β1-induced tubular epithelial-to-mesenchymal transition through activating β-catenin signaling. The FHL2-positive cells were observed both in renal tubule and interstitium in mice with obstructive nephropathy. However, the potential role and mechanisms for FHL2 in fibroblast activation and kidney fibrosis remains to be clarified.

**Methods:** The regulation and function of FHL2 in TGF-β1-stimulated fibroblast activation were examined in cultured NRK-49F cells. Mice with fibroblast-specific deletion of FHL2 were generated by mating FHL2−/− mice with S100a4-Cre transgenic mice. Mouse model of kidney fibrosis was established by unilateral ureteral obstruction (UUO).

**Results:** TGF-β1 induced FHL2 mRNA and protein expression in a time- or dose-dependent manner in cultured cells. Ecoprotein expression of FHL2 increased α-smooth muscle actin (α-SMA), type I collagen and fibroactinin expression, nevertheless knockdown of FHL2 via small interfering RNA partially suppressed TGF-β1-stimulated fibroblast activation. The regulation and function of FHL2 in TGF-β1-stimulated fibroblast activation were examined in cultured NRK-49F cells. Mice with fibroblast-specific deletion of FHL2 were generated by mating FHL2−/− mice with S100a4-Cre transgenic mice. Mouse model of kidney fibrosis was established by unilateral ureteral obstruction (UUO).

**Conclusions:** Our results suggest that FHL2, through activating β-catenin signaling, plays a critical role in mediating TGF-β1-induced fibroblast activation and contributes to the development and progression of kidney fibrosis, and FHL2 could be a potential future therapeutic target for chronic kidney disease.

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

**FR-PO363**

Fibroblast-Specific p90RSK Promotes Kidney Fibrosis **Ling Lin**,1 Chaowen Shi, Kebin Hu. Penn State University College of Medicine, Hershey, PA.

**Background:** The 90 kDa ribosomal s6 kinases (RSKs) are a group of serine/threonine kinases that regulate diverse cellular function, such as cell growth, cell motility, and cell survival. There are 4 RSK isoforms (RSK-1-4), of which RSK1 is also designated as p90RSK and predominantly expressed in the kidney. p90RSK is recently shown to promote diabetic endothelial dysfunction and atherosclerosis, however, the role of p90RSK in the development and progression of chronic kidney disease has never been investigated in vivo.

**Methods:** We generated a novel fibroblast-specific p90RSK transgenic mouse strain and investigated the role of p90RSK in kidney fibrosis.

**Results:** We examined the expression of phospho-specific and total p90RSK during the course of chronic kidney injury in the classic unilateral ureter obstruction (UUO) model. It’s found that p90RSK is dramatically activated, as indicated by phosphorylation of p90RSK, in the obstructed kidneys as early as 3 days after UUO; and the activation continued increasing until 14 days after UUO when the mice were sacrificed. Whereas, there is little difference in the level of total p90RSK between the obstructed and control kidneys. Intriguingly, double immune staining analysis found that the activation of p90RSK in the interstitium is largely induced in the FSP-1-positive fibroblasts. We generated fibroblast-specific p90RSK transgenic mice, p90RSK-Tg, and found that this mouse has normal phenotype as the littermate control. However, when UUO was induced in the p90RSK-Tg mice, it was found that p90RSK-Tg mice display significantly worse tubular damage, and dramatically increased deposition of extracellular matrix components such as collagen and fibronectin than that of their littermates. Western blot analysis also showed that p90RSK-Tg mice had decreased E-cadherin expression and de novo activation of alpha-SMA comparing to their littermates.

**Conclusions:** It is clear that fibroblast-specific p90RSK activation promotes kidney fibrosis, possibly, through the epithelial-to-mesenchymal transition mechanism.

*Funding:* NIDDK Support

**FR-PO364**

A Novel, Highly Specific TGFβ1 Inhibiting Antibody Demonstrates Antifibrotic Activity without Cardiotoxicity **Stefan Wawersik**, Thomas Schurpf, Abhishek Datta, Christopher Littlefield, Christopher Chapron, Kathy Y. Morgan, Constance Martin, Kimberly Long, Allan Capilli, Kaleigh Pavlik, Justin W. Jackson, Gregory Carven, Alan Buckler. Scholar Rock Inc, Cambridge, MA.

**Background:** Transforming growth factor-β1 (TGFβ1) has diverse biological functions, including regulation of immune response and tissue homeostasis. TGFβ1 activation has been associated with diseases including kidney fibrosis, where chronic activation is a key driver. Because of high homology between the TGFβ1 growth factor and its close relatives TGFβ2 and TGFβ3, truly TGFβ1-specific inhibitors have remained elusive. Pan-TGFβ inhibition, on the other hand, can cause dose-limiting heart valvulopathies, leading to concerns with long-term dosing. TGFβ1 are expressed as pro-proteins that are proteolytically cleaved into a C-terminal growth factor and an N-terminal prodomain that remains noncovalently associated with the growth factor, preventing receptor binding. This latent TGFβ1 complex resides on cells or in the extracellular matrix until it is activated by integrins, freeing the growth factor and allowing receptor binding.

**Methods:** To identify TGFβ1-specific antibodies, we targeted the prodomain, which shares much lower homology to TGFβ2 and TGFβ3 than the growth factor.

**Results:** We identified SR-AB1, a monoclonal antibody that binds latent TGFβ1 with no detectable binding to latent TGFβ2 or TGFβ3. SR-AB1 blocks latent TGFβ1 activation by ωVβ6 or ωVβ8 integrins, providing specificity unachieved by biologics that target the TGFβ1 growth factor/receptor interaction. SR-AB1 further inhibits latent TGFβ1 complexed with all four known TGFβ1-presenting molecules, allowing targeting of TGFβ1 in multiple tissues. SR-AB1 blocks activation of endogenous TGFβ1 in a number of primary cells, including dermal myofibroblasts and hepatic stellate cells. Critically, while pan-TGFβ inhibitors show evidence of valvulopathy or other cardiotoxicity, SR-AB1 is free of such toxicities in 1 and 4 week rat studies. Finally, we tested the in vivo efficacy of TGFβ1 inhibition via this novel mechanism in the UUO model of kidney fibrosis, showing that SR-AB1 suppresses fibrosis to levels similar to those achieved by pan-TGFβ inhibition.

**Conclusions:** Our data show that isoform-specific inhibition of latent TGFβ1 is effective in a preclinical fibrosis model and has a superior safety profile compared to pan-TGFβ inhibition.

*Funding:* Commercial Support - Scholar Rock, Inc.
FR-PO366

The Role of β-catenin/Foxo in Renal Fibrosis

Padmasheere Rao,1 Min Pang,3 Xi Qiao,1 Hong Yu,1 Hai long Wang,1 Min Hui,2 Qi Cao,1 Yiping Wang,1 Chong H. P. ng,3 Brian J. Nankivel,1 Vincent W. Lee,1 Stephen I. Alexander,1 Guoping Zheng,1 David C. Harris,1,4 Centre for Transplant and Renal Research, Westmead Institute for Medical Research, University of Sydney, Sydney, NSW, Australia; 2Centre for Kidney Research, Children’s Hospital at Westmead, Sydney, NSW, Australia; 3Shanshi Medical University, Tianjin, China; 4Westmead Hospital, Westmead, NSW, Australia; 5Department of Tissue Pathology and Diagnostic Oncology, ICPMR, Westmead Hospital, Westmead, NSW, Australia.

Background: TGF-β causes fibrosis by cross-talk with major profibrotic pathways. β-catenin is a common co-factor in different TGF-β signalling pathways. β-catenin binds to TGF-β to activate profibrotic genes, while β-catenin also binds to Foxo in competition with TGF-β. We propose that promoting β-catenin/Foxo will protect against β-catenin/TGF-β mediated profibrotic changes and kidney fibrosis.

Methods: Human kidney biopsies from kidney transplant and diabetic nephropathy patients were assessed for β-catenin/Foxo and β-catenin/TGF-β interactions in relation to kidney fibrosis. Mouse tubular epithelial C1.1 cells were treated with TGF-β1 or without and ICG-001 (siSM), an inhibitor of β-catenin/TGF-β1. Foxo1 and TFC1 were knocked out by CRISPR/Cas9-mediated gene knockout. We evaluated kidney fibrosis in vivo in the unilateral ureteric obstruction (UUO) model. Profibrotic changes were examined by Western blot and immunofluorescence. Dualink - Proximity Ligation Assay (PLA) and co-immunoprecipitation assays (co-IP) were used to examine β-catenin/Foxo and β-catenin/TGF-β interactions.

Results: PLA of human kidney biopsies showed that β-catenin/Foxo correlated negatively (r=-0.785) whilst β-catenin/TGF-β correlated positively (r=0.679) with kidney fibrosis score (P<0.01). co-IP and PLA showed that ICG-001 promoted β-catenin/Foxo interaction by inhibiting β-catenin/TGF-β binding in TGF-β1-treated C1.1 cells. TGF-β1-induced β-catenin/TGF-β activity and expression of fibrotic genes (vimentin, N-cadherin, αSMA) were reduced by ICG-001 and TFC1 knockout, while Foxo1 knockout prevented the reduction of the fibrotic gene expression.

Conclusions: These results indicate that β-catenin/Foxo plays a protective role against TGF-β1’s profibrotic activity by inhibiting β-catenin/TGF-β interaction and thereby preventing kidney fibrosis.

Funding: Government Support - Non-U.S.

FR-PO367

Inhibition of p300/CBP-Associated Factor Attenuates Renal Tubulointerstitial Fibrosis through Modulation of NF-κB and Nrf2

Gungjin Chung,1,2 Zhilian Li,1,3 Soojung Kim,4 Seok Joon Shin,1 Cheol Whee Park,2 Chul Woo Yang,2 Yong-Soo Kim,1 Eun Sil Koh.2 Division of Nephrology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN; 2Department of Internal Medicine, The Catholic University of Korea College of Medicine, Seoul, Republic of Korea; 3Department of Nephrology, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China; 4Department of Biochemistry, The Catholic University of Korea College of Medicine, Seoul, Republic of Korea.

Background: p300/CBP-associated factor (PCAF), a histone acetyltransferase, is involved in many cellular processes such as differentiation, proliferation, apoptosis and reaction to cell damage by modulating the activities of several genes and proteins through acetylation of either histones or transcription factors. Here, we examined a pathogenic role of PCAF and its potential as a novel therapeutic target in the progression of renal tubulointerstitial fibrosis induced by unilateral ureteral obstruction.

Methods: After UUO surgery, male C57BL/6 mice were administered either the PCAF inhibitor garcinol or a vehicle by intraperitoneal injection once a day for 3 or 7 days. Renal tubular epithelial cells (HK-2) were transfected with siRNA-PCAF and analyzed for expression of pro-fibrotic factors.

Results: Administration of garcinol reversed an increase in renal expression of total PCAF and histone 3 lysine 9 acetylation, and it reduced positive areas of trichrome and α-smooth muscle actin and collagen content in UUO kidneys. The increased mRNA levels of transforming growth factor-β1, matrix metalloproteinase (MMP) 2, MMP9 and fibronectin in obstructed kidneys was significantly reduced by garcinol treatment. Furthermore, garcinol suppressed nuclear factor-kB (NF-κB) pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6 whereas it elevated nuclear expression of nuclear factor erythroid-derived 2-like factor 2 (Nrf2) and levels of Nrf2-dependent antioxidants including heme oxygenase-1, catalase, superoxide dismutase 1 and NADPH:quinone oxidoreductase-1. In addition, garcinol treatment resulted in reduction of TUNEL-positive cells and increased ratio of Bcl-2 to Bax in obstructed kidneys. PCAF siRNA in HK-2 cells inhibited the expression of type IV collagen and fibronectin when stimulated with TNF-α.

Conclusions: Our results suggest that inhibition of the inordinately enhanced PCAF may mitigate renal fibrosis by redressing the aberrant balance between inflammatory signaling and antioxidant response through modulation of NF-κB and Nrf2.

Funding: Government Support - Non-U.S.

FR-PO368

The Lysine Methyltransferase SETDB1 Inhibits Renal Myofibroblast Differentiation

Victoria G. Shuttleworth,2 Neil S. Sheerin,3 Ian Logan.3 1Newcastle University, Newcastle upon Tyne, United Kingdom; 2Newcastle University, UK, Newcastle Upon Tyne, United Kingdom; 3newcastle hospitals, Newcastle, United Kingdom.

Background: Renal fibrosis is characterised by accumulation of myofibroblasts expressing alpha-SMA. These cells deposit extracellular matrix that replaces normal kidney tissue leading to chronic kidney disease and organ failure. TGF-β1 is critical to myofibroblast transdifferentiation, signalling through transmembrane receptors, resulting in SMAD3 phosphorylation. Phosphorylated SMAD3 undergoes nuclear translocation to regulate transcription of profibrotic genes, such as alpha-SMA. Regulatory mechanisms governing these events are unknown, but SMAD3 may utilise co-regulators from other pathways. For this reason, we screened for methyltransferases involved in TGF-β1 signaling. We identify SETDB1 as a new repressor of SMAD3 and TGF-β1 induced transdifferentiation.

Methods: siRNA Screen. siRNAs targeting 48 human methyltransferases were transfected into cells harboring a TGF-β1-responsive pCAGA12-luc reporter gene. These were treated with TGF-β1, prior to reporter gene assay. Immunoprecipitation, HKC-8 cells were starved in serum-free medium and treated with TGF-β1. SETDB1 immunoprecipitation was performed on nuclear fractions. Immunofluorescence. HKC-8 cells starved in serum-free medium were treated with TGF-β1 prior to immunofluorescence with SMAD3 and SETDB1 antibodies. Human primary renal fibroblasts were transfected with either control or SETDB1 siRNA then treated with TGF-β1 and subjected to immunofluorescence for alpha-SMA, or light microscopy to evaluate morphology.

Results: 1 siRNA screening identified SETDB1 as a strong co-repressor of SMAD3, even in the presence of TGF-β1-2 Immunoprecipitation showed an interaction between SETDB1 and SMAD3 in nuclear fractions. No interaction was observed without TGF-β1 or control immunoglobulins 3 TGF-β1 promoted both SMAD3 and SETDB1 nuclear translocation, demonstrating co-localisation 4 Primary renal fibroblasts transfected with either control or SETDB1 siRNA then treated with TGF-β1 and subjected to immunofluorescence for alpha-SMA, or light microscopy to evaluate morphology.

Conclusions: 1 SETDB1 is a new SMAD3 co-repressor 2 TGF-β1 treatment promotes a specific interaction between with SMAD3 and SETDB1, in the nucleus 3 SETDB1 inhibits myofibroblast differentiation in human renal fibroblasts

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

Underline represents presenting author.
FR-PO369
Calcineurin A-Alpha regulation of Nox2 via NFkB Is Involved in Cyclopodine-Induced Nephrotoxicity Asawathy Miriam Cherivan,1 Robert S. Hoover,2,3 Clintoria R. Williams.1,2 Emory University, Atlanta, GA; Emory University, Atlanta, GA.

Background: The calcineurin inhibitor cyclopodine (CsA) is an effective immunosuppressant and dramatically improved the outcomes of transplant patients. However, one long-term consequence of CsA and other calcineurin inhibitor treatments is nephrotoxicity attributed to oxidative damage. Calcineurin has two primary isoforms of the catalytic subunit - CaNα and CaNβ. The renal phenotype of CaNα-/- mice substantially mirrors CsA nephrotoxicity whereas CaNβ-/- mice do not. However, mechanisms downstream of CaN that are involved in nephrotoxicity are poorly understood. Since NADPH oxidase-2 (Nox2) derived oxidative stress has been implicated in CsA nephrotoxicity, we hypothesized that inhibition of CaN by CsA stimulates Nox2 upregulation and promotes oxidative stress.

Methods: To test this hypothesis, WT mice were administered CsA or vehicle alone daily for 6 weeks. Kidneys were then collected for analysis of CaN isoform activity, Nox2 expression and ROS generation. In addition, Nox2 regulation was investigated in kidneys from CaNα-/-, CaNβ-/- and WT mice. Since Nox2 may be transcriptionally regulated via the NFκB pathway, fibroblasts derived from CaNα-/-, CaNβ-/- and WT mouse kidneys were treated with the NFκB inhibitor, calicheamicin phophylester (CAPE).

Results: In WT mice, CaNα was the predominant isoform bound to calmodulin, consistent with previous in vitro findings showing that CaN is the basally active isoform. CaN-calmodulin association was disrupted with CsA treatment and was accompanied by enhanced Nox2 expression. Consistently with our in vivo findings, Nox2 upregulation and ROS generation occurred only in CaNααβ mice. Interestingly, NFkB, but not NFAT activation was observed. In CaNα-/- renal fibroblasts, NFkB inhibition prevented Nox2 and ROS upregulation.

Conclusions: Our findings demonstrate that CaNα plays a key role in Nox2 regulation and ROS generation. Additionally, loss of CaNα activity, such as with CsA, promotes Nox2-mediated oxidative stress via an NFκB-dependent mechanism. These novel findings provide additional evidence of divergent CnA isoform signaling pathways. Therefore, selective ablation of CaNα and not CaNβ could improve the long-term outcomes of transplant patients.

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

FR-PO370

Background: Inflammation is activated in proteinuric models, and may contribute to long term interstitial fibrosis. We investigated whether the NLRP3 inflammasome pathway is involved in the pathogenesis of CKD in the Adriamycin (ADR) model.

Methods: Adult male Munich-Wistar rats were given ADR (5 mg/kg iv) and either no therapy or Allopurinol (Allo), used as a NLRP3 inhibitor, 36 mg/kg/day (ADR±Allo). Control rats (C) received saline only. After 4 weeks, we assessed body weight (BW, no therapy or Allopurinol (Allo), used as a NLRP3 inhibitor, 36 mg/kg/day (ADR+Allo).

Control rats (C) received saline only. After 4 weeks, we assessed body weight (BW, no therapy or Allopurinol (Allo), used as a NLRP3 inhibitor, 36 mg/kg/day (ADR+Allo). To long term interstitial fibrosis. We investigated whether the NLRP3 inflammasome could improve the long-term and not CnA κ B-dependent mechanism. These studies demonstrated that a major mechanism by which CsA inhibits Nox2 expression and ROS generation. In addition, Nox2 regulation was investigated in kidneys from CnA-κ-/-, CnA-ß-/- and WT mice. Since Nox2 may be transcriptionally regulated via the NFκB pathway, fibroblasts derived from CnA-κ-/-, CnA-ß-/- and WT mouse kidneys were treated with the NFκB inhibitor, calicheamicin phophylester (CAPE).

Results: In WT mice, CnA was the predominant isoform bound to calmodulin, consistent with previous in vitro findings showing that CnA is the basally active isoform. CnA-calmodulin association was disrupted with CsA treatment and was accompanied by enhanced Nox2 expression. Consistently with our in vivo findings, Nox2 upregulation and ROS generation occurred only in CnA-κ-/- mice. Interestingly, NFkB, but not NFAT activation was observed. In CnA-κ-/- renal fibroblasts, NFkB inhibition prevented Nox2 and ROS upregulation.

Conclusions: Our findings demonstrate that CnA is involved in chronic kidney disease (CKD). The beneficial effects of CsA may contribute to this beneficial effect. Allo may help to prevent or limit the progression of CKD. FAPESP/CNPq.

Funding: Government Support - Non-U.S.

FR-PO371
Oleanolic Acid Alleviates Renal Fibrosis through Regulating the Expression of miR-141 Mingjiang Wei, Jiaqi Yin. The First Affiliated Hospital of Soochow University, Suzhou, China.

Background: Renal fibrosis is characterized by the abnormal metabolism of extracellular matrix (ECM). However, ECM's abnormal metabolism mechanism has not been understood clearly. Recent studies suggested that metabolic regulation of ECM remodeling was associated with some miRNAs, such as miR-141, miR-21, miR-136 and so on. MiR-141 is the most important of them which control the ECM’s metabolism. Both the cell signal pathway of TGF-β/Smads and the ECM’s metabolism enzyme MMP-9 play important roles in renal fibrosis through effecting ECM’s metabolism. So we hypothesize that miR-141 regulation the ECM's metabolism via both TGF-β/Smads and MMP-9. Oleanolic acid (OA) is the main extract of Achyranthes bidentate, which could reduce the symptoms of chronic kidney disease and improve the renal function. We have proved that OA can decrease the degree of renal fibrosis through regulating the metabolism of ECM.

Therefore, we speculated that OA could lessen the excessive accumulation of ECM by enhancing the expression of miR-141.

Methods: Thirty-two healthy Balb/c mice performed unilateral ureteral obstruction (UUO) surgery to induce ECM accumulation. Mice were randomly divided into 4 groups: sham-operated group (n=8), OA group (n=8), OA (25mg.Kg⁻¹) (n=8), Lotsin (25mg.Kg⁻¹) group (n=8). Daily OA and Lotsin was applied to mice by oral gavage for 10 days after surgery. Then all mice were killed and renal tissue were obtained for further analysis.

Results: We showed that OA group revealed obviously pathological injury including renal interstitial fibrosis compared with the model group by HE staining. The expression of TGF-β1, Smad2/3, ColIV, FN were downregulated and the expression of MMP-9 was upregulated compared with the model group by immunohistochemistry (P<0.05). Real-time quantitative PCR demonstrated that OA group increased significantly the expression of miR-141 and MMP-9, while obviously decreased the expression of TGF-β1, Smad2/3, ColIV and FN, compared with the model group (P<0.05).

Conclusions: In summary, our study provides that OA could regulate the expression of miR-141 to release the abnormal accumulation of ECM through impacting TGF-β/Smads. Our results provided another hand, OA could increase the expression of miR-141 to inhibit the excessive accumulation of ECM via upregulating the expression of MMP-9. OA may have beneficial effects on inhibiting the development of renal fibrosis.

Funding: Government Support - Non-U.S.

FR-PO372
RIPK3 Inhibition Alleviates Folic Acid-Induced Kidney Fibrosis of C57BL/6 Mouse Ying Shi,1 Yongli Zhao,1 Chunling Huang,2 Xinning Chen,2 Carol A. Pollack.1 The Second Hospital of Dalian Medical University, Dalian, China; 1College of Medicine, the University of Sydney, Sydney, NSW, Australia.

Background: Current therapies for renal fibrosis are largely ineffective. Therefore, identification of novel therapeutic targets is essential. RIPK3 is identified as a crucial regulator of necrosis, apoptosis and inflammation, which have been well recognised to be involved in renal fibrogenesis. To date, the role of RIPK3 in renal fibrosis has not been reported.

Methods: C57BL/6 wild-type and RIPK3 gene knock out (RIPK3-/-) mice and two conventional strategies were used in the study. 1. Folic acid was administrated i.p. to induce kidney injury in both WT and RIPK3-/- mice for 28 days; 2. C57BL/6 WT mice injected with folic acid were treated with Dabrafenib (RIPK3 inhibitor) or vehicle respectively for 28 days. Kidneys were harvested from above experiments and kidney fibrosis was assessed by measuring 24 hour of urinary albumin excretion and urinary albumin creatinine ratio (UACR) by ELISAs. Kidney histological change and ECM deposition was assessed by PAS, Masson’s trichrome, picrosirius red staining and immunohistochemistry. MCP-1, TGF-β and a-SMA RNA expression level were detected by quantitative RT-PCR analysis.

Results: RIPK3 blockade reversed folic acid induced 24 hour urinary albumin excretion and decreased UACR compared to WT or vehicle control groups treated with folic acid. Histological analysis showed that folic acid resulted in increased collagen accumulation and ECM deposition, whereas, RIPK3 inhibition attenuated ECM deposition and renal fibrosis. Similar results were also elucidated by immunohistochemistry on ECM components type I, III, IV Collagens and Fibronectin expression in renal interstitium. In addition, quantitative RT-PCR demonstrated Dabrafenib treated mice and RIPK3-/- mice inhibited the mRNA expression of TGF-β1 and a-SMA.

Conclusions: These results suggest that RIPK3 blockade may be a potential novel target in renal fibrosis.

Funding: Government Support - Non-U.S.

FR-PO373
Nuclear Localization of Phosphatase and Tensin Homolog (PTEN) Causes Cell Cycle Arrest and Is Associated with Kidney Fibrosis Amanda K. Ajay, Akinwande A. Akinfolarin, Joseph V. Bonventre, Venkata Sabbishetti, Brigham and Women’s Hospital, Boston, MA.

Background: PTEN is a lipid-tyrosine phosphatase that modulates various cellular processes including growth, survival and metabolism. Though the antagonistic effects of overexpression of PTEN on phosphatase and tensin homolog (PTEN) is well known, the localization of nuclear PTEN is not known. Some studies have demonstrated that nuclear PTEN regulates DNA damage response followed by genotoxic stress and maintains genomic stability.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
stability. In this study, we investigated the function of nuclear PTEN in renal epithelial cells followed by DNA damage repair in vitro and in vivo.

Methods: HK2 cells were treated with aristolochic acid (AA) for 48 hrs and cell cycle and nuclear PTEN was assessed. HEK293 cells stably expressing wild-type-GFP-PTEN, NLS-GFP-PTEN, mutant (NLS-GFP-C124S-PTEN) were developed and treated with 5 mg/ml AA for 48 hrs and cell cycle analysis was performed. Bilateral ischemia/reperfusion (IR: 20 min) was performed in C57Bl6 mice and mice were sacrificed at 21 days post IR. Kidney fibrosis was evaluated by Masson’s Trichrome and alpha-smooth muscle actin (α-SMA) staining. Immunostaining of PTEN was performed. The HK2 cells were transfected with siRNA and treated with 10 μg/ml TGFβ1 localization following AA treatment. Cells stably expressing cyclophilin PTEN exhibited G2/M arrest, while cells expressing nuclear PTEN rather displayed G1/S arrest. In mice, proximal tubular cells in fibrotic kidneys displayed elevated levels of nuclear PTEN staining.

Conclusions: Nuclear PTEN induces cell cycle arrest and is elevated after DNA damage in tubular epithelial cells in vitro and in vivo.

FR-PO374
Thymosin β4 Has Cell-Specific Effects on Renal Fibrosis Jiazhong Yang,1 Jie Wu, Yang1, Haijun Yang,2 Agnes B. Fogo3. Vanderbilt University Medical Center, Nashville, TN;1 Wanjue Christian Hospital, Wanjue, GuangWong-Do, Republic of Korea.

Background: Thymosin β4 (Tβ4) is a G-actin sequestering protein with effects on angiogenesis, cell migration and matrix. We previously showed that Tβ4 is increased in sclerotic glomeruli after 5/6 nephrectomy, but exogenous Tβ4 treatment ameliorated interstitial fibrosis after unilateral ureteral obstruction (UUO). In this study, we investigated the impact of renal fibrosis of Tβ4 knockdown in different cell types.

Methods: Endothelial cell Tβ4 knockdown mouse (Tβ4 endo-KD) were generated by mating Tβ4 shRNA loxP mice with SCL Cre mice, with SCL Cre negative mice as control (endo-Cont). We also generated inducible macrophage Tβ4 knockdown mice (Tβ4 endo-KD) for Tβ4 KD mice via Tβ4 macF knocks. Mating Tβ4 shRNA loxP mice with LyS Cre mice, inducing Tβ4 KD by targeting Tβ4 with LyS Cre negative mice as control. Injury was induced by UO and/or folic acid (FA), with in vitro study of primary macrophages.

Results: In UO and FA models, Tβ4 endo-KD mice had significantly decreased peritubular capillary density vs control. After UO at day 14, vascular permeability and interstitial fibrosis were significantly decreased in Tβ4 endo-KD. Endothelial-mesenchymal transition was also decreased in Tβ4 endo-KD vs control. In contrast, in the FA model, Tβ4 endo-KD mice had significantly increased collagen I mRNA, and slower recovery rate of tubular injury, measured by urinary KIM-1/Cre and NGAL/Cr, vs control. The hypoxia markers, HIF1 and HIF2 mRNA levels, were significantly higher in Tβ4 endo-KD mice vs control. Knockdown of Tβ4 in cultured macrophages reduced P-c-Jun and enhanced Y-1, although in vivo in UO, interstitial fibrosis and macrophage infiltration were not different in Tβ4 mac-KD vs control.

Conclusions: We conclude that endothelial cell Tβ4 affects peritubular capillary density and endothelial cell function, while the contribution of endothelial Tβ4 to renal outcome depends on disease model, whether a state of nonreversible interstitial fibrosis vs. toxic acute tubular injury, with beneficial effects of knockdown of Tβ4 in the former, contrasting impaired recovery in the latter. Tβ4 also affects M2 macrophage transformation but knockdown of Tβ4 only in macrophages did not change interstitial fibrosis. We conclude that thymosin β4 has cell and context-specific renal effects.

Funding: NIDDK Support

FR-PO375
Pharmacological Induction of ARNT/HIF1β Attenuates Chronic Organ Failure Michael Zeisberg, Desiree Tampe, Gerhard A. Mueller, Bjorn Tampe. University Medical Center Goettingen, Goettingen, Germany.

Background: Injury in any organ triggers a complex signaling cascade, ultimately culminating in tissue fibrosis and organ failure. Prompted by various studies across multiple organs demonstrating that preconditioning regimens to pre-emptively induce endogenous reparative mechanisms protect from later injury, we here aimed to gain insights into the molecular mechanisms underlying successful preconditioning, and to explore whether such pathways could be utilized to inhibit progression of chronic organ failure.

Methods: The effect of picomolar versus nanomolar FK506 was assessed in multiple models of chronic injury in the kidney (UOU), heart (AT II infusion) and liver (CCl4 injection). Using murine and human cell cultures, molecular mechanisms were analyzed by qRT-PCR, Western blotting and immuno staining.

Results: Based on existing transcriptional profiling data, enrichment analysis and array-based screening, we identified a novel protective mechanism that is controlled by the transcription factor ARNT (synonym HIF1β), which effectively inhibits progression of chronic kidney injury in both, preconditioning as well as intervventional regimes. We further expect that ARNT expression itself is controlled by the FKB127/XY1 transcriptional repressor complex, and that disruption of such FKB127/XY1 complexes by either depletion of FKB127 or YY1, or by picomolar FK506 concentrations at sub-immunosuppressive doses increases ARNT expression, leading to transcriptional ARNT activation. On a molecular level, we provide evidence that supraphysiological ARNT levels induce formation of distinct ARNT homodimers independent of hypoxia or xenobiotic signaling. For the first time, we detect ARNT homodimers in mammalian cells, facilitating unique transcriptional properties of ARNT/ARNT by direct targeting of a palindromic E-box binding motif (5'-CACGTCG -3') core sequence) within the proximal ALK3 promoter. Subsequent activation of ALK3-dependent canonical BMP signaling responses attenuate chronic organ failure in models of chronic kidney, cardiac and liver injury.

Conclusions: We report a novel organ protective mechanism that depends on ARNT/HIF1β homodimers, which can be pharmacologically modulated and targeted by immunophilin ligand FK506.

FR-PO376
Increased Sodium Chloride Cotransporter Expression in a Rat Renal Fibrosis Model Ito Sakuya,1 Yasuke Kaida,1 Yosuke Nakayama,1 Eisei Sohara,2 Shinichi Uhida,2 Kei Fukami.1 1Department of Medicine, Division of Nephrology; 2Department of Medicine, Kurume University, Kurume, Japan; 2Kurume University, School of Medicine, Kurume, Japan; Tokyo Medical and Dental University, Tokyo, Japan; Department of Medicine, Kurume University School of Medicine, Kurume, Japan.

Background: Antihypertensive therapies such as renin-angiotensin system (RAS) inhibitor and diuretics are the promising therapeutic strategy for inhibiting the progression of chronic kidney disease (CKD). The salt-sensitive hypertension is associated with the progression of CKD through the activation of the sodium chloride cotransporter (NCC). However, changes in the expression of NCC in the distal tubule of the different CKD stages are unknown. Thus, we investigated the blood pressure and the expression of NCC in the distal tubule of rats with mild to severe renal failure induced by nephrectomy (NX).

Methods: Sprague Dawley (SD) rats were randomly allocated into the control and CKD groups. We assigned the NX rats to three groups by the several degrees of kidney exsanguination: sham (n=4), mild CKD (n=3), moderate CKD (n=4), severe CKD (n=3). The NX and sham-operated rats were sacrificed at 4 weeks after operation. We examined the blood pressure, renal function, and urinary albumin excretion in rats with remnant kidney. Further, we explored the expression of NCC in renal tubule of the remnant kidneys by western blotting and immuno staining.

Results: Systolic blood pressure was significantly higher in the moderate and severe CKD rats compared with those in the sham-operated rats at 4 weeks after operation (148.3±17.9, 149.3±19.7 vs 114.8±12.8 mmHg; P<0.05, respectively). However, there was no difference of blood pressure between the mild CKD and the sham-operated rats (119.2±22.9 vs 114.8±12.8 mmHg; P=0.79). Serum blood urea nitrogen (BUN) and creatinine (Cr) levels, and urinary albumin excretion were significantly increased in all stages of CKD rats at 4 weeks after operation. The expression of total NCC was gradually up-regulated with the progression of CKD in the remnant kidney model.

Conclusions: In this study, increased NCC protein expression was observed in the remnant kidney model, which might induce the salt-sensitive hypertension in CKD. Therefore, the thiazide diuretics might be useful for controlling blood pressure in CKD patients. Further studies are needed to clarify the precise mechanisms of the increased NCC and its therapeutic strategy in CKD patients with hypertension.

FR-PO377
Targeting mTORC2/PKCα Inhibits Fibroblast Activation and Kidney Fibrosis Involving Blockade of Autophagic Flux Jiafan Ren, Chunsun Dai. Nanjing medical university, Nanjing, China.

Background: Our published study reported that mTORC2 plays a critical role in fibroblast activation and kidney fibrosis. However, the role and mechanisms for PKCα, one of the major downstream targets of mTORC2, in regulating fibroblast activation and kidney fibrosis remain to be determined.

Methods: Rat kidney interstitial fibroblasts (NRK-49F) were stimulated with TGFβ1 and kidney fibrosis was induced by unilateral ureter obstruction (UO) in CD1 mice. Go6976, a synthetic compound which selectively inhibits PKCα signaling, was employed.

Results: Here, we found that TGFβ1 could activate PKCα in cultured NRK-49F cells in a time-dependent manner. Blocking PKCα signaling with either Go6976 or PKCα small interfering RNA could markedly suppress TGFβ1-induced fibroblast activation. Additionally, Go6976 treatment could impair autophagic flux exhibited as decreased autophagosome-lysosome fusion and autophagic degradation accompanied by increased SQSTM1/p62 and LC3-II in NRK-49F cells. Similarly, 3-Methyladenine (3-MA) and Autophagy inhibitor, could markedly suppress TGFβ1-induced fibroblast activation. In UO kidneys, PKCα signaling was activated in the interstitial myofibroblasts and blocking PKCα with Go6976 could significantly ameliorate kidney fibrosis as well as inflammatory infiltration in the UO kidneys compared to those treated with vehicle. Administration of Go6976 in mice could induce the accumulation of SQSTM1/p62 and LC3-II in the UO kidneys, suggesting the blockade of autophagic flux in the fibrotic kidneys.

Conclusions: Together, these results suggest that blockade of PKCα attenuates chronic kidney fibrosis. Future studies are needed to clarify the precise mechanisms of the increased NCC and its therapeutic strategy in CKD patients with hypertension.

Funding: Government Support - Non-U.S.
FR-PO378

PBI-4050 Reduces Renal Injury and Anemia in a Mouse Model of Adenine-Induced CKD

Background: PBI-4050 is in clinical development in Phase IIb for the treatment of adenine-induced chronic kidney disease (CKD) in the context of Focal Segmental Glomerulosclerosis (FSGS). The purpose of this study was to investigate the effects of PBI-4050 in a model of adenine-induced CKD.

Methods: Eight-week-old male C57BL/6 mice were fed standard chow, or a diet supplemented with 0.25% adenine. Following one week of adenine diet, daily doses of PBI-4050 (200 mg/kg) or vehicle (vehicle) were administered by oral-gavage for three weeks. Longitudinal renal function was assessed by plasma creatinine via HPLC. At endpoint, blood analysis, plasma electrolyte and erythropoietin levels were measured in blood obtained by cardiac puncture. Tubulointerstitial inflammation/fibrosis and overall renal injury score were assessed in Masson’s trichrome and PAS-stained kidney sections. Pro-inflammatory and pro-fibrotic gene expression and fibronectin expression were measured in kidney cortex samples by qPCR and western immunoblotting respectively.

Results: PBI-4050 treatment reduced adenine-induced polyuria and maintained urinary osmolality. Renal function assessed by plasma urea and creatinine were significantly increased and four-fold and two-fold respectively in vehicle treated mice, while PBI-4050 lowered these values. Hematocrit, hemoglobin and mean corpuscular volume were significantly decreased in CKD-mice, while PBI-4050 maintained these levels in addition to increasing plasma erythropoietin levels. Renal pro-inflammatory gene expression was equally upregulated in both adenine-groups, while Masson’s trichrome staining, e-SMA mRNA and fibronectin protein expression were significantly upregulated in vehicle treated mice and were decreased with PBI-4050. PAS-staining revealed decreased tubular injury and cyst formation in the adenine-PBI-4050 group compared to adenine-vehicle.

Conclusions: PBI-4050 treatment for three weeks decreased the severity of several adenine-induced sequelae including tubular injury, tubulointerstitial fibrosis and anemia. Taken together, these data reinforce its use as a potential renoprotective therapy.

Funding: Commercial Support - Prometic Life Sciences Inc.

FR-PO379

A Role for IL-27 in Limiting Renal Fibrosis

Background: Pro-inflammatory and pro-fibrotic gene expression and fibronectin expression were measured in kidney cortex samples by qPCR and western immunoblotting respectively. There was increased four and two-fold respectively in vehicle treated mice, while PBI-4050 lowered these values. Hematocrit, hemoglobin and mean corpuscular volume were significantly decreased in CKD-mice, while PBI-4050 maintained these levels in addition to increasing plasma erythropoietin levels.

Results: PBI-4050 treatment reduced adenine-induced polyuria and maintained urinary osmolality. Renal function assessed by plasma urea and creatinine were significantly increased and four-fold and two-fold respectively in vehicle treated mice, while PBI-4050 lowered these values. Hematocrit, hemoglobin and mean corpuscular volume were significantly decreased in CKD-mice, while PBI-4050 maintained these levels in addition to increasing plasma erythropoietin levels. Renal pro-inflammatory gene expression was equally upregulated in both adenine-groups, while Masson’s trichrome staining, e-SMA mRNA and fibronectin protein expression were significantly upregulated in vehicle treated mice and were decreased with PBI-4050. PAS-staining revealed decreased tubular injury and cyst formation in the adenine-PBI-4050 group compared to adenine-vehicle.

Conclusions: PBI-4050 treatment for three weeks decreased the severity of several adenine-induced sequelae including tubular injury, tubulointerstitial fibrosis and anemia. Taken together, these data reinforce its use as a potential renoprotective therapy.

Funding: Commercial Support - Prometic Life Sciences Inc.

FR-PO380

Relation of Uric Acid with Rapid Kidney Function Decline and Development of Kidney Disease: The Jackson Heart Study

Background: Longitudinal studies have established an association between Th17 cells and alternatively activated macrophages (M2), which is associated with increased odds for RKFD (OR 1.8; 95% CI 1.25-2.49; p = 0.0013) and suggested a potential risk for incident CKD (OR, 1.39; 95% CI 0.89-2.16; p = 0.14). There was no interaction between sex and uric acid on both RKFD (p = 0.12) and incident CKD (p = 0.70).

Conclusions: These data identify a role for IL-27 in modulating clinically relevant risk factors for development and progression of chronic kidney disease (CKD) has been mixed. We evaluated the relationship of uric acid level with rapid kidney function decline (RKFD) and incident CKD among 3,702 Jackson Heart Study participants who had complete measures of uric acid at baseline (2000-2004) and estimated glomerular filtration rate (eGFR) available at both baseline and Exam 3 (2009-2013).

Methods: RKFD was defined as a decline in eGFR of ≥30% between Exams while incident CKD was defined as having eGFR < 60 mL/min/1.73 m² at Exam 3 with a 25% eGFR decline. Associations were evaluated using multiple logistic regression models. Odds ratios (OR, 95% confidence [CI]) were reported per 1 standard deviation (SD) increment.

Results: Mean baseline uric acid and eGFR were 5.4 ± 1.6 mg/dL and 95.9 ± 19.9 mL/min/1.73 m², respectively. During a median follow-up of 8.1 years, 422 (11.4%) and 268 (7.5%) participants experienced RKFD and developed incident CKD, respectively. In multivariable logistic regression, 1 SD increase in baseline uric acid concentration was associated with increased odds for RKFD (OR 1.8; 95% CI 1.25-2.49; p = 0.0013) and suggested a potential risk for incident CKD (OR, 1.39; 95% CI 0.89-2.16; p = 0.14). There was no interaction between sex and uric acid on both RKFD (p = 0.12) and incident CKD (p = 0.70).

Conclusions: These data identify a role for IL-27 in modulating clinically relevant risk factors for development and progression of chronic kidney disease (CKD).

Funding: Other NIH Support - The Jackson Heart Study is supported by contracts HHSN268201300046C, HHSN268201300047C, HHSN268201300048C, HHSN268201300049C, HHSN268201300050C from the National Heart, Lung, and Blood Institute and the National Institute on Minority Health and Health Disparities.
Augmented Association between Blood Pressure and Proteinuria in Hyperuricemic Patients with Non-Nephrotic Chronic Kidney Disease

Kentaroh Koka, Yuji Tsuyoshi, Ryo Tamami, Yusuke Ohya, University of the Ryukus, Nishihara-cho, Japan.

Background: High serum uric acid levels (HU) may enhance susceptibility to hypertensive renal damage via disrupted autoregulation system of glomerular hemodynamics. However, effect of HU on the relationship between blood pressure (BP) levels and proteinuria is unknown in patients with chronic kidney disease (CKD).

Methods: A total of 109 patients with non-nephrotic CKD (55 men and 54 women) who underwent renal biopsy were recruited. Arteriolar hyalinosis was semiquantitatively assessed via arteriole grading. We examined the correlation between BP and urine protein levels (g/gCr) according to the presence of higher uric acid (HU) levels (mg/dl), defined as ≥7 in men and 5 in women, which were the levels from which risk of hyalinosis is ≥.

Results: The median for age, BP, estimated glomerular filtration rate (eGFR), and serum creatinine were 49.9 years, 124/74 mmHg, and 1.73 m², respectively. In the patients with HU (n=58), log-transformed systolic BP was significantly correlated with log-transformed urine protein (r=0.49, p=0.0001). In contrast, there was no significant correlation between them in those without it (n=51). In the multiple regression model (R²=0.18, p=0.0009), interaction of HU and log-transformed systolic BP for proteinuria was significantly correlated with logarithm-transformed urine protein (β=3.0, p=0.04) independent of age, sex and potential confounding factors. However, its statistical significance was completely disappeared after additional adjustment with arteriolar hyalinosis index.

Conclusions: These results suggested that HU might potentiate the susceptibility for hypertensive glomerular damage via disrupted autoregulation in non-nephrotic CKD patients.
FR-PO385
Evaluation of Glomerular Filtration Rate Change as an Indicator of Development of Incident CKD Using Support Vector Machine: Community-Based Prospective Cohort Study
Fieichiro Kanda,1 Bogdan I. Epureanu,2 Kaname Suwa,4 Kei Nakajima,1 Kanagawa University of Human Services, Yokosuka, Japan; 'Tokyo Kyosai Hospital, Meguro, Japan; 'University of Michigan, Ann Arbor, MI; 'Saitama Health Promotion, Saitama, Japan.

Background: Chronic kidney disease (CKD) is a risk factor for cardiovascular disease and death. To decrease the number of CKD patients, it is important to identify people at high risk of developing CKD among healthy people from the public-health viewpoint. We investigated the role of estimated glomerular filtration rate (eGFR) change in the development of CKD in a community-based prospective cohort study using the support vector machine (SVM).

Methods: A total of 3295 healthy people (male, 72.7%) were enrolled in this prospective cohort study for 6 years (Saitama Cardiometabolic Disease and Organ Impairment Study) in Japan. The outcome event was incident CKD 6 years later. Subjects were categorized on the basis of eGFR change over 3 years by 10%.

Results: The mean±SD age was 38.8±10.1 years; eGFR, 81.8±17.3 ml/min/1.73m²; and eGFR change over 3 years, -15.0±18.5%. Multivariate logistic regression models showed the relationship between change in eGFR (0%) - 10%, adjusted odds ratio 3.89 (95%CI: 2.0, 7.56); -20%, 40.3 (20.5, 79.0); -30%, 124.8 (59.9, 260.1); -40%, 297.9 (119.8, 741.1). Interaction between eGFR change and eGFR was also observed (p<0.0001). A receiver operating characteristic curve showed a cutoff value of -12.4% for CKD prediction. The use of SVM enabled the identification of high-risk patients and showed that cutoff values differ depending on eGFR: eGFR 90, eGFR change =0.0001). A receiver operating characteristic curve showed a cutoff value also observed (p<0.0001). A receiver operating characteristic curve showed a cutoff value

Conclusions: eGFR change tends to be associated with the risk of CKD. The cutoff values for the prediction of CKD may differ depending on eGFR in the general population. The composite index of eGFR and eGFR change may have high potential use for detecting high-risk people for CKD.

FR-PO386
Lipodystrophy Increases the Risk of Developing CKD in HIV-Infected Patients in Switzerland: the LIPOKID Study
Yassine R. Bouatou,2 Françoise Hamelin,1 Yves Vaucher,3 Yasmine R. Bouatou,2 Françoise Hamelin,1 Yves Vaucher,3
1 Geneva University Hospital, Geneva, Switzerland; 2Saitama, Japan

Background: Antiretroviral therapy (ART) improved HIV patient survival. However, metabolic complications such as dyslipidemia or lipodystrophy (LD) are the hallmark of first generation ART. Growing evidence points towards a role of lipid disturbances in chronic kidney disease (CKD). Also, as the HIV population is aging, identification of risk factors for (CKD) is crucial since both classical and HIV-related risk factors for CKD are highly prevalent among these patients. We studied the cumulative exposure to LD as an independent risk factor for CKD in HIV patients.

Methods: All patients from the Swiss HIV Cohort Study with an estimated glomerular filtration rate (eGFR) > 60 ml/min/1.73 m² at baseline (i.e. at entry in the cohort) and more than 3 months of follow-up from January 2002 to December 2015 were included. The primary endpoint was defined as a sustained eGFR < 60 ml/min/1.73 m². The secondary endpoint was sustained albuminuria (dipstick). Cox regression models were used to measure the risk to develop CKD associated with cumulative exposure to different patterns of LD.

Results: Among the 5'384 patients included, 4'246 did not have LD at entry in the cohort. 31.0% developed at least once LD during their follow-up after a median time of 17.1 months (IQR: 9.45-2.2 months) and 252 (4.7%) reached the primary endpoint after a median follow-up of 43.7 months from baseline (IQR: 18.5-89.3 months). Overall exposure to LD increased significantly the risk of an eGFR < 60 ml/min/1.73 m² in univariate analysis with a hazard ratio (HR) 2.25 (95% confidence interval (CI): 1.68-3.10; p<0.0001). After adjustment for main confounders, LD increased the risk of eGFR < 60 ml/min/1.73 m² by a HR 1.98 (95% CI: 1.31-2.99; p = 0.0001). LD was not significantly associated with the development of albuminuria.

Conclusions: LD might be a risk factor for eGFR decline independently of previously reported risk factors for CKD.

FR-PO387
Artificial Intelligence Improves CKD Progression Forecasts
Luca Neri, Francesco Belloccchio, Carlo Barbieri, Flavio Mari, Ulrich Tschuluna, Stefano Stuard. Fresenius Medical Care, Bad Homburg, Germany.

Background: Accurate CKD progression forecasts are key to tailor interventions to real patients needs. Current prognostic tools rely on few dominant variables (e.g. eGFR, albuminuria) and do not incorporate potentially important patterns of association (e.g. interactions). Hence, their performance is suboptimal for high and low risk patients (i.e. early stages of CKD). We developed a risk score addressing such weaknesses with machine learning.

Methods: CKD patients (stages 3-5) registered in EuCidR (2011-2015) entered the study cohort. Entropies were Kidney Failure (KF) within 2 and 5 years. The algorithm was derived with random forest (RF) and tested in a partition of the original sample which was not used to develop the model. The RF algorithm exploited 82 variables. To reflect real-life clinical practice, in the validation study, the algorithm calculated a risk score for each patient based on non-missing variables abstracted from electronic clinical charts. We computed model AUC and calibration curves. We compared the predictive accuracy of RF against Tanger’s Kidney Failure Risk Score (KFRS)

Results: Among 4064 patients, 2685 and 1672 patients had 2 and 5 years of follow up (fig. 1). Most influential variables for KF at 2 years were eGFR, its rate of change, proteinuria, body mass, haemoglobin, Charlson’s index, phosphate. Most influential variables for KF at 5 years were blood pressure, CKD-BMD markers, eGFR, proteinuria, serum albumin, heart rate. RF outperformed KFRS both in the whole sample and among CKD3a patients (Fig 1).

Conclusions: Contrary to KFRS, the performance of RF was stable at different CKD stages and was less dependent on initial GFR and albuminuria. Differences in forecast accuracy between RF and KFRS equations may lead to very large reductions in healthcare cost and clinical risk due to unnecessary medical encounters.

FR-PO388
Time-Centered Approach to Understanding Progression of CKD

Background: Traditional approaches to modeling risk of CKD progression do not provide estimates of the time it takes for disease progression to occur by stage of CKD, or the extent to which risk factors may differentially affect the time spent in various CKD stages.

Methods: We used mixed models to estimate person-specific trajectories of renal function among 3682 participants of Chronic Renal Insufficiency Cohort (CRIC), a longitudinal study of persons with CKD. We then used these trajectories to estimate time spent in each CKD stage and compared these times according to combinations of risk factors associated with disease progression.

Results: During 9.5 years of median follow-up, participants spent longer in earlier than later CKD stages, ranging from 9.5 yrs in stage 3 to 0.7 yrs in stage 5 (Figure 1). Risk factors were associated with larger differences in duration in the earlier vs. later stages of CKD. For example, median duration of CKD was over 8 years shorter in stage 3a, 6 years shorter in stage 3b, but only 5.3 months shorter in stage 5 for those with proteinuria >1 g/g (vs. <1 g/g) [Figure 1]. Participants with controlled diabetes (AIC < 7.5%) and without proteinuria spent the longest time in CKD stage 3 [Figure 2a], but spent similar amount of time in stage 5 as participants with uncontrolled diabetes and proteinuria. We also found profound differences in the time spent in CKD stages by presence or absence of proteinuria and uncontrolled systolic BP (a140 mm Hg) [Figure 2b].

Conclusions: We found marked variations in the time spent in the different stages of CKD based on different risk factors. Time-based metrics of CKD progression may help convey prognostic information to patients and guide clinical decisions, such as timing of access placement and RRT.

Funding: Other NIH Support - NHLBI
FR-PO389
Long Term Effects of Intensive Low Salt Diet Education on Deterioration of Glomerular Filtration Rate among Non-Diabetic Hypertensive Patients with CKD
Anna Lee,1 Ho Jun Chin,2 SNBH, Gyeonggi-do, Democratic People's Republic of Korea; 2Seoul National University Bundang Hospital, Seong nam, Republic of Korea.

Background: We conducted a prospective cohort study to investigate whether lower dietary salt intake and the intensive low salt diet education are effective to reduce the rate of GFR decline among hypertensive CKD patients.

Methods: This study included 171 participants in the previous open-label, case-controlled, randomized clinical trial including 245 hypertensive CKD patients who took an intensive low salt diet education.

Results: Follow-up was 57±18.7 weeks. 47 (20.4%) patients reached the endpoint (log) uUMOD concentrations were significantly associated with (log) eGFR and (log) proteinuria (r=0.554 and r=-0.429, p<0.001 resp.). In a multivariable Cox-regression analysis, the two quartiles with the lowest uUMOD concentrations were at increased risk for ESRD/rapid eGFR loss with a hazard ratio (HR) of 3.589 (lowest quartile, uUMOD ± 2.6 µg/mL, 95%-confidence interval (CI) 1.002-12.992, p=0.049) and 5.409 (second lowest quartile, uUMOD 2.7-7.45 µg/mL, 95%-CI 1.444-20.269, p=0.011) in comparison to the highest quartile (≥ 11.45 µg/mL), respectively. In ROC-analysis, uUMOD predicted the endpoint with good sensitivity (74.6%) and specificity (76.6%) at an optimal-cut-off at 3.5 µg/mL and area-under-the-curve of 0.786 (95%-CI 0.712-0.860, p<0.001).

Conclusions: uUMOD was independently associated ESRD/rapid loss of eGFR. It might serve as a robust predictor of rapid kidney function decline and help to better schedule arrangements for future treatment.

FR-PO389 Urinary Uromodulin Independently Predicts ESRD and Rapid Kidney Function Decline in CKD Patients
Dominik Steubl, Klinikum rechts der Isar, Munich, Germany. Group/Team: Munich Uromodulin Study Group.

Background: Urinary uromodulin (uUMOD), exclusively secreted by the ascending limb of the loop of Henle and therefore a marker of tubular function has been shown to be a strong predictor of long term CKD progression and cardiovascular mortality. Data on risk factors predicting rapid progression to end-stage-renal-disease (ESRD) or rapid kidney function decline in chronic kidney disease (CKD) are rare but urgently needed to plan treatment. This article describes the predictive value of uUMOD for rapid progression of CKD.

Methods: We assessed uUMOD, demographic/treatment parameters, estimated glomerular filtration rate (eGFR) and proteinuria in 230 CKD patients stage I-V. ESRD was registered at the end of a follow-up of one year as the outcome variables. Association between logarithmic (log) uUMOD and (log) eGFR/proteinuria was calculated using linear regression analysis adjusted for demographic parameters. We performed multivariable Cox regression analysis to evaluate uUMOD as a predictor. Therefore, patients were categorized into quartiles. The predictive value was further assessed using receiver-operating-curve (ROC) analysis.

Results: Follow-up was 6.1±2.6 years. 501 (20.4%) patients reached the endpoint. (log) uUMOD concentrations were significantly associated with (log) eGFR and (log) proteinuria (r=0.554 and r=-0.429, p<0.001 resp.). In a multivariable Cox-regression analysis, the two quartiles with the lowest uUMOD concentrations were at increased risk for ESRD/rapid eGFR loss with a hazard ratio (HR) of 3.589 (lowest quartile, uUMOD ± 2.6 µg/mL, 95%-confidence interval (CI) 1.002-12.992, p=0.049) and 5.409 (second lowest quartile, uUMOD 2.7-7.45 µg/mL, 95%-CI 1.444-20.269, p=0.011) in comparison to the highest quartile (≥ 11.45 µg/mL), respectively. In ROC-analysis, uUMOD predicted the endpoint with good sensitivity (74.6%) and specificity (76.6%) at an optimal-cut-off at 3.5 µg/mL and area-under-the-curve of 0.786 (95%-CI 0.712-0.860, p<0.001).

Conclusions: uUMOD was independently associated ESRD/rapid loss of eGFR. It might serve as a robust predictor of rapid kidney function decline and help to better schedule arrangements for future treatment.

FR-PO391 Anemia Is a Risk Factor for Incident ESRD
Santosh Saraf,6 Jesse Y. Hus,3 Jing Chen,1 Teresa K. Chen,2 Michael J. Fischer,4 L. Lee Hamm,5 Rupal Mehta,6 James H. Sondheimer,1 Matthew R. Weir,2 Xiaoming Zhang,4 Ana C. Ricardo,6 James P. Lash,6 Johns Hopkins University School of Medicine, Baltimore, MD; 7Northwestern University, Feinberg School of Medicine, Chicago, IL; 8Tulane School of Medicine, New Orleans, LA; 9Tulane University School of Medicine, New Orleans, LA; 10University of Illinois Hospital and Health Sciences Center, Chicago, IL; 11University of Illinois at Chicago, Chicago, IL; 12University of Maryland School of Medicine, Baltimore, MD; 13University of Pennsylvania, Philadelphia, PA; 14Wayne State University School of Medicine, Detroit, MI.

Background: Although anemia is a consequence of chronic kidney disease (CKD), anemia itself may accelerate CKD progression. However, the data regarding the impact of anemia on the progression of CKD are inconsistent.

Methods: We used Cox proportional hazards to examine the association of baseline anemia on the World Health Organization criteria of anemia (Hgb <12 g/dL in women and <13 g/dL in men) with incident end-stage renal disease (ESRD) and all-cause death using data from the Chronic Renal Insuficiency Cohort Study.

Results: The study included 3,919 participants with CKD (mean age 58 years, 45% female, 42% white, 42% black, 13% Hispanic, mean estimated glomerular filtration rate (eGFR) 45 ml/min/1.73 m², and median proteinuria 0.19 g/24 h). At study entry, 1,859 (47.4%) of participants had anemia. Compared to individuals without anemia, those with anemia were older, more likely to be black or Hispanic, have lower mean eGFR and more anemia itself may accelerate CKD progression. However, the data regarding the impact of anemia on the progression of CKD are inconsistent.

The study included 3,919 participants with CKD (mean age 58 years, 45% female, 42% white, 42% black, 13% Hispanic, mean estimated glomerular filtration rate (eGFR) 45 ml/min/1.73 m², and median proteinuria 0.19 g/24 h). At study entry, 1,859 (47.4%) of participants had anemia. Compared to individuals without anemia, those with anemia were older, more likely to be black or Hispanic, have lower mean eGFR and more

Conclusions:

(a) Adjusted for center
(b) Further adjusted for age, sex, race/ethnicity, education, income
(c) Further adjusted for systolic blood pressure, waist circumference, cardiovascular disease, HgbA1c, phosphate, C-reactive protein, eGFR, proteinuria, ACE-inhibitor/ARB, beta blocker, erythropoiesis stimulating agent

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO392
The Association between Kidney Function and Genetic Polymorphisms among Japanese Male Employees Takahiro Imazumi, Sawako Kato, Shoichi Maruyama. Nagoya University Graduate School of Medicine, Nagoya, Japan.

Background: Previous studies have implicated several single nucleotide polymorphisms (SNPs) in predisposition to chronic kidney disease (CKD). Though arteriosclerotic disease is deeply involved in the incidence of CKD, whether SNPs related to arteriosclerosis are involved in CKD remains unclear. The purpose of this study was to identify SNPs that confers susceptibility to CKD and to examine whether the risk allele accumulation is associated with CKD.

Methods: We conducted a cross-sectional study using data of 4814 male workers which contained 432 participants with CKD to examine the association between eGF and 59 candidate polymorphisms (17 CKD and 42 arteriosclerotic diseases). We defined the genetic risk score (GRS) as the total number of risk alleles that showed a significant association in this examined, and analyzed the relationship with CKD (eGF < 60 ml/min/1.73m2).

Results: We found eight candidate SNPs with P value < 0.05 (CXCCL1 rs3732379, SHROOM3 rs17319721, MTP rs1808059, PPARG rs4474172, APOA5 rs662799, BRAP rs782886, SPATA1L rs2467853, and MCP1 rs3062411) in the multivariable linear regression adjusted for age, BMI, systolic blood pressure, and fasting blood glucose. Among these 8 SNPs, BRAP rs782886 and SPATA1L rs2467853 were significantly associated with eGF (false discovery rate < 0.05). GRS was significantly associated with CKD [ Odds ratio, 1.17, 95% confidence interval, 1.09-1.26]. C-Statistics improved from 0.77 to 0.80 by adding SNPs significant in this study (P = 0.006). However, adding GRS significantly improved IDI and cNRI (0.0057, P = 0.0002, 0.212, 0.0 < P < 0.001, respectively).

Conclusions: After adjustment for clinical factors, kidney function was associated with BRAP rs782886 and SPATA1L rs2467853 and the GRS for CKD that we developed was associated with CKD.

Funding: Commercial Support - Toyota motor corporation Support - Non-U.S.

FR-PO393
Fibroblast Growth Factor 23 and Kidney Function Decline: The Health Aging and Body Composition Study David A. Drew, Ronit Katz, Stephen Kritchevsky, Joan H. Ix, Michael Shlipak, Anne B. Newman, Linda F. Fried, Mark J. Sarnak, Orlando M. Gutierrez. 1San Francisco VA Medical Center, San Francisco, CA; 2University of Pittsburgh, Pittsburgh, PA; 3Temple Main Medical, MA; 4Wake Forest School of Medicine, Winston-Salem, NC.

Background: Fibroblast growth factor 23 (FGF-23) is a potential biomarker for kidney disease. Previous studies have shown FGF-23 to be a risk factor for incident end-stage renal disease (ESRD); however, there are less data on the association of FGF-23 with earlier kidney related outcomes.

Methods: The FGF-23 study was initiated using an initial ELISA assay in 2,496 participants of the Healthy Aging and Body Composition Study, a cohort of well-functioning older adults. Kidney function was estimated by assaying cystatin C at the commencement of renal replacement therapy or reaching eGFR <10 ml/min, death, loss to follow-up, or December 2014 were sampled in this retrospective observational study. Estimated Glomerular Filtration Rate (eGFR) as measured by CKD-EPI formula was collected for all patients from study start date (date of Ultrasound) until the study end which included diagnosis of CKD confirmed at medical record review). The hazard ratio (HR) for CKD was estimated with Cox proportional hazards modeling adjusting for age, BMI, systolic blood pressure, and fasting blood glucose. Results: Of the 3061 patients registered in the SKS, 1419 patients had US imaging of the kidneys. GFR was associated with cystatin C at baseline and years 3 and 10. The associations between FGF-23 and decline in kidney function remained significant estimated glomerular filtration rate (eGFR) decline ≥30% or ≥3 ml/min/year and incident CKD (incident eGFR <60ml/min/1.73 m2 and a ≥3 ml/min/year decline) were evaluated. Models were adjusted for demographics, baseline eGFR, urine albumin/creatinine ratio, comorbidity, and serum calcium, phosphorus and parathyroid hormone.

Results: The mean (SD) age was 75 (3) years, with 52% female, and 38% black. There were 405 persons with 30% decline, 702 with > 3 ml/min/year decline, and 536 with incident CKD. In fully adjusted continuous models, FGF-23 concentrations were not associated with kidney function decline (OR [95%CI] = 0.99 [0.82, 1.19] for ≥30% decline and OR= 1.16 [0.99, 1.36] for ≥3 ml/min/year decline), or incident CKD (IRR= 1.05 [0.91, 1.22]) per two fold higher FGF-23 level). In quartile analysis, the highest quartile of FGF-23 was significantly correlated with incident CKD (IRR= 1.26 [1.02, 1.57] for highest vs lowest quartile).

Conclusions: Higher FGF-23 concentrations were not consistently associated with decline in kidney function or incident CKD in community-dwelling older adults.

Funding: NIDDK Support, Other NIH Support - National Institute on Aging (NIA). Contracts N01-AG-6-2101; N01-AG-6-2103; N01-AG-6-2106; NIA grant R01-AG0288050

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

Underline represents presenting author.

502

FR-PO394

Background: Premenopausal women who undergo bilateral oophorectomy are at an increased risk for morbidity and mortality. Given the potential benefits of estrogen on renal structure and function, we hypothesized that women who undergo bilateral oophorectomy are at an increased risk of chronic kidney disease (CKD).

Methods: All premenopausal women who underwent bilateral oophorectomy for a noncancerous condition before age 50 years from 1/1/1988 to 12/31/2007 in Olmsted County, MN were identified and age-matched (±1 year) to referent women who did not undergo oophorectomy. We defined in 2 ways: (1) serum creatinine-based definition (Cr > 1.1 mg/dl on two occasions, greater than 90 days apart) and (2) medical record diagnosis of CKD (screening for diagnosis codes and confirmation by medical record review). The incidence (IRR) for CKD was estimated with Cox proportional hazards models using age as the time scale. Women with CKD before index were excluded from the analyses. Inverse probability weighting was used to balance the two cohorts with respect to 17 chronic diseases at the time of oophorectomy (or index date), age, education, race, BMI, smoking, and calendar year.

Results: There were 1,653 women with bilateral oophorectomy and 1,637 referent women, and the median length of follow-up was 14 years in both cohorts. Using the serum Cr-based definition, 69 referent women and 120 women with bilateral oophorectomy developed CKD, with an adjusted HR of 1.48 (95% CI 1.10-1.99). The adjusted HR was higher in women who underwent oophorectomy at age ≥45 years (HR 1.74 (95% CI 1.15-2.63). In a subgroup analysis of women without any chronic diseases at the index date, the risk of CKD remained significant (HR 1.85, 95% CI 1.12-3.05). Using the diagnosis of CKD confirmed at medical record review, 43 referent women and 61 women with bilateral oophorectomy developed CKD, with an adjusted HR of 1.17 (95% CI 0.79-1.74).

Conclusions: Premenopausal women who undergo bilateral oophorectomy are at an increased risk of developing CKD, even after adjusting for multiple chronic conditions. This risk may be due to the abrupt drop in systemic estrogen levels after surgery. Further research into the mechanisms of renal injury and the correct dosage of hormone replacement after oophorectomy is needed.

Funding: Other NIH Support - The study used the resources of the Rochester Epidemiology Project, which is supported by the National Institute on Aging of the National Institutes of Health [R01 AG004875]. This study was also supported by funds from the Mayo Clinic Research Committee (to W.A.R.). W.A.R. was partly supported by the National Institutes of Health [R01 AG052425, P50 AG046170, U01 AG006786, and P01 AG048875].

FR-PO395
Non-Alcoholic Fatty Liver Disease Does Not Accelerate Progressive Renal Progression in Non-Dialysis CKD Raikumar Chinnadurai, Diana Vassallo, Philip A. Kalra. SALFORD ROYAL NHS FOUNDATION TRUST, Manchester, United Kingdom.

Background: Non-Alcoholic Fatty liver disease (NAFLD) is strongly associated with increased incidence and high prevalence of Chronic Kidney Disease (CKD). The association of NAFLD with renal disease progression in non-dialysis dependent CKD (NDD-CKD) has not been explored. Our aim is to access the impact of NAFLD on the rate of progression of CKD.

Methods: All patients recruited in the Salford Kidney Study (SKS)/Large prospective CKD database who had an ultrasound(UlS) of the liver performed between January 2000 and December 2014 were sampled in this retrospective observational study. Estimated Glomerular Filtration Rate (eGFR) as measured by CKD-EPI formula was collected for all patients from start date (date of Ultrasound) until the end date which included commencement of renal replacement therapy or reaching eGFR <60 ml/min, death, loss to follow-up or censoring at 31 December 2015. The rate of decline in eGFR was calculated by the slope of linear regression in the total sample and a matched group obtained after propensity score matching of all baseline characteristics. All analysis was undertaken in SPSS.

Results: Of the 3061 patients registered in the SKS, 1419 patients had US imaging of the liver, either bespoke or as part of a general abdominal scan, during the study period. After excluding patients based on pre-set criteria, a sample of 852 (183 NAFLD and 669 non-NAFLD) patients with complete datasets remained. By Propensity Score matching 138 patients with and without NAFLD were matched. At baseline, the median age of the study group was 66 years, and median eGFR was 33.5 ml/min/1.73m2. Patients with NAFLD had more hypertension, diabetes mellitus and hypercholesterolemia. Body Mass Index significantly higher in the NAFLD group 31.7±3.7 vs 30.0±3.5 kg/m2. Follow-up time was 73 months with no difference between groups(p=0.176). In terms of CKD progression, there was no difference in the rate of decline of eGFR between
CKD: Risk Factors for Incidence and Progression - I

FR-PO396

Particulate Matter Air Pollution and the Risk of Incident CKD and Progression to ESRD
Benjamin C. Bowe, Yan Xie, Tingting Li, Yan Yan, Hong Xian, Ziayi Al-Aly.

Methods: We linked the Environmental Protection Agency and the Department of Veterans Affairs databases to build an observational cohort of 2,482,737 United States veterans, and used survival models to evaluate the association of PM2.5 concentrations and risk of incident CKD, eGFR decline, and ESRD. County-level exposure was defined as baseline as the average annual PM2.5 concentrations in 2004, and separately as time-varying where it was updated annually and as cohort participants moved.

Results: Over a median follow-up of 8.52 years (IQR: 8.04–8.80), where exposure was defined at baseline (median 11.8 µg/m3; IQR: 10.1–13.7), a 10 µg/m3 increase in PM2.5 concentration was associated with increased risk of eGFR <60 ml/min/1.73m² (Hazard Ratio (HR)=1.21; 95% Confidence Interval (CI)=1.14–1.29); CKD (HR=1.27; CI=1.17–1.38); eGFR decline air pollution adversely impacted kidney health. Prior work examined the association of PM10 concentrations and risk of kidney outcomes. Exposure estimates derived from NASA's satellite data yielded consistent results.

Conclusions: Our findings demonstrate a significant association between exposure to ambient fine particulate matter and risk of incident CKD, eGFR decline, and ESRD.

Funding: Veterans Affairs Support

FR-PO397

Ambient Coarse Particulate Matter, Nitrogen Dioxide, Carbon Monoxide, and the Risk of Kidney Disease
Benjamin C. Bowe, Yan Xie, Tingting Li, Yan Yan, Hong Xian, Ziayi Al-Aly.

Methods: We merged multiple large databases including those of the Environmental Protection Agency and the Department of Veterans Affairs to build a longitudinal observational cohort of 2,201,969 United States veterans, and used survival models to evaluate the association of PM10 concentrations and risk of incident eGFR <60 ml/min/1.73m², incident CKD, eGFR decline ≥30%, and ESRD. Exposure was treated as time-varying where it was updated annually and as cohort participants moved.

Results: Over a median follow-up of 8.52 years (IQR: 8.05–8.80), an interquartile range (IQR) of NOx (10 µg/m3) was associated with increased risk of eGFR <60 ml/min/1.73m², HR=1.07 (CI=1.06–1.08), HR=1.09 (CI=1.08–1.10), and HR=1.09 (CI=1.08–1.10), respectively. An IQR increase in concentrations of PM10 NOx, and CO was associated with increased risk of incident CKD, HR=1.07 (CI=1.05–1.08), HR=1.08 (CI=1.06–1.10), and HR=1.10 (CI=1.06–1.11), respectively. An IQR increase of PM2.5 NOx, and CO concentrations was associated with increased risk of eGFR decline ≥30%, HR=1.08 (CI=1.07–1.10), HR=1.12 (CI=1.10–1.13), HR=1.09 (CI=1.08–1.10), respectively. An IQR increase in concentrations of PM10 NOx, and CO was associated with increased risk of ESRD; HR=1.09 (CI=1.06–1.12), HR=1.10 (CI=1.06–1.12), and HR=1.05 (CI=1.02–1.08), respectively. Spline analyses suggested a monotonic increasing relationship between PM10 NOx, and CO concentrations and risk of kidney outcomes.

Conclusions: Our results demonstrate that environmental exposure to higher levels of PM10 NOx, and CO is associated with increased risk of incident CKD, eGFR decline, and ESRD.

Funding: Veterans Affairs Support

FR-PO398

Urinary Iron and Oxidative Stress: Association with Megalin in CKD

Al-Aly.1,3 Hong Li,1,3 Yan Yan,1,3

Methods: We measured the initial serum Mg level in 418 children enrolled in the first cohort of the Chronic Kidney Disease in Children (CKD) study. Participants were grouped into low Mg (< 1.7 mg/dL, n=84, 20%), intermediate Mg (1.7–1.9 mg/dL, n=217, 52%) or high Mg (2.0–2.7 mg/dL, n=117, 28%) categories. Using parametric failure-time models, we evaluated the association between Mg level and CKD progression, defined as the time to the composite event of renal replacement therapy (dialysis or kidney transplant) or 50% decline in estimated glomerular filtration rate (eGFR) after adjustment for the following potential confounders: initial eGFR, proteinuria, age, sex, race, BMI, Tanner stage, anemia, hypertension, and CKD diagnosis.

Results: Median age was 11 years, 62% were male and 58% non-Hispanic white. Median eGFR and urine protein-to-creatinine (UPC) ratio were 45.3 ml/min/1.73m² and 0.4 mg/mg, respectively, 21% of the children had a glomerular diagnosis. The baseline characteristics of the patients in the three groups were not significantly different with regard to all potential confounders except initial eGFR and proteinuria. Participants in the low Mg group had a significantly higher baseline eGFR, and lower UPC ratio compared to those in the high Mg category (median [IQR]: 51 [41, 63] vs. 37 [29, 50] and 0.3 [0.1, 0.6] vs. 0.2 [0.1, 0.7], respectively). Mg levels were not significantly different for patients on diuretics (n=28), calcium inhibitors (n=14), or Mg supplements (n=7). After adjustment for potential confounders, the relative times to either 50% decline in eGFR or renal replacement therapy were not significantly different among Mg groups.

Conclusions: Hypomagnesemia (Mg <1.7 mg/dL) is associated with more rapid progression of pedal CKD. Higher Mg levels (Mg ≥2.0 mg/dL) do not correlate with more rapid progression of pediatric CKD either.

Funding: NIDDK Support, Private Foundation Support

FR-PO399

Magnesium and Progression of CKD in Children Enrolled in the CKD Study

Martin A. Turman,1,3 Aisha Betoko,1,3 George J. Schwartz,1,3 Susan L. Furth,1,3 Bradley A. Warday,1,3 Phoenix Children’s Hospital, Phoenix, AZ; 1The Children’s Mercy Hospital, Kansas City, MO; 2University of Rochester, Rochester, NY; 3Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; 4The Children’s Hospital of Philadelphia, Philadelphia, PA.

Background: Studies in adults with CKD demonstrate that lower magnesium (Mg) levels correlate with more rapid progression of CKD. We hypothesized that hypomagnesemia is associated with faster progression in children with CKD.

Methods: We measured the initial serum Mg level in 418 children enrolled in the first cohort of the Chronic Kidney Disease in Children (CKD) study. Participants were grouped into low Mg (< 1.7 mg/dL, n=84, 20%), intermediate Mg (1.7–1.9 mg/dL, n=217, 52%) or high Mg (2.0–2.7 mg/dL, n=117, 28%) categories. Using parametric failure-time models, we evaluated the association between Mg level and CKD progression, defined as the time to the composite event of renal replacement therapy (dialysis or kidney transplant) or 50% decline in estimated glomerular filtration rate (eGFR) after adjustment for the following potential confounders: initial eGFR, proteinuria, age, sex, race, BMI, Tanner stage, anemia, hypertension, and CKD diagnosis.

Results: Median age was 11 years, 62% were male and 58% non-Hispanic white. Median eGFR and urine protein-to-creatinine (UPC) ratio were 45.3 ml/min/1.73m² and 0.4 mg/mg, respectively, 21% of the children had a glomerular diagnosis. The baseline characteristics of the patients in the three groups were not significantly different with regard to all potential confounders except initial eGFR and proteinuria. Participants in the low Mg group had a significantly higher baseline eGFR, and lower UPC ratio compared to those in the high Mg category (median [IQR]: 51 [41, 63] vs. 37 [29, 50] and 0.3 [0.1, 0.6] vs. 0.2 [0.1, 0.7], respectively). Mg levels were not significantly different for patients on diuretics (n=28), calcium inhibitors (n=14), or Mg supplements (n=7). After adjustment for potential confounders, the relative times to either 50% decline in eGFR or renal replacement therapy were not significantly different among Mg groups.

Conclusions: Hypomagnesemia (Mg <1.7 mg/dL) is associated with more rapid progression of pediatric CKD. Higher Mg levels (Mg ≥2.0 mg/dL) do not correlate with more rapid progression of pediatric CKD either.

Funding: NIDDK Support, Private Foundation Support

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

Understanding represents presenting author.
FR-PO400

CKD Self-Management: Identifying Phenotypes and Associations with Renal and Cardiovascular Outcomes

Sarah J. Schrauben,1 Jesse Y. Hsu,1 Sylvia E. Rosas,2 Rajat Deo,2 Bernard G. Jaar,3 Georges Saab,2 Swati Lederer,2 Jing Chen,2 Ana C. Ricardo,2 James P. Lash,2 Harold I. Feldman,2 Amanda H. Anderson.1 1U Penn, Philadelphia, PA; 2CRIC, Bethesda, MD.

Background: In the effort to slow chronic kidney disease (CKD) progression and its complications, patients need to engage in self-management behaviors. This study evaluated CKD-SMB management behaviors (CKD-SMB) by identifying patterns of engagement into groups (or phenotypes), and evaluating the association of these phenotypes with renal and cardiovascular outcomes, and death.

Methods: Data from the Chronic Renal Insufficiency Cohort (CRIC) Study were analyzed using a clustering technique, latent class analysis (LCA), to identify CKD-SMB phenotypes stratified by diabetes status. The original CRIC cohort (N=3939) was the derivation cohort, and 1,560 participants subsequently recruited served as the validation cohort. LCA was based on the following measures of CKD-SMB: BMI, diet, physical activity, blood pressure, smoking status, and hemoglobin A1c (if diabetic), which were dichotomized into “recommended” and “not recommended”. Cox proportional hazards models calculated hazard ratios (HRs, 95% CI) of phenotypes for CKD progression, atherosclerotic and heart failure (HF) events, and death.

Results: Three CKD-SMB phenotypes were identified separately among diabetics (DM) and non-diabetics (ND) that varied by level of engagement in recommended CKD-SMB, with Phenotype I being the most engaged, Phenotype II moderately engaged, and Phenotype III, the least engaged. In multivariable-adjusted models, Phenotype III was strongly associated with CKD progression, atherosclerotic events, and death among both DM and ND, and Phenotype II was associated with atherosclerotic events in DM and with death in ND (Table). Conclusion: This study demonstrates there are potentially three CKD-SMB phenotypes that distinguish an individual for clinical outcomes. Given the rise of CKD and its complications, CKD-SMB phenotypes could identify high-risk groups and guide management.

Funding: NIDDK Support

Associations (HR, 95% CI) of Clinical Outcomes by CKD-SMB Phenotypes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>DM</th>
<th>ND</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FR-PO401

Factors Associated with Rapid CKD Progression in a Special Predialysis Population Under Strict Volume Control

Olimpia Ortega,1 Zosia K. Baranow,2 Melissa Vasquez,2 Diego Navazo, Rocio Camacho, Maria Sanchez, Cristina Di Gioia, Paolina Gallar, Aniana Oliet, Milagros Ortiz, Carmen Mon, Juan Carlos Herrero. Nephrology, Hospital Severo Ochoa, Leganes, Spain.

Background: Fluid overload has emerged recently as an independent predictor of chronic kidney disease (CKD) progression among patients with CKD. Fluid overload control has been our priority for many years in our predialysis outpatient unit using a strategy of strict volume control. The aim of this study was to analyse the hydration status achieved in our patient and to evaluate the independent factors associated with rapid CKD progression or the initiation of dialysis in this special population.

Methods: 99 patients with CKD stages 4 and 5 were enrolled and followed for 2.9 ± 1.4 years. All patients were under a strict volume control strategy based on clinical criteria. Body composition monitor was used to analyse the hydration status achieved in our patients. Patients were organized in tertiles of percentage annual GFR decline. Univariate and multivariate logistic regression analysis were used to evaluate the independent factors associated with rapid CKD progression (tertile 3, cutoff value=15%). Cox proportional hazard model was used to analyse the independent factors associated with the initiation of dialysis.

Results: Fluid overload in the whole population was 0.17 (±0.4 to 0.98) and median relative hydration status (fluid overload/ECW) was 1.4% (±2.25 to 5.2%). During the 4 year period 17 patients initiate dialysis and 3 patients died. Multivariate logistic regression analysis shows that only NT-proBNP levels (OR 1.01; 95% CI 1.00-1.03; p=0.04) and proteinuria (OR 1.60; 95% CI 1.12-2.39; p=0.03) were associated with rapid CKD progression (tertile 3). The independent factors associated with the initiation of dialysis were in addition to proteinuria (OR 1.00; 95% CI 1.00-1.00; p=0.005), proteinuria (HR 4.4; 95% CI 1.23-16.1; p=0.02) and low plasma albumin (HR 0.002; 95% CI 0.000-0.69; p=0.04), Fluid overload was not associated with rapid CKD progression nor with the start of dialysis.

Conclusion: A practically normohydration status can be achieved even in patients with advanced CKD using a strategy of strict volume control. In this setting, NT-proBNP levels, reflecting increased left ventricular filling pressure and not fluid overload by itself, are associated with rapid CKD progression and the initiation of dialysis.

FR-PO402

Biologic Use and Incident CKD in Rheumatoid Arthritis

Keiichi Sumida,1 Miklos Z. Molnar,2 Praveen Kumar Potukuchi,3 Fatima Hassan,2 Fridjof Thomas,4 Kunihiro Yamagata,4 Kamyar Kalantar-Zadeh,2 Csaba P. Kovessy,1 1Nephrology Center, Toranomon Hospital Kajigaya, Kawasaki, Japan; 2University of California Irvine, School of Medicine, Orange, CA; 3University of Tennessee Health Science Center, Memphis, TN; 4University of Tsukuba, Tsukuba, Japan.

Background: Rheumatoid arthritis (RA) is associated with reduced kidney function, possibly due to chronic inflammation or the use of nephrotoxic therapies. Little is known about the effects of RA therapy using novel non-nephrotoxic biologic agents on the risk of incident CKD.

Methods: In a nationwide cohort of 20,757 U.S. veterans with an eGFR ≥60 mL/min/1.73 m² who were newly diagnosed with RA between 2004 and 2006, with follow-up through 2013, we examined the association of the use of biologic agents with incident CKD (>25% decrease in eGFR reaching <60 mL/min/1.73m²) and change in eGFR (<−3, −3<−0 [reference], and ≥0 mL/min/1.73m²/year), using time-dependent Cox models and multilinear logistic regression models, respectively, with adjustment for potential confounders.

Results: After multivariable adjustment, patients receiving (vs. not receiving) biologic treatment had a lower risk of incident CKD (adjusted HRs [95% CI], 0.83 [0.72-0.96]) and progressive eGFR decline (adjusted multivarional ORs [95% CI] for eGFR slopes <-3 and −3<−0 mL/min/1.73m²/year, 0.82 [0.72-0.95] and 1.03 [0.95-1.12], respectively) (Figure). A significant deceleration of eGFR decline was also observed after biologic administration in patients treated with biologics (1.01±1.9 vs. 0.4±0.2 mL/min/1.73m²/year) before and after biologic use, respectively, P<0.001.

Conclusions: Biologic treatment was independently associated with lower risk of incident CKD and progressive eGFR decline. Clinical trials are warranted to test whether active interventions with biologic agents can prevent adverse renal outcomes associated with RA.

Funding: NIDDK Support

Association of biologic treatment with (A) incident CKD and (B) change in eGFR

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biologics</td>
<td>0.83 (0.72-0.96)</td>
</tr>
</tbody>
</table>

FR-PO403

Changes in Albuminuria and Subsequent Risk of Incident Kidney Disease

Keiichi Sumida,1 Miklos Z. Molnar,2 Praveen Kumar Potukuchi,3 Koshy K. George,2 Fridjof Thomas,4 Jun Ling Lu,4 Kunihiro Yamagata,4 Kamyar Kalantar-Zadeh,2 Csaba P. Kovessy,1 1Nephrology Center, Toranomon Hospital Kajigaya, Kawasaki, Japan; 2University of California Irvine, School of Medicine, Orange, CA; 3University of Queensland, Memphis, TN; 4University of Tennessee Health Science Center, Memphis, TN; 5University of Tsukuba, Tsukuba, Japan.

Background: Albuminuria is a robust predictor of CKD progression. However, little is known about the associations of changes in albuminuria with the risk of kidney events outside the settings of clinical trials.

Methods: In a nationwide cohort of 56,946 U.S. veterans with at least two albuminuria measurements and an eGFR ≥60 mL/min/1.73 m² between 2004 and 2006, we examined the associations of 1-year fold changes in albuminuria with incident CKD (>25% decrease of eGFR upon reaching <60 mL/min/1.73 m²) and rapid eGFR decline (eGFR slope <−5 mL/min/1.73 m² per year), assessed using Cox models and logistic regression models, respectively, with adjustment for potential confounders.

Results: The mean (SD) age was 64.2 (10.4) years; 97% were male; and 91% were diabetic. There was a near linear association between 1-year fold changes in albuminuria and incident CKD (Figure). The multivariable-adjusted hazard ratios (95% CI) of incident CKD associated with 1-year albuminuria fold changes of <0.5, 0.5<−0.75, 0.75<−1.25, and ≥1.25 (vs. 0.75<−1.25) fold were 0.82 (0.76-0.88), 0.93 (0.86-1.00), 1.12 (1.05-1.20), and 1.29 (1.23-1.38), respectively. Qualitatively similar associations were present for rapid eGFR decline (adjusted odds ratios [95% CI] for albuminuria changes <0.5, 0.5<−0.75, 1.25<−2, and ≥2 (vs. 0.75<−1.25) fold, 0.86 [0.78-0.94], 0.98 [0.89-1.07], 1.18 [1.08-1.28], and 1.67 [1.54-1.81], respectively.

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

Underline represents presenting author.
FR-PO404

Complications of RAAS Blockade in Patients with Advanced CKD

Miklos Z. Molnar,1 Adnan Nasert,2 Keiichi Sumida,3 Ariel R. Rieszenman,4 Barry M. Wall,5 Praveen Kumar Potukuchi,6 Abduzhappar Gaipov,3 Elani Streja,1 Kamyar Kalantar-Zadeh,3 Csaba P. Kovessydy,4 Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; 2Nephrology Center, Toranomon Hospital Kajigaya, Kawasaki, Japan; 3University of California Irvine, School of Medicine, Orange, CA; 4University of Tennessee Health Science Center, Memphis, TN; 5University of Tennessee Health Science Center - Memphis, Memphis, TN; 6Veterans Affairs Medical Center, Memphis, TN.

Background: Renin-Angiotensin-Aldosterone system inhibitors (RAASi) are associated with slower progression of chronic kidney disease (CKD) and lower mortality in patients with CKD, yet their discontinuation is frequent. The reasons for not using or for stopping RAASi in patients with advanced CKD are unclear.

Methods: We examined 15,966 US veterans initiating dialysis during 2007-2014, who displayed three RAASi use patterns in the last 3 years pre-dialysis: 1) never used (n=7,294), 2) discontinued in the last year before dialysis (n=6,833) and 3) uninterrupted use (n=1,839). We defined AKI as a >25% decrease in eGFR and hyperkalemia as a potassium >5.5 mmol/l during the 3 years prior to dialysis. Associations of RAASi use patterns with incidence of AKI and hyperkalemia were examined in logistic regression models adjusted for demographics, comorbidities, blood pressure and eGFR.

Results: Patients were 72±11 years old, 98% male, 23% African-American, and 65% diabetic. Compared to patients who never used RAASi, uninterrupted and interrupted RAASi use were associated with 16% and 72% higher multivariable adjusted risk of AKI [Figure Panel A], and with 11% and 81% higher multivariable adjusted risk of hyperkalemia [Figure Panel B], respectively.

Conclusions: RAASi before dialysis is associated with higher risk of AKI and hyperkalemia. These complications (especially hyperkalemia) may contribute to the discontinuation of RAASi in patients with advanced CKD. Additional studies are needed to determine if measures aimed at alleviating hyperkalemia and AKI could lead to higher RAASi use and improved outcomes.

Funding: NIDDK Support

FR-PO405

Association between Serum Albumin Level and Incidence of ESRD in Patients with Immunoglobulin A Nephropathy: A Possible Role of Albumin as an Antioxidant Agent

Kazuhiko Koga, Fukuoka, Japan; 2Kyushu University, Graduate School of Medical Sciences, Fukuoka City, Japan; 3National Fukuoka-Higashi Medical Center, Koga, Fukuoka, Japan.

Background: Serum albumin is the most abundant intravascular protein and the major intravascular antioxidant. The association between serum albumin and the incidence of end-stage renal disease (ESRD) in patients with IgA nephropathy (IgAN) is not fully understood.

Methods: We retrospectively investigated 1,352 patients who were diagnosed with IgAN by biopsy from seven institutions in Japan between October 1979 and December 2010. Patients were divided into three groups by tertile of serum albumin value: Low group, Middle group, and High group (≤3.9 g/dL, 4.0–4.3 g/dL, ≥4.4 g/dL, respectively). The association between serum albumin level and the incidence of ESRD was assessed using a Cox proportional hazards model. We also conducted an experiment of dihydroethidium staining for detection of decrease in intracellular superoxide anion induced by hydrogen peroxide in albumin-pretreated mouse mesangial cells.

Results: During the median 5.1-year follow-up period, 152 patients (11.2%) developed ESRD. Participants in Low group had a 1.88-fold (95% confidence intervals, 1.15–3.20) higher risk of the incidence of ESRD than those in High group after adjustment for age, sex, systolic blood pressure, urinary protein excretion, body mass index, estimated glomerular filtration rate, total cholesterol, triglycerides, and pathological parameters of the Oxford classification (M, E, S, T) and extracapillary proliferation (Ex). Furthermore, in in vitro experiments, generation of intracellular superoxide anion, a major form of reactive oxygen species, by hydrogen peroxide was significantly attenuated in albumin-pretreated mouse mesangial cells compared with γ-globulin-pretreated cells.

Conclusions: Low serum albumin level is an independent risk factor of ESRD in patients with IgAN. The mechanism could be explained by the antioxidant capacity of serum albumin.


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

Underline represents presenting author.
FR-PO407

Tracking of Microalbuminuria and A1c in a High-Risk Zuni Population

Vallabh O. Shah, V. Shane Pankratz, Robert G. Nelson, Donica M. Gahlate, Jeanette Bobelu, National Institutes of Health, Phoenix, AZ; University of New Mexico Health Science Center, Albuquerque, NM.

Background: The Zuni Indians are disproportionately affected by diabetes and chronic kidney disease, signaling a need for effective community-based prevention efforts. We previously reported on the epidemic of kidney disease and its intermediate phenotypes, and described the heritability of these conditions. Recently, through a Patient Center Outcomes Research Institute (PCORI)-funded study of home-based kidney care (HBKC), we rescreened 314 Zuni participants and examined changes in a constellation of markers of kidney disease and diabetes in a subset of these participants.

Methods: Summaries of the risk factors in the 155 participants (73 [47%] female; mean [SD] age at baseline 33.7 [11.5] years) at three key time points shown in the table 1.

Results: The development of ESRD in 7 individuals in this study set of 155 participants with longitudinal follow-up underscores the high incidence of renal disease in this population. These incident cases of renal disease occurred in 2081.7 person-years of follow-up, leading to an estimated incidence rate of CKD in this population of 3.8 (95% CI: 1.9 – 7.7) events per 1000 person years.

Conclusions: This analysis of a cohort of individuals from the PCORI studied at 3 time points over up to 14.3 years shows significantly increasing UACR and A1C levels, and a high incidence of kidney disease. These findings reinforce the need for interventions to modify risk factors for CKD progression, such as our PCORI-supported pilot HBKC intervention in this high-risk population, particularly amongst young adult Zuni.

Funding: Other U.S. Government Support

Table 1: Time 1 (Yr 2000) Time 2 (Yr 2007) Time 3 (Yr 2004)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C</td>
<td>6.1 (1.14)</td>
<td>6.1 (1.4)</td>
<td>7.0 (2.0)</td>
</tr>
<tr>
<td>UACR</td>
<td>35 (15.0)</td>
<td>35 (33.7)</td>
<td>40 (28.9)</td>
</tr>
</tbody>
</table>

*Mean (SD). Repeated measures analysis of variance models were performed to test for trends in risk factors over time (P<0.05 indicates statistical significance).

FR-PO408

Arsenic Exposure and Incident ESRD in the Southern Community Cohort Study (SCCS)

Keri L. Cavanaugh, Edmond K. Kabagambe, Jennifer Morse, Thomas G. Stewart, Aaron B. Bowman, Yaofang Zhang, William J. Blot, Tulat Alp Ikizler, Loren Lipworth, Vanderbilt University Medical Center, Nashville, TN; Vanderbilt University, Nashville, TN.

Background: Arsenic (As) is nephrotoxic at high doses. We hypothesized that long-term low to moderate exposure to As is associated with ESRD risk.

Methods: We conducted a nested case-control study within the SCCS, a prospective study of low income adults residing in underserved urban and rural communities with potentially high toxicant burden in the southeastern US (2002-2009). Among 125 (63 black, 62 white) randomly selected incident ESRD cases and 250 controls, matched on age, race, sex, and time of enrollment, baseline serum As was measured by inductively coupled plasma mass spectrometry. Data were modeled using conditional logistic regression, after log transformation of As. Generalized additive models examined the trends in risk factors over time (P<0.05 indicates statistical significance).

Results: Mean age at SCCS enrollment of cases and controls was 55 years, and 55% were female. Median (25th, 75th percentile) levels of As (ng/ml) were significantly higher among ESRD cases (0.56; 0.32, 0.85) than among controls (0.39; 0.26, 0.73). An increase in risk factors for CKD progression, such as our PCORI-supported pilot HBKC intervention in this high-risk population, particularly amongst young adult Zuni.

Funding: Other NIH Support - NIEHS P30ES000267–47; National Cancer Institute

Conclusions: These results provide support for the hypothesis that chronic low to moderate exposure to As may be an important novel modifiable contributor to ESRD risk. Further work incorporating urinary As and geographic exposure modeling is ongoing.

Funding: Other NIH Support - NIEHS P30ES000267–47; National Cancer Institute

FR-PO409

Total Nephron Number Decreases with the Stage of CKD – A Study in Japanese Subjects

Go Kanazaki, Victor G. Puelles, Luise A. Cullen-McEwen, Yusuke Okabayashi, Nobuo Tsuibo, Akira Shimizu, Takashi Yokoo, John F. Bertram, Department of Analytic Human Pathology, Nippon Medical School, Tokyo, Japan; Department of Nephrology and Clinical Immunology, University Hospital RWTH Aachen, Aachen, Germany; Division of Nephrology and Hypertension, The Jikei University School of Medicine, Tokyo, Japan; Department of Anatomy and Developmental Biology, Monash University, Melbourne, VIC, Australia.

Background: There is increasing evidence that low nephron number increases the risk for CKD. We have previously shown that nephron number predicts eGFR. However, changes in total nephron number across the stages of CKD have not previously been reported. In this study we assessed total nephron number and clinicopathological findings in Japanese subjects in order to determine the structural and functional changes associated with nephron loss in each CKD stage.

Methods: Kidneys from 58 Japanese subjects were collected at Nippon Medical School, Tokyo, Japan during autopsy and were divided into three groups; CKD stage 1 (n=13, eGFR>90 mL/min), CKD stage 2 (n=24, eGFR 89-60 mL/min), and CKD stage 3A-4 (n=21, eGFR 59.15 mL/min). Total nephron number (Nglomer) and mean glomerular volume (Vglomer) were estimated by design-based stereology. Single nephron eGFR (SNeGFR) was calculated as eGFR divided by two times the number of non-sclerotic glomeruli.

Results: Total nephron number per kidney was significantly lower in CKD stage 3-4 (293,198±110,087; means±SD; P<0.001) than in CKD stage 1 (591,377±238,149) and CKD stage 2 (505,303±132,917). Glomeruli were larger in CKD stage 3-4 (P<0.001) than in CKD stages 1 and 2. Kidney weights were similar in the three groups, even though subjects with CKD stage 3-4 had lower cortical volumes and total glomerular volume (combined volume of all non-sclerotic glomeruli) than with CKD stages 1 and 2. Although no differences in SNeGFR were observed between the three groups, SNeGFR/ Vglomer, which predicts glomerular capillary filtration, was reduced in CKD stages 2 and 3-4 (P<0.001).

Conclusions: Compared with subjects with eGFR>60 mL/min, CKD stage 3-4 patients had an apparent nephron deficit, with glomerular hypertrophy partially compensating for the nephron loss. Our findings also suggest that glomerular capillary filtration starts decreasing in stage CKD 2.

Demographic and renal functional and structural data with CKD stages

<table>
<thead>
<tr>
<th>Variable</th>
<th>CKD stage 1 (N=13)</th>
<th>CKD stage 2 (N=24)</th>
<th>CKD stage 3A-4 (N=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR</td>
<td>90.62±19.38</td>
<td>80.19±19.95</td>
<td>53.31±20.66</td>
</tr>
<tr>
<td>Nglomer</td>
<td>591,377±238,149</td>
<td>505,303±132,917</td>
<td>293,198±110,087</td>
</tr>
<tr>
<td>Vglomer</td>
<td>4.75±0.63</td>
<td>4.61±0.59</td>
<td>4.52±0.55</td>
</tr>
<tr>
<td>SNeGFR</td>
<td>39.01±9.02</td>
<td>37.64±8.43</td>
<td>36.41±7.94</td>
</tr>
</tbody>
</table>

*Underline represents presenting author.

mean±SD
FR-PO410

Intrarenal Renin-Angiotensin System Activity in Nighttime Is Associated with Renal Arteriosclerosis in Normotensive IgA Nephropathy Patients

Akihiko Ishigaki,1 Shinshuke Isobe,1 Takashi Matsuyama,1 Sayaka Ishigaki,1 Naoko Tsujii,1 Tomoyuki Fujikura,2 Takayuki Tsujii,1 Akihiko Kato,1 Hideo Yasuda,1 Hamamatsu University School of Medicine, Hamamatsu, Japan; 2Hamamatsu University School of Medicine, Hamamatsu, Japan; 3Hamamatsu University School of Medicine, Hamamatsu, Japan; 4Hamamatsu University School of Medicine, Hamamatsu, Japan; 5Hamamatsu University School of Medicine, Hamamatsu, Japan.

Background: Intrarenal renin-angiotensin system (RAS) activation especially in nighttime plays an important role in the development of hypertension and renal damage. However, the association between intrarenal RAS activation in daytime and nighttime and renal structural damages has not been clearly investigated in IgA nephropathy patients without hypertension.

Methods: We investigated the urinary angiotensinogen (U-AGT) excretion in daytime and nighttime that reflects intrarenal RAS activity and renal structural damages in 27 normotensive IgA nephropathy patients (age 39.2 ± 13.6 years, 10 men and 17 women, blood pressure 112.0 ± 11.8 / 70.0 ± 9.5 mmHg, estimated glomerular filtration rate (eGFR) 74.0 ± 17.3 ml/min/1.73m2, urinary protein excretion 0.58 ± 0.50 g/day). Renal structural damages of renal biopsy tissues were scored as follows: the levels of arteriolar hyalinosis; the proportion of arterioles affected (0: absent, 1: 1-25%, 2: 26-50%, 3: 51-100%), the levels of arteriosclerosis in arcuate and interlobular arteries (0: normal, 1: intima thickness and less than media thickness, 2: intima thickness and more than media thickness), and percentages of global sclerosis (GS) and tubulointerstitial fibrosis, as described previously.

Results: The levels of arteriosclerosis were significantly and positively associated with U-AGT excretion levels in daytime and nighttime. On the other hand, the levels of arteriolar hyalinosis and percentages of GS and tubulointerstitial fibrosis were not correlated with the U-AGT excretion levels in daytime and nighttime. Multiple linear regression analysis revealed that the levels of arteriosclerosis tended to be associated with U-AGT excretion levels in daytime, when age, sex, body mass index (BMI), and eGFR were adjusted (β=0.33, p=0.079). Moreover, the levels of arteriosclerosis were significantly and positively associated with U-AGT excretion levels in nighttime after adjustment of age, sex, BMI, and eGFR (β=0.49, p=0.043).

Conclusions: In normotensive IgA nephropathy patients, the activation of intrarenal RAS especially in nighttime is associated with renal arteriosclerosis. Funding: Government Support - Non-U.S.

FR-PO411

Performance Evaluation and Potential Utility of Urinary L-FABP as a Point of Care Device in CKD

Ananya Saha,1 Ian Read,2 Philip A. Kalra,2 Sandip Mitra.3 Central University Manchester Hospitals NHS Foundation Trust, Manchester, United Kingdom; 2Salford Royal Hospital NHS Trust, Salford, Manchester, United Kingdom.

Background: Liver-type fatty acid binding protein (L-FABP) is expressed by the proximal renal tubule during oxidative stress. Urinary L-FABP is released with tubular damage & is an established biomarker in acute kidney injury. However its value in Chronic Kidney Disease (CKD) & its progression has not been defined. We evaluate the clinical performance of a semi-quantitative point of care (POC) device for the detection of urinary L-FABP & assess the value of urinary L-FABP as a biomarker at different stages of CKD.

Methods: We report the baseline analysis of ELUDE, a multicentre study involving patients with CKD. Urine samples were tested for urinary protein creatinine ratio (PCR) in mg/mmol and urinary L-FABP using a semiquantitative POC & a quantitative ELISA (ng/g). A concomitant serum sample was analysed to calculate estimated glomerular filtration rate (eGFR) in ml/min/1.73 m2. CKD was staged as per KDOQI.

Results: In 624 CKD participants, 15% had CKD1 (eGFR 77±11.0; PCR 10±210.3), 13% CKD2 (eGFR 51±8.5; PCR 46±89.9), 25% CKD3 (eGFR 36±5.5; PCR 72±120.4), 33% CKD4 (eGFR 22±4.5; PCR 139±19.1) & 15% CKD5 (eGFR 11±2.4; PCR 265±282.2). The mean urinary L-FABP ELISA measurement was 21.0 μg/gCr. L-FABP levels increased with advancing stages of CKD (1- 2: 11.2±9.1, 3: 20.6±13.7, 4: 25±45.1, 5: 62.5±33.6 μg/gCr). L-FABP correlated negatively with eGFR (r=−0.516, p<0.001) and positively with uPCR (r=0.567, p<0.001). The association of L-FABP with eGFR was more pronounced at advanced stages of CKD. In an adjusted linear regression model for prediction of eGFR, L-FABP was an independent predictor in CKD stages 4 (β=−0.215, p=0.021) & 5 (β=−0.241, p=0.03) whereas only was an independent predictor in CKD 5 (β=−0.091, p=0.021). Derived L-FABP measurements correlated well with eGFR (r=0.656, p<0.001).

Conclusions: The study findings suggest that in advanced stages of CKD, L-FABP may be a more reliable predictor of eGFR than proteinuria. High levels of urinary L-FABP in advanced CKD 4 & 5 could reflect dominant tubular damage & atrophy & may act as a useful biomarker of progressive disease. Longitudinal follow-up data from this study will further inform these findings. POC device used in this study provides a reliable way of measuring urinary L-FABP & may be of utility in the clinical setting. Funding: Commercial Support - CMIC Holdings LTD

FR-PO412

Soluble ST-2 and Galectin-3 and Risk of CKD Progression

Mariam L. Alam,1 Ronit Katz,2 Keith A. Bellovich,3 Zeenat Y. Bhat,4 Frank C. Brosius,2 Ian H. de Boor,5 Crystal A. Gadgebeku,3 Debbie S. Gibson,1 Jennifer J. Hawkins,2 Jonathan Himmelfarb,2 Bryan R. Kestenbaum,3 Matthias Kretzler,4 Susan P. Steigerwald,2 Nisha Bansal,7 1University of Arizona, Tucson, AZ; 2University of Michigan, Ann Arbor, MI; 3Mt. Sinai Hospital Medical Center, Detroit, MI; 4Temple University, Philadelphia, PA; 5Wayne State University, Detroit, MI; 6Kidney Research Institute, Seattle, WA; 7University of Washington, Seattle, WA.

Background: Cardiac biomarkers soluble ST-2 (sST-2) and galectin-3 may reflect inflammation and fibrosis. sST-2 and galectin-3 have been shown to be associated with cardiovascular events, but less is known about their associations with kidney disease. We examined associations of sST-2 and galectin-3 with kidney function decline in a chronic kidney disease (CKD) cohort.

Methods: The Clinical Phenotyping Phenotyping and Resource Biobank (CPRPROBE) and Seattle Kidney Study (SKS) are prospective studies of CKD patients. We measured serum concentrations of sST-2 and galectin-3 at baseline. Outcomes were 1) progression to end-stage renal disease (ESRD) (need for dialysis/transplant or eGFR <15 ml/min/1.73m2) and 2) annualized relative change in eGFR. We used Cox regression and generalized estimating equation models to study the association of biomarker levels with kidney outcomes, adjusting for eGFR, urine ACR (UACR), demographics, cardiovascular disease, diabetes, body mass index, blood pressure and anti-hypertensive use.

Results: Among the 561 participants in CPRPROBE, the mean age was 55 ± 16 years, 42% were male and 35% had diabetes. Baseline eGFR was 55 ± 31 ml/min/1.73m2 and median UACR was 217 (interquartile range [IQR] 16, 885) mg/g. Among the 280 SKS participants, the mean age was 62 ± 13 years, 82% were male and 56% had diabetes. Baseline eGFR was 42 ± 16 ml/min/1.73m2 and median UACR was 118 (IQR 15, 626) mg/g. Incidence rates of ESRD were 5.41 (110 events) and 3.73 (30 events) per 100 person-years in CPRPROBE and SKS, respectively. Higher sST-2 was associated with a greater annual decline in eGFR in both CPRPROBE and SKS, but was not associated with progression to ESRD. Higher galectin-3 was associated with an increased risk of ESRD in CPRPROBE only (Table).

Conclusions: Higher levels of sST-2 and galectin-3 are associated with progression of CKD, highlighting possible shared cardiac and renal mechanisms that contribute to these diseases. Funding: NIDDK Support
Conclusions: SCT with concurrent CKD is associated with an increased risk for GFR decline and renal requirement for dialysis in our cohort. More detailed studies are needed to determine risk factors for progression in this patient population.

FR-PO414
Factors Associated with Clinically Significant CKD and Their Clinical Utility in Primary Care Clinics in Singapore (Qian Jan Lew,1 Francis N. Nguyen,4 John C. Allen,1 Ngiap chuan Tan,2 Tazeen H. Jafar,1 1Duke-NUS Medical School, Singapore, Singapore; 2Singapore General Hospital PolyClinics, Singapore, Singapore; 3SingHealth PolyClinic, Singapore, Singapore; 4SingHealth, Singapore, Singapore.

Background: Chronic kidney disease (CKD) is a major global public health challenge, including Southeast Asia. Factors associated with CKD in Singapore were determined by analyzing historical data on all individuals ≥ 40 years visiting 4 government polyclinics in Singapore from 1st Jan 2012 to 31st Dec 2015.

Methods: Clinically significant CKD patients had CKD-EPI serum creatinine-based estimated glomerular filtration rate < 60 ml/min/1.73 m² or 1+ dipstick proteinuria sustained ≥ 3 months. Multivariable and stepwise logistic regression analysis and receiver operator characteristic curve analysis were conducted for the outcome of clinically significant CKD.

Results: About 25.9% (95% CI: 25.6-26.2%) of the 88,765 individuals screened at Singapore PolyClinics (mean (SD) age of 65.9 ± 11.1 years, and 53.3% women) had clinically significant CKD. Age (OR=1.06, 95% CI: (1.06-1.07) / year); body mass index [1.02 (1.02-1.03) / kg/m²]; male vs female [1.23 (1.17-1.27)]; Malay [1.31 (1.24-1.38)] and Indian [0.80 (0.74-0.87)] vs Chinese; public vs private housing [1.25 (1.18-1.34)]; ever vs never smoker [1.08 (1.01-1.15)]; presence of hypertension [2.89 (2.69-3.11)], diabetes [7.23 (6.95-7.52)], or stroke [1.36 (1.27-1.45)] vs none were independently associated with clinically significant CKD. However, only age, presence of diabetes and hypertension incrementally added to the area under the curve of the 0.808 (95% CI: 0.805-0.811) for clinically significant CKD.

Conclusions: Clinically significant CKD prevalence is high in primary care clinics in Singapore. Our results highlight the factors associated with clinically significant CKD and underscore the need for targeted screening of CKD in Southeast Asia.

Funding: Clinical Revenue Support

FR-PO415
Long-term Prognosis and Predictive Factors of Non-Remission in IgA Nephropathy after Tonsillectomy and Steroid Pulse Therapy (TSP) for IgA Nephropathy (IgAN) is widely performed in Japan. However, the efficacy of TSP remains controversial, partly because even though IgAN is a chronic nephritis, most studies set the primary outcome as complete remission (CR) at 1 year after TSP and do not address long-term outcome. Therefore, we followed patients who had undergone TSP for a minimum of 3 years to clarify the long-term results and predictive factors of non-remission (NR) following TSP.

Methods: This retrospective, single-center, cohort study included 63 patients who were monitored for at least 3 years after TSP for IgAN at Shinshu University Hospital. The frequency of CR (urinary total protein ≤ 0.3 g/24h and urinary red blood cells ≤ 5/ high-power field) was assessed at 1 and 3 years following TSP. Using statistical methods, the predictive factors of NR at 3 years were investigated with relation to physical examination, serology, and urinalysis items.

Results: CR was observed in 29 (46%) patients at 1 year of follow-up. Of these, 6 (10%) experienced a recurrence and 23 (36%) maintained CR at 3 years. Among the 34 (54%) patients with NR at 1 year, 10 (16%) exhibited late remission and 24 (38%) remained unchanged at 3 years. Overall, tubulointerstitial fibrosis was significantly more severe in NR patients than in CR patients (P<0.01). Among the 29 patients who showed CR at 1 year, tubulointerstitial fibrosis in patients with a recurrence at 3 years was significantly more severe as well (P<0.05). The most useful factor for predicting NR at 3 years was the well known tubulointerstitial injury marker urinary N-acetyl-b-D-glucosaminidase (U-NAG) according to receiver operator characteristic (ROC) analysis (cut-off: 4.35 U/gCr; sensitivity: 83%; selectivity: 75%; area under ROC curve: 0.817). Even in patients with CR at 1 year, those whose U-NAG was >4.35 U/gCr were more likely to relapse within 3 years (P<0.05).

Conclusions: At 3 years following TSP for IgAN, both recurrence and late remission are observed in relatively many patients. The severity of tubulointerstitial fibrosis is considered to be related to TSP resistance, and U-NAG represents a useful predictor of long-term prognosis.

FR-PO416
Epidural Fat Is Associated With Traditional CV Risk Factors and Renal Function in Patients with Moderately Severe CKD (GCKD) (Turgay Saritas, Jonas Schmoe, Jennifer Nadal, Matthias Schmid, Rolf Janka, Christoph Wanner, Kai-Uwe Eckardt, Jürgen Floege, Markus P. Schneider, Georg Schlieper,1 University of Bonn, Bonn, Germany; 2University Hospital RWTH Aachen, Aachen, Germany; 3University Hospital RWTH Aachen, Aachen, Germany; 4University of Erlangen-Nuremberg, Erlangen, Germany; 5University Hospital Wuerzburg, Wuerzburg, Germany; 6University of Erlangen-Nuremberg, Erlangen, Germany; 7Nephrology and Hypertension, University of Erlangen-Nuremberg, Erlangen, Germany; 8University of Bonn, Bonn, Germany; 9MTZ DuDita Karlstraße, Düsseldorf, Germany.

Background: Pathological increase of epidural adipose tissue (EAT) has been proposed as a novel, imaging-based predictor of CV events. How traditional CV risk factors associate with EAT enlargement in patients with moderately severe chronic kidney disease (CKD) has not been examined yet.

Methods: We analyzed data from 257 patients from CARVIDA (CARdioVascular In Depth Aspects) which is a multi-center sub-study of the German Chronic Kidney Disease (GCKD) study. Patients were enrolled on the basis of an eGFR of 30-60 ml/min/1.73 m² or overt proteinuria, and EAT was measured by computed tomography. Multivariable association of EAT with CV risk factors (age, gender, BMI, smoking, diabetes mellitus, hypertensive nephropathy, cholesterol, HDL, eGFR [CKD-EPI equation] and urine albumin-to-creatinine (UACR)) was assessed using linear regression analysis. Framingham 10-year CV disease risk score and ACC-AHA 10-year atherosclerotic CV disease (ASCVD) risk score were calculated for each patient.

Results: EAT showed a median level of 121 cm² (IQR: 81-162 cm²) in moderately severe CKD patients. Of note, lower eGFR was independently associated with increased EAT (OR 0.997 (95% CI: 0.994-0.999), p<0.05). Finally, EAT correlated with estimated 10-year risk for CV disease by Framingham ( spearman rho = 0.257, p =0.002; median risk score: 18.5%) and ASCVD ( spearman rho =0.192, p =0.020; median risk score: 13.7%).

Conclusions: Epidural fat is associated with traditional CV risk factors in the presence of CKD. Moreover, we observed that lower eGFR is also associated with EAT. EAT may thus be an integrative risk marker and follow-up of our patients will determine whether assessment of EAT improves the prediction of CV events in CKD.

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

Associations between Cardiovascular Risk Factors and Epicardial Fat Volume as obtained from Multivariable Adjusted Linear Regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.02</td>
<td>1.00 - 1.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>1.30</td>
<td>1.18 - 1.42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>1.04</td>
<td>1.03 - 1.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoker</td>
<td>1.14</td>
<td>1.08 - 1.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pre-Medications</td>
<td>1.03</td>
<td>1.01 - 1.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current Medicines</td>
<td>1.03</td>
<td>1.01 - 1.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.02</td>
<td>1.00 - 1.04</td>
<td>0.037</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.02</td>
<td>1.00 - 1.04</td>
<td>0.037</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>1.09</td>
<td>1.00 - 1.19</td>
<td>0.037</td>
</tr>
<tr>
<td>HDL</td>
<td>1.03</td>
<td>0.98 - 1.07</td>
<td>0.037</td>
</tr>
<tr>
<td>eGFR</td>
<td>0.98</td>
<td>0.90 - 1.06</td>
<td>0.037</td>
</tr>
<tr>
<td>ACUR</td>
<td>0.99</td>
<td>0.90 - 1.00</td>
<td>0.037</td>
</tr>
</tbody>
</table>

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

Underline represents presenting author.

FR-PO417
C-Reactive Protein Mediates the Association between Central Obesity and Microalbuminuria among Persons with the Metabolic Syndrome, Especially in African Americans Satyesh K. Sinha,1 Magda Shaheen,1 Deyu Pan,2 Keith C. Norris,2 Susanne B. Nicholas,2 Charles R Drew University of Medicine and Science, Los Angeles, CA; 2None, Westchester, CA; 1University of California Los Angeles, Los Angeles, CA.

Background: C-reactive protein (CRP), an inflammatory marker, is associated with the metabolic syndrome (MetS) and chronic kidney disease (CKD). However, little is known about the racial disparities of the effect of CRP on the association between individual components of the MetS and microalbuminuria (MA).

Funding: None

Associations between Cardiovascular Risk Factors and CRP (ng/ml) as obtained from Multivariable Adjusted Linear Regression
Methods: We analyzed National Health and Nutrition Examination Surveys (NHANES) data, (1999-2010) for adults (aged ≥20 years) with MetS (N=5700). We used multiple logistic regression to assess the independent relationship between MetS components and MA, adjusting for age, gender, race/ethnicity and estimated glomerular filtration rate (eGFR). We used the Sobel-Goodman mediation tests to examine the extent of how CRP influenced the effect of MetS components on MA by race/ethnicity. We examined the association between CRP and MA and tested the ability of CRP to reclassify risk using the net reclassification index with and without CRP.

Results: In the multivariate model, CRP, as well as central obesity, blood pressure, fasting plasma glucose, and high-density lipoprotein (HDL), were independent predictors of MA, p<0.05. The mediation test showed that the proportion of total effect of the MetS components on MA mediated by CRP, t=0.11 for HDL and 0.40 for central obesity, p=0.05. These levels varied by race/ethnicity. The mediation effect of CRP for central obesity (highest prevalence in African Americans; AA) was highest for AAAs (0.94) compared to Whites (0.55) or Hispanics (0.18), p<0.05. The addition of CRP to the model reduced the effect size of MetS components, demographics and eGFR resulted in net reclassification improvement of 0.11 (standard error=0.03, p=0.002) but no significant change in the prediction of MA (receiver-operating characteristics area under the curve, without CRP=0.66, with CRP=0.67).

Conclusions: We conclude that CRP mediates the association between MA and both HDL and central obesity. Importantly, for AAs, CRP mediates the relationship between MA and central obesity.

Grant Support: Supported in part by NIH grants U54-MD-008149, UL1TR001024, P30AG021684, U54MD007598, and S21 MD00103.

Funding: Other NIH Support - U54-MD-008149, UL1TR001024, P30AG021684, U54MD007598, and S21 MD00103.

FR-PO418

A New Way to Assess CKD Progression: Correlation of Renal Ultrasound Measurements to Co-Morbidities, CKD Stages, and Total Renal and Parenchymal Cortical Volume Harish R. Alappan,1 Raj Alappan,3 Raj Sehgal,3 Emory University - Undergraduate, Atlanta, GA; 2Radiology Institute, Atlanta, GA; 3Renal Associates, LLC, Columbus, GA.

Background: Correlating Renal Ultrasound (US) data to co-morbidity and Chronic Kidney Disease (CKD) stages is sparse. Kidney’s volumetric US data and trends have not been reported previously in CKD stages.

Methods: Initial CKD evaluation was conducted at Renal Associates. Clinical data and renal US done at the center were analyzed. Using the M7-Mindray US System, the same radiographer did the imaging and the same radiologist read images. 612 renal US images from Aug. 2014 to Jan. 2016 were analyzed. The Renal and Medullary sagittal, transverse and AP axis and cortical thickness for the right (RK) and left (LK) kidneys were measured in cm. Using Total Renal (TRV), and the Medullary (MV) volume, the Cortical (CV) volume was calculated. Using a correction constant for each kidney (RK uncertainty 0.4891, LK uncertainty 0.4886) the true renal Cortical tissue Volume (RCV) was determined for each kidney.

Results: Overall study (n=612): mean age was 63.87 yrs., 339 (55.3%) females, BMI 31.23, Cr 1.49 mg/dL, eGFR 60 ml/min/1.73m2. For 1mL of the RCV(cm3), the true renal Cortical tissue Volume (RCV) was determined for each kidney. RK and LK=0.4886) the true renal Cortical tissue Volume (RCV) was determined for each kidney.

Cortical thickness and volumetric corrected Renal Cortical Volume in cm3

<table>
<thead>
<tr>
<th>Cortical thickness</th>
<th>Volume corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>RK</td>
<td>0.4886</td>
</tr>
<tr>
<td>LK</td>
<td>0.4886</td>
</tr>
</tbody>
</table>

Conclusions: This study is the first of its kind that correlates renal measurements on renal US data to co-morbidity and Chronic Kidney Disease (CKD) stages. Kidney’s volumetric US data and trends have not been reported previously in CKD stages.

Funding: Other NIH Support - U54-MD-008149, UL1TR001024, P30AG021684, U54MD007598, and S21 MD00103.

FR-PO419

Change in Creatinine-Based Estimated GFR versus Cystatin-C-Based Estimated GFR and Renal Outcome in Patients with CKD Su Hyun Kim,6 Junseok Jeon,3 Jinjung Kim,4 Hye Ryong Jang,1 Yoon-Goo Kim,1 Dae Joong Kim,1 Ha Young Oh,1 Wooseong Huh,2 Jung eun Lee,1 3None, Seoul, Republic of Korea; 4Samsung Medical Center, Seoul, Republic of Korea; 5Seoul National University Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; 6Samsung medical center, Seoul, Republic of Korea; 7Samsung medical center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea.

Background: Many studies have demonstrated that an early change in estimated glomerular filtration rate (eGFR) predicts the risk of chronic kidney disease (CKD) progression. However, there are few studies comparing prognostic power of creatinine-based eGFR slope (eGFRcys slope) and cystatin-C-based eGFR slope (eGFRcys slope). This study examined which eGFR slope during first-year was superior in identification of high-risk group of progression to end-stage renal disease (ESRD) in patient with CKD.

Methods: From October 2010 to November 2016, patients who had simultaneous measurements of serum creatinine and cystatin-C more than 3 times for 1 year were identified. We calculated baseline eGFR values and first-year eGFR slopes using CKD-EPI formula and linear regression analyses. The patients with baseline eGFR ≥ 60 ml/min/1.73m2 were excluded. We defined a rapid progression as eGFR slope < -5 mL/min/1.73m2/year. We assessed association between first-year eGFR slopes and progression to ESRD (defined as initiation of dialysis or kidney transplantation) by cox proportional hazard model.

Results: Total 857 patients were included. Forty-five percent of patients had diabetes. Baseline eGFRcys were 36.7 (25.8 – 47.2) ml/min/1.73m2 and eGFRcys were 36.5 (25.3 – 49.1) ml/min/1.73m2. During follow-up of 2.4 (1.3 – 3.3) years, 78 (9.1%) events occurred. Both eGFRcys slope and eGFRcys slopes were associated with higher risk of ESRD independently of baseline eGFR (HR = 0.95 [0.93 – 0.97], HR = 0.96 [0.95 – 0.98], respectively). Both creatinine and cystatin-C based-rapid progression were associated with increased risk of ESRD (HR = 2.25 [1.44 – 3.52], HR = 1.77 [1.10 – 2.86], respectively). In subgroup analyses of rapid progression group by creatinine (N = 295), eGFRcys slope was not associated with risk of ESRD (HR = 0.99 [0.96 – 1.03], P = 0.68). Whereas, eGFRcys slopes contributed to further discrimination of higher risk of ESRD in subjects with rapid progression by cystatin-C (HR = 0.96 [0.93 – 0.98], P = 0.002).

Conclusions: These findings suggest that eGFRcys slope may be superior to eGFRcys in identification of high-risk group in patient with CKD.

Funding: Commercial Support - Randox Teoranta, Meenmore, Dungloe, County Donegal, F49 TV6v, Ireland.

FR-PO420

Laboratory Indices and Serum Biomarkers Associate with Prior Renal Functional Decline in CKD William P. Martin,1 Serika D. Naicker,2 Eibhlin M. Mecole,2 Susan Lough,2 Sarah Cormican,1 Maria Megarvey,1 Ciaran Richardson,2 Ivan Mecolln1, John Lamont,1 John P. Ferguson,1 Peter Fitzgerald,1 Matthew D. Griffin,1 Regenerative Medicine Institute, National University of Ireland, Galway, Ireland; 2Randox Teoranta, Meenmore, Dungloe, Ireland; 3Randox Laboratories Limited, 55 Diamond Road, Crumlin, United Kingdom; 4HRB Clinical Research Facility, Galway, Ireland.

Background: Prediction of renal functional decline in chronic kidney disease (CKD) is limited. We evaluated the relationship between laboratory indices and results from a novel serum biomarker chip assay with recent rate of decline of renal function.

Methods: Patients were recruited from nephrology clinics at a tertiary referral center during 2014 and 2015, where they provided a serum sample for biomarker quantification with a novel multi-analyte chip assay. Relationships between laboratory indices and serum biomarkers at recruitment with slope of MDRD eGFR prior to recruitment were investigated using a custom weighted least squares algorithm adjusting for age, sex, and first eGFR during the study period.

Results: 170 subjects were identified (135 (79.4%) with native CKD, 35 (20.6%) with kidney transplants (KTs)). Mean age was 60.09 ± 17.38 years. 69 (40.6%) subjects were female. Native CKD stages were: 5 (17.2%) CKD1, 17 (12.6%) CKD2, 19 (14.1%) CKD3a, 40 (29.6%) CKD3b, 34 (26.2%) CKD4, and 10 (7.4%) CKD5. Median [IQR] number of eGFR measurements was 17.0 [10.8, 27.3] over 3.2 [2.4, 3.7] years prior to first eGFR during the study period. Rate of eGFR decline was -2.59 ± 0.52 mL/min/1.73m2/year in native CKD and KT subjects, respectively (p = 0.035). Analysis results for selected laboratory and biomarker indices are summarized in the Table.

Conclusions: Multiple serum biomarkers measured simultaneously with a novel chip assay and several laboratory indices were strongly associated with prior renal functional decline in CKD subjects. Retrospective eGFR trends may be of value for identifying biomarker signatures associated with rapid renal functional decline.

Funding: Commercial Support - Randox Teoranta, Meenmore, Dungloe, County Donegal, F49 TV6v, Ireland.
Association of serum laboratory indices and biomarkers with slope of MDRD eGFR by multivariable regression.

| Serum Laboratory Indices | β (SEM) | p
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>1.2 (0.08)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Phosphate</td>
<td>1.09 (0.08)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Albumin</td>
<td>1.11 (0.08)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.16 (0.08)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cystatin</td>
<td>1.15 (0.08)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

FR-PO421
Non-Steroidal Anti-Inflammatory Drug (NSAID) Use and ESRD in the Southern Community Cohort Study (SCCS)
Fabian Bock,1 Edward in the Southern Community Cohort Study (SCCS)

Methods: We assembled a case-cohort study from the SCCS, comprising 292 incident ESRD cases, identified by Indian nephrologists between January 2015 and December 2017, and a probability sample of 1453 SCCS participants, who donated a blood sample and had serum creatinine measured. Data were collected at baseline on regular use (2 times/week) of prescription and OTC analgesics, including NSAIDs. The analysis was restricted to those who reported using any analgesic. The association of NSAID use with ESRD was estimated with a logistic regression model adjusted for age, sex, smoking, hypertension, diabetes, arthritis, baseline eGFR, aspirin, acetaminophen, and an estimated propensity score (PS). The PS is the covariate-adjusted probability of being an NSAID user and was calculated with predictors of NSAID use as covariates.

Results: At enrollment, mean (SD) age was 53 (8) and 55 (9) years among ESRD cases and subcohort controls, and 78% and 62%, respectively, were black. Median (25th, 75th percentile) baseline eGFR of cases and controls was 78 (59, 109) and 98 (83, 113) ml/min/1.73 m² respectively. Overall, NSAID, aspirin and acetaminophen use were reported by 38%, 33% and 36% of ESRD cases, respectively, compared to 53%, 40% and 33% of controls. Table 1 shows the distribution of analgesic use by baseline eGFR. In adjusted analyses, compared to non-NSAID analgesic users, the OR (95% CI) for the association between NSAID use and ESRD was 0.83 (0.54-1.27).

Conclusion: Among analgesics users, 25% of cases with baseline eGFR<60 used NSAIDs, but NSAID use was not significantly associated with risk of ESRD.

Funding: Other NIH Support - National Cancer Institute (R01CA092447) and American Recovery and Reinforcement Act (R01CA092447-08S1), Other U.S. Government Support

Table 1: Selected demographic details of ICCD study subjects (n=1567)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean ± SD or No. of subjects (% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50 ± 12.0</td>
</tr>
<tr>
<td>Male sex</td>
<td>2,065 (80.0)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.5 ± 5.8</td>
</tr>
<tr>
<td>Waist/Hip ratio</td>
<td>0.8 ± 0.2</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>131 ± 18.9</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>83 ± 15.9</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>45 ± 17.8</td>
</tr>
<tr>
<td>Education: graduates and above</td>
<td>470 (19.0)</td>
</tr>
<tr>
<td>Residence: rural or semi-urban</td>
<td>598 (59.8)</td>
</tr>
<tr>
<td>Household exposure to dust, chemicals, animals etc.</td>
<td>529 (30.7)</td>
</tr>
<tr>
<td>Skin pigment</td>
<td>536 (54.4)</td>
</tr>
<tr>
<td>Family history of kidney disease present</td>
<td>149 (6.8)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>106 (6.7)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>474 (28.0)</td>
</tr>
<tr>
<td>History of use of anti-inflammatory drugs or medications</td>
<td>377 (24.5)</td>
</tr>
<tr>
<td>History of AKI</td>
<td>154 (9.8)</td>
</tr>
<tr>
<td>History of NSAID use after diagnosis of kidney disease</td>
<td>483 (31.1)</td>
</tr>
<tr>
<td>Smoking history</td>
<td>491 (31.3)</td>
</tr>
<tr>
<td>History of vaccination against Hepatitis B</td>
<td>408 (29.3)</td>
</tr>
<tr>
<td>Medical insurance available</td>
<td>431 (27.5)</td>
</tr>
<tr>
<td>Monthly income (USD)</td>
<td>273 (40.1)</td>
</tr>
<tr>
<td>Vitamin D supplementation</td>
<td>38.3 (13.8, 65.1)</td>
</tr>
</tbody>
</table>

FR-PO422
Indian Chronic Kidney Disease (ICKD) Study: A Prospective Cohort Study of CKD Patients in India
Ashok K. Yadav,1 Vivek Kumar,2 Shobhit Bhanali,3 Gopesh K. Modi,2 Sishir D. Gang,4 Jai Prakash,5 Dipankar Sircar,3 Sreeth Prameswaran,6 Narayan Prasad,7 MANISHA SAHAY,8 Santosh Varughese,1 Shivendra Singh,9 Vivekanand Jha.10 Banaras Hindu University, Varanasi, India;1 Samarpan Kidney Institute & Research Ctr., Bhopal, India; Nephrology, PGIMER, Chandigarh, India; George Institute for Global Health, New Delhi, India;1 IPGMER, SSKM Hospital, Kolkata, India;1 JIPMER, Pondicherry, India; MULTIBHAI PATEL UROLOGICAL HOSPITAL, Nadiad, India; OSMANIA HOSPITAL, HYDERABAD, India;7 Postgraduate Institute of Medical Education and Research, Chandigarh, India;8 SGPGIMS CAMPUS, Lucknow, India;10 Nephrology, CMC, Vellore, India.

Background: The Indian Chronic Kidney Disease (ICKD) study (https://ickd.georgem Institute.org.in/) is a multi-centric, prospective, observational cohort study of early stage CKD patients in India which will ascertain rate and factors influencing progression of CKD in India.

Methods: Adult subjects with mild to moderate CKD [estimated glomerular filtration rate (eGFR) 30-60 ml/min/1.73m² or eGFR >60 ml/min/1.73m² with proteinuria/albuminuria] are eligible for enrolment. Approximately 5000 subjects would be enrolled over 18 months. Time to 50% decline in eGFR, need of renal replacement therapy, CVD event or death are primary end points. A central bio-repository with serial biological samples is coupled with this cohort. Socio-economic aspects of treatment will also be studied.

Results: A total of 1567 subjects have been enrolled in the ICKD cohort till May 2017. The cause of CKD could not be ascertained in 25% of subjects. Chronic glomerulonephritis, diabetic kidney disease and chronic interstitial nephritis are causes for CKD in 16.5%, 18% and 17% of subjects, respectively. Tables 1 shows selective demographic characteristics of enrolled subjects. Majority are males belonging to rural areas with occupation exposure to sand, dust, chemicals or animals etc. 24% subjects had used alternative drugs and 10% had history suggestive of AKI in the past.

Conclusion: This is the first and most comprehensive description of an early stage CKD cohort from a developing country.

Funding: Government Support - Non-U.S.

FR-PO423
GDF-15 and FGF-23 Are Associated with Mortality in Type 2 Diabetic Patients with Microalbuminuria
Marie Fridmesh-møller,1 Bernt Johan Von Scholten,1 Henrik Reinhard,1 Tine Hansen,1 Frederik Persson,1 Hans-Henrik Parving,2 Peter Rossing,1,3 Steno Diabetes Center Copenhagen, Gentofte, Denmark;3 Rigshospitalet, Copenhagen, Denmark; Copenhagen University Hospital, Copenhagen, Denmark

Background: We evaluated growth differentiation factor 15 (GDF-15) and fibroblast growth factor 23 (FGF23) reflecting different aspects of renal pathophysiology as determinants of decline in estimated glomerular filtration rate (eGFR), incident cardiovascular disease (CVD) and all-cause mortality in patients with type 2 diabetes (T2D) and microalbuminuria, but without clinical coronary artery disease

Methods: Prospective study including 200 patients. GDF-15 and FGF23 were measured at baseline. Adjusted Cox models included sex, age, LDL cholesterol, smoking, HbA1c, creatinine, systolic blood pressure urine albumin excretion rate (UAER) and for FGF23 also 25(OH)Dvitamin D. Main outcome measures: A decline in eGFR of >30%, at any time point during follow-up was the predefined endpoint of CKD progression. Hazard ratios (HR) were provided per 1 SD increment of log-transformed values of the variables.

Results: Patients were (± SD) 59 ± 9 years old, GFR 91.1 ± 18.3 ml/min/1.73m² and UAER (IQR) 103 (39–230) mg/24-h. During a median 6.1 years follow-up, there were 40 incident CVD events, 26 deaths and a total of 42 patients reached the renal endpoint after 4.9 years (median). Higher GDF-15 was a determinant of decline in eGFR >30% in unadjusted (HR (95% CI) 1.7 (1.3-2.4); p=0.001) and adjusted (HR 1.7 (1.1-2.5); p=0.018) models, a predictor of CVD in the unadjusted model (HR 1.4 (1.0-1.9); p=0.034) and of all-cause mortality in unadjusted (HR 1.8 (1.3-2.6); p=0.001) and adjusted (HR 1.9 (1.2-2.9); p=0.003) models. Higher FGF-23 was associated with all-cause mortality in unadjusted (HR 1.5 (1.1-2.0); p=0.010) and adjusted (HR 1.6 (1.1-2.2); p=0.011) models.

Conclusion: In patients with T2D and microalbuminuria, GDF-15 was independently associated with decline in kidney function and all-cause mortality, and higher FGF23 was associated with all-cause mortality.

FR-PO424
Cigarette Smoking Exacerbated the Pathology of Diabetic Nephropathy with Severity of Interstitial Inflammation Infiltration: A Multi-Center Study in Male Adults
Qian Q. Han,1 Ween China Hospital, ChengDu, Sichuan, China.

Background: Cigarette smoking have been identified as a progression factor in various kidney diseases, but no exact statement has been shown in DN at present. So we aim to investigate the association between cigarette smoking and renal injury of biopsy-proven diabetic nephropathy (DN) in male adults from Southwest China to provide more evidence for management.

Methods: A total number of 171 male adult patients with DN proven by renal biopsy from multicenter in Southwest China were recruited in our study. The patients are divided

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
into three groups according to smoking state: non-smoker, ex-smoker, and current smoker. Clinical and pathological characteristics of all three groups were collected. Logistic regression analyses, with or without multivariable adjustments for other risk factors for DN, were used to evaluate the risk of pathology of DN based on the smoking status.

**Results:** Cigarette smoking is associated with the pathology of DN. Both the unadjusted regression analyses and the multivariable adjusted regression analyses suggested cigarette smoking was a risk factor for severity of glomerular lesions (p = 0.030 & 0.030 respectively) and interstitial inflammation infiltration (p = 0.009 & 0.009 respectively) when compared with non-smoking group, and arterial hyaline, which suggesting no smoking or cessation of smoking is recommended. Especially, both unadjusted (p = 0.01, OR = 14.73) and multivariable adjusted (p = 0.01, OR = 17.50) regression analyses strongly significantly suggested that smoking was risk for interstitial inflammation. When analysing the subgroups divided by eGFR and urine protein, the results were still significant.

**Conclusions:** Smoking may be an independent risk factor for glomerular lesions, interstitial inflammation infiltration of DN, while persistent smoking is a risk factor for arterial hyaline, which suggesting no smoking or cessation of smoking is recommended for patients with diabetic nephropathy.

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

---

**FR-PO425**

Self-Reported Tobacco, Alcohol, and Illicit Drug Use and Progression of CKD: The CRIC Study

**Methods:** The associations of tobacco, alcohol, and illicit drug use with risk of chronic kidney disease (CKD) progression and all-cause mortality have not been well studied among patients with CKD.

**Methods:** The Chronic Renal Insufficiency Cohort (CRIC) Study is a prospective cohort study of 3939 adults with CKD recruited from seven US clinical sites. Self-reported questionnaires annually assessed current smoking, weekly drinking (consumed alcohol ≥1 days per week), any marijuana use, and any hard illicit drug use (use of cocaine, heroin, or methamphetamine). CKD progression was defined as halving of estimated glomerular filtration rate (eGFR) or initiation of dialysis or kidney transplant. Deaths were confirmed by death certificate. Multiple time-dependent Cox regression was used to assess the associations of drug use with progression of CKD and all-cause mortality.

**Results:** Over an average 5.4-year follow-up, 1287 participants had CKD progression and 1001 died. Current smoking and hard illicit drug use were significantly associated with increased risk of CKD progression or all-cause mortality (Table). Among patients with CKD, current smoking and hard illicit drug use may increase the risk of CKD progression and all-cause mortality.

**Conclusions:** Among patients with CKD, current smoking and hard illicit drug use have a significant association with increased risk of CKD progression or all-cause mortality.

**Funding:** NIDDK Support

---

**FR-PO426**

Lower School Educational Level Is Associated with Lower eGFR in Patients with Moderately Severe CKD: The GCKD Study

**Methods:** We analyzed data from 5111 patients of the German CKD (GCKD) study, who were enrolled on the basis of an eGFR of 30-60 ml/min or overt proteinuria. Patients were divided into three categories according to their school educational level: "low" (completed ≤ 9th grade), "intermediate" (10th grade) and "high" (a 12th grade). In adjusted logistic regression analyses, were stratified for sex, age, smoking status (never, weekly, and daily), diabetes diagnosis, and body mass index. For education, the odds ratio of being in a lower category of eGFR for low education had lower eGFR (median eGFR 43 vs. 51 ml/min, p < 0.001). However, autoimmune disease was more prevalent and UACR was higher (median 78 vs. 48 mg/g) in patients with high education (p < 0.001). An association was also found between low education and low annual household income, and the prevalence of diabetes mellitus, hypertension, coronary heart disease, stroke, and arthropathy (p < 0.001). Similar significant differences were observed by comparing patients with low income vs. high income (median household income: < 25,000 €; 25,000 to <50,000 €; 50,000 to <100,000 €; ≥ 100,000 €). An ordinal logistic regression was run to determine the association of education and income on eGFR (<30, 30-44, 45-59, >60 ml/min) and urine albumin-to-creatinine ratio (UACR) (<30, 30-300, >300 mg/g) adjusted for multiple confounders.

**Results:** In comparison with those who had high school education, patients with low education had lower eGFR (median eGFR 43 vs. 51 ml/min, p < 0.001). However, autoimmune disease was more prevalent and UACR was higher (median 78 vs. 48 mg/g) in patients with high education (p < 0.001). An association was also found between low education and low annual household income, and the prevalence of diabetes mellitus, hypertension, coronary heart disease, stroke, and arthropathy (p < 0.001). Similar significant differences were observed by comparing patients with low income vs. high income (median household income: < 25,000 €; 25,000 to <50,000 €; 50,000 to <100,000 €; ≥ 100,000 €). An ordinal logistic regression was run to determine the association of education and income on eGFR (<30, 30-44, 45-59, >60 ml/min) and urine albumin-to-creatinine ratio (UACR) (<30, 30-300, >300 mg/g) adjusted for multiple confounders.

**Conclusions:** Within the GCKD cohort, low education level but not income was independently associated with lower eGFR. Furthermore, low education and low income were associated with a greater burden of comorbidities.

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

---

**FR-PO427**

Hyperfiltration Predicts Rapid GFR Decline in a General Non-Diabetic Population and in Type 2 Diabetes

**Methods:** We investigated whether a higher GFR predicts a steeper long-term GFR decline in two diverse populations, Pima Indians with type 2 diabetes (N=319) and non-diabetic Danes in Norway (the Renal Iohexol Clearance Survey [RENIS], N=1594).

**Background:** An abnormally high glomerular filtration rate (GFR), or renal hyperfiltration, may predispose individuals to subsequent rapid GFR decline in diabetes, prediabetes, obesity, and hypertension. This hypothesis remains controversial; however, in diabetes, it is supported by clinical trials showing that treatments that acutely reduce the GFR, such as ACE inhibitors and sodium-glucose cotransport inhibitors, may reduce medium-term GFR decline.

**Methods:** We investigated whether a higher GFR predicts a steeper long-term GFR decline in two diverse populations, Pima Indians with type 2 diabetes (N=319) and non-diabetic Danes in Norway (the Renal Iohexol Clearance Survey [RENIS], N=1594). Because spurious correlations between initial values (e.g., GFR level) and subsequent changes may bias ordinary regression methods, we assessed this relationship as the correlation between the random intercept and random slope in a linear mixed model. This method separately estimates the error term (e.g., the day-to-day variation in the GFR) and random effects, eliminating bias because of regression to the mean.

**Results:** The mean (SD) baseline GFRs were 149.4 (43.3) and 104.0 (20.1) ml/min, and the median (IQR) follow-up times were 9.1 (4.0-15.0) and 5.6 (5.2-6.0) years in the Pima and RENIS cohorts, respectively. Higher baseline GFR (within a narrow normal range) was associated with a higher baseline GFR (a higher intercept) in both cohorts in multivariable adjusted linear mixed regression models with a random intercept and slope (p=0.001). The adjusted correlation between the random intercept and random slope was -0.42 (95% confidence interval, -0.55 to -0.26) in the Pima cohort and
0.32 (-0.40 to -0.23) in the Renins cohort, demonstrating that higher baseline GFRs were associated with a steeper GFR decline.

Conclusions: Renal hypertrophy predicts accelerated long-term GFR decline in type 2 diabetes and in the general non-diabetic population.

Funding: NIDDK Support, Commercial Support - Boehringer Ingelheim, Government Support - Non-U.S.

FR-PO428

Predictors of Net Acid Excretion in the Chronic Renal Insufficiency Cohort (CRIC) Study Landon C. Brown, Allison Luciano, Jane F. Pendergast, Pascale Khairallah, Cheryl A. Anderson, James H. Sondheimer, L. Lee Harno, Ana C. Ricardo, Pandarangana S. Rao, Mahboob Rahman, Edgar R. Miller, Daohang Sha, Wei Xie, John R. Asplin, Harold I. Feldman, Myles S. Wolf, Julia J. Scialla. 1Duke University School of Medicine, Durham, NC; 2University of California San Diego, La Jolla, CA; 3Wayne State University School of Medicine, Detroit, MI; 4Tulane University School of Medicine, New Orleans, LA; 5University of Illinois at Chicago, Chicago, IL; 6University of Michigan Health System, Ann Arbor, MI; 7Case Western Reserve University, Cleveland, OH; 8Johns Hopkins University, Baltimore, MD; 9University of Pennsylvania, Philadelphia, PA; 10Lutherink Corp, Chicago, IL.

Background: In prior work, higher urine net acid excretion (NAE) was associated with lower risk of chronic kidney disease (CKD) progression in patients with diabetes. In order to (1) evaluate potential mechanisms underlying associations between NAE and outcomes, and (2) assess modifiable components for future intervention, we now investigate individual predictors of NAE in the CRIC Study.

Methods: CRIC is a cohort of adults with entry estimated glomerular filtration rate (eGFR) of ≥45 ml/min/1.73m2. 24h NAE was measured as the sum of urine NH4 and titratable acidity in a subset, excluding those with urine pH <4 or ≥7.4 (n=978). We identified individual variables and sets of variables associated with NAE across the domains of demographics, comorbidities, laboratory measurements, diet, body composition, and medications using linear regression and domain-specific model adjusted R2. Results: Mean ± SD NAE was 33.2 ± 17.4 mEq/day and was higher among those with diabetes (p=0.06) vs. without diabetes (n=482, 34.4 ± 18.7 vs. 31.9 ± 15.9 mEq/day, p<0.02). Multiple variables associated with NAE in models adjusted for age, sex, eGFR, race/ethnicity, and body surface area (Table). By domains, most variance was explained by demographics, body composition, and laboratory values including kidney function and serum bicarbonate. Among medications, several metabolically active agents including biguanides and allopurinol associated with NAE.

Conclusions: NAE relates to body composition and metabolic factors in addition to diet. This study may help explain previously observed associations between NAE and kidney outcomes in diabetes.

Funding: NIDDK Support

FR-PO429

Association of Low Bicarbonate with Increased Risk of Mortality, Dialysis, and Hospitalization in CKD Patients Jerry M. Buyea, David A. Bushinsky, Elizabeth Li, Sarah McNulty, Gerrit Klaren, 1PharmaStat, LLC, Newark, CA; 2Tricida, Inc, South San Francisco, CA; 3Tricida, Inc., South San Francisco, CA; 4University of Rochester Medical Center, Rochester, NY.

Background: Low bicarbonate has been associated with a higher risk of mortality, dialysis, and hospitalizations in CKD patients. Here we estimate these risks across different levels of low bicarbonate, compared to normal, in a database of 59,710 patients with stage 3-5 CKD (ICD9 585.4, 585.5) or eGFR <60 mL/min/1.73m2.

Methods: 24h NAE was measured as the sum of urine NH4 and titratable acidity in a subset, excluding those with urine pH <4 or ≥7.4 (n=978). We identified individual variables and sets of variables associated with NAE across the domains of demographics, comorbidities, laboratory measurements, diet, body composition, and medications using linear regression and domain-specific model adjusted R2

Results: Mean ± SD NAE was 33.2 ± 17.4 mEq/day and was higher among those with diabetes (p=0.06) vs. without diabetes (n=482, 34.4 ± 18.7 vs. 31.9 ± 15.9 mEq/day, p<0.02). Multiple variables associated with NAE in models adjusted for age, sex, eGFR, race/ethnicity, and body surface area (Table). By domains, most variance was explained by demographics, body composition, and laboratory values including kidney function and serum bicarbonate. Among medications, several metabolically active agents including biguanides and allopurinol associated with NAE.

Conclusions: NAE relates to body composition and metabolic factors in addition to diet. This study may help explain previously observed associations between NAE and kidney outcomes in diabetes.

Funding: NIDDK Support

FR-PO430

The Association of Metabolic Acidosis with Renal Progression in CKD: Results from the KNON-CRD Study Hye Jin Kim, Hyunjin Ryu, Eunjong Kang, Miyeon Han, Curie Ahn, Kook-Hwan Oh. 1Department of Internal Medicine, Dongsuk University College of Medicine, Gyeongju, Republic of Korea; 2Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea; 3Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea.

Background: Metabolic acidosis, usually manifested by low serum bicarbonate level, is prevalent in chronic kidney disease (CKD). However, its relationship to long-term outcomes is unclear in Korean CKD patients. The purpose of the present study is to evaluate serum bicarbonate as a risk factor for renal outcomes, cardiovascular events and mortality in large-scale Korean CKD cohort patients.

Methods: Among the subjects recruited in the Korean CRD Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNON-CRD) between 2011 and 2016, we analyzed 1,809 participants who measured for serum bicarbonate levels. Serum bicarbonate level was categorized as low, lower normal, higher normal, and high (≤22, 22.26, 26.1-29.1, ≥30 mEq/L, respectively) groups. Metabolic acidosis was defined as serum bicarbonate <22 mEq/L. The primary outcome was renal events defined as doubling of serum creatinine, 50% reduction in eGFR from the baseline values, or end-stage renal disease. The secondary composite outcome consisted of cardiovascular events and death.

Results: Patients were 53.6±12.3 years old. The mean serum bicarbonate level was 25.7±3.7 mEq/L. A total 240 (13.3%) patients had metabolic acidosis. Patients were followed for 36.3±17.5 months. After adjustment, there was no significant association between serum bicarbonate and renal outcomes. There was significant interaction of serum bicarbonate with eGFR (interaction P=0.029). In an analysis with adjustment, in a subgroup with eGFR ≥45 mln/1.73m2, the risk of developing renal outcomes was significantly increased with decreasing (HR 0.91, 95% CI 0.87-0.94; P<0.001) and the low bicarbonate group was associated with a HR of 1.72 (95% CI 1.26-2.32; P<0.001) compared with lower normal group. Serum bicarbonate was not independently associated with renal outcomes in those with eGFR <45ml/m1.73m2 (HR 0.92; 95% CI 0.78-1.08; P=0.407). Serum bicarbonate was independent associated with secondary outcomes neither in eGFR ≥45 (HR 0.96; 95% CI, 0.89-1.04; P=0.339) nor in eGFR <45/m1/1.73m2 (HR 0.90; 95% CI, 0.79-1.02, P=0.086).

Conclusions: In a cohort of participants with CKD, metabolic acidosis was an independent risk factor for renal progression, particularly for those with advanced decreasing kidney function.

Funding: Government Support - Non-U.S.

FR-PO431

Urinary Citrate Concentrations in a Multi-Ethnic Asian Population of Healthy Participants and CKD Patients Clara L. Ngoh, Boon Wee Teo. 1Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore; 2Department of Medicine, University Medicine Cluster, National University Health System, Singapore, Singapore.

Background: Hypocitraturia is a risk factor for nephrolithiasis. Urinary metabolomics from non-Asian centres have suggested that urinary citrate is important for chronic kidney disease (CKD) progression. We studied clinical associations between urinary citrate concentrations and CKD in a multi-ethnic Asian population.

Methods: Data of 187 CKD patients and 87 healthy participants from the Asian Kidney Disease Study and the Singapore Kidney Function Study were used. Four ethnic groups (Chinese, Malay, Indian and Others) were included. Glomerular filtration rate (GFR) was estimated using the CKD Epidemiology Collaboration (CKD-EPI) equation. Urine citrate concentration was assayed using fluorescence mass-spectrometry. Hypocitraturia was defined as 24-hour urinary citrate excretion (UCE) ≤320 mmol.

Results: The mean 24-hour UCE in healthy controls and patients were 336 (209 - 443) mmol and 143 (63 - 208) mmol (CKD 1 and 2) 63 (17 - 93) mmol (CKD 3) and 21 (4 - 39) mmol (CKD 4 and 5) respectively (P<0.001). Hypocitraturia was first observed when eGFR <9 <12 mln/1.73 m2. Hypocitraturia was also significantly associated with dietary protein intake (P=0.045), eGFR <45 (P<0.001), metabolic acidosis (P<0.001)
and 24-hour proteinuria (P <0.001). In each CKD strata, Malay patients had the lowest 24-hour U albumin/Cr ratio (7 ± 24 mg/umol, P=0.025), while adjusting for age, eGFR, diabetic protein intake and chronic medications. In the Malay population, 24-hour U was also associated with a history of coronary artery disease (P <0.001), but was not a risk factor for urolithiasis (P=0.590). In healthy controls, there were no ethnic disparities.

The pH-sensitive metabolite citrate is observed in early CKD, with Asian ethnic disparities in terms of degree of UCE reduction. This has prognostic implications for renal and cardiac function. Further urinary metabolomics studies should focus on UCE to identify key signature differences between different Asian ethnic groups.

FR-PO432
Acid Retention Worsens as CKD Progresses to More Advanced Stages
Nimrit Goraya,1,2 Jan Simoni,1 Lauren N. Sager,3 Donald E. Wesson,4,5
1Diabetes Health and Wellness Institute, Dallas, TX; 2Biostatistics, Baylor Scott & White, Temple, TX; 3Surgery, Texas Tech University Health Sciences Center, Lubbock, TX; 4Internal Medicine, Texas A and M School of Medicine, Temple, TX; 5Internal Medicine, Baylor Scott and White Health, Temple, TX.

Background: Acid (H⁺) retention, even without metabolic acidosis by plasma acid-base parameters, mediates eGFR decline in animal models of chronic kidney disease (CKD) and worsens with declining GFR. Patients with reduced eGFR but no metabolic acidosis also have H⁺ retention (Wesson, et al. JAPN 300:F330) and preliminary studies showed that H⁺ retention worsened as eGFR decreased over 10 years (Goraya, et al. NIDDK 25:S9A, 2015). Because recent study supports that dietary H⁺ reduction slows nephropathy progression, more advanced CKD patients might require more aggressive dietary H⁺ reduction if their H⁺ retention is indeed greater. Consequently, we further tested the hypothesis that H⁺ retention worsens with declining eGFR by comparing cross-sectional data of H⁺ retention across CKD stages 1 through 4.

Methods: Twenty-six stage 1, 40 stage 2, 36 stage 3, and 36 stage 4 macroalbuminuric, non-diabetic CKD subjects had H⁺ retention measured by comparing the observed to the expected increase in plasma [HCO₃⁻] in response to retained H⁺, dose urine (urine-urine) excretion two hours after an oral NaHCO₃ bolus (0.5 mg/kg bw), assuming 50% body weight HCO₃⁻ space of distribution. Specifically, H⁺ retention = [retained HCO₃⁻ /0.5 x body weight] – observed increase in plasma [HCO₃⁻] x (0.5 x body weight). So, the greater the difference between the expected and observed increase in plasma [HCO₃⁻] the greater the amount of “unaccounted” H⁺ which was assumed to have been HCO₃⁻ that had been titrated by retained H⁺.

Results: Cystatin C-calculated eGFR in ml/min/1.73m² was as follows: CKD 1 =101±8, CKD 2=76±6, CKD 3= 40±7, and CKD 4=23±5. The Bonferroni correction reduced the number of significant group comparisons for H⁺ retention. Accordingly, H⁺ retention was greater in CKD 2 vs. CKD 1 (17.4±8.9 vs. 3.0± 14.0 mmol, p=0.001), in CKD 3 vs. CKD 2 (24.9±15.4 vs. 17.4±8.9 mmol, p=0.007), but not for CKD 4 vs. CKD 3 (32.2±10.5 vs. 24.9±15.4 mmol, p=0.0108).

Conclusions: These cross-sectional data show that H⁺ retention increased significantly and progressively from CKD stages 1 through 3 and, along with the previous longitudinal data, support that H⁺ worsens as eGFR decreases. Greater H⁺ retention in patients with lower eGFR might contribute to their faster eGFR decline and its resolution might require more aggressive dietary H⁺ reduction to optimize eGFR preservation.

FR-PO433
Acid Retention Revealed by Urine Citrate Excretion Might Identify CKD Patients for Whom Dietary Alkali Is Kidney Protective
Nimrit Goraya,1,2 Jan Simoni,1 Lauren N. Sager,3 Donald E. Wesson,4,5
1Diabetes Health and Wellness Institute, Dallas, TX; 2Biostatistics, Baylor Scott & White, Temple, TX; 3Surgery, Texas Tech University Health Sciences Center, Lubbock, TX; 4Internal Medicine, Baylor Scott & White Health, Temple, TX; 5Internal Medicine, Texas A and M School of Medicine, Temple, TX.

Background: Despite data showing that dietary alkali slows eGFR decline in chronic kidney disease (CKD) stage 3 (CKD 3) patients with mild metabolic acidosis (plasma total CO₂ [PTCO₂] >22 mM) (Goraya, et al. KI 86:1031, 2014) and in CKD stage 2 (CKD 2) JASN 26:S5A, 2015), because of no metabolic acidosis (Goraya, et al. AP 300:F330; Mahajan, et al. KI 78:303, 2010), KDIGO recommends alkali for only CKD patients with PTCO₂ < 22 mM. We tested the hypothesis that urine excretion of pH sensitive metabolites of H⁺, such as citrate, might identify acid retained CKD stage 4 patients who cause lower eGFR decline in animal models of CKD, in patients for whom dietary alkali provides kidney protection but for whom current guidelines do not recommend alkali therapy.

Methods: Macroalbuminuric, non-diabetic subjects with CKD stage 1 (CKD 1) and PTCO₂ > 24 mM (n=26), 2 CKD stage 2 (n=20), > 24 mM (n=40), and CKD stage 3 with PTCO₂ < 22 mM (n=36), had urine samples measured at entry to determine creatinine and 8h urine citrate excretion (8h U citV). H⁺ retention was calculated as follows:

\[ H⁺ \text{ retention} = \frac{\text{retained } \text{HCO}_3^-}{0.5 \times \text{body weight}} - \text{observed increase in plasma } [\text{HCO}_3^-] \times (0.5 \times \text{body weight}) \]

where the observed increase in plasma [HCO₃⁻] was measured at 8h U citV.

Results: PTCO₂ was similar in CKD 2 (26.2±6.0 mmol) and CKD 1 (26.8±0.7 mmol) but was lower in CKD 3 (22.8±7.7 mmol). Bonferroni correction required p-value significance < 0.0083 for within-group comparisons of H⁺ retention and 8h U citV. H⁺ retention was greater in CKD 2 than CKD 1 (17.4±8.9 vs. 3.0±14 mmol, p=0.010) and PTCO₂ that for CKD 3 (24.9±15.4 mM) was higher than both CKD 1 (p=0.001) and CKD 2 (p=0.001).

Conclusions: Lower than CKD 1 urine citrate increase was present in CKD 2 and CKD patients for whom alkali therapy has been kidney protective but whose PTCO₂ was not less than 22 mM. Hypocitraturia is observed in early CKD, with Asian ethnic disparities in terms of degree of UCE reduction. This has prognostic implications for renal and cardiac function. Further urinary metabolomics studies should focus on UCE to identify key signature differences between different Asian ethnic groups.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author. 513
in eGFR, despite adjustment for age and BMI (p=0.05) as compared to those with none or mild CKD.

Conclusions: Among Veterans with CKD, the presence of moderate to severe SA is associated with a faster decline in eGFR and increased risk of 30% decline in eGFR over 2 years, but findings are of borderline statistical significance. Completion of 3-year follow-up as planned will provide additional power to make more definitive conclusions regarding the association between SA and CKD progression in this population.

Funding: Veterans Affairs Support

FR-PO436

Urinary Epidermal Growth Factor (uEGF) and Monocyte Chemoattractant Protein-1 (uMCP1) as Biomarkers of Renal Involvement in ANCA-Associated Vasculitis (AAV) Wenjun Ju,1 Catherine Najem,2 Viji Nair,1 David D. Cuthbertson,3 Rennie L. Rhee,2 Laura H. Mariani,3 Jeffrey P. Krischer,3 Matthias Kretzler,1 Peter A. Merkel,2 University of Michigan, Ann Arbor, MI; 1University of Pennsylvania, Philadelphia, PA; 2University of South Florida, Tampa, FL Group/Team: Vasculitis Clinical Research Consortium and NEPTUNE Network

Background: EGF mediates distal tubular epithelial cell function and regeneration. MCP-1 recruits leukocytes to areas of inflammation. This study examined the utility of uEGF and uMCP-1 as biomarkers of renal disease in AAV.

Methods: uEGF and uMCP-1 (normalized to urine creatinine) were measured at enrollment, an active renal disease visit (index), 1-2 visits prior to and after the index, and at 1 year follow-up utilizing urine samples from a multicenter longitudinal cohort of patients with AAV. Chronic kidney disease (CKD) was defined as eGFR< 60 mL/min/1.73 m2 for ≥3 months. Index visit was defined as the first visit with a new/worse BVAS/WG renal item since prior visit. To assess the association of each biomarker with disease activity, a mixed effect model was used, adjusting for ANCA type (MPO or PR-3), urinary albumin/creatinine ratio (ACR), eGFR, visit type. To assess time to CKD, a Cox proportional hazard model was used, adjusting for demographics, ANCA type, ACR, and eGFR.

Results: At baseline, 165/544 patients had CKD. After adjusting for sex, age, race, ANCA type, eGFR, and albumin/Cr, for each unit increase in baseline uEGF/Cr there was a lower risk of CKD [HR=0.62, (0.43, 0.88), p=0.01)]. Higher baseline uMCP-1/Cr didn’t predict risk of CKD [HR=1.14, (0.88, 1.48), p=0.33)]. 112 patients had active renal disease. uEGF/Cr levels did not significantly differ between pre-, post- and index visits. Compared to index visit, uMCP-1/Cr was lower at pre- and post-index visits (p=0.04 and p<0.01).

Conclusions: In AAV, uEGF predicts progression to CKD independently of ACR and uMCP-1, but uEGF, correlates with renal disease activity. uEGF and uMCP-1 are useful biomarkers in AAV.

Funding: NIDDK Support, Other NIH Support - Rare Diseases Clinical Research Network- Vasculitis Clinical Research Consortium U54 AR057319, North American Nephrotic Syndrome Network U54DK083912.

FR-PO437

Neighborhood Socioeconomic Status and Incident ESRD Mild R. Saunders,2 Esteban A. Cedillo-Couve1, Lawrence J. Appel,1 Jiang He,1 Edward J. Horwitz,2 Jesse Y. Hsu,10 Martha L. Davilugus,1 Michael J. Fischer,2 Ana C. Ricardo,2 Hernan Rincion-Choles,1 Susan P. Steigerwald,1 Daohang Sha,7 James H. Sondheimer,1,11 James P. Lash,4 Cleveland Clinic, Cleveland, OH; 3Johns Hopkins Medical Institutions, Baltimore, MD; 4Solon, OH; 5Tuane School of Public Health and Tropical Medicine, New Orleans, LA; 6University of Pennsylvania, Philadelphia, PA; 7University of Chicago, Chicago, IL; 8University of Illinois Hospital and Health Sciences Center, Chicago, IL; 9University of Illinois at Chicago, Chicago, IL; 10University of Michigan, Ann Arbor, MI; 11University of Pennsylvania, Philadelphia, PA; 12Wayne State University School of Medicine, Detroit, MI Group/Team: On behalf of CRIC Investigators

Background: Although individuals with lower socioeconomic status (SES) are disproportionately affected by end-stage renal disease (ESRD), the association of neighborhood SES with incident ESRD has not been thoroughly evaluated. Using data from the Chronic Renal Insufficiency Cohort Study, we evaluated the relationship between neighborhood SES and ESRD.

Methods: Cox proportional hazards to examine the association between neighborhood SES quartiles and incident ESRD. We constructed a neighborhood-level SES summary measure using z scores for 6 census-derived variables using a validated approach.

Results: Among 3291 adults with CKD (mean eGFR 45 ml/min/1.73m2, median proteinuria 0.19 g/24h), 41% were non-Hispanic white, 42% non-Hispanic black, 13% Hispanic. At study entry, compared to those in the highest quartile SES neighborhood Q4, individuals in lowest SES quartile neighborhoods (Q1) were more likely to be younger, female, non-Hispanic black or Hispanic, current smokers, have lower healthy eating scores and physical activity (p<0.001 for each). In addition, Q1 individuals had lower eGFR, higher proteinuria, and were more likely to have diabetes, hypertension, and cardiovascular disease; however, they were as likely as those in Q4 counterparts to be on aspirin, statin, and ACE/ARB. During median follow-up of 6.8 years, there were 878 ESRD events. Multivariable analyses are summarized below.

Conclusions: While individuals in low SES neighborhoods had a greater burden of kidney disease risk factors and higher ESRD rates, likelihood of reaching ESRD was explained in part by individual SES.

Funding: NIDDK Support

FR-PO438

Human Kidney Tubule Cytosine Methylation Changes Can Improve Models for CKD Progression Caroline A. Glueck,2 Chengxiang Qiu,3 Sang Youb Han,2 Jing Huang,2 Ae Seo Deok Park,4 Ti-An Ko,1 Ioannis Mantzaris,5 Yong Chen,3 Amit K. Verma,1 Matthew Palmer,1 Katalin Susztak,1 Albert Einstein College of Medicine, Bronx, NY; 1Inje University, GoYang, Republic of Korea; 2Montefiore Medical Center, Bronx, NY; 3Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; 4The Children's Hospital of Philadelphia, Philadelphia, PA; 5University of Pennsylvania, Philadelphia, PA.

Background: Chronic Kidney Disease (CKD) progresses at variable rates. Patients who progress rapidly are more likely to reach end stage renal disease (ESRD). Current models to predict CKD progression are centered on baseline GFR, age, and comorbidities. These clinical phenotypes do not explain the pathophysiology of progression and cannot account for environmental influence on progression. Cytosine methylation is a stable, cell type specific and environmentally responsive epigenetic signal that affects gene expression patterns. The aim of this project was to determine if genome wide cytosine methylation changes can improve baseline models for CKD progression and identify novel pathways underlying CKD progression.

Methods: Biobanked human kidney tissue was microdissected to isolate kidney tubules. The data set included 69 human kidney tubule samples with associated cross-sectional and longitudinal clinical data. Histomorphology for samples were graded on 20 independent parameters. Genome wide cytosine methylation was analyzed using the Illumina Infinium 450K chip. Transcript level changes were determined using the Affymetrix RNA microarray. Subject-specific adjusted GFR slopes were determined using best linear unbiased prediction to account for random variation. Variables for CKD progression models were selected by a machine learning regression analysis method, “LASSO”, to improve model accuracy and reduce model overfitting. Methylation and

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
transcript levels were added to baseline linear regression models and both R² and aakka information criteria were used to evaluate model fitness.

Results: The final model (M1) for CKD progression based on LASSO-selected variables included: baseline GFR, age, albuminuria (dipstick), CKD stage, diabetes, height, and vessel intimal fibrosis. Adding the top gene transcript level to M1 (M2) improved model fitness, Finally, addition of the methylation level at the top genomic loci to M2 (M3) further improved model fitness.

Conclusions: Human kidney tubule cytosine methylation levels may improve CKD progression models even after gene expression levels are included. Methylation changes in kidney tissue may be useful biomarkers for CKD progression and may be functionally important in CKD progression.

Funding: NIDDK Support

FR-PO439

Urineal Epidermal Growth Factor Predicts Rapid GFR Decline in the General Non-Diabetic Population

Jon V. Norvik,1,2 Wenjun Ju,1 Vijji Nair,1 Vidar T. Stefansson,1 Jørgen Schei,1,3 Trond G. Jenssen,1 Marit Solbø,4 Matthias Kretzler,2 Bjørn O. Eriksen,5 Toralf Melsom,4 Östlund University Hospital, Oslo, Norway; 1.U:Michigan, Ann Arbor, MI; 2.The Arctic University of Norway, Tromsø, Norway; 3.University Hospital of North Norway, Tromsø, Norway; 4.University of Michigan, Ann Arbor, MI; 5.University of Tromsø, Tromsø, Norway.

Background: Biomarkers are needed to distinguish people at high risk to develop chronic kidney disease (CKD) for early and targeted clinical care. Lower levels of urinary epidermal growth factor (uEGF) have been associated with increased tubular atrophy, interstitial fibrosis and rapid progression in CKD of various etiologies. We investigated whether lower uEGF predicted risk for rapid glomerular filtration rate (GFR) decline in the general population.

Methods: In the Renal Iohexol Clearance Survey of Tromsø 6 (RENIS-T6), we measured GFR by iohexol-clearance in 1,594 middle-aged persons without diabetes or chronic kidney disease. Of these, 1,299 (81%) had a follow-up GFR measurement after a median of 5.6 years in the RENS-Follow Up and a random sample of 87 persons had a third GFR measurement. uEGF levels at baseline were measured using an ELISA assay. We used a linear mixed model with random intercept and slope to assess the relationship between uEGF and change in GFR and a multiple logistic regression model to examine the association between uEGF and rapid GFR decline (defined as annual GFR decline ≥ 3 mL/min/1.73 m²).

Results: The mean (SD) annual GFR decline rate was -0.86 (2.13) mL/min/1.73 m². Lower baseline uEGF was independently associated with a steeper GFR decline rate (β = -0.16 (95% confidence interval (CI) -0.26 to -0.05) mL/min/1.73 m² per 1 SD decrease in log-transformed uEGF after adjusting for CKD risk factors such as urinary albumin-to-creatinine ratio (ACR)). The annual GFR decline rate for participants with uEGF levels below the median was -1.00 (95% CI -1.14 to -0.86) mL/min/1.73 m² compared to -0.71 (95% CI -0.86 to -0.56) mL/min/1.73 m² for those above the median value (P = 0.006), adjusted for sex, age, and ACR. The multivariable adjusted odds ratio for rapid decline was 1.91 (95% CI 1.27 to 2.88) for those with uEGF below the median level.

Conclusions: Lower uEGF levels predicted rapid GFR decline in the general non-diabetic population.

Funding: Government Support - Non-U.S.

FR-PO440

Rate of GFR Decline and Incident CKD among Primary Care Patients with Normal or Mildly Reduced Renal Function

Farrukh F. Scherrer,1,3 Jenssen,1,4,3 Eriksen,5 Melsom,4 Ju,5 Mindset,4,3 Ju,5 Viji,1 Nair,1 Solbø,4 Kretzler,2 Eriksen,5 Melsom,4 Melsom,4 Scherrer,1,3

Background: Rapid GFR decline is associated with adverse outcomes. The risk factors associated with the rate of GFR decline in association with incident CKD among primary care patients with normal or mildly reduced GFR are not well defined.

Methods: From an academic primary care patient registry containing electronic health record data, we identified 2,219 adults with at least three GFR values (calculated using the CKD-EPI equation) between July 1st 2008 – June 30th 2016. We required patients to have an initial (baseline) GFR value between 60-119 mL/min/1.73 m². Rapid GFR decline was defined as a decline in eGFR of ≥ 5 mL/min/1.73 m² per year and incident CKD was defined as an eGFR of <60 mL/min/1.73 m². The clinical and socio-demographic characteristics were compared using chi-square tests and independent samples t-tests. Adjusted logistic regression models were computed to measure the associations between covariates among rapid decliners stratified by baseline eGFR of 60-89 (mildly reduced) and 90-119 (normal) mL/min/1.73 m².

Results: Rapid GFR decline was significantly associated with incident CKD, older age, black race, unmarried status, lower neighborhood socioeconomic status (nSES), hypertension, type 2 diabetes, current smoking and initial eGFR (p < 0.001). Incident CKD was significantly associated with unmarried status (p < 0.028), and type 2 diabetes (p = 0.0001) in rapid decliners and with anxiety (p = 0.005) and depression (p = 0.5) in slow decliners. Older age, hypertension and initial GFR were significantly (p < 0.0001) associated with incident CKD in both groups. Multivariate logistic regression analysis resulted in consistent associations with rapid GFR decline and mildly reduced baseline eGFR, revealed only older age being significantly associated with incident CKD (OR = 1.04 [1.01-1.08]).

A separate multivariate logistic regression model among rapid decliners with a normal baseline eGFR revealed only type 2 diabetes being significantly associated with incident CKD (HR = 3.38 [1.35-10.89]).

Conclusions: Among primary care patients with normal or mildly reduced GFR (who are typically not referred to nephrology), patient characteristics associated with incident CKD differ by the rate of GFR decline and by the baseline eGFR. Our findings identify high risk patients in primary care and would inform development of risk prediction models for incident CKD.

Funding: NIDDK Support

FR-PO441

The Effect of Statin Therapy on Clinical Outcomes in Patients with CKD: The Results from the KNOW-CKD and KNOW-CKD: Risk Factors for Incidence and Progression - II


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

Underline represents presenting author.

515
FR-PO443
Self-Reported Snoring Is Associated with Incident CKD Development: A Community-Based Prospective Cohort Study
Jaekeol Kwon, Heebyung Koh, Ki Heon Nam, Seong yeong An, Tae-Hyun Yoo. Department of Internal Medicine, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, Republic of Korea.

Background: Reports have shown sleep disordered breathing symptoms including habitual snoring to be clearly associated with the development of metabolic derangements and vascular diseases. However, the relationship between habitual snoring and renal function is not well investigated. Therefore, this study aimed to evaluate the association between habitual snoring and the development of incident chronic kidney disease in a cohort of subjects with normal renal function.

Methods: Data were retrieved from the Korean Genome and Epidemiology Study (KoGES), a prospective community-based cohort study. A total of 9304 subjects with normal renal function were included in the analysis. Subjects were classified into three groups, based on self-reported snoring frequency at baseline: non-snorer, infrequent snorer, frequent snorer. The primary endpoint of study was development of CKD, defined as estimated glomerular filtration rate < 60 mL/min/1.73 m².

Results: The mean age was 52 years. The non-snorer, infrequent snorer, frequent snorer groups each included 3573(38.4%), 3856(41.4%) and 1875(20.2%) subjects. Cox Proportional Hazard model analysis revealed that snoring was an independent risk factor for incident CKD development [HR, 1.21; 95% CI, 1.007-1.468; P = 0.0032]. Individual factors even after adjusting for confounding factors including the presence of metabolic syndrome and eGFR at baseline.

Conclusions: Snoring may increase the risk of CKD development in subjects with normal renal function. Managing sleep quality could play a role in preserving renal function.

FR-PO444
The Effects of Coffee Intake on the Incident CKD in General Population
Heebyung Koh, Ki Heon Nam, Meiyun Wu, Youngnam Nam, Seung Hyeok Han. 1Department of Internal Medicine, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, Republic of Korea; 2Department of Internal Medicine, College of Medicine, Severance Biomedical Science Institute, Brain Korea 21 PLUS, Yonsei University, Seoul, Republic of Korea.

Background: Coffee intake has been linked to many cardiovascular diseases, and smoking is a well known risk factor of incident chronic kidney disease (CKD). However, studies on coffee consumption and development of chronic kidney disease (CKD) in general population.

Methods: Using the database from the Korean Genome and Epidemiology Study (KoGES) from 2001 to 2014, we analyzed 9644 subjects with normal renal function. Coffee consumption was categorized into 5 groups: 0/wk (<2232), 1-<6 cups/wk (<618), 1-6 cups/wk (<6190), 1 cup/day (≥6245), and a 2 cups/day (≥2439). All measurements such as systolic blood pressure, body mass index, estimated glomerular filtration rate (eGFR), fasting glucose, hemoglobin, and lipid profiles during follow-up period were treated as time-varying covariates. The primary outcome was incident CKD defined as an eGFR < 60 mL/min/1.73 m².

Results: The mean age was 52.0 years and 4594 (47.6%) were male. At baseline, higher coffee consumers were younger, had lower blood pressure, and had lower prevalence of hypertension and diabetes as compared to non-smokers or lower consumers. Time-averaged blood pressure was also lower as coffee consumption was increased. A multivariable logistic regression model showed that high coffee consumption independently associated with low systolic blood pressure (β = −0.52, P < 0.001). During a mean follow-up of 124.8 months, 839 (8.6%) participants developed CKD. The incident CKD occurred in 168 (16.5%) in former- or current-smokers as compared to 164 (13.6%) in never-smokers (P = 0.057). In a multivariable Cox regression analysis after adjustment of confounding factors, coffee consumption of ≥1 cup/day was significantly associated with a lower risk of CKD development [HR, 0.71; 95% CI, 0.50-0.99; P = 0.045]. This finding was significant even after adjustments were made for confounding factors including age, sex, body mass index, smoking status, comorbidities, use of antihypertensive agents, eGFR, and overt proteinuria. SRB of < 110 mmHg (hazard ratio, 0.76; 95% confidence interval (CI), 0.55-1.05; P = 0.076) and those with SBP of 130-139 mmHg (HR, 0.62; 95% CI, 0.42-0.91; P=0.015) were significantly associated with a lower risk of the composite endpoint as compared to SBP of 130-139 mmHg. In contrast, HRs for the composite outcome were significantly higher in patients with SBP of 150 to 159 mmHg (HR, 1.47; 95% CI, 1.20-1.5; P=0.0049) and those with SBP of a 160mmHg (HR, 2.00; 95% CI, 1.36-3.09; P=0.002) than in patients with SBP of 130-139 mmHg. There was no difference in the risk of primary outcome between SBP categories of 120-129, 130-139, and 140-149 mmHg.

Conclusions: In this study, we found a significant linear relationship between SBP and adverse renal outcomes in patients with CKD. Thus, lowering the BP target below the levels proposed by the current guideline may be beneficial to attenuate deterioration of kidney function.

FR-PO446
Smoking Is a Risk Factor for the Progression of CKD: From the Korean Cohort Study for Outcome in patients With CKD
Meiyun Wu,1 Seung Hyeok Han.2 1Department of Internal Medicine, College of Medicine, Severance Biomedical Science Institute, Brain Korea 21 PLUS, Yonsei University, Seoul, Republic of Korea; 2Department of Internal Medicine, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, Republic of Korea.

Background: Smoking is a risk factor of developing incident chronic kidney disease (CKD). However, most studies included relatively healthy participants without CKD and studies on the association between smoking and deterioration of kidney function in patients with CKD are scarce. Therefore, we aimed to evaluate the effect of smoking on kidney disease progression and dose-response relationship by pack-years in these patients. Methods: Using the KoreanN cohort study for Outcome in patients With Chronic Kidney Disease (KoGES-CKD) is a nation-wide prospective observational cohort study from 9 centers in Korea. A total of 2218 patients were included in the final analysis. Patients were categorized into never-, former-, and current-smokers. Primary outcome was a composite definition eGFR of a 50%, initiation of dialysis, or kidney transplantation.

Results: The mean age was 53.6±12.3 years and 1356 patients (61.1%) were male. Compared to never-smokers, former- or current- smokers had higher prevalence of diabetes (38.4% vs. 29.6%, P < 0.001) and cardiovascular disease (14.3% vs. 7.8%, P < 0.001) at baseline. In addition, these patients had higher blood pressure (128±16.7 vs. 127.0±15.8 mmHg, P = 0.007), lower eGFR (48.6±27.9 vs. 52.3±22.6 mL/min/1.73m², P = 0.004) and higher level of proteinuria [1.6 (0.2-1.8) vs. 1.2 (0.1-1.2) g/d, P < 0.001] than never-smokers. During a mean follow-up duration of 36.7±18.2 months, primary outcome occurred in 197(10.5%) subjects developed CKD in the non-snorer, infrequent snorer and frequent snorer groups each included 3573(38.4%), 3856(41.4%) and 1875(20.2%) subjects. This finding was significant even after adjustments were made for confounding factors, including age, sex, body mass index, smoking status, systolic blood pressure, eGFR at baseline.

Conclusions: In this study, we found a significant linear relationship between SBP and adverse renal outcomes in patients with CKD. Thus, lowering the target BP below the levels proposed by the current guideline may be beneficial to attenuate deterioration of kidney function.
The primary outcome was development of CKD defined as estimated glomerular filtration rate ≥ 1.33 ml/min/1.73 m².

Results: In the SSE and non-SSE groups, the mean ages of the subjects were 49.5 ± 7.4 and 51.6 ± 7.9 years, the numbers of male subjects were 289 (14.0) and 466 (16.7), and the mean estimated glomerular filtration rates (eGFR) were 95.1 ± 12.7 and 93.9 ± 12.8 ml/min/1.73 m², respectively. Among the subjects in the SSE group, the duration of SSE showed a significant positive correlation with BMI and HbA1c. Cox analysis revealed that SSE was a significant risk of CKD development even after adjustments were made for confounding factors (Hazard ratio, 1.15; 95% confidence interval, 1.02-1.3; P = 0.049).

Conclusions: Secondhand smoking significantly increased the risk of CKD development. In addition, factors such as obesity and insulin resistance may be affected by SSE. Avoiding SSE may have an effect on preventing the development of CKD.

FR-PO448
Significance of Cardio-Ankle Vascular Index in the Long-Term Renal Prognosis for Patients with Non-Diabetic CKD Akiko Shimizu, Hideo Okonogi, Tetsuya Kawamura, Shinya Yokote, Masahiro Suyama, Kei Matsumoto, Kentaro Koike, Nobuo Tsuibo, Yoichi Miyazaki, Masato Ikeda, Makoto Ogura, Takashi Yoko. Division of nephrology and hypertension, The Jikei university school of medicine, Tokyo, Japan.

Background: Cardio-ankle vascular index (CAVI) is a non-invasive index of arterial stiffness and, theoretically, independent of blood pressure at the time of measurement. Although the role of CAVI as a predictor of cardiovascular events has been reported, few studies have considered the renal prognosis. The present retrospective cohort study was undertaken to investigate the association between CAVI and the long-term renal prognosis in patients with non-diabetic chronic kidney disease (NDDCKD).

Methods: We included 44 NDDCKD patients (CKD stages 1, 2, 3, and 4, and follow-up period ≥ 2 years), who were diagnosed for first time renal biopsy (RBx). Renal outcome was defined as reaching 30% decline in eGFR from baseline. We analyzed the association between CA VI and outcome, and risk factors affecting the incidence of outcome, by Cox proportional hazard model, receiver-operating characteristic (ROC) analysis, and Kaplan–Meier analysis.

Results: As a result, a median follow-up time was 86 months (range, 27–101 months), and 176 (20.4%) patients reached outcome. Baseline CAVI, eGFR, hypertension and uric acid were significantly associated with outcome by univariate Cox analysis (p < 0.05). By ROC analysis, the areas under the curve for diagnosis of the future outcome by baseline CAVI was 0.838 (p = 0.0007), and CAVI cut-off value was calculated as 7.50 (Sensitivity 93%, Specificity 62%). Then CAVI≥7.5 (CAVI-C) and eGFR were independently associated with outcome by multivariate Cox analysis, (Hazard ratio (HR) 7.3, 95% confidence interval (CI) 1.2-141, p = 0.05, and HR 0.97, 95%CI 0.94-0.99, p = 0.05, respectively). Furthermore, Kaplan–Meier analysis showed that outcome-free survival was significantly lower in HCAs VI group compared with CAVI≥7.5 group (Log-rank test, p = 0.0017).

Conclusions: These results indicated that CAVI at the time of RBx was independently associated with long-term renal prognosis in NDDCKD patients.

FR-PO449
CKD Patients Are Exposed to More Proton Pump Inhibitors (PPIs) Compared to Non-CKD Patients in a Tertiary Single Center. Heejeong Lee, Songhee Oh, Haeyoung Lee, Jin seok Jeon, Dong Cheol Han, Soon hyo Kwon. 1 Soon Chun Hyang Univ. Hospital, Seoul, Republic of Korea; 2 Soon Chun Hyang University Hospital, SEOUL, Republic of Korea; 3 Soon Chun hyang university hospital, SEOUL, Republic of Korea; 4 Soonchunhyang University Hospital, SEOUL, Republic of Korea.

Background: Proton pump inhibitor (PPI) is associated with incident chronic kidney disease (CKD), CKD progression and end-stage renal disease (ESRD). However, the extent of PPI in CKD patients comparing to non CKD patients is still unclear.

Methods: We conducted a retrospective study on patients (>18 years old) who received PPI in a single tertiary out-patient clinic (750 beds, Seoul, South Korea) from Jan. 2014 to Dec. 2015. PPIs need doctor’s prescription in South Korea.

Results: Our sample consisted of 9,112 patients. Females were 50.3% and were 10.4 years older. Among CKD patients, 721 (7.9%) were categorized as stage 3 or 4, 176 (1.9%) were stage 5 or ESRD. Total 7 types of PPIs were prescribed. During the study period, median duration of PPI usage was 120 days [interquartile range, 63-271] in CKD 3-4 group, 105 days [56-271] in CKD 5-ESRD group and 90 days [56-175] in non-CKD group. Patients with CKD stage 3 or 4 took longer duration of PPI than non-CKD patients (p = 0.001). Main departments of medicines which prescribed PPIs in CKD group were gastroenterology (39.4%), cardiology (28.2%), nephrology (15.1%) and neurology (4.2%). Compared to the non-CKD group, the CKD stage 3 or 4 and CKD stage 5 or ESRD group was taking more drugs simultaneously (6.9 ± 4.8 vs 2.4 ± 1.6, p < 0.0001). Total 242 patients were examined in the first week of life. Additional ultrasound images were taken at six months of age in all babies. Total kidney volume, renal cortical and pyramid thickness were measured.

Conclusions: In premature babies the average kidney volume increased significantly from 32 weeks to 37 weeks PMA (post menstrual age) (6.89 ± 0.4 vs 10.38 ± 0.29, p = 0.0001). However, at 37 PMA the kidney volume and the pyramid/cortex ratio were still significantly smaller in premature babies compared to term babies (10.38 ± 0.29 vs 12.85 ± 0.48, p ≤ 0.0001; 2.22 ± 0.08 vs 2.79 ± 0.08, P = 0.0001 respectively). Premature infants
had also a significantly lower eGFR (73.6 vs. 79.3 mL/min/1.73 m²; p = 0.03). By 6 months the average kidney volume was no longer different between premature and term babies due to significant catch-up growth of the premature kidney. The pyramid/cortex ratio remained significantly lower in the premature babies than term babies (2.01±0.05 vs 2.5±0.10, p = 0.0006). In term babies the medulla region continued to develop and mature, while the pyramid/cortex ratio remained significantly lower in the premature than in the term babies (2.01±0.05 vs 0.05). For premature babies the pyramid/cortex ratio didn’t change significantly from birth to 6 months suggesting the medullary growth was significantly impaired.

**Conclusions:** Taken together, these results suggest that premature birth has sustained effects on postnatal renal medulla development and remodelling with potentially negative impact on renal function later in life.

**FR-PO453**

**Urinary Epidermal Growth Factor as a Prognostic Marker for the Progression in Children with Alport Syndrome**

Bailong Li,1 Fangru Ding,1 Fang Wang,2 Vijay Nair,1 Matthias Kretzler,2 Wenjun Ju1,2 Jie Ding.1 1Peking University First Hospital, Beijing, China; 2University of Michigan, Ann Arbor, MI.

**Background:** Alport syndrome (AS) is a rare hereditary kidney disease manifested with progressive renal failure, vast majority of the cases are caused by defects in type IV collagen genes. Considerable variation exists in terms of disease progression among patients with AS. Identification of patients at high risk of rapid progression remains an unmet need. Urinary epidermal growth factor has been shown to be independently associated with risk of progression to end stage kidney disease (ESKD) or 40% reduction of baseline eGFR in multiple independent adult CKD cohorts. In this study we aim to assess the prognostic value of uEFG in children with AS.

**Methods:** 117 pediatric patients with AS and 72 healthy children (3-18 year-old) were included in this study. uEFG was measured in duplicates in baseline urine samples using ELISA (R&D) and concentration was normalized by urine creatinine (uEFG/Cr). In patients with longitudinal follow up data (n=38), progression was defined as decreased kidney function (CKD stage increase) during follow-up period (average follow-up 29.2±16.18 months). The area under the receiver operating characteristic (ROC) curve was used to assess the discriminative power of the marker.

**Results:** uEFG/Cr decreases with age in both healthy children and pediatric patients with AS. The decrease rate of uEFG/Cr with age was faster in AS patients. uEFG/Cr is significantly correlated with GFR (r=0.75, p<0.001), after adjustment for age. In 38 patients with longitudinal follow-up, we observed a significant correlation between uEFG/Cr and eGFR slope (r=0.58, p<0.001). Patients with lower uEFG/Cr level with an increased risk of progression to a higher CKD stage. uEFG distinguished progressors from patients who do not show CKD stage advance with an AUC of 0.89, versus 0.80 by GFR and 0.79 by ACR.

**Conclusions:** Our work suggested that uEFG/Cr may be used as a biomarker for accelerated kidney function decline in pediatric patients with AS. It may help to identify patients at high risk of progression for targeted clinical care and improve the patients stratification in interventional trials. Future validation with more patients and longer follow-up time will be required.

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

**FR-PO454**

**Analysis of the Plasma Proteome Reveals Dysregulation of Molecular Pathways in Patients with Stage 4 CKD**

Kulikowski,1 Sylwia Wasiaek,2 Laura Tsuijikawa,3 Christopher Halliday,2 Stephanie Stotz,3 Dean Gilham,2 Ravi Jahaigard,2 Kamyar Kalantar-Zadeh,1 Richard A. Robson,2 Michael Sweeney,2 Jan O. Johansson,2 Norman C. Wong,3 ‘Christchurch Clinical Studies Trust, Christchurch, New Zealand; 3Resverlogix Corp, Calgary, AB, Canada; 1University of California Irvine, School of Medicine, Orange, CA; 2Resverlogix Inc., San Francisco, CA.

**Background:** Chronic kidney disease (CKD) is associated with progressive loss of renal function. To gain insight into molecular mechanisms and biological consequences of pathway dysregulation in CKD, plasma proteome profiling of stage 4 CKD patients was performed using a novel somamer-based approach coupled to bioinformatics.

**Methods:** Eight subjects with stage 4 CKD not on dialysis (mean eGFR=20 ml/min/1.73m²) and eight matched control subjects (mean eGFR=78.5 ml/min/1.73m²) participated in the study. Plasma samples were collected for analysis with the SOMAscan® 1.3K platform, which detects 1305 proteins in a multiplexed, sensitive and reproducible manner. Proteomics data were analysed with Ingenuity Pathway Analysis (IPA®).

**Results:** SOMAscan® proteome analysis of plasma from CKD versus control subjects identified 289 differentially expressed proteins (difference>10%, p<0.05), 191 of those proteins were upregulated by more than 50% in CKD plasma relative to controls. Many of the enriched markers correlate with CKD progression, including cystatin C, B2M, LCN2, LFABP and FGF23. Other differentially expressed proteins included S100A8 and S100A9, and their soluble receptors, adhesion molecules, metalloproteases, complement, coagulation and fibrinolytic factors. IPA® bioinformatics of the plasma proteome confirmed an upregulation of pathways known to be activated in CKD such as the inflammatory and immune response, endothelial dysfunction, thrombosis, renin-angiotensin system, calcification and oxidative stress.

**Conclusions:** This study provides an exhaustive list of plasma proteins that are dysregulated in stage 4 CKD. In combination with pathway analysis, this CKD plasma proteome contributes new knowledge of molecular processes that accompany CKD and potential new disease markers.

**FR-PO455**

**Mineralocorticoid Receptor Blockers and Renal Outcomes in Patients with Heart Failure and CKD**

Thomas Mavrakas,1,2 Nadia Giannetti,1 Ruth Sapir-Pichhadze,2 Alsan Alam.3 1Division of Cardiology, McGill University Health Centre, Montreal, QC, Canada; 2Division of Nephrology, McGill University Health Centre, Montreal, QC, Canada; 3Division of General Internal Medicine, Geneva University Hospitals, Geneva, Switzerland.

**Background:** The protective effect of mineralocorticoid receptor blockers (MRBs) against cardiovascular death or heart failure hospitalization has been demonstrated in patients with chronic kidney disease (CKD). However, safety concerns limit their use in this population. Furthermore, the effect of MRBs on CKD progression is unknown.

**Methods:** We conducted a retrospective cohort study including consecutive adult patients from the heart failure clinic of a tertiary care center who were already treated with an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker. The exposure of interest was treatment with MRBs by 6 months from registration to clinic. Persistent doubling of serum creatinine was the primary efficacy outcome. The composite of doubling of serum creatinine or potassium >6 mmol/l was the primary safety outcome. The composite of death from any cause, myocardial infarction, or admission for decompensated heart failure was the secondary outcome.

**Results:** A total of 314 patients who were prescribed MRBs were compared to 1116 patients who were never treated with MRBs. Among them, 121 and 408 patients, respectively, had CKD. MRBs were discontinued in 34/121 patients with CKD (28.1%) and 55/165 patients without CKD (33.3%) (p-value=0.35). While MRB treatment increased the risk of persistent creatinine doubling in patients without CKD, in CKD patients a protective trend was seen (p-value for interaction 0.02). Similarly, the primary safety outcome occurred more commonly with exposure versus non-exposure to MRBs in non-CKD but not in CKD patients (p-value for interaction 0.02). CKD status significantly affected MRB effect on renal outcomes; treatment with MRBs may be nephroprotective in heart failure patients with CKD.

**Funding:** Private Foundation Support
Remote Candidate Prognostic Biomarkers of CKD among People with Type 1 Diabetes Mellitus (TIDM) Jian Cal, Michael Merchant, Adam E. Gaweda, Michael E. Brier, Brad H. Rovin, Minghao Ye, Jan Wysocki, Mark E. Moltich, Daniel Battle, Jon B. Klein. 1University of Louisville School of Medicine, Louisville, KY; 2Ohio State University Wexner Medical Center, Columbus, OH; 3Northwestern University Feinberg School of Medicine, Chicago, IL; 4Rolley Rex VAMC, Louisville, KY. Group/Team: For DCCT/EDIC study and CKD Biomarkers Consortium.

Background: It has been difficult to identify biomarkers that antedate the development of CKD. We used a plasma proteomic approach to evaluate samples from participants in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications (DCCT/EDIC) with the goal to establish surrogate prognostic biomarkers of CKD in TIDM.

Methods: Samples from 23 cases (defined as participants who went on to develop CKD stage 3 (GFR<60mL/min/1.73m²) were examined prior to developing CKD. Two samples from these cases were analyzed; one early sample during DCCT and a later sample from each same subject during EDIC. 23 controls were participants in whom GFR remained well above 60mL/min/1.73m² after collection of the two matching samples during DCCT and EDIC. Samples were immunodepleted, trypsinized, labeled with 10-plex tandem mass tag (TMT), and analyzed by high resolution 2D-LCMS. The data were processed prior to Wilcoxon Rank-Sum difference testing (p-value <0.05). Candidate biomarker selection was based on fold-changes (FC, <1.5 and >1.5) to identify case/control DCCT and EDIC differences.

Results: When the case/control proteomic analysis was obtained during DCCT, cases and controls had similar age, sex, GFR, HBA1C, blood pressure, albumin excretion rate (AER) and duration of DM. During EDIC, about 15 years later, there were differences (p<0.01) in GFR (83.9 vs 101.9 mL/min/1.73m²), AER (810.5 vs 24g/mg24h) and HBA1C (9.5 vs 8.3) between cases and controls. 1,667 identified protein groups were quantified. Cross sectional cases/control proteome differences were observed during DCCT (n=12) and EDIC (n=103) study time frames. Nine proteins were observed with >1.5FC (DCCT, n=6; EDIC, n=3) that were unique in DCCT and EDIC. Two proteins showed significant differences between cases and controls in both cross-sectional and longitudinal proteome analyses. These differences in proteins were identified about 20 and 4yrs, respectively before the development of CKD.

Conclusions: In people with TIDM the plasma proteome, years prior CKD stage3, has unique proteins that are potential biomarkers of disease progression.

Funding: NIDDK Support, Veterans Affairs Support

Risk of ESRD and Mortality in Stage 3 CKD Using a Risk Estimator Youngjun Park, Nawsheen Chowdhury, Candace D. Grant, Shayan Shirazian, Department of Medicine, Division of Nephrology, NYU-Winthrop Hospital, Mineola, NY.

Background: Accurate assessment of the risk of end stage renal disease (ESRD) is important in determining which patients with chronic kidney disease (CKD) to prepare for renal replacement therapy (RRT). This can be challenging in earlier CKD when the short term risk for ESRD can be low but the lifetime risk is high. We applied a short term (2-year) risk calculation method to a population of stage 3 CKD patients and carried out an observational study to assess outcomes.

Methods: This is a cross-sectional study of 409 patients with stage 3 CKD. The ESRD risk estimation was determined using the 2 year risk estimator developed and validated by Tangri et al. A 2-year risk of progression to ESRD of <2.5% was considered low risk (LR) and a 2.5% was considered higher risk (HR). Patients were then organized into groups by age (<60, 60 to 79 and ≥80 years). Over the following 2 years development of ESRD and death were recorded.

Results: The average age for the entire group was 70±14 years, 68% were men, 78% were white, the mean GFR was 42 mL/min/1.73m² and the mean 2 year ESRD risk was 2.2%. The 2 year calculator determined 76% (n=311) of our entire stage 3 cohort to be LR. None of the LR group reached ESRD versus 5% of the HR group and 5% of the LR group died versus 10% of the HR group. The 2 year risk of ESRD progressively diverged with younger age with a 4.2% risk for patients <60, versus a 1.9% and 1.1% risk for patients 60 and 79 to 80, respectively (p<0.001). For patients younger than 60, 46% of them were at high risk compared to 10% in the a 80 year age group (p<0.001). We found none of the patients aged a 80 versus 4% of the younger patients aged >60 years reached ESRD. In contrast, 11% of the older patients versus 4% of the younger patients died.

Conclusions: These results show that in our population age had a significant impact on 2 year estimated ESRD risk. Risk determinations and outcomes showed progressively higher ESRD risk with younger age and a higher risk of death with older age. A validated risk calculator to assign patients to LR and HR groups appears to help predict clinical outcomes and might be a useful tool in guiding proper selection of patients for preparation for RRT.

Concomitant Acute Pyelonephritis and Obstruction Duration Affects Renal Outcome in Obstructive Uropathy by Urolithiasis Jung-ho Shin, So-hee Jeong, Jin Ho Hwang, Su Hyun Kim. Chung-Ang University Hospital, Seoul, Republic of Korea.

Background: Urolithiasis related obstructive uropathy is one of increasing causes of CKD, which is commonly encountered in clinical field. Obstruction release from urolithiasis can be easily delayed with a lack of suggested golden time to prevent renal function deterioration. Here, we investigated the clinical significance and renal outcomes of urolithiasis related obstructive uropathy.

Methods: This is a pilot study of 414 from 2315 patients in urolithiasis related obstructive uropathy cohort which is recruited between Jan. 2005 and Dec. 2015. Clinical outcomes were evaluated with respect to obstruction duration, acute kidney injury (AKI), and acute pyelonephritis (APN) accompanied by obstructive uropathy.

Results: Median duration of obstruction (elapsed time to release obstruction) was 5 days and APN was accompanied in 17.1% of patients. In the patients whose obstruction was relieved within 2 days from the symptom onset, 14.5% showed spontaneous release of obstruction. In the patients with concomitant APN, mean age was older (57.6 vs 52.5 years old, P<0.001), estimated GFR (eGFR) at the time of admission was lower (63.5 vs. 79.4 mL/min/1.73m², P<0.001) and the use of NSAIDs were lower (49.3% vs. 74.9%, P<0.001). The eGFR decrease of >30% from baseline (P<0.001) and eGFR decrease of >50% (P<0.001) was significantly more in patients with concomitant APN. The AKI grades by KDIGO showed worse renal outcome in advanced stage (P<0.001). The patients whose obstruction was released within 2 days from the symptom onset, showed more favorable outcome in eGFR decrease of >30% (P<0.019). When we adjusted gender, age, HT, DM, use of NSAIDs, APN, AKI grades, and obstruction release over 2 days for a multivariate analysis, APN (HR 2.2, CI 1.01-4.65; P=0.047) and the obstruction release after 2 days (HR 3.55, CI 1.34-9.38; P=0.011) were independently associated with eGFR decrease of >30%. Concomitant APN was also associated with eGFR decrease of >30% (HR 8.006, CI 1.86-34.38; P=0.005). The use of NSAIDs was associated with favorable renal outcomes.

Conclusions: In urolithiasis related obstructive uropathy patients, concomitant APN was strongly associated with renal function deterioration after obstruction release. The elapsed time to release obstruction also affected to renal function.
FR-PO461
Prevalence and Severity of Dental Plaque and Dental Calculus in Patients with CKD
Nanmita Kalra,1 Ujjwala Roy,1 Sunil Agarwal,2 Ashok K. Tripathi,3 Om P. Kalra,2 Orchid Medical Centre, Ranchi, India; 1Nephrology, Pt. B.D. Sharma University of Health Sciences, Rohtak, India; 2Medicine, University College of Medical Sciences and GTB Hospital, Delhi, India; 3Pedodontics, University College of Medical Sciences, Delhi, India; 4Biochemistry, University College of Medical Sciences, Delhi, India.

Background: Patients with CKD have impaired immune responses which may predispose them to various infections, such as dental plaque. Further, altered calcium-phosphorus balance and high prevalence of mineral bone disease may result in poor dental health including dental calculus, decayed and missing teeth. The goal of this study was to assess the status of dental plaque, dental calculus and missing teeth in patients with CKD.

Methods: 150 age and sex matched subjects were recruited under 3 groups, 50 in each. These included: Group A - healthy controls; Group B - patients with CKD stage 3 to 5 not yet on maintenance hemodialysis (MHD) and Group C - patients of CKD stage 5 who were on MHD for >1 month. Detailed examination of the teeth for dental plaque and dental calculus was done. Severity of dental plaque and dental calculus was recorded as follows: dental plaque score was calculated as total area covered by using dental plaque and calculus scores on a scale of 1 to 3. Dental plaque and dental calculus score was calculated after recording individual dental plaque and calculus score and dividing it by the number of teeth examined. Patients with history of recent tobacco use, diabetes mellitus, oral infection and drug intake such as calcium channel blockers, anticonvulsants, immuno-suppressants and allograft recipients were excluded.

Results: Mean dental plaque score and dental calculus score in patients with CKD were significantly higher as compared to healthy controls (p<0.001 for both). Mean dental plaque score was: healthy controls - 0.98±0.39, Group B: 1.5±0.52 and Group C: 1.81±0.53. Mean dental calculus score was: healthy controls - 0.91±0.56, Group B - 1.77±0.56 and Group C: 1.81±0.56. Further, it was found that the dental plaque score showed a progressive rise with increase in severity of kidney disease. Patients of CKD stage 5 who had been on MHD had significantly higher mean dental plaque score as compared to those with CKD stage 5 who had not yet been started on HD (p=0.029). Further, patients with CKD had higher number of missing teeth (Group B – 2.36±4.08, Group C – 2.64±3.60) as compared to healthy controls (1.10±2.28).

Conclusions: Patients with CKD have higher prevalence of dental plaque and dental calculus. The prevalence of dental plaque correlates with increase in severity of kidney disease. Higher prevalence of dental pathology may contribute to malnutrition in patients with CKD.

FR-PO462
Urinary Renin and Angiotensinogen for Predicting Antiproteinuric Effect of Angiotensin Receptor Blocker Do Hee Kim,1 Junseok Jeon,2 Hye Ryoun Jang,2 Jung eun Lee,2 Wooseong Huh,2 Hye-Young Kim,2 Dae Joong Kim,2 Ha Young Oh,2 Yoon-Goo Kim,2 Division of nephrology, Department of Medicine, Chungbuk National University Hospital, Cheongju, Republic of Korea; 3Division of nephropathy, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; 1Department of Medicine, Chungbuk National University College of Medicine, Cheongju, Republic of Korea.

Background: Although urinary angiotensinogen (AGT) and renin were reported to reflect the activity of intrarenal renin-angiotensin system which is known to be activated in proteimeic chronic kidney disease patients, the clinical value of urine AGT and renin during antiproteinuric therapy is yet to be determined. In this study, we investigated the clinical impact of baseline urinary AGT or renin on the antiproteinuric effect of angiotensin receptor blocker (ARB).

Methods: A multicenter, prospective observational cohort study was conducted in 205 patients with overt proteinuria (urinary protein/creatinine ratio [uPCR] ≥ 1 mg/mgCr) between April 2009 and December 2011. Low salt diet was thoroughly educated in all patients at the time of enrollment. Baseline urinary AGT/creatinine ratio (uAGT/ Cr), renin/creatinine ratio (uRen/Cr), and sodium/creatinine ratio (uNa/Cr) were measured before starting valsartan. The uPCR was followed up at 2 months and 6 months in all patients. A total of 60 patients were followed up for 5 years.

Results: The mean age of patients was 47.6 ± 12.5 years and 51.2% were male. The uPCR was 2.32 ± 1.43 mg/mgCr and the estimated glomerular filtration rate was 63.2 ± 22.8 ml/min/1.73m². The uNa/Cr was 1.30 ± 0.25 mg/mgCr. Natural logarithms of uAGT/Cr (ln[AGT/Cr]) and uRen/Cr (ln[uRen/Cr]) were significantly higher in 53 patients with uPCR decrement greater than 1mg/mgCr at 6 months. The uNa/Cr was higher in patients with uPCR decrement greater than 1 mg/mgCr at 2 months. Multivariable regression analysis identified ln(uNa/Cr) as a significant factor associated with the occurrence of uPCR decrement at 6 months (β = 0.206, P = 0.047). Ln(uRen/Cr) was identified as a predictive factor (OR 1.244, 95% CI 1.04-1.49, P = 0.018) for uPCR decrement higher than 1 mg/mgCr at 6 months in logistic regression analysis.

Conclusions: Our study showed that baseline ln(uRen/Cr) and uNa/Cr have the potential to be used as prognostic markers predicting antiproteinuric effect of ARB. The clinical importance of low salt diet education was also shown.

FR-PO463
AKI after Radical Nephrectomy as Risk Factor for CKD: Retrospective Analysis from an Italian Cancer Center Laura Cosmi,1 Camillo Porta,2 Fabio Maliberti,1 Marina Foramitti,1 Maurizio Gallieni.1 Azienda Istituti Ospitalieri di Cremona, Cremona, Italy; 2IRCCE San Matteo University Hospital Foundation, Pavia, Italy; 3Istituti Spatieri Cremona, Cremona, Italy; 4Ospedale San Carlo Borromeo - ASST Sant Paolo e Carlo - University of Milano, Milano, Italy; 5Nephrology and Dialysis, ASST Sant Paolo e Carlo, Milano, Italy.

Background: Radical nephrectomy is a significant risk factor for chronic kidney disease (CKD), and there are few reports on the renal outcome after radical nephrectomy for cancer. The aim of this study was to determine the incidence of AKI and whether postoperative AKI is associated with new-onset CKD after radical nephrectomy for renal cell cancer (RCC).

Methods: We conducted a retrospective study of 650 adult patients (>40 years old), from an Italian Cancer Centers with normal renal function who underwent unilateral radical nephrectomy for a solitary renal cortical tumour and were pathologically diagnosed with RCC between January 2010 and February 2017. Post-operative AKI was classed using risk, injury, failure, loss and end-stage kidney disease (RIFLE) criteria. CKD was defined as a decrease in estimated glomerular filtration rate (GFR) to <60 ml/ min/1.73 m².

Results: According to the RIFLE criteria, 195 of 216 patients fell into the AKI risk category 1, 16 patients fell into the AKI injury category and 5 patients fell into the AKI failure category. Multivariate analysis revealed as major result that higher preoperative GFR was an independent risk factor for postoperative AKI, although older age, male gender higher body mass index, smaller RCC size were independent risk factors too. New-onset CKD was more prevalent in the AKI risk group than in patients without AKI 1 year after surgery (56.1% versus 43.9%, respectively) and 3 years after surgery (52% versus 31%). Patients who experienced post-operative AKI had a 3.5-fold higher risk of new-onset CKD after multiple adjustments, that confirms our previous study.

Conclusions: AKI after radical nephrectomy in patients is a potent risk factor for new-onset CKD. Prevention of post-operative AKI, but also the assessment of kidney function pre-nephrectomy, is essential for reducing the incidence of CKD after nephrectomy.

FR-PO464
Elevated Time-Varying BP Is Associated with Greater Risk of Progression of CKD Than Elevated Baseline BP in Children with Non-Glomerular CKD Ben C. Reynolds,3 Jennifer Room,1 Christopher B. Pierce,2 Joseph T. Flynn,1 Mina Matsuda-Abedini,3 Susan L. Furr,1 Bradley A. Waryad,4 Rulan S. Parekh,5 Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; 2Johns Hopkins University School of Public Health, Baltimore, Maryland, MD; 3Royal Hospital for Children, Glasgow, Glasgow, United Kingdom; 4Seattle Children’s Hospital, Seattle, WA; 5The Children’s Hospital of Philadelphia, Philadelphia, PA; 6The Children’s Mercy Hospital, Kansas City, MO; 7The Hospital For Sick Children, Toronto, ON, Canada; 8The Hospital for Sick Children, Toronto, Toronto, ON, Canada.

Background: Effective treatment of hypertension in children with chronic kidney disease (CKD) slows the rate of progression to end stage renal disease (ESRD). Less clear is whether longitudinal (e.g. annual time varying) measures of blood pressure (BP) are associated with greater risk of progression. We quantified this risk with systolic or diastolic casual BP measurement > 90th centile at baseline or longitudinally in children with CKD.

Methods: Of 826 children (257 glomerular disease, 569 non-glomerular) enrolled in the CKiD cohort, we determined if BP <50th percentile was associated with an elevated risk of progression, severity of disease (CKD), and there are few reports on the renal outcome after radical nephrectomy for cancer. The aim of this study was to determine the incidence of AKI and whether postoperative AKI is associated with new-onset CKD after radical nephrectomy for renal cell cancer (RCC).

Results: Higher SBP percentile was associated with an elevated risk of progression, the time-varying metric estimating a higher magnitude of risk compared to time-fixed baseline measures (Table). Adjustment for potential confounders did not qualitatively change the risk in non-glomerular disease but nullified the estimate in glomerular disease. We quantified this risk with systolic or diastolic casual BP measurement > 90th centile at baseline or longitudinally in children with CKD.

Conclusions: Elevated time-varying systolic BP is associated with a greater risk of CKD progression than baseline BP in children with non-glomerular CKD. Clinicians can use updated BP to assess risk for progressive CKD and adjust management accordingly.

Funding: NIDDK Support
FR-PO466

Delayed Renal Recovery and Long-Term Renal Survival after Radical Nephrectomy for Renal Cell Carcinoma

Hee jung Park,1 Ha nee Jung,2 Tae won Lee,1 Hyun Seop Cho,2 Hyun-Jung Kim,3 Dong Jun Park,1 Eunjin Bae,2 Se-Ho Chang1 Gyeongsang National University Hospital, Changwon, SEOUL, Republic of Korea; 4Gyeongsang National University Hospital, Jinju-si, Gyeongsangnam-do, Republic of Korea; 3Gyeongsang national university hospital, Jinju, Jinju-si, Republic of Korea; 2School of Medicine, Gyeongsang National University, Jinju, Republic of Korea.

Background: Radical nephrectomy has been associated with chronic kidney disease (CKD). It is unclear whether delayed renal recovery after surgery affects long-term renal survival in patients undergoing radical nephrectomy for renal cell carcinoma. We assessed factors affecting the recovery of renal function.

Methods: We reviewed medical record database for all patients (>18 years old) who underwent radical nephrectomy for renal cell carcinoma between from January 2009 to December 2016. Among these, we included patients undergoing surgical nephrectomy after surgery. Renal outcome was defined as a doubling in serum creatinine or End stage renal disease. Estimated GFR were calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Delayed renal function was defined by creatinine did not decrease less than preoperative value.

Results: Among the 105 patients who met inclusion criteria, 70 (66.7%) were males. The median age at nephrectomy was 62 years (25-84 years). 60 (57.1%) was diagnosed with delayed renal recovery: The average serum creatinine was 0.85±0.22 mg/dL, and average estimated GFR was 102.89±29.46 ml/min/1.73m2. The average follow-up period was 39.55±24.48 months. Multiple linear regression analysis shows delayed renal recovery, baseline estimated GFR to be significantly associated with long-term renal survival (p=0.05, p=0.04, respectively). Hypertension and increased baseline creatinine were the factors affecting early recovery of renal function.

Conclusion: Our results suggest that hypertension and renal impairment for renal cell carcinoma patients may delayed renal recovery after radical nephrectomy, and adversely affect kidney function over a long term period.

FR-PO467

Renal and Metabolic Complications of Long-Term Total Parenteral Nutrition (TPN) in Pediatric Patients Presenting to Bari, Italy

Paolo Tomeo,1 Vladimir Tesar,2 Paolo Tommaso Di Noia,3 Maria luisa Russo,4 Grazziella D’arrigo,5 Giovanni Tripepi,1 Vladimir Tesar,4 Carmine Zoccali,6 Rosanna Coppo.4

1Children’s Hospital of Michigan, Detroit, MI; 2Children’s hospital of Michigan, Detroit, MI; 3Children’s Hospital of Michigan, Detroit, MI; 4Pediatric Nephrology, Children’s hospital of Michigan, Detroit, MI; Group/Team: Wayne state university.

Background: The number of children requiring prolonged TPN is increasing and yet very little is known about its potential long term complications. The objective of this study was to evaluate renal and metabolic complications of prolonged TPN in patients at our institution.

Methods: We did a retrospective chart review with prospective follow-up of 26 patients who, with the exception of one patient, were followed at our Children’s hospital Intestinal Rehabilitation Clinic. We included 1 patient to 15 (median of 4) years of age that had been on TPN for ≥ 6 months at the time of data collection. Patients were received ≥20% TPN and when other co-morbidities were excluded. Variables that were studied included anthropometric data, indication and duration of TPN, TPN formulation and daily volume, intestinal anatomy, details on oral nutritional supplements, current medications, blood and urine chemistry results, renal imaging results, and number of acute kidney injury (AKI) episodes.

Results: Of the 26 patients, 8 (31%) received 100% nutrition as TPN; 10 (38%) patients received a mean of 80% and 8 received 20%-80% nutrition as TPN. The median Duration of TPN administration was 4 years (Range 1-15). Recurrent AKI was the commonest complication in 24 (92%) patients with a median of 8 (range 4 - 40) episodes per patient. Other complications were hypertension (38%), echogenic kidneys on ultrasound examination (27%), renal size asymmetry (15%), hyperphosphatemia (15%), renal calcui (11%), phosphaturia, hypophosphatemia and nephrocalcinosis (4%), and recurrent acute infection or chronic endocarditis (4%). Hematological hyper transfusion, as defined by modified Schwartz eGFR=<$155ml/min/m2, was noted in 12 (46%) patients.

Conclusions: Children on long-term TPN are at risk of CKD due to recurrent AKI, hypertension, and glucomerular hyperfiltration. Appropriate renal and metabolic monitoring is recommended.
FR-PO469
Can Early Referral to Nephrologists Reduce All-Cause and Cardiovascular Mortality and How Long Can the Effect of Pre-Dialysis Nephrology Care Last after Dialysis Initiation? Yukimasa Iwata, Taisuke Tatatsuki, Daisuke Yoshihiko, Hiroki Okushima, Rei Tio, Tatsuya Sogo, Terumasa Hayashi. Osaka General Medical Center, Osaka-Shi, Japan.

Background: Although early referral (ER) to nephrologists before dialysis initiation has been recommended to improve overall survival in patients on maintenance dialysis, we don’t have any available data about how long the favorable effect of ER can last. Furthermore, its effect on cardiovascular (CV) mortality remains unclear. Thus, we conducted a single center retrospective cohort study of incident dialysis patients to investigate the effect of ER on all-cause and CV mortality and how long ER could sustain its favorable effect on mortality after dialysis initiation.

Methods: A total of 875 patients with accurate clinical data and outcomes were extracted from 1131 patients who started chronic dialysis treatment from 2006 to 2015. Clinical status at dialysis initiation, all-cause and CV mortality were compared by referral timing (ER, referred to nephrologists more than 6 months before dialysis initiation; LR, other than ER). Cox and interval Cox proportional hazard model was used to evaluate the predictor factors for outcomes and how long favorable effect of ER on mortality could last.

Results: Median age and eGFR at dialysis were 70 years and 5.4 ml/min/1.73m², respectively. 654 patients were referred early (ER). 275 patients died and 82 of those from CV disease during the follow-up period (median, 40 months). Although, ER group showed fewer all-cause and CV mortality (Log rank test; P=0.007, 0.019 respectively) than LR group (Figure1), multivariate Cox proportional analysis failed to show significant impact on all-cause and CV mortality. However, on the basis of the Kaplan-Meier curves, the excess overall survival among ER versus LR patients appeared limited to the several years of maintenance dialysis (Figure 1A). Thus, we built several interval Cox models: one for the first 6-months, one for the second 6-months, one for the third 6 months, one for the last 6-months after dialysis initiation.

Conclusions: ER was not associated with CV death, whereas ER may improve overall survival during early period after dialysis initiation.

FR-PO470
Urinary Neutrophil Gelatinase-Associated Lipocalin Is a Possible Indicator of Tubulointerstitial Fibrosis and Glomerular Sclerosis in the Patients Undergoing Renal Biopsy. Yoshifumi Hamasaki, Teruhiko Yoshida, Ryo Matsuura, Akihiro Tojo, Eisei Noiri, Masaomi Nangaku. The University of Tokyo, Tokyo, Japan.

Background: Renal tubulointerstitial fibrosis and glomerular sclerosis are common pathological changes occurring in association with chronic kidney disease (CKD). Non-invasive and reliable biomarkers which can predict the renal histological change will be helpful to decide the indication of renal biopsy. Neutrophil gelatinase-associated lipocalin (NGAL) is a promising marker of not only acute kidney injury but also chronic kidney disease. Thus, the training and validation phase of our ANNs considered therapy not ACEi or ARBs or immunosuppressive therapy that may influence the clinical course of the disease. Thus, the training and validation phase of our ANNs considered therapy exposure.

Funding: Government Support - Non-U.S.

Results: The first model to predict ESKD by 15 years of clinical outcome had accuracy 98%, precision 93%, recall 87% and F1-measure 87%. The second ANN to predict the number of years to achieve ESKD showed a RMSE (root mean squared error) of 2.68 years and a MAE(mean absolute error) of 1.12 years. The second ANN was trained and validated using all the training and validation set participants. Thus, the training and validation phase of our ANNs considered therapy exposure.

Funding: Government Support - Non-U.S.

Conclusions: We have developed a new clinical decision support system to estimate the risk of ESKD and its timing in IgAN patients. This tool showed an excellent performance. Interestingly, the VALIGA cohort included many patients who received or not how much of ARBs or immunosuppressive therapy that may influence the clinical course of the disease. Thus, the training and validation phase of our ANNs considered therapy exposure.

Funding: Government Support - Non-U.S.

Purpose: We evaluated the relationships between urinary markers and the results of postmortem diagnostic examination.

Results: Ninety-six patients were enrolled in this study. Urinary NGAL/Creat (uNGAL/Cre) was significantly correlated with the severity of TF and the percentage of sclerotic glomeruli (Spearman’s rank correlation coefficient r=0.38 and 0.28, p<0.01, respectively) in the moderate and severe group. The unpaired t-test showed t-ratio of 12.12 years.

Conclusions: uNGAL/Creat can last. Furthermore, its effect on cardiovascular (CV) mortality remains unclear. Thus, we conducted a single center retrospective cohort study of incident dialysis patients to investigate the effect of ER on all-cause and CV mortality and how long ER could sustain its favorable effect on mortality after dialysis initiation.

Funding: Government Support - Non-U.S.

Conclusions: We have developed a new clinical decision support system to estimate the risk of ESKD and its timing in IgAN patients. This tool showed an excellent performance. Interestingly, the VALIGA cohort included many patients who received or not how much of ARBs or immunosuppressive therapy that may influence the clinical course of the disease. Thus, the training and validation phase of our ANNs considered therapy exposure.

Funding: Government Support - Non-U.S.

Purpose: We evaluated the relationships between urinary markers and the results of postmortem diagnostic examination.

Results: Ninety-six patients were enrolled in this study. Urinary NGAL/Creat (uNGAL/Cre) was significantly correlated with the severity of TF and the percentage of sclerotic glomeruli (Spearman’s rank correlation coefficient r=0.38 and 0.28, p<0.01, respectively) in the moderate and severe group. The unpaired t-test showed t-ratio of 12.12 years.

Conclusions: uNGAL/Creat can last. Furthermore, its effect on cardiovascular (CV) mortality remains unclear. Thus, we conducted a single center retrospective cohort study of incident dialysis patients to investigate the effect of ER on all-cause and CV mortality and how long ER could sustain its favorable effect on mortality after dialysis initiation.

Funding: Government Support - Non-U.S.

Purpose: We evaluated the relationships between urinary markers and the results of postmortem diagnostic examination.

Results: Ninety-six patients were enrolled in this study. Urinary NGAL/Creat (uNGAL/Cre) was significantly correlated with the severity of TF and the percentage of sclerotic glomeruli (Spearman’s rank correlation coefficient r=0.38 and 0.28, p<0.01, respectively) in the moderate and severe group. The unpaired t-test showed t-ratio of 12.12 years.

Conclusions: uNGAL/Creat can last. Furthermore, its effect on cardiovascular (CV) mortality remains unclear. Thus, we conducted a single center retrospective cohort study of incident dialysis patients to investigate the effect of ER on all-cause and CV mortality and how long ER could sustain its favorable effect on mortality after dialysis initiation.

Funding: Government Support - Non-U.S.

Purpose: We evaluated the relationships between urinary markers and the results of postmortem diagnostic examination.

Results: Ninety-six patients were enrolled in this study. Urinary NGAL/Creat (uNGAL/Cre) was significantly correlated with the severity of TF and the percentage of sclerotic glomeruli (Spearman’s rank correlation coefficient r=0.38 and 0.28, p<0.01, respectively) in the moderate and severe group. The unpaired t-test showed t-ratio of 12.12 years.

Conclusions: uNGAL/Creat can last. Furthermore, its effect on cardiovascular (CV) mortality remains unclear. Thus, we conducted a single center retrospective cohort study of incident dialysis patients to investigate the effect of ER on all-cause and CV mortality and how long ER could sustain its favorable effect on mortality after dialysis initiation.

Funding: Government Support - Non-U.S.

Purpose: We evaluated the relationships between urinary markers and the results of postmortem diagnostic examination.

Results: Ninety-six patients were enrolled in this study. Urinary NGAL/Creat (uNGAL/Cre) was significantly correlated with the severity of TF and the percentage of sclerotic glomeruli (Spearman’s rank correlation coefficient r=0.38 and 0.28, p<0.01, respectively) in the moderate and severe group. The unpaired t-test showed t-ratio of 12.12 years.

Conclusions: uNGAL/Creat can last. Furthermore, its effect on cardiovascular (CV) mortality remains unclear. Thus, we conducted a single center retrospective cohort study of incident dialysis patients to investigate the effect of ER on all-cause and CV mortality and how long ER could sustain its favorable effect on mortality after dialysis initiation.

Funding: Government Support - Non-U.S.

Purpose: We evaluated the relationships between urinary markers and the results of postmortem diagnostic examination.

Results: Ninety-six patients were enrolled in this study. Urinary NGAL/Creat (uNGAL/Cre) was significantly correlated with the severity of TF and the percentage of sclerotic glomeruli (Spearman’s rank correlation coefficient r=0.38 and 0.28, p<0.01, respectively) in the moderate and severe group. The unpaired t-test showed t-ratio of 12.12 years.

Conclusions: uNGAL/Creat can last. Furthermore, its effect on cardiovascular (CV) mortality remains unclear. Thus, we conducted a single center retrospective cohort study of incident dialysis patients to investigate the effect of ER on all-cause and CV mortality and how long ER could sustain its favorable effect on mortality after dialysis initiation.

Funding: Government Support - Non-U.S.
modified albumin to ≤ 56 ± 1 % after in-vitro g-uanidylation whereas the binding of indoxyl sulfate to albumin from healthy control subjects and CKD patients. Thus, in-vitro post-translational guanidylation of albumin had a direct effect on the binding capacity of hydrophilic metabolites like indoxyl sulfate and tryptophan.

Conclusions: In conclusion, we established a mass spectrometry-based method for the characterisation of PTM and demonstrated the pathophysiological impact of a representative post-translational modification of plasma albumin. The approach described in this study may help to elucidate the pathophysiological role of protein modifications.

FR-PO473
Incidence and Outcomes of Syncope in Patients with CKD
Manish M. Sood,a David Massicotte-Azarnouch,b John Paul Kwuornuc, Megan K. McCullam,d Amit X. Garg, Ngam Lan,¢ Amber O. Molnar,d London Health Sciences Centre, London, ON, Canada; bMcMaster University, Hamilton, ON, Canada; cOttawa Hospital Research Institute, Ottawa, ON, Canada; dUniversity of Alberta, Edmonton, AB, Canada; eInstitute for Clinical Evaluative Sciences, Ottawa, ON, Canada.

Background: Syncope is common condition, occurring in roughly 1 in 3 people during their lifetime, and may be a sign of underlying illness. CKD patients may be at an elevated risk of syncope due to concurrent medical conditions, medication usage or the etiology of CKD itself. We set out to examine the incidence of first episode and recurrent syncope and its outcomes in patients with CKD > 66 years of age.

Methods: In a population-based, retrospective cohort study using administrative databases between 2006 and 2015. A total of 272,149 patients with no history of syncope, a urine albumin to creatinine ratio (ACR) and eGFR measure were included. First syncope by strata of eGFR and ACR was examined using Fine and Gray Models. Recurrent syncope strata was determined using negative binomial models (RRR). Models were adjusted for demographics, resource utilization, demographics and medications. Among those with syncope, the incidence of adverse outcomes (ACS, arrhythmia, stroke, fracture and death) was determined by eGFR strata.

Results: A total of 15,074 (5.5%) first and 36,710 (13.5%) recurrent syncope events occurred during the study period. Lower eGFR was associated with a higher risk of first episode of syncope [eGFR 60–90: sHR 1.24 (1.15–1.33), eGFR 45–60: sHR 1.45 (1.34–1.57), eGFR 30–45: sHR 1.49 (1.36–1.62), eGFR < 30: sHR 1.40 (1.25–1.57), eGFR < 15: sHR 1.93 – 2.48] whereas ACR was not. Recurrent syncope was associated with lower eGFR and higher ACR [sHR 60–90: RRR 1.21 (1.13–1.31), eGFR 45–60: RRR 1.46 (1.34–1.58), eGFR 30–45: RRR 1.58 (1.44–1.73), eGFR < 30: RRR 1.73 (1.53–1.94), eGFR < 90: referent; ACR 3–30: RRR 1.09 (1.04–1.13), ACR > 30: RRR 1.15 (1.06–1.24), ACR > 3 referent]. Among those with a first episode syncope event, the event rate (per 100 pt-yrs) of all adverse outcomes was higher with lower eGFR strata compared to normal eGFR (ACS: eGFR < 30: 2.44, eGFR > 90: 0.98, Arhythmia: GFR < 30: 21.63, eGFR > 90: 8.88, stroke: eGFR<30: 5.02, eGFR > 90: 2.32, fracture: eGFR<30: 25.58, eGFR > 90: 10.23).

Conclusions: First episode and recurrent syncope events are associated with lower eGFR and only marginally with a higher ACR. The risk of all adverse events (cardiovascular, fracture and death) is higher post-syncope in patients with eGFR < 30.

FR-PO474
A First Assessment of Urinary Peptide Biomarkers Predictive of Cardiovascular Complications in Children with CKD
Valerie Brunchault,a Germany; bGermany; cU1048, classifier was not validated.

Results: These results indicate that urinary peptides could be used as a non-invasive tool for the early prediction of CVD complications associated to CKD in children. An additional 250 patients from the 4C study will now be used to refine and confirm these results. [Equal contribution JPS and JK]

Funding: Government Support - Non-U.S.

FR-PO475
Relationships between CKD and Progression of Left Ventricular Diastolic Dysfunction
Yoshisuke Miyajima, Tadashi Toyama, Shinji Kitajima, Akinori Hara, Yasunori Iwata, Norihiko Sakai, Miho Shimizu, Kengo Furuchi, Takashi Wada. Kanazawa University Hospital, Kanazawa, Japan.

Background: CKD is known as a risk factor for heart failure, but its role on the left ventricular diastolic dysfunction as a preliminary stage of heart failure has not been adequately studied.

Methods: To investigate the relationship between CKD and progression of left ventricular diastolic dysfunction, we included patients who received echocardiography examination in Kanazawa University Hospital for more than twice with intervals of more than one year. We excluded patients who had been diagnosed with heart failure disease, moderate valvular heart disease and structural heart disease. Patients were examined their left ventricular peak velocity of blood flow across the mitral valve (E) and their diastolic peak velocities of mitral annulus (E'); E/e' ratio was used as an index of left ventricular diastolic function, and E/e' ratio > 14 was defined as left ventricular diastolic dysfunction.

Results: A total of 1,163 subjects were included and the average observation period was 3.2 years. Compared to the patients with the estimated GFR a90 mL/min/1.73 m2 as a reference, hazard ratios (95% confidence intervals) for the development of diastolic dysfunction were 1.25 (0.87–1.81), 1.51 (0.96–2.38), 2.06 (1.25–3.40), and 3.54 (2.13–5.88) for patients with eGFR 60–89 mL/min/1.73 m2, 45–59 mL/min/1.73 m2, 30–44 mL/min/1.73 m2, <30 mL/min/1.73 m2, respectively.

Conclusions: Left GFR and proteinuria were risk factors for the development of left ventricular diastolic dysfunction.

FR-PO476
Impaired Delivery of Cholesterol to Hepatocytes by Serum from CKD Patients: Implications for the Associated CVD Risk
Daniel E. Carl,a Graham T. Gipson,1 Shobha Ghosh,2 Salvatore Carbone,3 Dave L. Dixon,4 Ion S. Jovin,5 McGuire VAMC/VCU, Richmond, VA; 3VCU, Richmond, VA; 4Virginia Commonwealth University, Richmond, VA; 5Virginia Commonwealth University School of Pharmacy, Richmond, VA; 6Internal Medicine, Virginia Commonwealth University, Richmond, VA.

Background: Mortality in CKD patients is largely due to the development of CVD but the underlying mechanisms have not been elucidated. The flux of cholesterol from macrophage foam cells and its ability to deliver cholesterol to primary hepatocytes is now considered as a major contributor to development of CVD. Ability of the serum components to remove cholesterol from macrophage foam cells and deliver it to the liver for final elimination are the two critical steps in regulating cholesterol flux. Herein, we evaluated the ability to modifications of cholesterol to primary hepatocytes was determined and compared between groups using the Mann-Whitney Test. Correlations between kidney function parameters, CEC and uptake by hepatocytes were performed using the Spearman’s nonparametric rank test.

Results: CEC was significantly higher with serum from patients with CKD (Stages 3 and 4; P=0.001) compared to that from healthy subjects (Panel A). However, the ability of this effluxed FC to be delivered to hepatocytes was significantly lower in patients with CKD (Panel B, Stages 3 and 4; P<0.001). eGFR was inversely associated with CEC (Panel C) and positively associated with hepatocyte uptake (Panel D).

Conclusions: The above data that indicate impaired delivery of cholesterol to the liver for final elimination from the body likely underlies the development of CVD in CKD patients. Studies are in progress to determine if this decrease in hepatocyte uptake in CKD is related to changes in the structure of cholesterol carrying serum components (e.g., HDL or albumin) by reduced kidney function.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO477

Blockade of the Chemokine Receptor CX3CR1 with a Single Chain Antibody Reduces the Progression of Atherosclerosis and Glomerulosclerosis in Mice
Steven W. Kerr,1 Valentina Berger,2 Jorge L. Villalona,3 Rajvee Dave,3 Hong Wang,3 Margaret M. O’Neill,3 Joshuaine Toth,3 Mary McFarland,2 Lynn Pantages,2 Xintie Nie,4 Hu Sheng Qian,1 John Broadwater,2 Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT; 3Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT; 4Boehringer Ingelheim company, Danbury, CT; 2Boehringer Ingelheim, Ridgefield, CT; 5Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT; 6Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT; 7Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, AL.

Background: The fractalkine receptor CX3CR1 regulates leukocyte trafficking during inflammation and is associated with cardiovascular disease risk. We developed a high-affinity, selective, single chain antibody that targets human CX3CR1, designated BI655088. Since cardiovascular disease is the major cause of morbidity and mortality in patients with chronic kidney disease, we used a cardiorenal model to evaluate atherosclerosis and renal parameters.

Methods: Therefore, BI655088 was administered at 30mg/kg i.p. 2x/wk for 12 weeks to hyperlipidemic ApoE−/− mice expressing the human CX3CR1 gene and induced renal insufficiency by performing a unilateral nephrectomy.

Results: BI655088 significantly reduced atherosclerotic plaque area by 28% compared to vehicle-treated mice with no change in total cholesterol or triglycerides. In renal parameters, BI655088 was significantly higher in men than in women and positively correlated with age. UOCR was also higher in subjects with BMI ≥25 kg/m2 than BMI <25 kg/m2 median 0.48 (IQR 0.24, 1.13) g/g vs. 0.37 (0.21, 0.85) g/g; P<0.001, as well as in hypertensive compared to normotensive subjects 0.56 (0.27, 1.31) g/g vs. 0.35 (0.20, 0.77); P<0.001 and smokers compared to non-smokers 0.50 (0.24, 1.18) g/g vs.0.43 (0.23, 0.99) g/g; P<0.002. UOCR was positively associated with the same risk factors except BMI. In multivariable logistic regression analysis, both eGFR and UOCR were independent risk factors for having UOCR above median (eGFR: odds ratio (OR) 0.83 (0.79-0.88) per 10 ml/min/1.73 m2; UOCR: OR 2.05 (1.91-2.19)) per 0.5mg/mmol.

Conclusions: UOCR was positively associated with CV risk factors, and the association between eGFR and UOCR was independent of these factors and UACR. Our data indicate that increased UOCR may serve as a novel biomarker of atherosclerosis and kidney dysfunction, thereby supporting further research.

Funding: Government Support - Non-U.S.

FR-PO479

Increased Levels of Platelet Microparticles in CKD Patients with Acute Coronary Syndrome
Jørgen P. Mørberg,1 Kristina Lundwall,3 Fariborz Mobarez,2 Hakan Wallen,1 Stefan H. Jacobson,1 Jonas Spaak,1,3 Danderyd Hospital, Stockholm, Sweden; 2Karolinska Institutet, Solna, Sweden; 3Dept of Clinical Sciences, Karolinska Institutet, Danderyd hospital, Stockholm, Sweden.

Background: Patients with CKD have worse outcome after an acute coronary syndrome (ACS). Traditional and nontraditional risk factors, underutilization of coronary intervention, less active secondary prevention and lower adherence to medications all contribute to the poor prognosis. Microparticles MPs are circulating small sized vesicles shed from various cells upon activation, and they may induce biologically response and inter-cellular cross-talk. Platelet MPs(PMPs) are the most abundant MPs, and levels increase following myocardial infarction and in diabetes mellitus, hypertension, and CKD. We hypothesized that ACS patients with CKD had further elevated PMPs compared with non CKD patients.

Methods: 52 patients with ACS were included and fasting blood was acquired the day after admittance. Patients were divided in three groups according to serum C-reactive protein: CKD patients with non CKD patients.

Results: Levels of PMPs were elevated in CKD 4-5 patients compared with non CKD patients.

Conclusions: In ACS patients, levels of PMPs as well as levels of PMPs expressing platelet activation markers CD40 ligand(CD154) and P-selectin(CD62P) were higher in both CKD groups, compared with non CKD patients.

Funding: Government Support - Non-U.S.

FR-PO480

cGFR Trajectories and Risks of Death and Cardiovascular Events in Adults with Type 2 Diabetes
Ken B. Dara,1,2 Sterling McPherson,1,2 Brad Dieter,1 Radica Z. Alicic,1 Katherine R. Tuttle,1 Providence Health Services, Spokane, WA; 2Washington State University, Spokane, WA; 3University of Washington School of Medicine, Seattle, WA.

Background: Diabetes is the most common cause of chronic kidney disease (CKD) worldwide. Most with diabetes and CKD will experience death or a cardiovascular disease (CVD) event before reaching end-stage kidney disease. Decline in estimated glomerular filtration rate (eGFR) may be an antecedent of such events. The aim of this study was to

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
determine the relationship of eGFR decline with death and CVD events among persons with type 2 diabetes.

Methods: The ACCORD trial tested intensive control of glycemia in adults with type 2 diabetes. In our study, group-based modeling classified eGFR trajectories of 10052/10251 (98%) ACCORD participants with at least 2 eGFR (CKD-EPI) measurements. Trajectory classification was based on individual trajectory fit within a hypothesized class structure (both in number and classes of each function).

Cox proportional hazards models examined the risk of the primary ACCORD outcome (CVD death, myocardial infarction, stroke) by eGFR trajectory assignment.

Results: Participants were followed up to 7 years. Baseline characteristics included: age 62.7±6.6 (mean±SD) years; women 38% (3857/10052); White race 62% (6281/10052); diabetes duration 10.7±7.6 years; HbA1c 8.3±1.1 %; eGFR 84.0±17.5 mL/min/1.73m²; and urine albumin-to-creatinine ratio 13, 6-43 (median, IQR). Approximately 109 (109/10251, 0.01% of participants were classified in the lowest trajectory class with eGFR values persistently <60 mL/min/1.73m². In the next trajectory class, 21% (2101/10052) were classified with initial eGFR values above, but falling below, 60 mL/min/1.73m² over time. Three additional classes were defined with eGFR above 60 mL/min/1.73m² throughout the study. Fully-adjusted models controlled for baseline eGFR (isolating the independent effect of the trajectory slope), age, sex, race, diabetes duration, HbA1c, albuminuria, and treatment. Hazards for the primary outcome were greater for the two lowest compared to the highest eGFR trajectory class (HR, 1.52; 95% CI=1.07-2.18; p=0.03 and HR, 1.42; 95% CI=1.06-1.90; p=0.02). More rapid eGFR decline in persons with type 2 diabetes independently predicted significantly greater risk of death and CVD events.

FR-PO481
Prevalence of Secondary Hyperparathyroidism among Patients with Diabetic Nephropathy Mahmoud H. Imam,1 Ahmed W. Elshourbagy,2 Amira Mohamady,3 Rizk sayad rizk Sarhan.2 Internal medicine, University Benha, Benha, Egypt; 2Internal Medicine Department, Benha University, Benha, Egypt; 3Internal Medicine Department, Benha faculty of medicine, Benha, Egypt.
Background: Both SHPT and diabetes mellitus has increased the risk for cardiovascular complication mainly through vascular calcification and endothelial dysfunction. The prevalence of SHPT among diabetic nephropathy patients was not previously studied. The aim of this study is to evaluate the prevalence of SHPT among diabetic nephropathy patients attended to diabetes and nephrology outpatient clinic.

Methods: In this retrospective study, 437 diabetic patients were enrolled in this study from 264 diabetic patients who were taking digoxin and nephropathy outpatient clinics in our tertiary care hospital in Jeddah from Jan 2014 to Feb 2017. Inclusion criteria were: [1] Age ≥18 years, [2] Patient had diabetic nephropathy and was diagnosed based on the presence of urinary albumin/creatinine ratio (uACR) ≥30 mg/g = 24 hours’ proteinuria measurement = 300 mg/g. Exclusion criteria were: [1] patients were already receiving cinacalcet and/or [2] patients had undergone neck surgery for parathyroidectomy. The intact parathyroid hormone 25 vitamin D level, uACR and other kidney and biochemical investigation results were obtained from patients’ medical records. Patients were divided into two groups: those with euparathyroidism (an iPTH level less than 65 pg/mL) and those with hyperparathyroidism with iPTH level above or equal to 66 pg/mL.

Results: Three hundred and seventy-four patients (85.5%) had an iPTH level ≥66 pg/mL and those with hyperparathyroidism with iPTH level above or equal to 66 pg/mL. The rate of change of estimated glomerular filtration rate (eGFR) was calculated using linear regression.

For all participants, 1 kg/m² increase in handgrip strength was significantly associated with 0.14 score increase in total scores of QOL and 0.05 score increase in physical domain of QOL in adjusted analysis. One time increase in 30-second chair stand was significantly correlated with 0.14 score increase in psychological domain of QOL. The QOL was assessed using the Taiwan version of the WHOQOL-BREF. Clinical outcomes included commencing dialysis, major adverse cardiovascular events (MACES), and first hospitalization.


FR-PO483
Association of Physical Activity with Cardiovascular and Renal Outcomes and Quality of Life in CKD Yi-chun Tsai,1 Hung-Chun Chen,2 Shang-Jyh Hwang,1 Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; 2Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan.
Background: Patients with chronic kidney disease (CKD) are more readily prone to have impaired physical activity than the general population. The aim of this study is to examine the relationship between physical activity and adverse clinical outcomes and quality of life (QOL) in CKD.

Methods: This cohort study enrolled 161 patients with CKD stages 1-5 from February 2013 to September 2013 and followed up until June 2016. Physical activity was measured using high handgrip strength, 30-second chair stand, and 2-minute step. The QOL was assessed using the Taiwan version of the WHOQOL-BREF. Clinical outcomes included commencing dialysis, major adverse cardiovascular events (MACES), and first hospitalization.

Results: Of all participants, 1 kg/m² increase in handgrip strength was significantly associated with 0.14 score increase in total scores of QOL and 0.05 score increase in physical domain of QOL in adjusted analysis. One time increase in 30-second chair stand was significantly correlated with 0.14 score increase in psychological domain of QOL. Over a mean follow-up period of 29.1±11.2 months, 37 (23.0%) reached commencing dialysis, 11(6.8%) had MACES, and 50(31.1%) had first hospitalization. High handgrip strength (hazard ratio (HR): 0.89, 95% CI: 0.84-0.96) and high 2-minute step (HR: 0.04, 95% CI: 0.01-0.95) were significantly associated with decreased risk for commencing dialysis in multivariate analysis. Thirty-second chair-stand was negatively associated with MACES (HR: 0.65, 95%CI: 0.47-0.89) and first hospitalization (HR: 0.84, 95%CI: 0.74-0.95).

Conclusions: Physical activity is a potential predictor of QOL and clinical outcomes in CKD.
FR-PO484

Real Life Insights into the Use of Mineralocorticoid Receptor Antagonists in Patients with Diabetic and Non-Diabetic CKD with and without Heart Failure

Gabriele Haas, Jonathan Korn, Alain Gay, Bayer AG, Berlin, Germany; IMS Health, Frankfurt, Germany; Bayer AG, Berlin, Germany; QuintilesIMS, Frankfurt, Germany.

Background: Mineralocorticoid receptor antagonists (MRAs) are part of the treatment practice for patients with heart failure (HF) and/or hypertension. This study aimed to evaluate real-life MRA utilization in patients with chronic kidney disease (CKD) with or without diabetes mellitus (DM), HF and hypertension, respectively.

Methods: This retrospective cohort study used the US claims database PharMetrics Plus between 10/2008 and 09/2014. 2,291,143 patients ≥18 years with a first CKD diagnosis and 5,899 patients who initiated MRAs were included in two cohorts. Demographic characteristics, comorbidities, clinical events, medication use, and healthcare costs are reported for the overall cohorts and stratified by diagnosis: CKD only, CKD-DM, CKD-HF and CKD-DM-HF, and MRA treatment (no MRA treatment, MRAs for ≥6 and ≥6 months).

Results: We identified 114,129 CKD, 77,012 CKD-DM, 15,567 CKD-HF, and 22,435 CKD-DM-HF patients. The results showed low MRA usage in the population of interest. Overall, 2.3% of patients used MRAs. Use within the four diagnostic groups was 1.3%, 1.9%, 5.7%, and 6.7%, respectively. Hypertension was present in 78.5% of the overall population and in 94.1% of MRA patients. HF was present in 16.6% of the overall population and in 46.6% of MRA users. 27.6% of patients who took MRAs had CKD stage 4, 5 or end-stage renal disease. MRA users generally presented with higher rates of comorbidities, medication use, and higher healthcare costs. One-year persistence with MRA was less than 50%.

Conclusions: The use of MRAs in CKD patients is low and seems to be driven by the presence of hypertension and HF. Yet, MRAs are also given to CKD patients beyond stage 4, 5 or end-stage renal disease. MRA users generally presented with higher rates of comorbidities, medication use, and higher healthcare costs. One-year persistence with MRA was less than 50%.

FR-PO485

Impact of Transcatheter Aortic Valve Implantation on Renal Function


Background: Chronic kidney disease (CKD) is very prevalent in patients with aortic valve disease. Decreased renal function as a consequence of diminished cardiac output may contribute to this patient’s renal dysfunction. Given the potential reversibility of this mechanism after valve correction, the aim of this study was to verify the impact of percutaneous transcatheter aortic implantation (TAVI) on kidney function.

Methods: We performed a retrospective analysis of 233 consecutive patients who underwent TAVI and were included in single center prospective registry between November 2008 and May 2017. Estimated Glomerular Filtration Rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula and we considered 3 groups according their eGFR (mL/min/1.73 m²): Group 1: eGFR ≥60; Group 2: 30≤eGFR<60; Group 3: eGFR<30. Patients on dialysis were excluded from the analysis. Prevalence of stage 3 chronic kidney disease was 2.3%. Use within the four diagnostic groups was 7.5%.

Results: In the overall cohort, 27.6% of patients who took MRAs had CKD. Yet, MRAs are also given to CKD patients beyond stage 4, 5 or end-stage renal disease. MRA users generally presented with higher rates of comorbidities, medication use, and higher healthcare costs. One-year persistence with MRA was less than 50%.

Conclusions: The use of MRAs in CKD patients is low and seems to be driven by the presence of hypertension and HF. Yet, MRAs are also given to CKD patients beyond stage 4, 5 or end-stage renal disease. MRA users generally presented with higher rates of comorbidities, medication use, and higher healthcare costs. One-year persistence with MRA was less than 50%.

Funding: Commercial Support - Bayer AG

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

Underline represents presenting author.
FR-PO488
Relationship of eGFR and ACR to Concurrent Abnormalities in a Global Consortium Lesley Inker, CKD Prognosis Consortium, Baltimore, MD.

Background: CKD is associated with many vascular and laboratory abnormalities. We describe the continuous relationship between abnormalities and CKD staged by eGFR and albuminuria (ACR; A1:<30, A2:30-299, A3:a300 mg/g).

Methods: Using 12 CKD and 29 general population or high risk (GP/HR) cohorts, we performed random-effects meta-analyses for associations between eGFR (CKD-EPI creatinine equation, expressed as a linear spline with knots at 30, 45, 60, 75, 90 and 105) and the following parameters: systolic blood pressure (SBP, N=629,247), hemoglobin (N=405,633), bicarbonate (N=45,001, CKD cohorts only), phosphorus (N=128,769), parathyroid hormone (PTH, N=47,667), calcium (N=266,009), potassium (N=404,318), and total number of abnormalities (N=17,975, CKD cohorts only). Analyses were adjusted for demographics, comorbid conditions, and ACR stage. We assessed whether associations were modified by ACR stage and by diabetes including interaction terms.

Results: The CKD cohorts were 52% female and 3% black, with mean age 67 (SD 14). The GP/HR cohorts were 53% female and 4% black, with mean age 53 (SD 18). In the CKD cohorts, lower eGFR was associated with lower hemoglobin and bicarbonate, and higher potassium, phosphorus, PTH and total number of abnormalities. (Figure) For the CKD cohorts, lower eGFR was associated with lower hemoglobin and bicarbonate, and higher potassium, phosphorus, PTH and total number of abnormalities. (Figure) For phosphorus, there appeared to be a sharper increase in risk below eGFR <30. Associations with eGFR were relatively flat for SBP and calcium. There was no qualitative differences in associations by level of ACR or diabetes. In the GP/HR cohorts, there was a continuous association between eGFR and potassium; for hemoglobin, phosphorus and PTH, associations were present at eGFR <59, <51 and <70, respectively. Albuminuria was a weak risk factor for metabolic abnormalities.

Conclusions: There was a graded association between potentially reversible metabolic abnormalities and level of GFR with similar associations by ACR stage.

Funding: NIDDK Support, Private Foundation Support

FR-PO489
Greater Variability in Kidney Function Is Associated with an Increased Risk of ESRD Yan Yan,1,2 Benjamin C. Bowe,1 Yan Xie,1 Tingting Li,1,2 Carlos E. Palant,3 Ziayi Al-Aly.1,2 Clinical Epidemiology Center, Research and Development Service, Veterans Affairs St Louis Health Care System, St. Louis, MO; 2Department of Medicine, Washington University School of Medicine, St. Louis, MO; 2Department of Surgery, Washington University School of Medicine, St. Louis, MO; 3Research and Medical Service, Veterans Affairs Medical Center, Washington, DC; 2George Washington University School of Medicine, Washington, DC.

Background: Intra-individual variability in kidney function is an independent predictor of all-cause mortality, providing additional prognostic information beyond baseline kidney function and prior slope; however, its prognostic significance for ESRD is not known.

Methods: To examine this question we assembled a cohort of 1,004,741 United States veterans with an eGFR above 60 ml/min/1.73m2 between October 2001-2002, where date of last measurement in this period was assigned T0, and used adjusted Cox Proportional Hazard models to examine the association between eGFR variability and risk of ESRD. Variability in kidney function was defined for each participant as the coefficient of variation of the regression line modeled on all outpatient eGFR measures during the three years before T0.

Results: After a median follow-up of 13.08 years, there were 2.76, 3.41, 4.01, and 5.57% cases of ESRD in the lowest to highest quartiles of eGFR variability, respectively. Compared with the referent category (lowest quartile), participants had a graded increase in risk of ESRD with a hazard ratio of 1.10 (95%CI: 1.06-1.13), 1.24 (1.20-1.28), and 1.73 (1.68-1.79) in quartiles 2, 3, and 4, respectively. Results were consistent across numerous sensitivity analyses.

Conclusions: Our results demonstrate that higher eGFR variability was associated with increased risk of ESRD.

Funding: Veterans Affairs Support

FR-PO490
Importance of eGFR Change as a Surrogate End Point of ESRD in a Randomized Controlled Trial Eisichiro Kanda,1 Enyu Inai,2 Fumiaki Kobayashi,1 Naoki Kashiwara,2 Masaomi Nangaku,1 Daiichi Sankyo Inc, Somerset, NJ; 2Kawasaki Medical School, Kurashiki City, Japan; 3Kumamoto University Graduate School of Medicine, Japan; 4National Cancer Institute, Tokyo, Japan; 5the University of Tokyo School of Medicine, Tokyo, Japan.

Background: A use of a validated surrogate endpoint instead of a clinical endpoint could make a sample size small and shorten trial period. We evaluated a usefulness of an estimated glomerular filtration rate (eGFR) change as a surrogate endpoint using data from the randomized controlled clinical trial [Olmesartan Reducing Incidence of End-Stage Renal Disease (ESRD in Diabetic Nephropathy Trial].

Methods: ESRD was defined as the true endpoint. eGFR changes over 1 to 3 years by 10% were defined as the surrogate endpoints. The relationship between eGFR changes and ESRD or the surrogate endpoints was evaluated using Cox proportional hazard models, which were adjusted for baseline characteristics. An effect of olmesartan on ESRD was compared with those on surrogate endpoints in terms of the ratio of the adjusted hazard ratio (aHR) of olmesartan to ESRD to those to surrogate endpoints by the bootstrap method.

Results: Diabetic kidney disease patients (n=566; male, 69.1%) were included in this analysis. Average age±SD, 59±1.1 years; eGFR 37±8.8 ml/min. The Cox proportional hazard models with spline curves showed the relationships between eGFR changes over 1 years and 2 years and ESRD (Figure 1). The ratios of aHR to ESRD to aHRs to surrogate endpoints near 1 were -30% or -40% over 2 years: -30%, 1.01 (95%CI: 0.69-1.41); -40%, 1.0 (0.71-1.34). The events of eGFR changes of more than -30% showed good agreement with ESRD (0.6 < Cohen’s kappas). The total sample sizes were 1004 for estimating eGFR change of -40% over 1 year; 800 for that of -40% over 2 years, which were smaller than that (1922) for one estimating ESRD.

Conclusions: eGFR change of more than -30% to -40% over 2 years would be a useful surrogate endpoint of ESRD in DKD patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO491
Identification and Prevalence of Pediatric CKD in a Large National Insurance Database 
Zubin J. Modji,1 Ian T. Robinson,2 Tanushree Banerjee,2 Neil R. Powe,3 Sharon Saydah,1 Deborah Rolla,1 Rajiv Sara,3 Debbie S. Gipsón.1 1Centers for Disease Control and Prevention, Atlanta, GA; 2University of California, San Francisco, San Francisco, CA; 3University of Michigan, Ann Arbor, MI.

Background: Population-level surveillance of chronic kidney disease (CKD) in pediatrics is undeveloped. Children and adolescents with CKD are currently poorly identified in large databases, as existing surveillance systems focus primarily on adults. We examined 3 different claims-based algorithms to identify children and adolescents with CKD in a large, national, single-payer insurance database.

Methods: Using the ClininformaticsSM data from 2014, children and adolescents < 21 years with potential CKD were identified by 3 ICD-9 codes: 585-CKD codes alone, adult CKD stage-specific algorithm and a novel pediatric-specific CKD algorithm derived from chart review (N=110) at a large academic center. Patients were included if code was used at least once during the study period. Demographics were compared between patients identified via each method and concordance between methods was evaluated.

Results: 860, 8637, and 4294 children were identified via the 585-CKD, adult, and pediatric algorithms, respectively. Of all patients identified by at least 1 of the 3 methods, 44.6% were identified by both the adult and pediatric algorithms. All 860 patients identified by the 585-CKD algorithm were also identified by both adult and pediatric algorithms. Some code differences included prostatic obstruction, abnormal creatinine testing and acute renal failure in adult algorithm and specific genetic, autoimmune, and urologic disorders in pediatric algorithm. 144 patients were uniquely identified by the pediatric algorithm and 5861 were unique to the adult algorithm. Of the uniquely identified patients, those in the pediatric group were older, compared to the adult group (11 y vs 8 y). A higher prevalence of anemia was observed among patients uniquely identified by the pediatric algorithm compared to adult algorithm (43% vs 23%).

Conclusions: Adult and pediatric code algorithms examined identified substantially more potential patients with CKD than the 585-CKD algorithm. Refinement and validation of code algorithms for pediatric CKD as well as expansion to use of ICD-10 codes may be necessary to allow for current and historic case identification and pediatric CKD surveillance efforts.

Funding: Other U.S. Government Support

FR-PO492
Assessing Success in Transitioning of Young Adults from Pediatric to Adult Kidney Practice 
Cybele Ghossein,1 Craig B. Langman,1 Benjamin Joslin.2 1Feinberg School of Medicine, Northwestern University, Chicago, IL; 2Northwestern University Feinberg School of Medicine, Chicago, IL.

Background: Transfer from a pediatric to an adult medical setting is associated with many barriers. There are little data on patients’ assessment of the transition process itself. Three years ago at Lurie Children’s Hospital, we established a kidney transition program with the help of an adult nephrologist, physician assistant and social worker. After 18 months, we evaluated the patients’ perception of the program.

Methods: Patients who had transitioned from pediatric care and were seen at least once in the adult clinic were asked to take an established 5-point Likert scale survey. Survey questions addressed readiness to transition, the transition process itself, and the perception of adult care. Responses were categorized into Top 2 Box (“strongly agree” or “neutral,” or “positive.” Average, standard deviation and reader reliability were calculated. The readers also selected a word that best depicted each response and those most-common words were counted by question and overall.

Results: 17 out of 42 patients completed the survey. Average age at transition (mean ± SD) was 20 ± 2 years; the majority of patients (82%) felt ready to transfer to adult care but only 59% felt they were consulted on the timing. 88% of patients felt having a transition appointment and meeting the adult care providers in the pediatric setting to be valuable. Although 94% of patients ultimately felt comfortable in the adult care environment, 18% experienced noticeable differences in treatment recommendations. 13 semi-structured interviews were conducted. Overall, the patients responded positively (3±0, 100% reader reliability) to the transition. But, when asked what could have improved the transition, the word the patients used most was, “earlier.”

Conclusions: Young adults transitioning to adult care often feel ready to transition earlier than their transfer of care date. They subjectively benefit from a transition program that outlines the process of transferring their care. Communication regarding differences in treatment between pediatric and adult nephrology care is warranted.

Funding: Private Foundation Support, Clinical Revenue Support

FR-PO493
Spatial Analysis of CKD Prevalence in the US – A Joint Analysis of NHANES and KEEP 
Orrin Myers,1 V. Shane Pankratz,2 Keith C. Norris,3 Joseph A. Vassalotti,1 Mark L. Unruh,3 Christos Argyropoulos.1 1Icahn School of Medicine at Mount Sinai, New York, NY; 2UCLA, Marina Del Rey, CA; 3UNM Health Sciences Center, Albuquerque, NM.

Background: Chronic Kidney Disease (CKD) is a public health concern in the US, but it lacks a nationwide surveillance system that can describe regional variation. We investigate the feasibility of estimating county-level CKD prevalence from the large-scale community disease detection Kidney Early Evaluation and Program (KEEP).

Methods: KEEP participants were recruited from two-thirds of the nation’s counties but were self-selected after targeted recruitment. We combined KEEP (N=127,149) and NHANES samples (N=27,565) from 2001–2012 to estimate sampling weights. The weights reduce self-selection bias in KEEP when estimating county-level prevalence of CKD (eGFR<60 mL/min/1.73 m2).

Results: Nationwide prevalence of eGFR<60 was 8.9% (7.5-10.7) from KEEP and 6.8% (6.3-7.2) for NHANES. CKD prevalence was significantly higher in rural counties (Fig 1A), which also had higher uncertainty (Fig 1B).

Conclusions: A joint analysis of NHANES and KEEP produced estimates of eGFR<60 that are adjusted for selection bias. Our analysis found that CKD rates are higher in rural counties. This approach makes it possible to enhance spatial CKD surveillance systems.

FR-PO494
Reported Awareness of CKD in the United States According to KDIGO Risk Groups for Prognosis 
Joanne E. Rodrigue,1 Tanushree Banerjee,2 Delphine S. Tuot,3 Meda E. Pavkov,2 Vahakn B. Shahinian,3 Nilka Rios Burrows,2 Rajiv Sara,3 Neil R. Powe.1 1University of California, San Francisco, San Francisco, CA; 2Centers for Disease Control and Prevention, Atlanta, GA; 3University of Michigan, Ann Arbor, MI.

Background: Chronic kidney disease (CKD) awareness in high risk populations is a critical public health challenge. CKD is characterized by marked differences in prevalence across race/ethnicity. Trends in awareness among those at various risks of prognosis to CKD have not been well characterized in the general United States population overall, or by race/ethnicity.

Methods: Prevalence of reported CKD awareness was assessed among non-pregnant adults aged ≥20 years in the National Health and Nutrition Examination Survey 1999-2014 with affirmative response to the question “do you have a routine place to go for healthcare?” Participants with and without CKD were categorized into three KDIGO risk groups for prognosis to CKD: low, moderate, and high, based on eGFR and albuminuria. CKD awareness was defined by affirmative response to the question “have
you ever been told that you had weak or failing kidneys?" We determined the proportions of awareness overall, by risk groups, and by sex; ethnicity over time periods 1999-2004, 2005-2010, and 2011-2014. A propensity score for KDIGO risk groups was used to adjust for differences over time in demographics, hypertension, diabetes, and frequency of healthcare use.

Results: Among 23,762 adults, the adjusted proportion of reported CKD awareness across all risk groups increased from 1999-2004 to 2011-2014 (p-trend=0.04). Awareness among Mexican Americans at high risk, increased from 13.4% in 1999-2004 to 36.6% in 2011-2014, and among those at moderate risk 2.3% to 11.1% (combined p-trend=0.003). Awareness among non-Hispanic (NH) whites and NH blacks at high and moderate risk showed moderate increases over time, but the trend was not significant.

Conclusions: Overall, increases in reported awareness of CKD, particularly in Mexican-Americans at moderate and high risk of progression may be due to improvements in detection of disease or due to increases in the number of persons with CKD knowing they have the disease.

Funding: Government Support - Non-U.S.

Adjusted Prevalence of Awareness by Risk Groups

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>1.1 (0.9-1.2)</td>
<td>1.3 (1.0-1.6)</td>
<td>1.5 (0.9-2.1)</td>
</tr>
<tr>
<td>Mixed</td>
<td>3.1 (2.0-4.2)</td>
<td>4.5 (2.5-7.6)</td>
<td>5.1 (2.9-9.3)</td>
</tr>
<tr>
<td>High</td>
<td>4.4 (3.6-5.2)</td>
<td>9.8 (5.9-16.0)</td>
<td>9.8 (5.1-20.6)</td>
</tr>
</tbody>
</table>

FR-PO495

Racial Disparities in Trajectory of eGFR Decline in Patients with or at Risk for CKD

Susanne B. Nicholas,1 Bennett K. Daratha,1 Jenny I. Shen,1 Douglas S. Bell,1 Radica Z. Alicic,2 Katherine R. Tuttle,1 Keith C. Norris,3 LaBiomed at Harbor-UCLA, Torrance, CA; Providence Medical Research Center, Spokane, WA; University of Washington School of Medicine, Spokane, WA; Washington State University, Spokane, WA; Medicine, UCLA, Los Angeles, CA. Group/Team: UCLA-PHS CKD Registry Study Team.

Background: Blacks have a 3.5-fold greater prevalence of advanced chronic kidney disease (CKD) compared to non-Blacks. However, less is known about patterns of CKD progression in Blacks relative to non-Blacks in real world settings. UCLA and PHS have formed the largest combined electronic health record (EHR) based CKD and at-risk for CKD Registry. This study compares trajectories of estimated glomerular filtration rate (eGFR) between Blacks and non-Blacks in the UCLA CKD Registry.

Methods: Data in the UCLA CKD and at-risk CKD Registry were analyzed from 176,406 patients who had at least two eGFR measurements from 2006-2016. Mean baseline eGFRs were compared using independent samples t-tests. Trajectories of eGFR of Blacks versus non-Blacks across the 11 years of study were assessed using linear mixed models with random effects controlling for age and gender.

Results: Baseline characteristics of the overall cohort were: age 55±18 (mean±SD) years, CKD-EPI eGFR 90±24 mL/min/1.73m², 8% Black and 55% women. Among patients with baseline eGFR ≥60 mL/min/1.73m², Blacks had higher mean baseline eGFR (103±23 versus 94±19 mL/min/1.73m², p<0.001), and higher mean difference in eGFR (6.8 mL/min/1.73m²; 95% CI:6.6-6.9; p<0.001) than non-Blacks. Among patients with baseline eGFR 30-59 mL/min/1.73m², mean baseline eGFR was similar for Blacks and non-Blacks (40±8 versus 40±8 mL/min/1.73m², p=0.06). However, Blacks appear to have steeper trajectory of eGFR decline (mean difference in eGFR 1.8 mL/min/1.73m²; 95% CI:1.4-2.3; p<0.001).

Conclusions: The trajectories of eGFR differed between Blacks and non-Blacks depending on baseline eGFR ≥60 or 30-59 mL/min/1.73m², by a pattern shift from higher eGFR trajectories to lower, steeper eGFR trajectories. These data may signal critical windows for interventions to reduce disparities and improve kidney health in this high-risk group of Black patients.

Funding: Private Foundation Support

FR-PO496

Decreased Kidney Function Among a Rural Population in Veracruz, Mexico: A Cross-Sectional Study

Magdalena Madero,1 Diego J. Aguilar,2 Alejandro Raña,2 Alejandro Escobar,1 Antonio Villa,2 Gregorio T. Obrador.2 1National Heart Institute, Division of Nephrology, Mexico, Mexico; 2Universidad Panamericana School of Medicine, Mexico, D.F., Mexico.

Background: An epidemic of CKD of unknown origin (CKDu) has emerged in Central America, particularly in young male sugarcane workers. CKDu cases have been reported from Tierra Blanca, Veracruz, a region with similar environmental and socioeconomic characteristics to those described in Central America. To date, there are no epidemiologic reports of CKD hotspots in Mexico.

Methods: A cross-sectional study included adults with or without risk factors for CKD aged 20-60 from 3 communities in Tierra Blanca, Mexico. Sociodemographic, clinical, occupational and environmental data were collected from 613 participants. Standardized serum creatinine and albumin-creatinine ratio were measured; glomerular filtration rate (eGFR) was estimated using CKD-EPI equation. Patients were categorized with or without CKD according to KDIGO classification. Factors associated with lower eGFR were assessed using a multiple logistic regression model.

Results: Mean age was 41±11, and 200(32.6%) were men. Prevalence of CKD (G1-G5) was 24.9%, mostly driven by albuminuria (Figure 1), and was similar between male and female participants. Presence of DM or HTN was more frequent in the group with CKD (33.9% and 33.9%); nevertheless, 68 (44.4%) of the participants identified with probable CKD did not have a traditional risk factor. Independent factors associated with an eGFR <90 mL/min/1.73 m² were older age (OR=1.07; 95% CI:1.0-1.1), DM (OR=1.7; 95% CI:1.0-3.19), family history of CKD (OR=2.0; 95% CI:1.1-3.5) and history of sugarcane work (OR=2.2; 95% CI:1-4.3)

Conclusions: This is the first epidemiologic report of a possible CKDu hotspot in Mexico. A high prevalence of CKD in these communities was found. Moreover, almost half of the cases could be classified as oCKD. Non-traditional risk factors, such as the history of sugarcane work, were associated with lower eGFR. The cross-sectional nature of the study prevents etiologic interpretations; a longitudinal assessment to further characterize this possible CKD hotspot is being planned.

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

FR-PO497

Prevalence and Risk Factors for CKD in Adults of El Salvador

Carlos M. Orantes,1 Raul Herrera,1 Miguel M. Almaguer,2 Moises N. Diaz,1 Xavier F. Parada,1 Esmeralda G. Gavarrete Escobar,4 Luis C. Silva.1 ISSS, San Salvador; El Salvador; 1Instituto de nefrologia, La Habana, Cuba; 2Massachusetts General Hospital, Boston, MA; 3National Institute of Nephrology, La Habana, Cuba; 4National School of Public Health, Cuba, La Habana, Cuba; 5University of El Salvador, San Salvador, El Salvador; Renal Research Unit, National Institute of Health, San Salvador, El Salvador.

Background: An increase in deaths due to chronic kidney disease (CKD) has been observed in Central America. Mortality is 17 times higher in Nicaragua and El Salvador than in Cuba. Noted, CKD of unknown etiology (CKDu) is a major health problem in El Salvador.

Methods: A cross-sectional analytical epidemiological study was conducted in a sample of 4,817 participants aged ≥20 years obtained from the national survey on non-communicable diseases to determine the prevalence and risk factors for CKD and CKDu. Stages of CKD (CKD-EPI equation) were estimated from serum creatinine and spot urine albumin. CKD-1 & 2 was confirmed at three months. Data analysis included descriptive, analytical, and bivariate measures

Results: Risk factors: diabetes mellitus (DM) (12.5%); hypertension (HTN) 37%; family history of CKD 8.7%; family history of DM 21.8%, family history of HTN 40.3%; obesity 27.3%, dyslipidemia 27%; current smoker 7.8%; alcoholism 9.4%; agricultural occupation 31.2%; NSAIDs 3.8%; nephrotoxic plants 3.8%, direct exposure to agrochemicals 12.6%. CKD prevalence was 12.6 (11.0-14.4) (Figure 1), of this one-third was CKD3a (25.9-35.5). Associations found were (OR; 95%CI): Age >64 (17.3; 11.7-25.6), DM (3.6; 2.9-4.7), obesity (3.5; 2.8-6.0), HTN (3.5; 2.8-4.5), male (2.3; 1.8-2.9), rural residency (1.3; 1.0-1.8), dyslipidemia (1.3; 1.0-1.6). At least 5 years of: use of agrochemicals (2.5; 1.9-3.4), exposure to agrochemicals in residency & work (2.4; 1.7-3.4), any agricultural activity (2.0; 1.5-2.5), direct exposure to agrochemicals (1.8; 1.4-2.4), drinking river water (1.8; 1.4-2.3), storage of products and hardware for fumigation (1.5; 1.2-2.0).

Conclusions: Adults in El Salvador have a double burden of risk factors (traditional and non-traditional) that can act synergistically to cause CKD.

Funding: Government Support - Non-U.S.
Survival of Patients with CKD Stage 3-5 in Iceland

Amar J. Jonsson, Sigrun H. Lund, Runolfur Palsson, Olafur S. Indridason, Landspitali – The National University Hospital of Iceland, Reykjavik, Iceland; University of Iceland, Iceland.

Background: The purpose of this study was to estimate hazard ratio (HR) for death in patients with chronic kidney disease (CKD) stage 3-5 and to estimate the survival benefit of renal replacement therapy in CKD stage 5.

Methods: We obtained all Scr values from all clinical laboratories in Iceland for the years 2008-2013. Data on age, gender, diagnoses of common comorbid conditions (ICD-9 and ICD-10 codes) and Hba1c measurements were retrieved from electronic medical records. Information on initiation of renal replacement therapy was also obtained. The CKD-EPI equation was used to calculate eGFR. CKD was defined and staged according to the KDIGO classification system. Computerized algorithms were used to identify and exclude episodes of acute kidney injury. For CKD stage survival analysis, Cox regression model, using age as time scale was used to calculate hazard ratios adjusted for age, sex, hypertension, diabetes, coronary artery disease and acute kidney injury. For hazard ratio calculations for stage 5 with RRT compared to no RRT we used cox regression model, using age as time scale was used to calculate hazard ratios adjusted for age, sex, hypertension, diabetes, coronary artery disease and acute kidney injury. For hazard ratio calculations, we used cox regression model with time on study, adjusted for age as continuous variable, sex, hypertension, diabetes and coronary artery disease.

Results: We retrieved 1,230,563 Scr values for 183,931 individuals aged 18 years and older. The median age was 62 years (range: 18 – 108) and 47.5% were men. A total of 131,52(7.2%) patients had CKD, 8951 (4.9%), 3252 (1.8%), 798 (0.4%) and 151 (0.08%) in stage 3A, 3B, 4 and 5, respectively and 234 patients received RRT. Compared to individuals without CKD, the adjusted hazard ratio for death for CKD stage 3a, 3b, 4 and 5 were 0.94 (95%CI: 0.88 – 1.00), 1.15 (95%CI: 1.05 - 1.26), 1.84 (1.59 - 2.14) and 3.06 (2.41 – 4.09) respectively in men and 0.85 (95%CI: 0.80 – 0.91), 0.98 (95%CI: 0.90 - 1.07), 1.60 (1.38 – 1.85) and 4.48 (3.18 – 6.30) in women, respectively. For individuals with stage 5 and receiving RRT the HR for death was: 0.43 (95%CI: 0.27 - 0.68) compared to those that did not receive RRT. For individuals aged 65-74 the HR was 0.80 (95%CI: 0.52 – 1.29) and for individuals aged 75 or older the HR was: 0.32 (95%CI: 0.17 – 0.57).

Conclusions: This nationwide study, comprising the majority of the Icelandic populations does not confirm increased risk of death with stage 3a and 3b as previously reported. Renal replacement therapy seems to improve survival for patients with CKD stage 5, particularly for the aged.

Funding: Government Support - Non-U.S.

Temporal Changes in the Pattern of Kidney Disease: Analysis Based on 40,759 Biopsy-Proven Cases in China From 2003 to 2014

Haixian Zhu, Jin-Hua Hou, Minlin Zhou, Dandan Liang, Si-Jia Shao, Ye Liu, Zhi-Hong Liu, National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, Nanjing China, Nanjing, China.

Background: Global burden of disease showed that spectrum of disease in China has changed from infectious disease to non-infectious disease over the past 20 years and the latter has become one of the most leading public health problems. Epidemiologic studies reveal the temporal changes in the pattern of kidney disease, which might reliably inform future hypothesis driven studies and public health interventions. Thus, in this study we aimed to determine the temporal trends in kidney disease in 40,759 cases from 2003 to 2014.

Methods: We identified all patients with a native kidney biopsy specimen referred to the National Clinical Research Centre of Kidney Diseases in Jinling Hospital between 2003 and 2014. Temporal era was categorized into three consecutive 4-year time intervals (2003–2006, 2007–2010, and 2011–2014) and patients age was categorized into four intervals (14-24, 25-44, 45-59, and ≥60).

Results: In total, 40,759 cases with renal biopsy were analyzed. The mean age of the patients were 36.59±14.12 years old and 52.0% was male. Mean age of renal biopsy patients increased continuously and he proportion of patients over 60 years old mounted up from 5.6% to 9.9%. Primary glomerulonephritis (PGN), Secondary glomerulonephritis (SGN), Tubulointerstitial disease (TIN) and inherited kidney disease accounted for 67.1%, 26.4%, 2.9% and 2.5% respectively among cases of renal biopsy. IgA nephropathy (IgAN) (52.7%) was most common in PGN, immune-mediated disease accounted for 59.20% in SGN. The proportions of IgAN and focal segmental glomerulosclerosis (FSGS) had a downward tendency (P<0.001); while the proportion of membranous nephropathy (MN) increased significantly (P<0.001). Lupus nephritis and Henoch-Schönlein purpura nephritis this kind of immune-mediated diseases decreased significantly (P<0.001), diabetic nephropathy increased by nearly one year (P<0.001) from 2011 to 2014.

Conclusions: PGN remained the predominant kidney disease in China, of which, IgAN was the most common one. What was noteworthy was that the proportion of MN increased significantly, with a maximum increase in adolescent patients. The changing spectrum of kidney disease presented in this study provided a certain reference and basis for clinical diagnosis, prevention and epidemiological study.

Consistency of the Obesity Paradox across Different Stages of CKD in Over 2 Million Veterans

Melissa Soochoo, Elani Streja, Yoshitsugu Ohi, Connie Rhee, Christina Park, Hamid Moradi, Csaba P. Kovesda, Kamyrar Kalantar-Zadeh, UC Irvine, Orange, CA; University of Tennessee Health Science Center, Memphis, TN.

Background: The inverse relationship between body mass index (BMI) and mortality, also known as the “obesity paradox”, has been described for both dialysis and non-dialysis dependent CKD patients. However, the relationship of BMI with mortality across all increasing CKD stages (including early CKD), is less well-known.

Methods: We investigated a cohort of 2.1 million US veterans with a BMI measurement between 2005-2006. CKD stages were created according to eGFR (estimated glomerular filtration rate) at the time of BMI measurement. Using Cox models adjusted for age, gender, race and diabetes status, we examined the relationship of BMI with all-cause mortality across strata of CKD stage.

Results: Patients were 64±14 years old, 5% female, 15% African-American, and 36% diabetic with a mean BMI 29.6 kg/m² and median[IQR] eGFR 75[61, 91] mL/min/1.73m². Patients were followed for a median[IQR] follow-up of 10.6[6.9, 11.1] years. We observed a reverse J-shaped association across all CKD stages compared to the referent BMI 25–<30 kg/m², where BMI≥40 kg/m² was associated with a higher risk of mortality across all CKD strata, except for CKD Stage 5 patients [HR(95%CI): 1.00[0.90, 1.12]. The relationship of BMI≥40 kg/m² with mortality incrementally declined towards the null across worsening kidney stages. However, across all stages of CKD, BMI≥25 kg/m² was persistently associated with the highest risk of mortality. [Figure]

Conclusions: The relationship of morbidity obesity with a higher risk of mortality in US veterans attenuates across worsening CKD stages, further supporting the notion of an “obesity paradox”. Further studies are needed to understand the underlying mechanism of this relationship and whether weight management strategies are indicated in patients with worsening kidney disease.

Funding: NIDDK Support, Veterans Affairs Support

Consistency of the Obesity Paradox across Different Stages of CKD in Over 2 Million Veterans

Melissa Soochoo, Elani Streja, Yoshitsugu Ohi, Connie Rhee, Christina Park, Hamid Moradi, Csaba P. Kovesda, Kamyrar Kalantar-Zadeh, UC Irvine, Orange, CA; University of Tennessee Health Science Center, Memphis, TN.

Background: The inverse relationship between body mass index (BMI) and mortality, also known as the “obesity paradox”, has been described for both dialysis and non-dialysis dependent CKD patients. However, the relationship of BMI with mortality across all increasing CKD stages (including early CKD), is less well-known.

Methods: We investigated a cohort of 2.1 million US veterans with a BMI measurement between 2005-2006. CKD stages were created according to eGFR (estimated glomerular filtration rate) at the time of BMI measurement. Using Cox models adjusted for age, gender, race and diabetes status, we examined the relationship of BMI with all-cause mortality across strata of CKD stage.

Results: Patients were 64±14 years old, 5% female, 15% African-American, and 36% diabetic with a mean BMI 29.6 kg/m² and median[IQR] eGFR 75[61, 91] mL/min/1.73m². Patients were followed for a median[IQR] follow-up of 10.6[6.9, 11.1] years. We observed a reverse J-shaped association across all CKD stages compared to the referent BMI 25–<30 kg/m², where BMI≥40 kg/m² was associated with a higher risk of mortality across all CKD strata, except for CKD Stage 5 patients [HR(95%CI): 1.00[0.90, 1.12]. The relationship of BMI≥40 kg/m² with mortality incrementally declined towards the null across worsening kidney stages. However, across all stages of CKD, BMI≥25 kg/m² was persistently associated with the highest risk of mortality. [Figure]

Conclusions: The relationship of morbidity obesity with a higher risk of mortality in US veterans attenuates across worsening CKD stages, further supporting the notion of an “obesity paradox”. Further studies are needed to understand the underlying mechanism of this relationship and whether weight management strategies are indicated in patients with worsening kidney disease.

Funding: NIDDK Support, Veterans Affairs Support
FR-PO501

Weight Loss in Veterans with CKD after Enrollment in a Weight Management Program
Niraj Desai,1 Cameron D. Carter,2 Mirela A. Dobre,2 Khaldoon Shaheen,2 Sankar D. Navaneethan,1 Mahboob Rahman,2 Baylor College of Medicine, Houston, TX; 3Case Western Reserve University, Cleveland, OH; 4Cleveland VA Medical Center, Cleveland, OH; 5VA Greater Cleveland HCSB; 6VA Cleveland HCSB, Cleveland, OH.

Background: Though obesity is common in patients with CKD, interventions to reduce weight have not been well studied in this population. We examined the relationship between enrollment in a weight management program and weight loss across strata of eGFR.

Methods: We conducted a retrospective, observational analysis of patients enrolled in Managing Overweight/Obesity for Veterans Everywhere (MOVE!), a multidisciplinary weight management program within the Veteran’s Affairs Medical Centers. Mean weight loss, and change in BMI for MOVE! participants was calculated comparing baseline weight measured upon enrollment to final weight measured at the last visit to the program. A control group not enrolled in MOVE! was evaluated for weight change over a similar time period. Paired t testing was used to assess statistical significance.

Results: 4935 veterans (age 59.5 +/- 9.4 yrs, weight 119.1 +/- 21.3 kg, BMI 37.4 +/- 6.5 kg/m², 18% black, 67% diabetic) were enrolled in MOVE! between 2006 and 2011. Mean weight loss was 1.0 +/- 6.4 kg/patient (p<0.001) and mean decrease in BMI was 0.33 +/- 2.1 kg/m² (p<0.001) after an average of 7.6 +/- 11.4 visits to the program. In an age, gender, BMI and weight matched cohort (n=4795), mean weight loss was 0.05 +/- 4.7 kg (p=0.438) and mean decrease in BMI was -0.05 +/- 1.7 kg/m² (p=0.438). Mean weight loss and decrease in BMI was similar for each stratum of eGFR in the intervention group of Korea; 6Seoul National University College of Medicine, Seoul, Republic of Korea; 3Cleveland VAMC, Case Western Reserve University, Cleveland, OH; 7Seoul National University Hospital, Seoul, Republic of Korea.

Conclusions: Enrollment in a multidisciplinary weight management program is associated with minimal weight loss across all strata of eGFR.

FR-PO502

Weight Loss Has an Additive Effect on the Anti-Proteinuric Effects of Angiotensin II Receptor Blockers in Hypertensive Patients with CKD
Shin-Young Ahn,1 Dong Ki Kim,2 Seung Seok Han,3 Jung Iwan Park,2 Bumsoo Cho,1 Chun Soo Lim,4 Ho Jun Chin.3 Division of Nephrology, Department of Internal Medicine, Seoul, Republic of Korea; 2Konkuk University, Seoul, Republic of Korea; 3Korea University Medical Center; 4Korea University Guro Hospital, Seoul, GYEONGGI-DO, Republic of Korea; 5Korea University Guro Hospital, Seoul, Republic of Korea; 7Seoul National University College of Medicine, Seoul, Republic of Korea; 6Seoul National University Hospital, Seoul, Republic of Korea.

Background: Because weight gain and obesity contribute to the development of chronic kidney disease (CKD) and end stage renal disease (ESRD), weight reduction is a lifestyle intervention that has been introduced for the prevention and management of CKD. Obesity with obesity sometimes exhibit a slow progression of renal deterioration. We investigate the additive anti-proteinuric effect of weight reduction on the usage of an angiotensin II receptor blocker and the potential mechanisms of the beneficial effect in hypertensive CKD patients.

Methods: This study is a subanalysis of data from an open-label, randomized, controlled clinical trial (NCT01552954). Among the 235 participants, the body weight of 227 participants was measured and 24h urine samples were collected at baseline and after 16 weeks. The participants were assigned to subgroup according to changes in their body weight.

Results: Fifty-eight participants (25.7%) were assigned to group 1 (a 1.5% decrease in body weight after 16 weeks), 32 participants (14.1%) were group 2 (a 0.5% - 0.1% decrease in body weight), and 136 participants (60.2%) were group 3 (at 0.0% increase in body weight). Over the study period, unintentional weight loss independently increased the probability of reduced albuminuria (Group 1, RR 2.634, 95% CI 1.913 - 20.315, p=0.002). The relationship between weight loss and a decrease in albuminuria was even more significant in several subgroups, including participants who were female, younger (< 65 years), non-obese and obese (BMI ≥ 18.5 kg/m²), as well as those who had a CKD stage ≥ 3 (a 45 ml/min/1.73m²), consumed a low salt diet (urinary sodium excretion < 200 mEq/day) and a low protein diet (< 1.2 g/kg/day), and had a low baseline level of albuminuria (< 200 mg/day). Among the urinary cytokines, only podocalyxin levels decreased significantly in participants who lost weight (p=0.013).

Conclusions: Intent to lose unintentional weight loss has additive effect on the anti-proteinuric effects of treatment with ARBs in hypertensive CKD patients, which is possibly related to the reduced damage of podocytes. Therefore, physicians could consider suggestion of weight reduction to hypertensive CKD patients even if they are not obese.

Funding: Private Foundation Support

FR-PO503

Daily Sedentary Time and Physical Activity Are Independently Associated with ESRD Risk
Jacob M. Taylor,2 Edmond K. Kabagambe,2 Thomas G. Stewart,3 Jennifer Morse,1 Edward D. Siew,2 William J. Blot,2 Loren Lipworth,2 Talat Alp Ikizler2 Biostatistics, Vanderbilt University Medical Center, Nashville, TN; 3Medicine, Vanderbilt University Medical Center, Nashville, TN.

Background: Lifestyle factors, such as sedentary time and physical activity, could influence kidney outcomes and thereby contribute to the risk of end stage renal disease (ESRD).

Methods: We analyzed a case-cohort study from the Southern Community Cohort Study (SCCS) which recruited ~86,000 low-income blacks and whites in the southeastern US (2002-2009). 546 incident ESRD cases, identified by linkage with the US Renal Data System through March 2015, and a probability sample of 4049 SCCS participants, who donated a blood sample and had serum creatinine measured, were included. Demographic, medical, and lifestyle information, including detailed sedentary time and physical activity data, were obtained via questionnaire at baseline. Sedentary time was calculated as h/day from daily sitting activities, while physical activity was calculated as met-hrs and derived from engagement in light, moderate, and vigorous activities. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of sedentary time and physical activity with ESRD were computed from multivariable Cox models that included the two variables and age, sex, race, education, income, body mass index, eGFR, smoking, history of diabetes, hypertension, and hypercholesterolemia.

Results: At baseline, the mean (SD) was 55.5 (8.8) years for age and 96 (24) ml/min/1.73m² for eGFR. Median (25%; 75%) percentile for sedentary time and physical activity were 7.9 (5.5, 11.4) hrs and 15.7 (8.6, 29.1) met-hrs, respectively. Most participants were women (58%), black (67%), reached high school (65%), had high income (61%), were overweight or obese (77%), were current/former smokers (58%), and had hypertension (61%), while 25% had diabetes and 39% had hypercholesterolemia. After median follow-up of 9.7 years (range 0.08-12.8), risk of ESRD increased per IQR increase in sedentary time (HR=1.13, 95% CI 1.09-1.16), while risk decreased per IQR increase in physical activity (HR=0.93, 95% CI 0.90-0.97) in adjusted analysis.

Conclusions: In this population at high risk for ESRD, sedentary time appears to increase the risk of ESRD, whereas physical activity is inversely associated with ESRD risk. Sedentary time and physical activity independently associate with ESRD risk.

Funding: Other NIH Support - National Cancer Institute, Veterans Affairs Support, Other U.S. Government Support

FR-PO504

Conventional Measures of Body Composition Underestimate Sarcopenia and Overestimate Obesity in CKD
Susan Ziolkowski,4 Lin Jong,2 Glenn M. Chertow,2 Mary B. Leonard.1 Stanford School of Medicine, Stanford, CA; 2Stanford University School of Medicine, Palo Alto, CA; 3Nephrology, Stanford University, Stanford, CA.

Background: Fat and lean mass are directly correlated. Therefore, conventional definitions of sarcopenia (S) based on lean mass fail to capture low lean relative to fat, i.e. relative sarcopenia (RS) in those with greater adiposity. Recent data suggest RS better predicts incident morbidity than does S. Percent body fat (%BF) overestimates the prevalence of obesity if lean mass is low, while body mass index (BMI, kg/m²) can underestimate. Fat mass indexed to height (kg/m²) helps to address this limitation. Percentage of body fat (%BF) overestimates the prevalence of obesity if lean mass is low, while body mass index (BMI, kg/m²) can underestimate.

Methods: DXA appendicular lean mass index (ALMI, kg/m²) and BMI were assessed in 13,980 NHANES participants. ALMI, FMI, and ALMI relative to FMI were expressed as sex- and race/ethnicity-specific standard deviation scores compared with young adults (T-scores) and for age. S was defined as ALMI T-score < -2, and RS as ALMI relative to FMI T-score < -2. Excess adiposity was defined using sex- and race/ethnicity-specific BMI cutpoints and conventional BMI and %BF cutpoints. GFR was estimated using creatinine (sGFRc) and cystatin C (eGFRc).

Results: The prevalence of RS was higher than the prevalence of S, especially in CKD stages 3b (17 vs 6%) and 4 (43 vs 6%) using eGFRc; these stages were associated with the highest FMI, accounting for the higher prevalence of RS vs S. In multivariable logistic regression, CKD stage was independently associated with lower ALMI relative to FMI for age, adjusted for smoking, physical activity and cardiovascular disease (OR stage 3b AT age=1.99, stage 5=2.38, vs eGFRc < 90; p trend=0.05). The prevalence of obesity increased with CKD stage through stage 4, and was lower in stage 5 using FMI, BMI and %BF definitions. BMI and %BF under- and overestimated obesity prevalence, e.g., in CKD Stage 4, the prevalence of obesity was BMI: 42%, FMI 55%, %BF = 72%; S was not associated with obesity by FMI, adjusted for race, age, diabetes, liver disease, physical activity and cardiovascular disease.

Conclusions: In CKD, S underestimates muscle deficits and %BF overestimates the prevalence of obesity. CKD is independently associated with low lean mass relative to fat mass (RS) but is not associated with excess adiposity. Further studies are needed to determine the impact of low RS and excess adiposity (as defined by BMI) relate to morbidity and mortality in CKD.

Funding: NIDDK Support
FR-PO505
Association between Circulating Fibroblast Growth Factor 21 and Body Composition in CKD [Mari Okada,1 Takahiro Masuda,1 Marina Kohara,1,2 Hiromichi Yoshizawa,1 Atsushi Miki,1 Sakai Nakagawa,1 Ken Ohara,1 Takuya Murakami,1 Erika Hishida,1 Hiroaki Miyoga,1 Miwa Shuto,1 Yuku Watanabe,1 Osamu Saito,1 Tetsu Akimoto,1 Shigeaki Muto,1 Makoto Kuro-o,2 Daisuke Nagata,1 1Division of Nephrology, Department of Internal Medicine, Jichi Medical University, Shimotsuke, Japan; 2Division of Anti-aging Medicine, Center for Molecular Medicine, Jichi Medical University, Shimotsuke, Japan.

Background: Fibroblast growth factor 21 (FGF21) is a liver-derived hormone that induces responses to stress including activation of the sympathetic nervous system and the hypothalamus-pituitary-adrenal axis. Circulating FGF21 levels increase in the progression of chronic kidney disease (CKD), but the mechanism has not yet been fully evaluated. In this study, we examined the association between circulating FGF21 and body composition in predialysis CKD patients.

Methods: Seventy-two predialysis CKD patients were enrolled in this study (age 51.3 ± 17.1 years, male 51.4%, estimated glomerular filtration rate [eGFR] 66.3 ± 28.3 ml/min/1.73m²). Body composition was measured by bioelectrical impedance analysis (BIA). Patients were divided into low- and high-FGF21 groups by the median value. Multivariable logistic regression analysis was used to examine the association between serum FGF21 levels and body composition.

Results: The median value of serum FGF21 was 131 pg/mL. Age (55.6 ± 15.4 vs. 45.2 ± 17.0 years, *p = 0.05), body mass index (BMI) (26.1 ± 5.7 vs. 23.7 ± 4.3 kg/m²), systolic blood pressure (129 ± 18 vs. 116 ± 15 mmHg), percentage of fat mass (FM/kg) (30.9 ± 1.3% vs. 34.4 ± 1.3%, *p = 0.034) and skeletal muscle (26.7 ± 6.8 vs. 25.7 ± 6.8 kg, *p = 0.024) were higher in the high-FGF21. On the other hand, percentage of fat mass (26.6 ± 10.6 vs. 25.1 ± 9.3%, *p = 0.264) and serum albumin (3.2 ± 0.9 vs. 3.8 ± 0.7 g/L) were lower in the high-FGF21. The ratio of ECM to total body water (ECW/TBW) (0.387 ± 0.021 vs. 0.376 ± 0.023) were higher, and sFGFR (55.2 ± 27.0 vs. 79.2 ± 24.5 ml/min/1.73m²) and serum albumin (3.2 ± 0.9 vs. 3.8 ± 0.7 g/L) were lower in the high-FGF21. On the other hand, percentage of fat mass (26.6 ± 10.6 vs. 25.1 ± 9.3%, *p = 0.264) and skeletal muscle (26.7 ± 6.8 vs. 25.7 ± 6.8 kg, *p = 0.024) were similar among the groups. In logistic regression analysis, ECM/TBW was an independent risk factor for high-FGF21 level (odds ratio 1.38: 95% confidence interval 1.04-1.96, *p = 0.024) even after adjustment for gender, BMI, systolic blood pressure, and percentage of fat mass.

Conclusions: In predialysis CKD patients, higher circulating FGF21 level is associated with increase in ECM/TBW. This result indicates that fluid retention is a novel indicator for circulating FGF21 levels.

Funding: Government Support - Non-U.S.

FR-PO506
Association of Body Composition with Frailty Status among Patients with Moderate to Advanced CKD [Cynthia Delgado,1 Kirsten L. Johansen.1 1University of California, San Francisco, San Francisco, CA; 2Medicine, Division of Nephrology, University of California, San Francisco, San Francisco, CA; 3Medicine, Nephrology Section, San Francisco Department of Veterans Affairs, San Francisco, CA.

Background: Frailty disproportionately affects individuals with chronic kidney disease (CKD) and is associated with hospitalization and loss of independence. The Frailty Index (FI) is a standard measure of frailty and is calculated by dividing the number of individual comorbidities by the available life expectancy. This study examines the association of frailty measures, as defined by the FI, with body composition in patients with CKD.

Methods: We enrolled 68 patients with CKD stage III-IV over the age of 18 who were receiving nephrology care. Frailty was defined according to the Fried Frailty index, which includes 5 criteria (weak grip, exhaustion, weight loss, low physical activity, slow gait). Participants meeting three or more criteria were considered frail (F); those meeting 1-2 criteria were intermediate frail (IF); and those not meeting any frailty criteria were not frail (NF). We performed whole-body bioelectrical impedance spectroscopy (BIS) to estimate ICW/kg as a proxy for muscle mass (ICW), fat mass (FM) and extracellular water (ECW) as a percentage of total body weight. We used ANOVA to compare frailty status (F, IF and NF) and logistic regression analysis with NF participants as the reference group to determine if body composition was associated with frailty status after adjusting for covariates.

Results: Participants’ mean age was 67 ± 8, and 93% were male. The majority of participants met at least one frailty criterion; 49% were IF and 25% were F. ICW/kg was lower among IF (0.28 ± 0.3 L/kg) and F (0.26 ± 0.3 L/kg) than among NF participants (0.29 ± 0.03 L/kg, *p=0.05). In regression analysis, higher percent muscle mass (ICW/kg) (OR 0.38 per 1%, 95%CI 0.17, 0.83) and percent FM (FM/kg) (OR 0.76 per 1%, 95%CI 0.58, 0.98) were associated with lower odds of frailty.

Conclusions: Among FICKSIT participants, higher muscle and fat mass were associated with lower odds of frailty.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO507
Frailty Affects Treatment Decisions and Outcomes for Patients with CKD [Reid Whitlock,2 Frederick Eng,1 Ranveer S. Brar,1 Claudio Rigatt,2 Paul Komenda,2 Clara Bohm,2 Navdeep Tangri.2 1Seven Oaks General Hospital, Winnipeg, MB, Canada; 2University of Manitoba, Winnipeg, MB, Canada.

Background: Frailty is common in patients with Chronic Kidney Disease (CKD) and leads to accelerated aging. While there have been several studies examining frailty in patients with earlier stages of CKD and those on dialysis, little is known about the prevalence and impact of frailty on outcomes in patients with advanced CKD. We sought to determine the agreement between 3 different frailty measures and the association of these measures with dialysis modality decisions and mortality.

Methods: We studied 508 patients with advanced CKD who were enrolled in CKD clinics at 4 centers. We collected demographics, comorbid conditions, and laboratory results in addition to objective [Modified Fried Frailty Criteria (Fried) and Short Physical Performance Battery (SPPB)], and subjective measures (physician and nurse impression) of frailty. Our primary outcomes were choice of dialysis modality and all-cause mortality.

Results: Our cohort had a median age of 68 (interquartile range: 58, 77) and was 42.9% female. Estimates of frailty prevalence varied as 49.9% of the cohort were considered frail according to SPPB, 29.9% according to Fried, 33.4% according to physician impression, and 28.7% according to nursing impression. Agreement between objective frailty assessments (κ = 0.48) and subjective frailty assessments (κ = 0.46) was moderate. The objective frailty measures were not associated with choice of dialysis modality. In contrast, the subjective physician impression of frailty was associated with choosing hemodialysis (OR 3.74 [95% CI: 1.02-13.66]). The subjective frailty measures were not associated with choice of dialysis modality. Frailty measured objectively using Fried trended toward an association with mortality (OR 1.94 [95% CI: 0.97-3.88]).

Conclusions: In summary, we have demonstrated that the definition of frailty is important, as there is limited agreement between frailty construct and important differences in the relationship of each construct with clinical outcomes. Patients diagnosed as frail by Fried were more likely to die, and patients considered frail by physicians were more likely to choose in-center hemodialysis. Further research to understand the longitudinal trajectory of frailty and its impact on therapeutic choices, morbidity, mortality, and quality of life after initiation of dialysis is needed.

Funding: Government Support - Non-U.S.

FR-PO508
Recalibration and Validation of the Charlson Comorbidity Index in an Asian Population: The National Health Insurance Service – National Sample Cohort Study [Jae shin Choi,1 Myoung-Hee Kim,2 Yong Chul Kim,3 Jung Nam An,4 Jae Yoon Park,5 Dong Ki Kim,1 Yun Kyu Oh,6 Yon Su Kim,7 Chun Soo Lim,1 Jung Pyo Lee.3 1Seoul National University Hospital, Seoul, Republic of Korea; 2Eulji University, Seongnam-si, Gyeonggi-do, Republic of Korea; 3Seoul National University Boramae Medical Center, Agonseong, Seoul, Republic of Korea; 4Dongguk University Ilsan Hospital, Gyeonggi-do, Republic of Korea.

Background: Weights assigned to comorbidities to predict mortality may vary based on the type of index disease and advances in the management of comorbidities. We aimed to develop a modified Charlson comorbidity index (CCI) in an Asian nationwide database (mCCI-A), thereby predicting their mortality more precisely.

Methods: The main data source used in this study was the National Health Insurance Service-National Sample Cohort (NHIS-NSC) constructed from the National Health Insurance claims between January 1, 2002 and December 31, 2013 in Korea. Of the 1,025,340 individuals included in the NHIS-NSC, 55,513 patients who were hospitalized at least once were analyzed for this study. mCCI-A score were calculated by summing up the weights which were assigned to individual comorbidities according to their relative prognostic significance determined by multivariate Cox proportional hazard model. The modified index was validated in the same cohort.

Results: The Cox proportional hazards model provided reassigned severity weights for 17 comorbidities that significantly predicted mortality. Both the CCI and the mCCI-A were correlated with mortality. However, the mCCI-A showed modest but significant increases in e statistics compared with the CCI. The analyses using continuous net reclassification improvement(cNRI) revealed that the mCCI-A improved net mortality risk reclassification by 23.1% (95% CI, 22.0-24.3; P<0.001).

Conclusions: The mCCI-A facilitates better risk stratification for mortality in Korean inpatients compared with the CCI, suggesting that it may be a preferred index for use in clinical practice and the statistical analysis of epidemiological studies.
FR-PO509
Self-Reported Sleep Problems and Mortality among US Adults with and without CKD: NHANES 2007-2010

Monica Shing, Jennifer L. Bragg-Gresham, Hal Morgenstern, Delphine S. Touit, Deborah Rolkia, Nilka Rios Burrows, Neil R. Powe, Rajiv Saran. CDC, Atlanta, AL; Centers for Disease Control and Prevention, Atlanta, GA; Priscilla Chan and Mark Zuckerberg San Francisco General Hospital & University of California SF, San Francisco, CA; University of California, San Francisco, San Francisco, CA; University of Michigan, Ann Arbor, MI.

Background: Sleep problems are associated with several medical conditions including kidney disease. However, little research has been done assessing associations of sleep problems with mortality. We estimated the effects of self-reported sleep problems on mortality, by CKD status, among nationally representative, US adults.

Methods: A sample of 11,338 adults, ages 20+, from the mortality-linked National Health and Nutrition Examination Survey (NHANES, 2007-2010) with complete data on estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (UACR) were included in the analysis. Data on self-reported sleep problems were obtained from questionnaires. CKD was defined as eGFR < 60 ml/min/1.73 m² or UACR > 30 mg/g. Cox regression, stratified by CKD status, was used to estimate hazard ratios (HR; 95% CIs) for mortality over a median of 34 months of follow-up, adjusting for survey year, age, sex, and race/ethnicity. A combined model including all the subjects was investigated (not shown) to test for differences in associations by CKD status.

Results: Self-reported sleep problems were common among participants with CKD. Among individuals with CKD, 4 of the 5 sleep problems were positively associated with mortality, adjusting for demographic factors (table). For diagnosed sleep disorders and <6 hours sleep per night, these associations in CKD patients were stronger than in persons without CKD (though both p-values for interaction were >0.15). Nocturia and >9 hours of sleep per night, these associations in CKD patients were stronger than in persons without CKD (though both p-values for interaction were >0.15). Nocturia and >9 hours of sleep were associated with mortality in patients with and without CKD.

Conclusions: If these findings are replicated in other studies with more extensive control for confounders, especially among CKD patients, efforts should be made to understand if ameliorating sleep problems improves wellbeing and survival.

FR-PO510
Association of Chronic Insomnia with Mortality and Adverse Renal Outcomes among US Veterans

Chu Lai, Amado X. Freire, Miklos Z. Molnar, Kamyar Kalantar-Zadeh, Csaba P. Kovacesky. UTHSC at Memphis, Memphis, TN; University of California Irvine, School of Medicine, Orange, CA; University of Tennessee Health Science Center, Memphis, TN.

Background: Chronic insomnia is highly prevalent in the world. Its effects on the sympathetic-adrenal system could potentially worsen hypertension and cause metabolic abnormalities. However, there is lack of evidence of the association between insomnia and adverse renal outcomes.

Methods: We examined associations of chronic insomnia (defined as the presence of ICD9 codes 307.42, 307.49 and 780.52 and long-term use of insomnia medications) with all-cause mortality, end-stage kidney disease (ESRD), and mortality. To date limited information exists regarding the risks of adverse events in ADPKD patients with advanced CKD. The objective of this study was to determine the risks of CKD-related adverse outcomes in ADPKD patients compared to non-ADPKD patients.

Results: We examined data from the Canadian Study of Prediction of Death, Dialysis and Interim Cardiorenal Events (CanPREDDICT) cohort. CanPREDDICT was a prospective pan-Canadian cohort study from 2008-2013 involving 28 facilities caring for patients with advanced CKD (eGFR 15-45 ml/min/1.73 m²) with adjudicated outcomes. We used Cox proportional hazards and Fine and Gray models to examine the risk of CV (defined as coronary artery disease or CHF), infection, ESKD, or all-cause mortality in a propensity-score matched (4:1) cohort of non-ADPKD and ADPKD patients.

Conclusions: ADPKD patients with advanced CKD are at higher risk of ESKD and cardiovascular events compared to non-ADPKD patients. These findings suggest that judicious monitoring, screening and treatment for adverse outcomes in ADPKD patients, especially related to cardiovascular disease, may be beneficial.

FR-PO511
The Risk of Adverse Events in Polycystic Kidney Disease Patients with Advanced CKD

Mamish M. Sood, Sonali N. De chickera, Adrea Levín, Mila Tang, Ayub Akbari. Ottawa Hospital Research Institute, Ottawa, ON, Canada; St. Paul's Hospital, Vancouver, AB, Canada; St. Paul's Hospital - University of British Columbia, Vancouver, BC, Canada; The Ottawa Hospital - University of Ottawa, Ottawa, ON, Canada; University of Ottawa, Ottawa, ON, Canada.

Background: Autosomal dominant polycystic kidney disease (ADPKD) leads to progressive chronic kidney disease (CKD) with a subsequent increasing risk of adverse events such as cardiovascular disease (CV), infections, end-stage kidney disease (ESKD) and mortality. To date limited information exists regarding the risks of adverse events in ADPKD patients with advanced CKD. The objective of this study was to determine the risks of CKD-related adverse outcomes in ADPKD patients compared to non-ADPKD patients.

Methods: We examined data from the Canadian Study of Prediction of Death, Dialysis and Interim Cardiorenal Events (CanPREDDICT) cohort. CanPREDDICT was a prospective pan-Canadian cohort study from 2008-2013 involving 28 facilities caring for patients with advanced CKD (eGFR 15-45 ml/min/1.73 m²) with adjudicated outcomes. We used Cox proportional hazards and Fine and Gray models to examine the risk of CV (defined as coronary artery disease or CHF), infection, ESKD, or all-cause mortality in a propensity-score matched (4:1) cohort of non-ADPKD and ADPKD patients.

Results: Among a total of 2,270 patients, 105 with ADPKD were matched with 416 non-ADPKD patients with a baseline mean age and eGFR of 62.6 (SD 14.0) years and 27.8 (SD 9.0) ml/min/1.73 m², respectively. During a total of 1,680 person-years of follow time (median follow-up 3.8 years), there were a total of 43, CV, ESKD, 117 infections and 39 all-cause mortality events. ADPKD was associated with a higher risk of cardiovascular events (9.5% vs. 7.9%, HR 1.46 [95%CI: 1.33, 1.62], p<0.001) and rapid loss of kidney function (odds ratio: 2.41 [95%CI: 1.66, 3.48], p<0.001), and rapid loss of kidney function (odds ratio: 1.29 [95%CI: 1.07, 1.56], p=0.01). ADPKD was associated with a higher risk of all-cause mortality (6.7% vs 7.7%, HR 0.87 [95%CI: 0.40-1.91) compared to non-ADPKD. There were no differences in the types of infections (urinary, respiratory, hematologic or other) between the two groups (p=0.585).

Conclusions: ADPKD patients with advanced CKD are at higher risk of ESKD and cardiovascular events compared to non-ADPKD patients. These findings suggest that judicious monitoring, screening and treatment for adverse outcomes in ADPKD patients, especially related to cardiovascular disease, may be beneficial.

FR-PO512
Renal Resistive Index and Systematic Arterial Stiffness in the General Population

Xiaohong Fan, Xuemei Li, Peking Union Medical College Hospital, Chinese Academy of Medicine Sciences & Peking Union Medical College, Peiking, China.

Background: Recent studies show that increased renal resistive index (RRI) is associated with kidney disease progression and cardiovascular disease (CVD). Greater arterial stiffness is also considered to be an independent predictor for CVD onset and associated with steeper decline in kidney function. RRI is presumed to be dependent on the sex difference existed even when adjusting for other factors. In all participants, the sex difference existed even when adjusting for other factors. All participants, baPWV was independently associated with increased RRI in multivariable analyses after adjustment for potential confounders. The other determinants of RRI in the general male population.

Methods: This study consisted of 1589 subjects ages between 35 and 85, recruited for a cross-sectional health survey in Pinghu, a suburb of Beijing, China in 2014. All subjects underwent assessment of ultrasonographic RRI and measurement of brachial-ankle pulse wave velocity (baPWV). Multiple linear regression modeling was performed to explore the RRI risk factors and the relationship between RRI and baPWV.

Results: The mean age of the study population was 53.7±9.1 years, 48.7% were males. RRI was positively associated with age (r=0.43; P<0.001). RRI in women was significantly higher than in men (0.62±0.05 vs. 0.60±0.06; P<0.001) at all age groups, the sex difference existed even when adjusting for other factors. All in participants, baPWV was independently associated with increased RRI in multivariable analyses after adjustment for potential confounders. The other determinants of RRI in the general male population.
population were age, sex, systolic and diastolic blood pressure, body mass index, estimated glomerular filtration rate and hemoglobin A1c (Table 1).

Conclusions: There was significantly association between systematic arterial stiffness and internal RRI. The sex difference affect needs to be investigated in the future.

Funding: Government Support - Non-U.S.

Table 1: BaPWV was significantly associated with increased renal resistive index.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group</th>
<th>All patients (n=358)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, Female vs. Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BaPWV, mm Hg</td>
<td>0.023</td>
<td>0.002</td>
<td>0.026</td>
</tr>
<tr>
<td>aPWV, mm Hg</td>
<td>0.001</td>
<td>0.001</td>
<td>0.026</td>
</tr>
<tr>
<td>qe-paw 1'y</td>
<td>0.002</td>
<td>0.015</td>
<td>0.021</td>
</tr>
<tr>
<td>RRI, per 100</td>
<td>0.007</td>
<td>0.007</td>
<td>0.011</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.005</td>
<td>0.009</td>
<td>0.011</td>
</tr>
<tr>
<td>RRI, per h/mg</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>(GFR, per 100)</td>
<td>0.002</td>
<td>0.003</td>
<td>0.003</td>
</tr>
<tr>
<td>(BMI, per 100)</td>
<td>0.004</td>
<td>0.005</td>
<td>0.006</td>
</tr>
</tbody>
</table>

FR-PO513

The Association between Plasma PCSK9 Concentrations and CKD

Jaeun Kim,1 Eun Hui Bae,1 Seong Kwon Ma,2 Soo Wan Kim,2 Chonnam National University Hospital, Gwangju, Republic of Korea; Chonnam National University Medical School, Gwangju, Republic of Korea.

Background: Dyslipidemia commonly appear in patients with chronic kidney disease (CKD) presenting with unique characteristics. The proprotein convertase subtilisin/kexin type 9 (PCSK9) is a regulator of the low-density lipoprotein receptor and plasma cholesterol concentrations. We studied the association of circulating PCSK9 concentrations with both estimated glomerular filtration rate (eGFR) and serum lipid parameters in patients at different stage of CKD.

Methods: Plasma PCSK9 concentrations measured by ELISA in 90 non-diabetes patients at different stage of CKD. We assessed their lipid profile including total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and plasma cholesterol concentrations. We studied the association of circulating PCSK9 with eGFR, age, sex, systolic and diastolic blood pressure, body mass index, and proteinuria.

Results: The mean plasma level of PCSK9 was 309.7 ± 74.6 ng/ml in the 90 patients. Plasma PCSK9 concentration has a positive correlation with UACR (r=0.264, P=0.020) and triglyceride (r=0.316, P=0.007), but not with total cholesterol (P=0.142), eGFR (P=0.058), LDL-C (P=0.319), CRP (P=0.101), ApoA1 (P=0.380), ApoB (P=0.805), ApoA1/B (P=0.893) and CRP (P=0.457). In the patients with UACR ≥1 g/gCr, plasma PCSK9 levels increase compared to patient with UACR <1 g/gCr (361.9 ± 60.3 ng/ml vs. 299.3 ± 73.2 ng/ml, P=0.008). Plasma PCSK9 level was independently associated with existence of diabetes and statin/fibrate medication. The concentrations of PCSK9 according to CKD stages were 273.0 ± 56.5 g/ml in the CKD stage 1, 317.5 ± 98.4 g/ml in the CKD stage 2, 306.6 ± 68.7 g/ml in the CKD stage 3, 333.1 ± 85.6 g/ml in the CKD stage 4, and 306.0 ± 64.3 g/ml in the CKD stage 5 without dialysis, respectively. The levels of PCSK9 in patients with CKD stage 1 were lower than those of other stages (P=0.032).

Conclusions: Plasma PCSK9 concentrations are related to proteinuria, but not associated to eGFR in patient with CKD.

FR-PO514

The Risk of Venous Thromboembolism in Patients with Albuminuria and Normal or Reduced Kidney Function

David Massicotte-Armstrong,1 Amit B. Reddy,2 Alejandro Lazo-Langner,2 Amber O. Molnar,2 Ngan Lam,2 Deborah Lynn Zimmerman,4 Amit X. Garg,1 Ziv Harel,3 Jeffrey Perl,1 Ron Wald,3 Manish M. Sood.4 London Health Sciences Centre, London, ON, Canada; McMaster University, Hamilton, ON, Canada; Ottawa Health Research Institute, Ottawa, ON, Canada; St. Michael’s Hospital, Toronto, ON, Canada; University of Alberta, Edmonton, AB, Canada; Western University, London, ON, Canada; University of California Irvine, School of Medicine, Orange, CA.

Background: Chronic kidney disease (CKD), defined by the presence of either albuminuria and/or reduced kidney function, is associated with a higher risk of venous thromboembolism (VTE). Whether the risk of VTE differs in CKD patients with albuminuria and normal or reduced kidney function remains unclear.

Methods: We conducted a retrospective population-based cohort study of 694,956 patients in Ontario, Canada between 2002 and 2012. We included patients with a measurement of albuminuria (albumin-to-creatinine ratio, ACR) and serum creatinine (for estimated glomerular filtration rate, eGFR). The primary outcome was the time to a first VTE event examined across differing levels of albuminuria and kidney function using adjusted Cox proportional hazard models and accounting for all-cause mortality was examined in Cox models adjusted for demographics, comorbidities, medication use, baseline estimated GFR and proteinuria.

Results: Patients were 66±11 years old, 96% were men, 59% were African American and 55% were diabetic. The baseline estimated GFR was 36±21 ml/min/1.73m². Higher DPI was associated with higher mortality (Figure). Compared to the second quartile, the hazard ratios (95%CI) of mortality associated with quartiles 1, 3 and 4 of DPI were 1.24 (0.76-2.01), 1.41 (0.88-2.26) and 2.17 (1.38-3.37), respectively.

Conclusions: In patients with moderate and advanced NDD-CKD, high DPI is associated with higher all-cause mortality. Further studies are needed to determine the amount of DPI providing optimal outcomes in this patient population.

Funding: NIDDK Support

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

354
The Effect of High Alcohol Consumption on Incidence of Proteinuria Was Different by Gender: A Retrospective Cohort Study

Yoshitaka Iseki,1,2 Hideaki Watanabe,3 Kenichi Fujimoto,3 Koichi Asahi,3 Toshihide Morita,4 Toshiki Yoshida,3 Shouichi Yamagata,3
1Department of Nephrology, Osaka University Graduate School of Medicine, Suita, Japan; 2Health and Counseling Center Osaka University, Toyonaka, Japan; 3Steering Committee for the Research on the Preventing of Chronic Kidney Disease in Specific Health Check and Guidance in Japan, Fukushima, Japan.

Background: Several studies reported that mild to moderate alcohol consumption reduced the risk of proteinuria, whereas a protective effect of heavy alcohol consumption is controversial. The aim of this retrospective cohort study was to assess an association between high alcohol consumption and the incidence of proteinuria in males and females.

Methods: Participants who underwent annual health check examinations in 78,327 males and 78,369 females; age 65 years; eGFR 75 ml/min/1.73m² and 76 ml/min/1.73m², respectively. Incidence of proteinuria was observed in 4,991 males and 3,040 females during 1.9 (1.0-2.1) years of the observational period. The association between alcohol consumption and incidence of proteinuria was U-shaped in males and J-shaped in females (Figure).

Results: Background of participants in 78,327 males and 78,369 females; age 65 years; eGFR 75 ml/min/1.73m² and 76 ml/min/1.73m², respectively. Incidence of proteinuria was observed in 4,991 males and 3,040 females during 1.9 (1.0-2.1) years of the observational period. The association between alcohol consumption and incidence of proteinuria was U-shaped in males and J-shaped in females (Figure).

Conclusions: The effect of high alcohol consumption on incidence of proteinuria was different between males and females. The association was J-shaped in female and U-shaped in males, respectively, suggesting that females were more vulnerable to alcohol than males.

Funding: Government Support - Non-U.S.
FR-PO519
Iron Status and Mortality Risk in Diabetic and Non-Diabetic Veterans with CKD Monique E. Chu,1,2 Jared Hansen,1,3,4 Helena B. Peters,1,5 Brian C. Sauer,1,2 Veterans Health Administration, Salt Lake City, UT;1 University of Utah, Salt Lake City, UT.

Background: The mortality risk associated with abnormal iron balance has not been compared between diabetic and non-diabetic CKD populations.

Methods: We performed a historical cohort study using the Veterans Affairs Informatics and Computing Infrastructure. We identified a pre-dialysis CKD cohort (MDRD eGFR <60 mL/min/1.73 m²) with at least one set of iron indices between 2006-2015. The clinical characteristics were determined from the ICD-9 codes and laboratory data during the baseline period, defined as the year preceding the first available iron indices. Patients with ESRD, genetic and chronic disorders affecting iron metabolism were excluded. The cohort was divided into 4 iron groups based on the joint quartiles (Q) of transferrin saturation (Tsat) and ferritin: functional iron deficiency (FID), 1st Tsat Q + 3rd-4th ferritin Qs; Low Iron (LI), 1st Tsat+ ferritin Qs, High Iron (HI), 4th Tsat-ferritin Qs; and Reference (R), 2nd-3rd Tsat-ferritin Qs. Matching weights were used to determine the effects of FID, HI, and LI on all-cause mortality, using R as the reference. Diabetes was examined as a potential effect modifier.

Results: Of the 1,159,371 Veterans with CKD, 148,611 met the inclusion criteria. The meanSD for age and eGFR were 72±11 years and 43±11 mL/min/1.73 m², respectively. The median (IQR) Tsat and ferritin values were 20 (14, 26)% and 119 (64, 196) ng/mL. Of the study cohort, 42% could not be categorized into any of the 4 iron groups. In the remaining 83,439 Veterans, the prevalence for FID, HI, LI, and R were 13%, 17%, 20%, and 50%, respectively. After matching weights were implemented, the covariates were evenly distributed among the iron groups. During the meansSD follow-up period of 4.0±2.7 years, FID exhibited the greatest risk for all-cause mortality [Risk Ratio, RR (95% CI); 1.21 (1.17, 1.25)], after being stratified by the diabetes status and matching for age, sex, BMI, dyslipidemia, eGFR, albumin, hemoglobin, eGFR, and CV history. The RRs for mortality with HI and LI were similarly increased, 1.09 (1.06, 1.13). The association between iron status and mortality risk was not modified by the diabetes status.

Conclusions: Abnormal iron status, particularly FID, is associated with increased all-cause mortality risk in pre-dialysis CKD, regardless of the diabetes status. Further studies are needed to investigate the underlying mechanism.

Funding: Veterans Affairs Support, Private Foundation Support

FR-PO521
Functional Iron Deficiency and Incident Diabetes Risk in US Veterans with Pre-Dialysis CKD Monique E. Chu,1 Jared Hansen,1,3,4 Helena B. Peters,1,5 Brian C. Sauer,1,2 Veterans Health Administration, Salt Lake City, UT;1 University of Utah, Salt Lake City, UT.

Background: While the association between iron overload and diabetes is well established, the possible adverse metabolic effect of iron deficiency, both functional and absolute, has not been investigated in any population, including those with CKD.

Methods: We performed a historical cohort study using the national data from the Veterans Affairs Informatics and Computing Infrastructure. We identified a non-diabetic, pre-dialysis CKD cohort (MDRD eGFR <60 mL/min/1.73 m²) with at least one set of iron indices between 2006-2015. The clinical characteristics were determined from the ICD-9 codes and laboratory data during the baseline period, defined as the year preceding the first available iron indices. Patients with diabetes, ESRD, genetic and chronic disorders affecting iron metabolism were excluded. The cohort was divided into 4 iron groups based on the joint quartiles (Q) of transferrin saturation (Tsat) and ferritin: functional iron deficiency (FID), 1st Tsat Q + 3rd-4th ferritin Qs; Low Iron (LI), 1st Tsat+ ferritin Qs, High Iron (HI), 4th Tsat-ferritin Qs; and Reference (R), 2nd-3rd Tsat-ferritin Qs. Incision diabetes was determined by the ICD-9 codes. Matching weights were used to determine the effect of iron status on incident diabetes, using R as the comparison group.

Results: Of the 1,159,371 Veterans with CKD, 68,728 met the inclusion criteria. The meanSD for age and eGFR were 74±12 years and 43±11 mL/min/1.73 m², respectively. The median (IQR) Tsat and ferritin values were 18 (13, 23)% and 98 (53, 150) ng/mL. Of the study cohort, 44% could not be categorized into any of the 4 iron groups. In the remaining 38,428 Veterans, the prevalence for FID, HI, LI, and R were 12%, 21%, 20%, and 47%, respectively. After matching weights were implemented, the covariates were evenly distributed among the iron groups. During the meansSD follow-up period of 4.0±2.7 years, only FID was associated with increased risk for incident diabetes [Risk Ratio, RR (95% CI); 1.20 (1.09, 1.33)], after successful matching for age, sex, race, BMI, hyperlipidaemia, CV history, albumin, hemoglobin, and eGFR. The RRs for HI and LI were 0.98 (0.90, 1.07) and 1.04 (0.95, 1.13), respectively.

Conclusions: FID, but not absolute iron deficiency, is associated with increased risk for incident diabetes in CKD. Further studies are needed to investigate the underlying mechanisms.

Funding: Veterans Affairs Support, Private Foundation Support

FR-PO522
Review of Safety of IV Iron Therapy in Patients with Non-Dialysis CKD (CKD-ND) Vikki M. Meyer,1 Richard P. Cooper,2 Sunil Bhandroid.1 1HEY Hospitals, Hull, United Kingdom;2 Hull and East Yorkshire Hospitals NHS Trust and Hull York Medical School, East Yorkshire, United Kingdom;3 Hull and East Yorkshire NHS Trust, Hull, United Kingdom.

Background: Anaemia in patients with Chronic Kidney Disease not on dialysis therapy (CKD-ND) is common, and often necessitates the use of intravenous iron products to correct both functional and absolute iron deficiency and iron deficiency anaemia. There has been a large increase in use but concerns on safety have been correctly raised. JAMA highlighted a high rate of 'anaphylaxis' in parenteral iron administration and mortality related to anaphylaxis. Short term reactions are known to occur including acute anaphylactic and lable iron reactions (Fischbahn effect) while longer term effects include elevated oxidative stress, possible increased risk of infections, and risk of iron overload.

Methods: This retrospective observational single-centre study, examined our experience of short term adverse effects with parenteral iron administration in CKD-ND using two preparations, Monofer and Cosmofer. Our database recorded patients’ demographics, iron administered, baseline haemoglobin, iron parameters, clinical observations and side effects. A total of 909 doses of Monofer (1g-1.5g) and 870 doses of Cosmofer (1g-1.5g) were administered to 1271 patients with a mean age of 68.67y for Cosmofer and 65.6y for Monofer, with no known allergies.

Results: Cosmofer: a total of 1 anaphylactic event in 870 doses (0.11%) occurred and infusion discontinued due to hypotension and respiratory distress. Other reactions consisted of headache (2), diaphoresis (1), vomiting (1), flushing (2) and numbness (1). A total of 5 reactions, vomiting (1), lethargy (1), constipation (1), flare up eczema (1) and one collapse requiring discontinuation of infusion, hydrocortisone, oxygen support, but no other intervention. Reactions requiring drug discontinuation were Cosmofer, 1 in 870 doses; and Monofer, 1 in 899 doses, which incidentally was the same patient in both cases.

Conclusions: Hyper-sensitivity reactions can occur in anyone receiving intravenous iron and at any time. Vigilance during administration is important and in the immediate 30 minutes following the infusion as per EMA guidelines. At present the balance between the benefits and the risks remains in favour of iron replacement and patients should be reassured until new data is available but care should be taken. More studies are required to delineate the short and longer term safety of iron therapy.

Funding: Government Support - Non-U.S.
FR-PO523
Serum Fibroblast Growth Factor-23 Levels Are Associated with an Increased Risk of Developing Anemia in Patients with Non-Dialysis CKD

Methods: Serum Fibroblast growth factor-23 (FGF23) is an established biomarker of aluminum accumulation in patients with chronic kidney disease (CKD). Several cross-sectional studies have suggested possible association between FGF23 and anemia in these patients. Thus, we further explored this relationship and examined whether FGF23 levels can predict the future development of anemia in a large-scale prospective cohort study.

Background: Among 2,238 patients with non-dialysis CKD enrolled in the KoreaN cohort study for Outcome in patients With Chronic Kidney Disease (KNOW-CKD), 2,089 patients who measured hemoglobin, hepcidin, iron profiles and intact FGF23 (iFGF23) level were included in the analysis. Anemia was defined as a hemoglobin level of < 13.0 g/dL in male and < 12.0 g/dL for female, respectively.

Results: The mean age was 53.6 ± 12.2 years and 1,275 (61.0%) patients were males. At baseline, anemia was found in 925 (44.3%) patients. Log iFGF23 significantly correlated with hepcidin, but inversely with iron profiles and hemoglobin. A multivariate logistic regression analysis showed that log iFGF23 was independently associated with anemia (odds ratio [OR], 1.12, 95% confidence interval [CI], 1.03-1.23, P = 0.01). Among 1,164 patients without baseline anemia, 295 (25.3%) patients developed anemia during a median follow-up duration of 21 (interquartile range, 7-38) months. In the fully adjusted multivariable Cox models, risk of developing anemia was significantly higher in the 3rd (hazard ratio [HR], 1.74; 95% CI, 1.17-2.59; P = 0.007) and 4th (HR, 1.73; 95% CI, 1.15-2.59; P = 0.02) quartile of iFGF23 as compared to the 1st quartile. Similar association was observed in a model when iFGF23 was treated as a continuous variable.

Conclusions: We showed that high serum iFGF23 levels are associated with an increased risk of developing anemia in patients with non-dialysis CKD. Our findings suggest that serum iFGF23 levels may emerge as an independent predictor of anemia.

FR-PO524
Serum 1,25 Dihydroxyvitamin D Is Independently Associated with Erythropoietin Deficiency and Endogenous Erythropoietin Resistance in Patients with CKD

Methods: Serum vitamin D levels were measured in 409 patients with CKD (glomerular filtration rate [eGFR] < 60 ml/min/1.73m2) who were not on dialysis therapy. Patients on exogenous EPO therapy and patients with iron deficiencies were excluded. Endogenous EPO resistance was assessed by calculating the ratio of endogenous EPO to hemoglobin (Hb)

Background: Erythropoietin (EPO) deficiency and resistance to endogenous EPO is a significant pathophysiologic feature of anemia in chronic kidney disease (CKD). 1,25 dihydroxyvitamin D [1,25(OH)2D] deficiency is known to contribute to anemia of CKD. We aimed to investigate the associations between serum 1,25(OH)2D, EPO deficiency and endogenous EPO resistance in patients with CKD.

Results: In univariate analysis, serum 1,25(OH)2D was correlated with the Hb level (r = 0.705, P < 0.001), endogenous EPO level (r = 0.254, P < 0.001) and the endogenous EPO/Hb ratio (r = -0.132, P = 0.007). Multiple regression analysis revealed that the serum 1,25(OH)2D level remained significantly associated with the Hb level (β = -0.530, P < 0.001), endogenous EPO level (β = 0.127, P = 0.025) and the endogenous EPO/Hb ratio (β = -0.106, P = 0.035), even after adjusting for other confounding factors, including the levels of parathyroid hormone and the inflammatory marker C-reactive protein.

Conclusions: The serum 1,25(OH)2D level exhibited significant associations with anemia, EPO deficiency and endogenous EPO resistance in CKD patients. These associations were independent of secondary hyperparathyroidism and inflammation status.

FR-PO525
Serum Fibroblast Growth Factor-23 Levels Are Associated with an Increased Risk of Developing Anemia in Patients with Non-Dialysis CKD

Methods: Serum Fibroblast growth factor-23 (FGF23) is an established biomarker of aluminum accumulation in patients with chronic kidney disease (CKD). Several cross-sectional studies have suggested possible association between FGF23 and anemia in these patients. Thus, we further explored this relationship and examined whether FGF23 levels can predict the future development of anemia in a large-scale prospective cohort study.

Background: Among 2,238 patients with non-dialysis CKD enrolled in the KoreaN cohort study for Outcome in patients With Chronic Kidney Disease (KNOW-CKD), 2,089 patients who measured hemoglobin, hepcidin, iron profiles and intact FGF23 (iFGF23) level were included in the analysis. Anemia was defined as a hemoglobin level of < 13.0 g/dL in male and < 12.0 g/dL for female, respectively.

Results: The mean age was 53.6 ± 12.2 years and 1,275 (61.0%) patients were males. At baseline, anemia was found in 925 (44.3%) patients. Log iFGF23 significantly correlated with hepcidin, but inversely with iron profiles and hemoglobin. A multivariate logistic regression analysis showed that log iFGF23 was independently associated with anemia (odds ratio [OR], 1.12, 95% confidence interval [CI], 1.03-1.23, P = 0.01). Among 1,164 patients without baseline anemia, 295 (25.3%) patients developed anemia during a median follow-up duration of 21 (interquartile range, 7-38) months. In the fully adjusted multivariable Cox models, risk of developing anemia was significantly higher in the 3rd (hazard ratio [HR], 1.74; 95% CI, 1.17-2.59; P = 0.007) and 4th (HR, 1.73; 95% CI, 1.15-2.59; P = 0.02) quartile of iFGF23 as compared to the 1st quartile. Similar association was observed in a model when iFGF23 was treated as a continuous variable.

Conclusions: We showed that high serum iFGF23 levels are associated with an increased risk of developing anemia in patients with non-dialysis CKD. Our findings suggest that serum iFGF23 levels may emerge as an independent predictor of anemia.
FR-PO527

Lack of Nephrologist Follow-Up after Nephrectomy for Kidney Cancer

Michael O. McCusker,1 Naima Carter-Montoe,1,4 Eric P. Cohen,1,2
1University of Maryland, Baltimore, MD; 2University of Maryland Medical Center, Baltimore, MD; 3Medicine, Baltimore VAMC, Baltimore, MD; 4School of Public Health, Baltimore, MD

Background: Medical renal disease often accompanies kidney cancer. The American College of Pathology recommends that the tissue surrounding a resected kidney cancer be examined to identify significant medical renal disease, much as is done for a kidney biopsy done for non-cancerous disease. This can inform regarding pathogenesis of kidney cancer and is immediately important for nephrologic management of patients who have had nephrectomy, partial or complete.

Methods: We tested a prospectively maintained database at the Baltimore Veterans Affairs Medical Center to determine the adequacy of follow-up in such cases. Sixty six patients were identified from 2010 through 2016, who had at least six months of follow-up after surgery.

Results: All but one were men and 46 were black. The average age was 64 +/- 7 (sd). Forty-one had total and twenty-seven had partial nephrectomies. Two patients had partial followed by contralateral total nephrectomy. Thirteen patients with oncocytomas were not included. In the pathology reports, six had no comment regarding the non-cancerous renal tissue. Eight more reported no abnormality, but twenty four showed moderate or worse medical renal disease of the non-cancerous renal tissue. As reported by others, micro and macrovascular disease were present in the non-cancerous tissue of the majority of cases. The average preoperative serum creatinine (s creat) of the patients was 1.3 mg/dl +/- 0.6 (sd). The average discharge s creat was 1.7 mg/dl +/- 0.9 (sd). (p<0.001 vs preoperative s creat). The average s creat at one year was 1.8 mg/dl +/- 1.2 (sd). Only 23 of these 66 patients had any nephrology follow-up after their surgery, and only 13 had measurement of proteinuria.

Conclusions: We conclude that although Pathologists usually provide some report of the non-cancerous renal tissue, this is still not always done. The majority of cases show significant medical renal disease in the surrounding non-cancerous kidney. Importantly, nephrologic follow-up of these patients with chronic kidney disease is deficient. Because of the known risks of CKD, it is prudent to ensure Nephrologist follow-up for patients who have had a nephrectomy for kidney cancer.

FR-PO528

Independent Associations of eGFR and Albuminuria with Cancer Incidence

Yejin Mok, Shoshana Ballew, Yingying Sang, Josef Coresh, Corinne Joshua, Elizabeth A. Platz, Kunihiro Matsushita, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Background: Cancer is a potential complication of chronic kidney disease (CKD) recently attracting attention. However, no previous studies have simultaneously investigated two key CKD measures, estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (ACR), for the risk of cancer incidence.

Methods: In 9,191 participants without prevalent cancer from the Atherosclerosis Risk in Communities (ARIC) study in 1996 to 1998, the associations of eGFR (based on creatinine and cystatin C) and ACR with overall and site-specific cancer incidence were evaluated with Cox proportional hazards model adjusted for conventional lifestyle and clinical risk factors for CKD and/or cancer.

Results: During a median follow-up of 14.7 years, 2,063 incident cancer cases occurred in 117,420 person years. eGFR was not associated with total cancer incidence after adjusting for risk factors. ACR was possibly positively associated after adjustment for age, sex, and race, but further adjustment for other potential confounders attenuated the association. By cancer site, a higher ACR was significantly associated with increased risk of lung and hematopoietic cancers (hazard ratio per 8-fold higher ACR was 1.29 [1.08-1.53] and 1.27 [1.02-1.59], respectively). The results were largely consistent in subgroups of sex, race, and current smoking status.

Conclusions: Kidney measures, particularly higher albuminuria, were modestly associated with cancer incidence. The association of ACR was especially robust for lung cancer and this finding is consistent with previous studies. Mechanisms underlying this association are not clear, and further studies exploring potential mechanism are needed.

FR-PO529

Prevalence and Mortality of CKD in Lymphoma: A Large Retrospective Cohort Study

Masamitsu Ubukata, Masaki Haru, Teruhiro Fuji, Akihito Ohta, Division of Nephrology, Department of Medicine, Tokyo Metropolitan Komagome Hospital, Bunkyo-ku, Japan

Background: The prevalence, incidence, and mortality of chronic kidney disease (CKD) in lymphoma patients have not been fully understood. The objective of this study was to evaluate the prevalence of CKD and its contribution to mortality in patients with lymphoma.

Methods: This was a retrospective cohort study on 429 consecutive lymphoma patients who were admitted or regularly visited our hospital from January 2013 to October 2016. The prevalence of CKD at enrollment was evaluated according to the modified Kidney Disease: Improving Global Outcomes (KDIGO) and proteinuria category. Dipstick proteinuria was classified into three grades: A1, A2, and A3+. eGFR (mL/min/1.73 m²) was classified into six stages: G1 for ≤ 90, G2 for 60–89, G3a for 45–59, G3b for 30–44, G4 for 15–29, and G5 for < 15. CKD was defined as eGFR < 60 mL/min/1.73 m² and/or proteinuria ≥ A1 that was sustained at least for 3 months. The severity of CKD was classified into the following four categories: no risk for G1A1 and G2A1; moderate risk for G1A2, G2A2, and G3A1; high risk for G1A3, G2A3, G3A2, and G3B1; and very high risk for G3A3, G3B2, G3B3, and G5. The cumulative mortality rate was estimated using the Kaplan-Meier method, with stratification into two groups based on the presence or absence of CKD. Further, a multivariate Cox proportional hazards regression model was used to calculate the hazard ratio (HR) and its 95% confidence interval (CI) for all-cause mortality, after adjustments for age, gender, pathology type, clinical stage of lymphoma, presence or absence of diabetes mellitus, hypertension, and cardiovascular disease.

Results: The mean follow-up period was 3.1 ± 1.0 years and the prevalence of CKD at study enrollment was 34.5%. The cumulative mortality rate was 20.7% and was significantly higher in the CKD group than in the group without CKD (36.4% vs. 18.9%, p < 0.02). In the multivariate analysis, mortality was significantly associated with CKD (HR 1.61; 95% CI 1.03–2.50), and this association was the most robust with very high risk CKD (HR 6.32; 95% CI 2.41–14.54).

Conclusions: CKD should be considered a risk factor for mortality among patients with lymphoma.
FR-PO530

Nephrologists’ Perspectives on Cancer Screening in Patients with CKD

Laura J. James,1,2 Germaine Wong,3 Jonathan C. Craig,4 Allison Tong.2
1None, Auambie, NSW, Australia; 2The University of Sydney, Sydney, NSW, Australia; 3Sydney School of Public Health, The University of Sydney, Westmead, NSW, Australia; 4University of Sydney/Children’s Hospital, Sydney, NSW, Australia; 5Centre for Kidney Research, Westmead, NSW, Australia.

Background: Cancer is a leading cause of morbidity and mortality in patients with chronic kidney disease (CKD). However, cancer screening practices are highly variable among nephrologists, which may reflect uncertainties around the benefits and harms of screening in this setting, and the competing risk of death from other causes. Therefore we aimed to describe nephrologists’ perspectives on cancer screening and understand the factors impacting their practice.

Methods: Semi-structured interviews were conducted with 21 nephrologists from 11 centres across Australia and New Zealand. Transcripts were analysed thematically.

Results: Five themes were identified: empowering patients to make informed decisions (respecting patient preferences, communicating evidence-based recommendations, creating awareness of consequences, preparing patients for transplantation); justifiable risk taking (avoiding undue consequences in vulnerable populations, ensuring cost effectiveness, warranted by long term immunosuppression, assurance of reasonable survival gains); prioritising current or imminent complications; ambiguity of evidence in supporting decisions (access to population-based data); and depending on a shared multidisciplinary approach (collaboration with primary health care, wary of inadequate dermatological services, generating targeted cancer preventative services).

Conclusions: Nephrologists approach decisions about cancer screening in patients with CKD based on patient preferences, assessment of risk, justifiable survival gains, and current health priorities. Evidence-based guidelines and specialist clinics that address cancer screening may support shared decision making about cancer screening in CKD.

Funding: Government Support - Non-U.S.

FR-PO531

Effectiveness of 12 Week Elbasvir/Grazoprevir (EBR/GZR) in Patients with Genotype 1 (GT1) Chronic Hepatitis C (HCV) and CKD

Flamm,3 Kowdley ,7 Steven Nwankwo,1 Bruce R. Bacon,2 Michael P. Curry,3 Steven Flamm,3 Kris V. Kowdley,7 Scott Milligan,4 Naoky Tsai.2 1Beth Israel Deaconess Medical Center, Boston, AL; 2Merck & Co, Lebanon, NJ; 3Merck Sharp & Dohme Ltd., Hoddesdon, United Kingdom; 4Northwestern Feinberg School of Medicine, Chicago, IL; 5Pharm ri mer Internation al, Bethesda, MD; 6Saint Louis University School of Medicine, Saint Louis, MO; 7Swedish Medical Center, Seattle, WA; 8Trio Health Analytics, La Jolla, CA; 9University of Hawaii, Kailua, HI.

Background: Elbasvir/grazoprevir (EBR/GZR) is recommended for use in the treatment of chronic HCV genotype (GT) 1 and 4 patients including those with renal impairment. The purpose of this study is to describe the real-world effectiveness of 12 week EBR/GZR in patients with GT1 chronic HCV and CKD.

Methods: Data were collected from US providers and specialty pharmacies through Trio Health’s disease management platform. Patients with CKD and GT1 HCV who initiated 12 week EBR/GZR therapy between Jan 28, 2016 (FDA approval) to Dec 31, 2016 were included in the analyses. CKD was defined as renal impairment of baseline eGFR <90 ml/min. Effectiveness was defined as attainment of per protocol sustained virologic response (SVR12) and liver transplant (LT); and 8 health states reflecting degree of CKD (Stages 1-5), liver fibrosis (F0-4), decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), and liver transplant (LT); and 8 health states reflecting degree of CKD (Stages 1-5), hemodialysis, and kidney transplant. Baseline patient characteristics and the proportion of TN GT1 patients achieving sustained virologic response (SVR) were collected from a real-world study of 124 TN GT1 patients with CKD who were treated with EBR/GZR between January and October 2016, using data from the TRIO Network. Data on the rate of progression of hepatic and renal disease, annual costs for each health state, utilities, and risk of cardiovascular events were obtained from published literature. The primary outcome was the incremental cost-utility ratio (ICUR); secondary outcomes included the lifetime incidence of DC, HCC, LT, ESLD mortality, and life expectancy.

Results: TN GT1 patients who received EBR/GZR were less likely to develop DC or HCC, receive a liver transplant, or die of liver-related causes compared to untreated patients, with a 2.4-year increase in life expectancy. Discounted costs and QALYs were both greater in patients receiving EBR/GZR compared to no treatment, with an ICUR of $5,897 QALY.

Conclusions: The model projected that EBR/GZR significantly reduces the incidence of liver disease complications compared to no treatment, using real-world patient characteristics and treatment outcomes. In addition, EBR/GZR was cost-effective for the treatment of CHC in patients with CKD.

Funding: Commercial Support - Merck & Co
FR-PO534

Hospital Acquired Infections after Major Surgery among Patients with Clinical Comorbidities: The Stockholm Creatinine Measurements (SCREAM) Project Junichi Ishigami,2 Marco Trevisan,3 Hong Xu,4 Josef Coresh,5 Kunihiro Matsushita,6 Juan J. Carrero.7

Methods: Using data from a random, sub-cohort of 958 older adults enrolled in the Cardiovascular Health Study, we evaluated whether spot urine uromodulin levels are associated with risk of infectious hospitalizations using Poisson and Cox regression analysis with several nested models.

Results: The mean age of participants was 78.1 years, mean eGFR was 70.9 ml/min/1.73m2 and 39.5% were men. The median (IQR) urinary uromodulin was 25.88 (17.25, 38.83) units. There were 592 infections hospitalizations among 362 participants during a median follow up of 9.2 years. Rates of hospitalizations (per100 person-years) decreased across higher quartiles of uromodulin: 7.4, 6.0, 5.8, and 5.6. Each doubling of uromodulin was associated with 20% lower number of infectious hospitalizations (Rate Ratio 0.80, 95% CI 0.66, 0.97) when adjusted for demographics, comorbidities and laboratory variables. Uromodulin levels were not associated with the hazard of first infection hospitalization or in a Cox regression when a model multiple events per person, each doubling of uromodulin was associated with 23% lower risk of infectious hospitalization (HR 0.77, 95% CI 0.64, 0.97) in adjusted analyses.

Conclusions: Higher levels of uromodulin are associated with lower rates of infection, a global immune defense that may not be limited to urinary tract infections alone.

Funding: NIDDK Support, Other NIH Support - NHLBI

Table 1: Prevalence of clinical comorbidity and relative risk of HAIs

| Clinical Comorbidity | % in the population | % among HAIs with (HR +95% CI) | Adjusted relative risk (95% CI) 
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease</td>
<td>20.4</td>
<td>24.1</td>
<td>1.5 (1.2-1.9)</td>
</tr>
<tr>
<td>Stroke</td>
<td>14.2</td>
<td>18.4</td>
<td>1.5 (1.2-1.9)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>22.8</td>
<td>26.3</td>
<td>1.5 (1.2-1.9)</td>
</tr>
<tr>
<td>CHF</td>
<td>13.3</td>
<td>16.6</td>
<td>1.5 (1.2-1.9)</td>
</tr>
<tr>
<td>CHD</td>
<td>12.9</td>
<td>15.8</td>
<td>1.5 (1.2-1.9)</td>
</tr>
</tbody>
</table>

The model was adjusted for each clinical comorbidity, age, sex, and type of surgery.

FR-PO535

Lactobacillus Plantarum 299v Prevents Clostridium difficile Infection in Patients Hospitalized in Nephrological and Transplantation Department Marcini Adamczak,1 Martina Parikh,3 Sylwia M. Dudzica, Agata Kujawa-Szewieczek, Katarzyna Kwiecien, Andrzezej Wieczek. Department of Nephrology, Transplantation and Internal Medicine, Medical University of Silesia, Katowice, Poland.

Background: Lactobacillus plantarum 299v (LP299v) has been introduced into the clinical practice in order to reduce gastrointestinal symptoms during antibiotic treatment. However, it remains controversial whether or not probiotics are also effective in the prevention of Clostridium difficile infections (CDI) among patients receiving antibiotics. The objective of this clinical, retrospective, single-center study was to analyze the CDI among patients receiving antibiotics and hospitalized in the period before, during and after cessation of LP299v use, as a prevention of CDI, in the nephrological and transplantation department.

Methods: Among 5341 patients hospitalized in the nephrological and transplantation department during three years 40 patients with CDI were diagnosed and enrolled in this study. From November 2013 to December 2014 prevention of CDI with oral use of LP299v was performed in all patients treated with antibiotics and after organ transplantation or receiving immunosuppressive drugs for any other reasons. For the further analysis the observation period was divided into three twelve-months periods: before, during LP299v use as the prophylactic manoeuvre against CDI and after cessation of such a prophylaxis

Results: A significant (p=0.001) reduction of the number of cases with CDI was found during LP299v use (period 2) (n=2; 0.11% of 1791 hospitalized patients) compared two others periods i.e. before and after cessation of such a prophylaxis (n=21; 1.21% of 1742 hospitalized patients and period and n=17; 0.94% of 1808 hospitalized patients, respectively).

Conclusions: Routine use of Lactobacillus plantarum 299v during treatment with antibiotics may prevent Clostridium difficile infection in the nephrological and transplantation department.

Funding: Government Support - Non-U.S.

FR-PO536

Plasma Biomarkers and Response to Intensive Blood Pressure Control: The ACCORD Trial Gisli N.nadkaRR,1 Martine Pollack-Zollman,1 Kim Sum Chauhan,1 Veena Rao,2 Priit Poojari,3 Aparna Saha,3 Chirag R. Parikh,3 Sharon G. Coca,1 Icahn School of Medicine at Mount Sinai, New York, NY; 2Yale University, New Haven, CT; 3Yale University and VAMC, New Haven, CT.

Background: Plasma biomarkers of inflammation [tumor necrosis factor 1 (TNFRI)]; monococyte chemotactic protein (MCP1) and interleukin 18 (IL18), renal injury [Kidney Injury Molecule 1 (KIM1) and fibrosis [YKL40] are associated with estimated glomerular filtration rate (eGFR) decline. There are limited data on association between these markers and response to intensive systolic blood pressure (SBP) control. We examined the relationship between baseline plasma biomarker levels and longitudinal SBP change in the ACCORD trial.

Methods: We used a multiplex platform to measure plasma biomarkers in baseline plasma specimens from randomly selected ACCORD trial participants with type 2 diabetes in intensive SBP arm (goal <120; n=260) vs. standard SBP arm (goal <140; n=269). We estimated the association between longitudinal SBP change and baseline biomarker tertiles after stratifying by intensive vs. standard SBP arm using linear mixed models.

Results: Mean age was 61.7 years, 46.6% were female and baseline eGFR was 88 ml/min. There were no significant differences between the intensive and standard SBP arm. Participants in the third tertile of KIM-1 had a higher SBP at baseline after adjusting for eGFR, UAER and demographics [-3.7 mmHg; SE 1.6]. After randomization, participants in the third tertile of KIM-1 in intensive SBP group had a smaller change in SBP compared to the first tertile [-5.1 mmHg; SE 1.5; p<0.001]. There were no associations with other biomarkers and SBP change in either arm. (Figure 1)

Conclusions: Higher levels of plasma KIM-1 at baseline are associated with attenuated SBP changes with intensive control. This findings indicate that subclinical renal tubular injury is associated with poorer response to intensive SBP control, even in persons with normal eGFR.

Funding: NIDDK Support
FR-PO537


Background: The control group in SPRINT targeted a blood pressure range of 130-140mmHg, which required down-titration of antihypertensive therapy when blood pressure was below 130mmHg on a single visit, or below 135mmHg on two consecutive visits. Such an approach would not be considered routine clinical care. We hypothesized that non-standard discontinuations of antihypertensive therapy in the control group, may have inflated the events rates and exaggerated the reported treatment effect.

Methods: Standard withdrawal of antihypertensive agents was defined as a withdrawal for systolic blood pressure less than 100mmHg at the current visit, or a related, related adverse event occurring between the previous and current visit. We evaluated the association of antihypertensive withdrawal with CV events on follow-up using the Cox proportional-hazards regression. We repeated the primary analysis comparing the time to first occurrence of a primary outcome between treatment groups, adjusting for non-standard withdrawal in blood pressure medication, treated as time dependent covariates, to estimate the effect of intensive versus standard blood pressure control.

Results: Non-standard withdrawal of antihypertensive agents occurred in 9.3% of patient visits in the control group, compared with 5.1% in the treatment group (p < 0.001), and was associated with an increased risk of the composite outcome, which was significant for 2 follow-up periods (HR 1.65; 95% CI, 1.26-2.16 for initial 3 months, HR 1.47; 95% CI, 1.12-1.95 for 3 to 6-month period), which was independent of blood pressure effect. After adjusting for non-standard withdrawal/reduction of antihypertensive agents, the intensive-treatment group was associated with a lower risk of the composite outcome measure, compared to standard care (HR 0.81; 95% CI, 0.67 to 0.97).

Conclusions: Targeting a systolic BP range (130-140mmHg) in the control group of SPRINT, rather than a conventional blood pressure threshold (<140mmHg), resulted in withdrawals of antihypertensive medications that would not be considered routine care. An analysis that adjusted for non-standard withdrawal of blood pressure medications during the trial resulted in a significant, but diminished, treatment effect of intensive blood pressure control (HR 0.81 versus 0.75), and the effect on heart failure became non-significant.

FR-PO538

Influence of Baseline Diastolic Blood Pressure (DBP) Level on the Effects of Intensive Blood Pressure Lowering on Cardiovascular (CV) Outcome in SPRINT Srinidhi Bedilu,1 Glen M. Chertow,2 Alfred K. Cheung,3 Mahboob Rahman,3 Tom Greene,4 Guo Wei,5 William E. Haley,5 William C. Cushman,4 Paul K. Whelton,6 Univ Utah, SLC, UT; 2Stanford Univ, Palo Alto, CA; 3Case Western Reserve University, Cleveland, OH; 4VAMC, Memphis, TN; 5Mayo Clinic, Jacksonville, FL; 6Tulane Univ, New Orleans, LA. Group/Team: For SPRINT Research Group.

Background: Lowering systolic blood pressure (SBP) in persons with low DBP might affect tissue perfusion and thereby, risk for CV events.

Methods: SPRINT tested the effects of SBP goal < 120 vs. < 140 mm Hg on CV outcomes in 9561 participants. We tested for effect modification by baseline DBP of the intervention on primary CV outcome (a composite of non-fatal MI, ACS not resulting in MI, stroke, CHF, or CV death).

Results: Mean age was 67.9 ± 9.4 years, with 35.6 % being women and 31.5 % Black. Means ± SD baseline SBP and DBP were 139.7 ± 15.6 and 78.1 ± 11.9 mm Hg, respectively. There were 562 primary outcome events over 29,277 person-years of follow-up. Adjusted for age, gender, race and the intervention arm, baseline DBP had a U-shaped association with the primary outcome (figure, panel A). Intensive SBP treatment reduced the risk of the primary outcome vs. standard treatment hazard ratio [HR] 0.76, 95% CI 0.64 to 0.89). P-value for the linear treatment by baseline DBP interaction did not approach statistical significance for the primary outcome (p = 0.85). HR for primary outcome across DBP quintiles are summarized in figure, panel B. HR for the primary outcome was 0.78 (95% CI 0.57 to 1.07) within the lowest DBP quintile and 0.74 (95% CI 0.61 to 0.90) within the upper four DBP quintiles (interaction p-value = 0.78).

Conclusions: While baseline low DBP was associated with increased risk of CV events, there is no evidence that the beneficial effects of the SPRINT intervention were modified by the level of baseline DBP.

Funding: NIDDK Support, Other NIH Support - NHLBI

FR-PO539

PTH, FGF23, and Effects of Intensive Blood Pressure Lowering in SPRINT Participants with CKD Charles Ginsberg,1 Timothy Craven,2 Michel Chonchol,3 Alfred K. Cheung,3 Mark J. Sarnak,1 Anthony A. Killeen,4 Kalani L. Raphael,5 Udayan Y. Bhatt,6 Jing Chen,7 Glenn M. Chertow,8 Barry I. Freedman,9 Suzanne Oparil,2 Barry M. Wall,7 Clinton B. Wright,1 Michael Shlipak,4 Joachim H. Ix,10 NINDS, Rockville, MD; 2The Ohio State University, Dublin, OH; 3University of Minnesota, Minneapolis, MN; 4VA Salt Lake City Health Care System, Salt Lake City, UT; 5San Francisco VA Medical Center, San Francisco, CA; 6VA Medical Center, Memphis, TN; 7University of Alabama at Birmingham, Birmingham, AL; 8Wake Forest University School of Medicine, Winston-Salem, NC; 9Tidale School of Medicine, New Orleans, LA; 10Stanford University School of Medicine, Palo Alto, CA; 11Tfts Medical Center, Boston, MA; 12UCSD, San Diego, CA; 13University of Utah, Salt Lake City, UT; 14University of Anschutz Medical Center, Aurora, CO.

Background: Serum FGF23 and PTH levels are elevated in CKD patients, and are associated with CVD events. Prior work has demonstrated that the association with CVD events may be modified by tubular resistance to FGF-23, thereby giving insight into kidney tubule function above and beyond eGFR. We hypothesized that the therapeutic benefits of intensive blood pressure (BP) control may also be modified by tubular resistance to PTH and FGF-23.

Methods: Among 2486 SPRINT participants with baseline eGFR < 60 ml/min/1.73m2, we measured intact FGF23 and intact PTH. We evaluated whether the effect of randomization to intensive vs. standard BP arms on CVD, HF events, and all-cause mortality was modified by serum PTH or FGF-23 levels.

Results: Mean age was 73 yrs, 60% were female, mean eGFR was 46 ml/min/1.73m2. Median [IQR] iFGF23 was 66 [52, 88] pg/ml, and median iPTH was 48 [35, 67] pg/ml. PTH modified the effect of intensive BP lowering for CVD events (p = 0.01) and HF (p = 0.003). In stratified analyses, intensive BP lowering was associated with lower risk of CVD (HR 0.68, 95% CI 0.45-1.00) and HF (HR 0.41, 95% CI 0.20-0.85) among patients with PTH >48 pg/ml; but not those with PTH <48 pg/ml. FGF23 did not modify the association of intensive BP control with any of the 3 outcomes.

Conclusions: Lower serum PTH levels may identify a subset of CKD patients who receive the greatest benefit from intensive BP lowering. Further work is necessary to elucidate if tubular resistance to PTH is the mechanism responsible for these findings.

Funding: NIDDK Support, Other NIH Support - NHLBI, NIA, NINDS, National Center for the Advancing Translational Sciences., Veterans Affairs Support.
Effect of Renal Function and Obstructive Sleep Apnoea on Nocturnal Blood Pressure in CKD Stage 3-4

**Background:** Many patients with chronic kidney disease (CKD) suffer from high nocturnal blood pressure (BP) and lack of nocturnal BP decrease. These are known to be associated with poorer outcome related to cardiovascular morbidity and mortality. Reasons for high nocturnal BP in patients with CKD are not known. In this case control study, we studied the effect of obstructive sleep apnoea (OSA) and renal function on nocturnal BP in CKD subjects.

**Methods:** Seventy patients with CKD 3-4 (eGFR 15-59 mL/min) from the Renal Outpatients Clinic, Holstebro Hospital were compared with 56 healthy age-matched controls. 24h ambulatory BP monitoring, blood samples (creatinine) and cardio respiratory monitoring (Apnoea Hypopnea Index, AHI) were performed in all participants.

**Results:** Non-dipping was seen in 44% (n=31) of CKD3-4 cases and 18% (n=10) of healthy controls. In this group had a more pronounced association (HR: 2.37, p<0.001). Among children with G (CKD), 44% were normotensive, 6% had daytime only HT, 20% had nocturnal only HT and 6% had diurnal HT. In models adjusting for age, gender and race, among NG children, presence of nocturnal only HT was significantly associated with outcome compared to normotensive children (HR: 1.80, p=0.02). The presence of diurnal HT in this group had a more pronounced association (HR: 2.37, p<0.001). Among children with G CKD, the presence of nocturnal only HT or daytime only HT was not significantly associated with outcome (HR: 1.60, p=0.30 and HR: 0.61, p=0.7), respectively, while the presence of diurnal HT was strongly associated with outcome (HR: 4.38, p<0.001).

**Conclusions:** Nocturnal hypertension is associated with a significantly faster decline in kidney function (GFR decline or RRT) when compared to normotensive patients with CKD. This outcome is even more pronounced in patients with diurnal HT. This confirms the utility of ABPM in patients with CKD. Identifying and controlling both daytime and nocturnal HT using ABPM may improve outcomes and delay CKD progression in this population.

**Funding:** NIDDK Support

---

**FR-PO542**

Nocturnal Hypertension Is Common and Is Associated with CKD Progression in the Chronic Kidney Disease in Children Study (CKiD) Cohort

**Background:** Hypertension (HT) affects nearly half of all children with chronic kidney disease (CKD) and is a major modifiable cause of end organ disease. 24 hour ambulatory blood pressure monitoring (ABPM) has demonstrated the significance of nocturnal HT on CKD progression among adults. In children with CKD, the effect of nocturnal HT on CKD progression is unknown.

**Methods:** Stratified by CKD etiology, we investigated the relationships between daytime or nocturnal HT (or both), and a composite outcome (defined as RRT or a 50% decline in eGFR) among CKD participants using Cox proportional hazards models. Daytime and nocturnal HT were defined as mean BP >95th percentile and/or load >25% for either systolic or diastolic BP within wake or sleep periods, respectively.

**Results:** 1195 ABPM studies from 693 CKiD participants were reviewed. In 501 children with non-glomerular (NG) CKD, 40% had nocturnal hypertension, 7% had daytime only HT, 19% had normal nocturnal HT, and 34% had diurnal HT. In 192 children with glomerular (G) CKD, 44% were normotensive, 6% had daytime only HT, 20% had normal nocturnal HT and 30% had diurnal HT. In models adjusting for age, gender and race, among NG children, presence of nocturnal only HT was significantly associated with outcome compared to normotensive children (HR=1.80, p<0.001). The presence of diurnal HT in the CKiD cohort had a more pronounced association (HR=2.37, p<0.001).

**Conclusions:** Children with G CKD, the presence of nocturnal only HT or daytime only HT was not significantly associated with outcome (HR: 1.60, p=0.30 and HR: 0.61, p=0.7), respectively, while the presence of diurnal HT was strongly associated with outcome (HR: 4.38, p<0.001).

**Funding:** NIDDK Support

---

**FR-PO543**

Ambulatory Blood Pressure and CKD Progression in the CKiD Cohort

**Background:** We evaluated mean arterial pressure (MAP) by ambulatory blood pressure monitoring (ABPM) in the CKiD cohort to investigate if low-normal MAP (<50th %ile) was associated with a decreased rate of CKD progression compared to conventional (50th-90th %ile) or high (>90th %ile) MAP.

**Methods:** The primary outcome was time to renal replacement therapy (RRT) or 50% decline in eGFR. The primary exposure was time-variant MAP. Analyses were stratified by glomerular and non-glomerular diagnosis. 3 Cox models were fit with conventional MAP as the primary exposure; another model was fit with low-normal MAP. All models were stratified by glomerular and non-glomerular diagnosis. The HR for the outcome compared to conventional MAP (95%CI: 1.35, 4.57); the HR for low-normal MAP was protective (0.42, 95%CI: 0.15, 1.15) (Figure 1). The HR for non-glomerular CKD with low normal MAP was 1.76 (95%CI: 1.25, 2.47) and 0.71 (95%CI: 0.42, 0.71) for low-normal MAP. After adjusting for other results were similar. Adjustment for proteinuria reduced the effect size but not the direction of association or glomerular significance.

**Conclusions:** Ambulatory MAP <90th %ile was associated with a more rapid progression of CKD in children. The benefit of MAP <50th %ile was slightly reduced after adjustment for proteinuria. The prevalence of ACEi/ARB use was lower among those with high MAP indicating potential for benefit with therapy.

**Funding:** NIDDK Support

---

**FR-PO540**

Effect of Renal Function and Obstructive Sleep Apnoea on Nocturnal Blood Pressure in Patients with CKD Stage 3-4

**Background:** Hypertension, Holstebro, Denmark

**Methods:** Effect of Renal Function and Obstructive Sleep Apnoea on Nocturnal Blood Pressure in Patients with CKD Stage 3-4

Hypertension, Holstebro, Denmark

**Background:** Many patients with chronic kidney disease (CKD) suffer from high nocturnal blood pressure (BP) and lack of nocturnal BP decrease. These are known to be associated with poorer outcome related to cardiovascular morbidity and mortality. Reasons for high nocturnal BP in patients with CKD are not known. In this case control study, we studied the effect of obstructive sleep apnoea (OSA) and renal function on nocturnal BP in CKD subjects.

**Methods:** Seventy patients with CKD 3-4 (eGFR 15-59 mL/min) from the Renal Outpatients Clinic, Holstebro Hospital were compared with 56 healthy age-matched controls. 24h ambulatory BP monitoring, blood samples (creatinine) and cardio respiratory monitoring (Apnoea Hypopnea Index, AHI) were performed in all participants.

**Results:** Non-dipping was seen in 44% (n=31) of CKD3-4 cases and 18% (n=10) of healthy controls. In this group had a more pronounced association (HR: 2.37, p<0.001). Among children with G (CKD), 44% were normotensive, 6% had daytime only HT, 20% had nocturnal only HT and 6% had diurnal HT. In models adjusting for age, gender and race, among NG children, presence of nocturnal only HT was significantly associated with outcome compared to normotensive children (HR: 1.80, p<0.001). The presence of diurnal HT in the group had a more pronounced association (HR: 2.37, p<0.001). Among children with G CKD, the presence of nocturnal only HT or daytime only HT was not significantly associated with outcome (HR: 1.60, p=0.30 and HR: 0.61, p=0.7), respectively, while the presence of diurnal HT was strongly associated with outcome (HR: 4.38, p<0.001).

**Conclusions:** Nocturnal hypertension is associated with a significantly faster decline in kidney function (GFR decline or RRT) when compared to normotensive patients with CKD. This outcome is even more pronounced in patients with diurnal HT. This confirms the utility of ABPM in patients with CKD. Identifying and controlling both daytime and nocturnal HT using ABPM may improve outcomes and delay CKD progression in this population.

**Funding:** NIDDK Support
FR-PO544

Reduction of Nocturnal Hypertension in Pediatric Renal Transplant Recipients Christine B. Sethna,1 Shari Gurusunge,1 Rachel Frank,2 Lulette Infante,2 Kevin E. Meyers,1 1Cohen Children’s Medical Center; New Hyde Park, NY; 2Cohen Children’s Medical Center, New Hyde Park, NY; 3Cohen Children’s Medical Center of New York, New Hyde Park, NY; 4The Children Hospital of Philadelphia and University of Pennsylvania, Philadelphia, PA.

Background: Nocturnal hypertension (nHTN) and non-dipper (ND) status are commonly found during ambulatory blood pressure monitoring (ABPM) in pediatric renal transplant recipients (Txp). These entities are associated with cardiovascular risk in adults. The aim was to investigate chronotherapeutic alteration of antihypertensive medication on nHTN and end-organ injury in ND Txp.

Methods: 33 ND Txp aged 5-21 with normal overall ABPM and eGFR >30 ml/min/1.73m² were randomized to intervention (enalapril, isradipine or propranolol added in the evening) or control (no medication change) in this open label, blinded endpoint clinical trial. ABPM, echocardiography for left ventricular mass index (LVMI) and pulse wave velocity (PWV) were performed at baseline, 3 and 6 months. ND was defined as a decline of <10% in average blood pressure (BP) from day to night. Differences were compared using Fisher’s, t-test and paired t-test by intention-to-treat analysis.

Results: ABPM, LVMI and PWV were similar between groups. Conversion to dipper status occurred in 43% vs 10% at 3 months (p=0.08) and 53% vs 8% (p=0.02) at 6 months for intervention and controls, respectively. Although all ABPM parameters at 3 and 6 months were lower in intervention compared with controls, only systolic night BP at 6 months showed a significant difference (114.9 ± 8.3 ± 8.3 mmHg, p=0.01). Changes over time in the intervention group are shown in the table. There were no significant changes over time in controls for ABPM, LVMI or PWV.

Conclusions: Reduction of nHTN and restoration of nocturnal dip in Txp is possible with chronotherapy. Future studies are needed with larger sample sizes to delineate the effect of improved nHTN on end-organ damage.

Funding: Private Foundation Support

FR-PO545

Ambulatory (ABP) Hypertension (HT) Over Time Is Associated with Subsequent GFR Decline in Children with CKD Joshua A. Samuels,1 Derek Ng,2 Shuai Jiang,2 Joseph T. Flynn,3 Susan L. Furth,3 Bradley A. Warady,3 Janis M. Dionne,1 1BC Children’s Hospital; University of British Columbia, Vancouver, BC, Canada; 2Johns Hopkins University, Baltimore, MD; 3McGovern Medical School at UTHHealth, Houston, TX; 4Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; 5Seattle Children’s Hospital, Seattle, WA; 6The Children’s Hospital of Philadelphia, Philadelphia, PA; 7The Children’s Mercy Hospital, Kansas City, MO.

Background: Ambulatory HT is associated with CKD stage. Longitudinal changes in ambulatory blood pressure (ABP) and their relationship to subsequent pediatric CKD progression is poorly described. We characterize changes in ABP and GFR over time in children in the CKiD cohort.

Methods: BP based on ABP and HT defined by CKiD ABP criteria. HT status could change following repeat ABP (every other year) and thus exposure varied over time. We quantified transitions from normotensive (NT) to HT, as well as the risk of progression to composite endpoint (GFR decline or 50% drop in GFR) by relative hazards (HR) using Cox proportional hazards models. Analyses adjusted for age, gender, and race and stratified by CKD diagnosis (i.e., glomerular (G=501) or non-glomerular (NG=192) etiology).

Results: A change in BP category was common. For G, 56% had HT at entry; 16% transitioned to a NT during ~6 years follow up. Of those with NT at entry, 20% transitioned to HT. For NG, 60% had HT at entry and 24% transitioned to NT. Among the 40% with NT at entry, 38% transitioned to HT. CKD progression was significantly greater during periods of HT compared to NT. Figure 1 displays the incidence of composite endpoint (GFR decline or RRT) by ABP status (HT= red; NT=blue) for G and NG CKD. Differences were significant by ABP (log rank p<0.001 for both groups). HT was associated with 2.81 times higher hazard of endpoint among children with G (95%CI: 1.51, 5.24) and a 2.09 times higher hazard among those with NG CKD (95%CI: 1.46, 2.99) in adjusted models. HRs remained significant when adjusted for proteinuria.

Conclusions: Ambulatory HT is common (~58%) in children with CKD. NT transitioned to HT more than vice versa in both G and NG children. Ambulatory HT was strongly associated with CKD progression.

Funding: NIDDK Support

FR-PO546

Comparison of Blood Pressure (BP) Methods and Setting in Children with CKD Tammy M. Brad,1 Shang-En Chung,1 Michelle N. Eakin,2 Andrea C. Goodman,3 Cozumel S. Pruette,2 Barbara A. Fivish,2 Shamar Tuchman,4 Susan R. Mendley,1 Kristin Rickert.2 1Children’s National Medical Center, Washington, DC; 2Johns Hopkins School of Medicine, Baltimore, MD; 3Johns Hopkins University, Baltimore, MD; 4University of Maryland, Baltimore, MD.

Background: Children with CKD are at greater risk for hypertension and high BP is a risk factor for CKD progression. Multiple methods exist to measure BP in clinical practice. We aimed to determine how differing methods of BP measurement:1) correlate with each other and 2) correctly identify hypertensive status.

Methods: Cross-sectional analysis of 116 children in the CKD: Hypertension Adherence in Teens (CHAT) study at baseline. Enrolled children were 11-19 years of age, had CKD, and were prescribed a BP medication. Children had a clinic BP, 3 consecutive
FR-PO547
Prevalence of Elevated Blood Pressure in Multiethnic School-Aged Children in New York City
Bernarda Viteri Baquerizo,1 Jeffrey M. Saland,2 Clare Ceballos1.1 Mount Sinai School of Medicine, New York, NY; 2Mount Sinai School of Medicine, New York, NY.

Background: Pediatric hypertension (HTN) is a public health problem defined by blood pressure (BP) ≥95th percentile relative to age, gender, and height on ≥3 occasions. Overweight increases the likelihood of elevated BP and HTN and is more common among minority, poor, and male children. These findings (28% overweight with 12% pre-hypertensive / 15% hypertensive range BP) were noted in School Based Health (SBH) centers by a team from this medical center 15 years ago. Our goal was to revisit these centers and a tertiary care hospital-based clinic to assess the quality of BP screening and follow-up if needed to begin iterative quality improvement (QI) toward reducing consequences of HTN on childhood development and early-onset organ damage.

Methods: Retrospective cross-section cohort, age 4-21 years, with at least one outpatient visit (SBH or hospital-based) between July 2015-June 2016. Results: 5739 patients had 8225 encounters. 215 (3.74%) patients had at least one visit with elevated BP, out of which only 16 (7%) had follow-up within the period described. About 3/4 of the visits were at the hospital-based clinics and 2.65% of patients with elevated BP were seen in this setting vs. 4.39% seen at SBH clinics (p-value = 0.003). Appropriate follow-up in patients with elevated BP treatment omission 14/126 seen at hospital-based clinics vs. 2/44 seen at SBH clinics. The children with or without elevated BP did not differ with respect to sex (female 52% and 48%, respectively), or AA race (40%), while Latinos were found in 46% patients with normal BP vs. 40% with elevated BP. Median age was 10 for the entire cohort. Obesity was noted in 63% of patients with elevated BP (median BMI 99th percentile), vs. 34% in patients with normal BP (median BMI 82nd percentile (p-value 0.001,CI -13.65 to -13.56), despite a slightly higher prevalence of patients classified overweight (BMI ≥85th percentile) in the latter group.

Conclusions: Although the rate of elevated BP in this population was somewhat lower than other reports of general screening programs, there is nonetheless a significant population of children with elevated BP and overweight as a risk factor for elevated BP. The lack of follow-up among this group of patients with elevated BP highlights the need to describe the association of laboratory markers and demographic information with hypertension in pediatric cHD patients from the PICCOLO MONDO Initiative.

FR-PO544
Association of Creatinine Levels and Hypertension in an International Cross-Sectional Database of Pediatric Patients on Chronic Hemodialysis: The PICCOLO MONDO Initiative Alice Topping,1 Ricardo Guerrero kanan,2 Ana C. Alvarez-Elias,3 Mara Medeiros,4 Jochen G. Raimann,3 Peter Kotanko,3 Maria E. Ferris,4 1Hospital Infantil de México Federico Gómez, MEXICO, D.F., Mexico; 2Instituto Nacional de Perinatología, Mexico, Mexico; 3Renal Research Institute, New York, NY; 4University of North Carolina at Chapel Hill, Chapel Hill, NC, MEXICO CHILDRENS HOSPITAL FEDERICO GOMEZ, Tláhuacpantla de Baz, Mexico.

Background: Hypertension is a concern when treating pediatric chronic hemodialysis (cHD) patients due its association with cardiovascular morbidity and mortality. We aim to describe the association of laboratory markers and demographic information with hypertension in pediatric cHD patients from the PICCOLO MONDO Initiative.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
FR-PO550

Background: FMD is a non-inflammatory vascular disease that in children unlike adults has no sex-prediction. FMD is under-recognized, under-diagnosed, with unclear pathogenesis. Doppler Ultrasounds (US), Magnetic Resonance Angiography (MRA), Computed Tomography Angiography (CTA), and Catheter Based Angiography (Ang) are used to make a presumptive diagnosis of FMD.

Methods: We did a retrospective analysis of the clinical features and radiological findings in 26 children diagnosed with FMD at the Children's Hospital of Philadelphia (CHOP), all are entered into the national FMDSA database and have institutional IRB consent.

Results: Mean age at diagnosis was 7.4 ± 4.7 yr (4m–17y). Family history HTN (54.2%) of FMD (8.3%), Caucasian (61.5%). Headache (46%) and HTN (89.7%) were the most prevalent symptoms and signs at presentation. US was a single site (7/25 (28%)) or multifocal sites 7/25 (28%) and invaded the main or first order renal branch in 17/25 (68%), but deep renal vessels were not seen. 2nd order branches were found in 7/25 (28%) (children Table). Only Ang showed deep vessel disease. US imaging was significantly less sensitive (28%) than Ang (p = 0.003) and was the least sensitive imaging technique. The NPV of Ang (48%) was also less than that of Ang (100%). The specificity and PPV of MRA imaging as well, but MRA imaging showed a lower NPV (40%) compared with Ang. This was the lowest NPV of the imaging modalities. MRA had a better sensitivity (62.5%) than US. Overall, 3D CTA had the best sensitivity (40%) when compared with Ang. This was the lowest NPV of the imaging modalities. MRA had a better specificity (62.5%) than US. Overall, 3D CTA had the best sensitivity (84.2%) and PPV (70%) compared with Ang but still had much lower specificity (70%) and PPV (84.2%) when compared with Ang.

Conclusions: Only Ang showed deep renal vascular disease. Ang should be done as part of the initial work-up of any child suspected of having renovascular FMD, no matter what the findings are on US, MRA, or 3D CTA.

Funding: Private Foundation Support, Clinical Revenue Support

Peripheral site of renal vasculature narrowing in 7/25 (28%) (more than 1 site often involved)

<table>
<thead>
<tr>
<th>Location</th>
<th>TotalInvasive (%)</th>
<th>Single-site site</th>
<th>Multifocal sites</th>
<th>Multi/Total</th>
<th>Patients p=n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd order</td>
<td>6.9 ± 1.1</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>1 (6)</td>
</tr>
<tr>
<td>3rd order</td>
<td>5.7 ± 0.6</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0 (0)</td>
</tr>
<tr>
<td>4th order</td>
<td>3.4 ± 0.7</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Peripheral</td>
<td>11.6</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

FR-PO551
Racial Disparities in Pediatric Hypertension Management - Christopher Cates,1,2 Bethany Crawford,1 John Lin, Nichola A. Hoffman, Thomas K. Davis,3 Vikas R. Dhandhukia,1 Laura Hesemann,1 Barnes Jewish Hospital, St. Louis, MO; 1University of Missouri School of Medicine, Columbia, MO; 2Washington University School of Medicine, St Louis, MO; 3Washington University in St. Louis, St. Louis, MO.

Background: African American (AA) adults have a higher prevalence of HTN and lower rates of control when compared to non-Hispanic whites (non-AA). Evidence for a similar disparity in pediatric populations is mixed though there are differences in hypertension-related morbidity. Studies assessing differences in HTN control between ethnic groups are lacking for pediatric patients. The goal of this study was to evaluate rates of HTN control among pediatric patients of different ethnicity.

Methods: All patients with a diagnosis of HTN seen between May 2012 and April 2013 at a pediatric nephrology clinic in an academic center were evaluated. Patients with resolved HTN, ESRD, or history of kidney transplant were excluded. Blood pressure control was recorded as documented by the treating physician. Data were collected to evaluate risk factors for uncontrolled HTN, including race, age, gender, stage of HTN, number of medications, BMI, and presence of CKD.

Results: Patients were identified as African American, 85 (67%) identified as Caucasian, Asian, or Other. Median age was 14 (range 5 months-20 years). Among all subjects, 83% were documented as having adequate BP control. However, the rate of control among AA subjects was 68% compared to 87% among non-AA subjects (p=0.012). When comparing racial groups, there was no difference in BMI group, CKD, family history, use of multiple anti-hypertensive medications, or stage of HTN.

Conclusions: In this pediatric cohort, AA subjects were less likely to have adequately-controlled blood pressure when compared to non-AA despite no difference in commonly-assessed risk factors for HTN or the number of medications prescribed. This parallels results obtained through population-based studies showing lower rates of blood pressure control among AA adults compared to non-AA and highlights the need to further address racial disparities in pediatric health care.

Blood Pressure Control and Risk Factors by Ethnicity

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>AA (n=126)</th>
<th>Non-AA (n=300)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>68%</td>
<td>87%</td>
<td>0.012</td>
</tr>
<tr>
<td>Overweight or obese</td>
<td>62%</td>
<td>60%</td>
<td>0.477</td>
</tr>
<tr>
<td>CKD</td>
<td>21%</td>
<td>20%</td>
<td>0.567</td>
</tr>
<tr>
<td>Family History of HTN</td>
<td>82%</td>
<td>76%</td>
<td>0.472</td>
</tr>
</tbody>
</table>

FR-PO552
 Ventricular Dysfunction in Children with Controlled Hypertension and CKD - Wacharee Seehunyong,1 Aura J. Arenas Morales,1 Arpit K. Agarwal,2 Marissa J. Defreitas,1 Chryso P. Katsoufis,1 Gaston E. Zilleruelo,1 Carolyn L. Abitbol,1 Sethuraman Swaminathan,2 Michael Freundlich,1 University of Miami/Pediatric Nephrology, Miami, FL; 2University of Miami/Pediatric Cardiology, Miami, FL.

Background: Hypertension (HTN) contributes to left ventricular hypertrophy (LVH) and dysfunction, and accelerates cardiovascular (CV) disease in chronic kidney disease (CKD), but the thresholds linking blood pressure (BP) with eventual CV events in children are unknown. Suggested targets for optimal therapy are <95th %ile BP reference values, but whether sustaining BP within these targets averts LVH and ventricular dysfunction in children is uncertain.

Methods: From 70 patients (14±6.0±2 years) with an initial diagnosis of HTN and available echocardiographic evaluation, 33 (14 on renin-angiotensin system blockers) with controlled BP <95th %ile and eGFR-based CKD stages 1 (n=16), 2 (n=10) and 5D (n=7) were analyzed.

Results: BP Z-scores (Zs) were similar in all groups. Echocardiogram revealed LVH in 19%, 20% and 43% in stages 1, 2-4 and 5D, and abnormal relative wall thickness (RWT >0.37cm) in 44%, 60% and 71% respectively. While systolic function remained normal, diastolic function E/A ratio was reduced in 13%, 20% and 71% of stages 1-2, 4-5D and declined across stages (p<0.05) (Figure 1). E/Em and E/Em abnormal Zs were uncommon. At least 1 abnormal diastolic function was present in 25%, 50% and 86% in above stages (p<0.05). LVMi Zs correlated positively with BMI Zs, E/E′ and Em/E′ Zs, and negatively with serum eCa (all p<0.05), but did not correlate with BP Zs. BP Zs did not correlate with any marker of diastolic function.

Conclusions: Despite controlled HTN, abnormal ventricular geometry and altered diastolic function were observed even in the earliest stages CKD. Other factors operative with declining kidney function may be responsible for the described changes. Longitudinal studies are needed to evaluate the effects of more stringent BP control on LVH and abnormal diastolic function in young CKD patients with HTN.

Funding: Clinical Revenue Support

FR-PO553
Epigenetic Clock and Biological Aging during Preeclampsia - Natasa Milic-2,3 Vesna D. Garovic,1 Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; 2Department for Medical Statistics and Informatics, School of Medicine University of Belgrade, Belgrade, Serbia; 1Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN.

Background: Preeclampsia is a pregnancy-specific disorder clinically characterized by hypertension (blood pressure a140/90 mmHg) and proteinuria (a300 mg per day).

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

Underline represents presenting author.

Poster/Friday
Aberrant placental aging and increased placental senescence have been demonstrated in pregnancy as well as the role of epigenetic mechanisms, such as DNA methylation, in control of maternal gene expression in normal pregnancies, which can be disrupted in preeclampsia. The aim of this study was to test the hypothesis that biological aging is accelerated in women with preeclampsia vs. those with normotensive pregnancies.

Methods: Biological age was measured by “epigenetic clock,” an estimate of DNA methylation age using the elastic net regression model, consisting of methylation values across 353 specific CpG sites that were found to vary with age. Data from the 450k methylation of 44 blood samples from preeclampsia (n=11), mean age 30.6 years and normotensive (n=34), mean age 31.4 years patients during the first and second trimesters and at the time of delivery were used to compare longitudinally the estimated DNA methylation (epigenetic) ages during preeclamptic and normotensive pregnancies.

Results: Biological age for women with normotensive pregnancies have not changed over the course of pregnancy (32±6 years for all time points). In contrast, biological age significantly increased over the course of preeclamptic pregnancies: first trimester, 30.48 years; second trimester, 31.49 years; and delivery, 32.69 years (p<0.05).

Conclusions: Our data suggest that preeclampsia may behave as a premature-aging-like state. These findings set the stage for future studies that may identify novel mechanistic pathways in preeclampsia.

FR-PO554

Fetal but Not Maternal APOL1 Genotype Is Associated with Increased Risk for Preeclampsia among African-Americans: Rebecca C. Hjorten,1,2 Kimberly J. Reidy,1 Claire L. Simpson,1 A. Z. Rosenberg, 2 Stacy Rosenblum,1 Csaba P. Kovacs,1,3 Frances A. Tyavsky,1 Joseph Myrie,1 Bianca L. Ruiz,1 Khyobeni Mozhui,10 Soulin Haque,1 Sandra E. Reznik,1 Frederick J. Kaskel,2 Jeffrey B. Kopp,2 Cheryl A. Winkler,2 Robert L. Davis,2 1Albert Einstein College of Medicine, Bronx, NY; 2Albert Einstein College of Medicine, Children’s Hospital at Montefiore, Bronx, NY; 3Albert Einstein College of Medicine, Bronxville, NY; 4Montefiore Medical Center, S. Green, NY; 5Montefiore Medical Center; 6St. Johns University, Queens, NY; 7NCI, NIH, Frederick National Laboratory, Frederick, MD; 8NIDDK, NIH, Bethesda, MD; 9UNIVERSITY OF TENNESSEE HEALTH SCI CTR, Memphis, TN; 10University of Tennessee, Memphis, TN; 11University of Tennessee Health Science Center, Memphis, TN; 12Nephrology and Hypertension, Cincinnati Children’s Hospital, Cincinnati, OH; 13Pathology, Johns Hopkins University, Baltimore, MD.

Background: African Americans are at increased risk for preeclampsia. Genetic variants in apolipoprotein L1 (APOL1) account for a substantial fraction of increased risk of kidney disease among African Americans. APOL1 is expressed in human placenta, and transgenic mice expressing APOL1 develop preeclampsia. The role of APOL1 variants in human preeclampsia has not been studied.

Methods: Two studies were performed evaluating maternal and fetal APOL1 genotypes in African American women with preeclampsia. At Albert Einstein College of Medicine (AECOM) affiliated Hospitals, we studied 122 pregnancies in African American women with preeclampsia. We used the CARTaGENE populational database, central hemodynamic and transgenic mice expressing APOL1 develop preeclampsia. The role of APOL1 variants in human preeclampsia has not been studied.

Results: In both studies fetal APOL1 high risk (HR) genotype was associated with preeclampsia in their mothers, relative risk at AECOM 1.65 (95% CI 1.11, 2.44) and odds ratio at UTHSC 1.92 (1.05, 3.59). In both studies, maternal APOL1 HR genotypes were not associated with preeclampsia. Gestational age, birth weight and Cesarman section did not vary by APOL1 genotype. Fetal APOL1 HR genotype births with preeclampsia were no more likely to have severe preeclampsia, but those mothers were more likely to have cerebral or visual disturbances (63% versus 37%, p = 0.04) and infants had lower APGAR scores at 5 minutes (8.0 versus 10.0, p < 0.01).

Conclusions: Fetal APOL1 high-risk genotype confers an increased risk for preeclampsia, likely by adversely affecting placental function. APOL1 genetic testing may have a clinical role to predict and perhaps improve pregnancy outcomes.
Impact of change of BW on HTN. Cox proportional hazard models was used to evaluate the effect of BW change on the incidental risk of hypertension.

**Results:** During follow-up, 4,445 (16.8 %) cases of hypertension newly developed (Q1: 1.5–10.8, Q2: 12.0–14.8, Q3: 14.8–22.0, Q4: 22.0–59.9, Q5: >59.9). When quintile 3 was set as a reference in adjusted model, the hazard ratios (HRs) for incidental hypertension exhibited a J-shaped relationship with the BW changes (Q1: 1.66 [95% CI: 1.17, 2.37], Q2: 1.96 [95% CI: 1.60–2.38], Q3: 1.00 [reference], Q4: 1.30 [95% CI: 1.10–1.54], and Q5: 3.39 [95% CI: 2.91–3.96], respectively).

**Conclusions:** The incidental risk of hypertension increased in weight loss as well as in weight gain which demonstrated J-shaped relationship. This finding further studies to investigate the incidental relationship between BW changes and hypertension.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No pregnancy (n=64,901)</th>
<th>Pregnancy ≤ 20 weeks or end only pregnancy (n=10,231)</th>
<th>Pregnancy &gt; 20 weeks (n=19,700)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>54.2±3.8</td>
<td>56.2±3.8</td>
<td>54.2±3.8</td>
</tr>
<tr>
<td>Age of first pregnancy</td>
<td>27.7±3.3</td>
<td>27.3±3.3</td>
<td>27.7±3.3</td>
</tr>
<tr>
<td>Bloods</td>
<td>7%</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>CVD risk factors</td>
<td>4%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Treatant hypertension</td>
<td>19%</td>
<td>19%</td>
<td>19%</td>
</tr>
<tr>
<td>Body weight index</td>
<td>-5.0±3.5</td>
<td>-5.0±3.5</td>
<td>-5.0±3.5</td>
</tr>
<tr>
<td>Body weight index</td>
<td>10±0.7</td>
<td>10±0.7</td>
<td>10±0.7</td>
</tr>
<tr>
<td>Heart rate</td>
<td>58.6±10.2</td>
<td>58.6±10.2</td>
<td>58.6±10.2</td>
</tr>
<tr>
<td>Adjusted central hemodynamic parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central systolic BP</td>
<td>131.1±13.7 (11.7)</td>
<td>131.1±13.7 (11.7)</td>
<td>131.1±13.7 (11.7)</td>
</tr>
<tr>
<td>Central diastolic pressure</td>
<td>81.0±10.2 (10.2)</td>
<td>81.0±10.2 (10.2)</td>
<td>81.0±10.2 (10.2)</td>
</tr>
<tr>
<td>Arterial index</td>
<td>31.2±9.3, 32.6</td>
<td>31.2±9.3, 32.6</td>
<td>31.2±9.3, 32.6</td>
</tr>
</tbody>
</table>

**FR-PO558**

**Characterizing the Burden of Hypertension in High Alpine Himalayan Villages of Nepal**

**Katherine Garlo,** 1 David M. Charytan. 2 Renal Division, Brigham and Women’s Hospital, Boston, MA; 2Brigham and Women’s Hospital/Harvard Medical School, Brookline, MA.

**Background:** Villages in the Ganesh Himal mountains are located in a remote high altitude regions of the Himalayas where there is limited access to basic resources and medical care. The burden of hypertension (HTN) has never been assessed in these communities. The primary objectives of this evaluation was to determine the prevalence of HTN while providing clinical care at medical camps with Himalayan Healthcare Hospitals.

**Methods:** We conducted a retrospective observational evaluation of adults ≥18 years living in Himalayan villages at a 15,000 feet elevation who attended HHC clinics during the spring medical trek of 2017. HTN was defined as systolic (SBP) and diastolic blood pressure (DBP) ≥140/90 mmHg. 21556 normotensive Korean men had been followed up from 2005 to 2013. Of these, the prevalence of HTN was measured using adjusted observed to expected prevalence ratios (PR).

**Results:** HTN was defined as systolic (SBP) and diastolic blood pressure (DBP) ≥140/90 mmHg in 43 patients (6.6%, mean age 65±13.8 years. 60%F) mean SBP among hypertensive patients was 172±19.8, 76%F, mean DBP 116±19.9 years, 75%F) received care at the spring medical trek of 2017. HTN was defined as systolic (SBP) and diastolic blood pressure (DBP) ≥140/90 mmHg. 21556 normotensive Korean men had been followed up from 2005 to 2013. Of these, the prevalence of HTN was measured using adjusted observed to expected prevalence ratios (PR).

**Conclusions:** In high elevation Himalayan villages of Nepal the prevalence of HTN with BP ≥140/80 mmHg was low but the severity of hypertension was high. Nearly one quarter of hypertensive individuals had albuminuria suggesting that end organ damage to the kidney is common. Our findings may under estimate the true prevalence of HTN given the predominance of females in the sample population and the high BP cut off. These findings have implications for public health policy in developing countries with limited resources.

| Table 1: Blood Pressure in Ganesh Himal Villages of the Himalayan Mountains |
|-----------------------------|-----------------------------|-----------------------------|
| SBP (mmHg)      | DBP (mmHg)      | Overall | Huntington | Lacs Village |
| Age (years) 18 | N | 60±4 | 56±4 | 49±4 |
| Age 25-34  | N | 60±4 | 56±4 | 49±4 |
| Age 35-44  | N | 60±4 | 56±4 | 49±4 |
| Age 45-54  | N | 60±4 | 56±4 | 49±4 |
| Age ≥ 55    | N | 60±4 | 56±4 | 49±4 |
| BP (50/30) | N (%) | 43 (6.9) | 46 (8.4) | 43 (7.6) |
| BP (50/30) | N (%) | 43 (6.0) | 46 (8.4) | 43 (7.6) |
| BP (150/50) | N (%) | 67 (10.4) | 65 (11.0) | 67 (10.4) |

**FR-PO559**

**Global Variation in Blood Pressure Control and Anti-Hypertensive Therapy in CKD Patients with Hypertension**

**Natalia Alencar de Pinho,** 1 Aderea Levin, 2 Masafumi Fukagawa, 3 Wendy E. Hoy, 4 Bruce M. Robinson, 5 Harold I. Feldman, 6 Luxia Zhang, 7 Kai-Uwe Eckardt, 8 Vivekanand Jha, 9 Koos-Haruo Oh, 10 Laura Solà, 11 J. Mayer, 12 Martin H. De Boer, 13 Maarten W. Taal, 14 Benedicte Stengel, 15 Arber Research Collaborative for Health, Ann Arbor, MI; 16 CASMU-IAMPP, Montevideo, Uruguay; 17 CESP INSERM, VILLEJUIF, France; 18 George Institute for Global Health, New Delhi, India; 19 Inserm ? CESP, Villejuif, France; 20 Medical University Innsbruck, Innsbruck, Austria; 21 Derby, United Kingdom; 22 Peking University Institute of Nephrology, Beijing, China; 23 Seoul National University Hospital, Seoul, Republic of Korea; 24 Paul Hospital and University of British Columbia, Vancouver, BC, Canada; 25 The University of Queensland, Brisbane, QLD, Australia; 26 Etkai University School of Medicine, Isehara, Japan; 27 University Medical Center Groningen, Groningen, Netherlands; 28 University of Erlangen-Nuremberg, Erlangen, Germany; 29 University of Pennsylvania, Philadelphia, PA. Group/Team: ISN iNET-CKD.

**Background:** Rates of blood pressure (BP) control in patients with CKD vary considerably worldwide. How differences in patient characteristics and antihypertensive treatment regimens relate to patterns of BP control is uncertain.

**Methods:** We used data from 14 studies participating in iNET-CKD, including 34,901 patients with gFR ≤60 ml/min/1.73m2 and HT (defined as either BP ≥140/90 mmHg or antihypertensive drug use) to compare the prevalence of uncontrolled BP (≥140/90) across 16 countries using adjusted observed to expected prevalence ratios (PR).

**Results:** Rates of uncontrolled BP varied from 28% to 61% (Figure 1). After adjusting for age, gender, DM, and GFR, prevalence ratios remained higher in cohorts from continental Europe, India, and Uruguay. Antihyp treatment use varied from 54% to 87% for RAAS inhibitors, 11% to 76% for diuretics, 26% to 75% for Ca channel blockers, and 22% to 68% for beta-blockers. In 8 out of 15 studies, >50% of patients with uncontrolled BP received <3 antihyp drugs. The number of prescribed antihyp classes was higher in cohorts from North America and Germany.

**Conclusions:** Global variation in BP control is partly explained by patient characteristics. Heterogeneity of antihyp treatment practices may also play a role and would be potentially modifiable.
Hypertension in High School Students: Genetic and Environmental Factors (HYGEF Study) Roberto Bigazzi,1 Chiara Lanzani,2 Laura Zago,1 Salvatore Lenti,1 Simone Fontana,1 Elisabetta Messaggio,1 Nausica Chiari,1 Roberta Batini,1 Fabio Sartini,1 Elena Brioni,1 Simona Delli carpin,1 Lorenza Citerio,2 Marco Simonini,2 Stefano Tentori,2 Filippo Cellai,2 Cristiano Magnaghi,2 Stefano Bagnoli,3 Vito M. Campese,1 Paolo Manunta,2 1USL NO, Livorno, Italy; 2Osp San Raffaele, Milan, Italy; 3USL SE, Arezzo, Italy; 4USC, Los Angeles, CA

Genotypes

Vito
Laura

Hypertension in High School Students: Genetic and Environmental

FR-PO560

Hypertension: Clinical and Translational

Whether genetic background in APOL1 affected individuals predicted sensitivity to disease, with studies suggesting a complex role in cardiovascular disease. We investigated recently, variants of the APOL1 gene have been associated with a higher rate of kidney disease and a complex role in cardiovascular disease. We sought to characterize HBP APOL1 AA individuals and their response to antihypertensive therapy.

Methods: HBP AA subjects from 4 trials (n=961) (PEAR1: NCT002465519 n=298, PEAR2: NCT02038552 n=190, GER1A n=280, and GER2A n=193: NCT 00055520) were evaluated at baseline after washout of BP meds. Genetic data was analyzed using Affymetrix or Illumina Human Omni-Quad Beadchips. APOL1 G1 and G2 variants were imputed using g1000 (PEAR1, PEAR2), or direct sequencing (GER1A, GER2A).

Genome wide association analyses included age, gender, baseline BP, and racial admixture as covariates.

Results: 14.0% (n=135) were positive for two APOL1 risk alleles. APOL1 AAs had similar baseline office, home, ambulatory day and night SBP and DBP measures vs. others (n=827). APOL1 AAs had significantly higher serum creatinine concentrations (0.93±0.24 vs 0.87±0.21 mg/dl, p=0.006) and lower eGFR (98.7±19.6 vs 104.8±18.7 ml/min, p=0.008). AAs with an APOL1 risk allele had a longer duration of HBP vs others (8.0±7.4 vs 6.7±7.5 yr, p=0.02). Subjects with an APOL1 risk allele had a greater SBP response to candesartan (12.1±2.7 vs 7.5±1.8 mmHg, p=0.03; GER2A), a trend toward greater DBP response (8.9±0.9 vs 6.3±1.2 mmHg, p=0.08), and a greater decline in albuminuria (-8.3±3.1 vs -3.7±4.3 mg/day, p=0.03). An intronic SNP rs17825860, within SDK1, predicted greater office SBP response (p=6.9 x 10^-6) in APOL1 AAs, and rs268658, an intronic SNP within DPP6, predicted greater office SBP response (p=3.2 x 10^-2) in APOL1 negative individuals.

Conclusions: HBP APOL1 AAs demonstrate early differences in eGFR and serum creatinine with a greater SBP response to angiotensin receptor blocker (ARB) before clinical evidence of cardiac or renal disease. Genetic variants of the podocyte protein SNPs, which are associated with potassium channels, may influence BP response to ARBs depending on APOL1 status.

Funding: Other NIH Support - NIGMS

FR-PO563

Derivation and Validation of an Uplift Model to Personalize Blood Pressure Treatment Strategy

Francis P. Wilson,1 Aditya Biswas,2 Chirag R. Parikh,3 1Yale School of Medicine, New Haven, CT; 2Yale University, New Haven, CT; 3Yale University and VAMC, New Haven, CT

Background: The Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that, for non-diabetic patients with cardiovascular risk factors, a more intensive systolic blood pressure lowering strategy (<120 mmHg) was superior to a standard blood pressure lowering strategy to prevent cardiovascular outcomes. However, absolute risk reduction was low suggesting that the vast majority of patients exposed to lower systolic BP will not directly benefit. Uplift modeling is a novel strategy to predict the marginal benefit of an intervention at the level of an individual allowing for personalized targeting of interventions.

Methods: We divided the SPRINT cohort into a 70% training and 30% validation set. Using deep-phenotyping via auto-encoders and a random forest uplift model, we predicted the marginal benefit of the intensive blood pressure compared to standard strategy. We then dichotomized this metric into two groups - “likely to benefit” and “unlikely to benefit”.

Conclusions: Use of an uplift-targeting approach in clinical practice would increase the efficacy of intensive blood pressure treatment, improve absolute risk reduction while simultaneously increasing the total number of cardiovascular events avoided at a population level.

Funding: NIDDK Support

Genetic Factors Predicting BP Response to Thiazides Differ in Hypertensive African Americans with and without APOL1 Genotypes

Patrick Cunningham,1 Zhiying Wang,2 Rhonda M. Cooper-Dell,3 Arlene Casamassima,1 1University of Chicago, Chicago, IL; 2University of Florida, Gainesville, FL; 3University of Houston, Houston, TX

Background: Essential hypertension (HBP) is common, and disproportionately affects African Americans (AAs) with higher rates of cardiovascular and renal disease. Recently, variants of the APOL1 gene have been associated with a higher rate of kidney disease, with studies suggesting a complex role in cardiovascular disease. We investigated whether genetic background in APOL1 affected individuals predicted sensitivity to thiazide diuretics in AA with HBP.

Methods: We combined AA patients from three HBP trials (PEAR1: NCT002465519 n=298, PEAR2: NCT01203852, n=190, and GER1A, n=280) to assess whether APOL1 genotype predicted BP response to thiazide diuretics. Subjects with elevated serum creatinine or significant proteinuria were excluded from these studies. Patient genetic data (n=570) was analyzed by Affymetrix or Illumina Human Omni-Quad Beadchip with correction for age, gender, baseline BP, and racial admixture. G1 and G2 variant alleles were detected by imputation using the g1000 data set (PEAR1, PEAR2), or by direct sequencing (GER1A). GWAS was performed on this data set to detect SNPs associated with differential response to thiazides.

Results: 14.9% of this combined HBP cohort (n=85) was positive for two APOL1 risk alleles. SBP or DBP at baseline and SBP or DBP response to thiazides, as measured by office or home cuff were similar between APOL1 positive and negative individuals. GWAS performed after adjusting for APOL1 genotype found that an intronic SNP rs111955547, located in ROBO2, was associated with a significantly decreased response to thiazides for office DBP (p=4.8 x 10^-10). Similarly, rs12943080, located in an intronic SNP in ROBO2, was associated with a significantly decreased response to thiazides for night-time SBP (p=5.0 x 10^-7).

Conclusions: Although HBP APOL1 AA individuals demonstrated similar BP responses to thiazides, genetic variants of ROBO2, which has a known role in podocyte development, as well as SNPs, which interact with TRPC6, positive for autosomal dominant FSGS, may identify individuals with poor response to thiazide diuretics.

Funding: Other NIH Support - NIGMS

APOL1 Hypertensive African Americans Show Greater BP Response and Urinary Albumin Reduction to Angiotensin Receptor Blockade with Different Genetic Predictors of Response versus Non-APOL1 Individuals

Patrick Cunningham,1 Zhiying Wang,2 Rhonda M. Cooper-Dell,3 Arlene B. Chapman,1,2 University of Chicago, Chicago, IL; 1University of Florida, Gainesville, FL; 2University of Houston, Houston, TX

Background: Hypertension (HBP) is common and disproportionately affects African Americans (AAs). HBP AAs typically are salt sensitive and respond more to thiazide diuretics, with a relatively suppressed renin-angiotensin-aldosterone axis. Variants of the APOL1 gene specific to AAs are associated with a higher rate of kidney disease and a complex role in cardiovascular disease. We sought to characterize HBP APOL1 AA individuals and their response to antihypertensive therapy.

Methods: HBP AA subjects from 4 trials (n=961) (PEAR1: NCT002465519 n=298, PEAR2: NCT02038552 n=190, GER1A n=280, and GER2A n=193: NCT 00055520) were evaluated at baseline after washout of BP meds. Genetic data was analyzed using Affymetrix or Illumina Human Omni-Quad Beadchips. APOL1 G1 and G2 variants were imputed using g1000 (PEAR1, PEAR2), or direct sequencing (GER1A, GER2A).

Conclusions: HBP APOL1 AAs demonstrate early differences in eGFR and serum creatinine with a greater SBP response to angiotensin receptor blocker (ARB) before clinical evidence of cardiac or renal disease. Genetic variants of the podocyte protein SNPs, which are associated with potassium channels, may influence BP response to ARBs depending on APOL1 status.

Funding: Other NIH Support - NIGMS
FR-PO564

Background: Majority of hypertension treatment decisions are made based on airport dialysis unit BP readings. Out of dialysis unit blood pressure readings are shown to be associated with left ventricular hypertrophy and mortality.

Methods: Ambulatory BP monitoring (ABPM) performed for 44 hours in between 2 dialysis sessions. ABPM BP recorded every 20 min during the day (7am to 11pm) and every 30 min during the night (11pm to 7am) in non-fistula arm. Hourly means were averaged to obtain interdialytic systolic and diastolic blood pressure readings over 44 hours. Less than 70% readings were excluded from the study. Along with BP means, Percent Time Elevation (PTE)-duration of day spent in high blood pressure state), dipping status at night, morning surge (the difference in systolic blood pressure during the first two hours after awakening and the lowest level recorded during night) and Pulse Pressure (PP) were assessed from ABPM data.

Results: Of 40 subjects, 68% were males. Average age was 54.5±12.3 years. 45% had diabetes, 98% had hypertension and 20% had IHD. 80% subjects had >40% PTE. In terms of dipping status, 7.5% had normal dipping (10-20% drop in SBP at night), 67.5% were non-dippers (<10% drop in SBP at night) and 25% had reverse dipping status (nocturnal BP higher than diurnal BP). In our study, 10% had >20% morning surge. We observed 27.5% had PP between 40 – 60 mm Hg, 45% had PP between 60 – 80 mm Hg, 22.5% had PP between 80 – 100 mm Hg.

Conclusions: Blood pressure readings obtained from ABPM helps to individualize hypertension management in relation to timing and selection of anti-hypertensive agent. Also, it helps to provide a targeted approach in treating dialysis patients with diurnal variations in BP on dialysis and non-dialysis days.

FR-PO565

Background: Evaluate cardiovascular risk (CVR) in healthy patients with clinical genetic test (Cardio inCode® test), and carotid echography.

Methods: cohort of 94 subjects (medium age 53 years 0.911, and male 73.5) We evaluate CVR with genetic test (Cardio inCode® that evaluated cardiovascular age -CVAGE- and global cardiovascular risk -GCVR-, using validated clinical and genetic score) and with carotid echography (intima-media thickness in left –IMTLC- and right –IMTRC- carotid). We evaluate levels of Glucose, Triglycerides, Total, HDL and LDL cholesterol, uric acid, creatinine (mg/dL) and creatinine clearance (ml/min) (MDRD-4 and CKD-EPI). We calculated the difference between cardiovascular (CVAGE) and biological age SPSS 20.0.

Results: Markers of CVR measure with Cardio inCode are associated with carotid and analytical parameters: Carotid: IMTLC is associated with AGE (r: 0.499, p= 0.001), CVAGE (r: 0.588, p= 0.001) and GCVR (r: 0.492, p= 0.001). IMTRC with AGE (r: -0.364, p= 0.001) and CVAGE (r: -0.361, p= 0.001) but MDRD not.

Metabolic parameters: GLUCOSE is associated with CVAGE (r: 0.272, p= 0.008), GCVR (r: 0.224, p= 0.031), IMTLC (r: -0.254, p= 0.020), IMTRC (r: -0.214, p: 0.051) and GCVR (r: 0.360, p= 0.001), GCVR (r: 0.453, p= 0.001), IMTLC (r: 0.400, p= 0.001), IMTRC (r: 0.24, p: 0.027) URIC ACID with CVAGE (r: 0.376, p= 0.001), GCVR (r: 0.353, p= 0.001) and IMTLC (r: 0.242, p= 0.060). Differences between CVAGE and biological age is associated with IMTLC (r: -0.294, p= 0.007) and GCVR (r: -0.363, p< 0.001). In 31.3% this difference is more than 10 years. No differences in biological age in this group.

Conclusions: Intima media thickness in left carotid is a good marker and better than in right carotid to evaluate CVR. CKD-EPI are better associated with CVR and Cardio inCode® than MDRD. Metabolic parameters (except cholesterol) are associated with Cardio inCode and intima media thickness. Difference between CVAGE and biological age are associated with cardiovascular risk. This difference depends on CVR, but not biological age. In healthy subjects we can evaluated CVR with Cardio inCode® and carotid echography.

FR-PO566
Short-Term Blood Pressure Variability Predicts Cardiovascular Events and All-Cause Mortality Better Than Office and Ambulatory Blood Pressure in Hemodialysis Patients Pantelis Sarafidis,1 Charalampos Loutriadis,1 Antonios Karpetas,2 George Tzanis,1 Georgios Koutroumpas,1 Athanasios Bikos,1 Vasilios Raptis,1 Christos Syrgas,1 Vasilios Liakopoulos,1 Aikaterini A. Papagianni,1 Department of Nephrology, Hippokration Hospital, Aristotel University of Thessaloniki, Thessaloniki, Greece; 2Therapeutiki, Hemodialysis Unit, Thessaloniki, Greece; 3Hemodialysis Unit, Achilleopouleion General Hospital, Volos, Greece; *Hemodialysis Unit, Pieria, Katerini, Greece; 1Section of Nephrology and Hypertension, 1st Department of Medicine, AHEPA Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece.

Background: Hemodialysis patients are subjected to severe blood pressure (BP) fluctuations during intra- and interdialytic periods. Long-term predialytic BP variability (BPV) is associated with increased cardiovascular risk. This is the first study to examine the prognostic significance of short-term BPV using ambulatory blood pressure monitoring (ABPM) in hemodialysis.

Methods: 170 patients underwent 48h ABPM during dialysis and a standard interdialytic interval and were followed for 28±11 months. BPV parameters calculated were: standard deviation(SD), weighted SD(wSD), coefficient of variation(CV), average real variability(ARV). The primary end-point was: combination of all-cause death, non-fatal MI or stroke. Secondary end-points were: (i) all-cause death (ii) cardiovascular death (iii) combination of cardiovascular death, MI, stroke, resuscitation after cardiac arrest, coronary revascularization or hospitalization for HF.

Results: In total, 37(21.8%) patients died and 46(27.1%) had cardiovascular events. Freedom from primary end-point was similar for quartiles of predialysis SBP, 48h SBP, and SBP-SD, but was progressively shorter for SBP-wSD (p=0.047), and SBP-ARV (81.4%, 81.0%, 73.8%, 51.2% p<0.001; Figure 1). Hazard Ratios for all outcomes were similar for quartiles of pre-dialysis SBP and 48h SBP but were progressively increasing with higher quartiles of 48h SBP-ARV (for primary outcome: Q1 reference; Q2:1.11, 95%CI:0.42-2.95; Q3:1.64, 95%CI:0.66-4.09; Q4:3.45, 95%CI:1.53-7.83).

Conclusions: Short-term BPV is associated with future cardiovascular events and mortality in hemodialysis patients, but office and ambulatory BP are not. These results add to evidence suggesting that BPV is independent cardiovascular risk factor in hemodialysis.

FR-PO567
Renal Functional Reserve Is Related to Exercise Heart Rate in Essential Hypertensive Patients: A Novel Link between the Kidneys and the Heart Aikaterini Damianakaki,1 Kyriakos Dimitriadis,1 Aglaia Chalkia,2 Konstantinos Tsiofis,1 Dimitrios Petras.2 1First Cardiology Clinic, University of Athens, Hippokration Hospital, Athens, Greece; 2Nephrology Department, Hippokration Hospital, ATHENS, Greece.

Background: Renal functional reserve (RFR) refers to the capacity of the kidney to augment its level of function under the influence of certain stimuli and it constitutes a valuable diagnostic tool for recognizing high risk patients for acute kidney injury (AKI).

Methods: Of 40 subjects, 68% were males. Average age was 54.5±12.3 years. 45% had diabetes, 98% had hypertension and 20% had IHD. 80% subjects had >40% PTE. Percent Time Elevation (PTE-duration of day spent in high blood pressure state), dipping status at night, morning surge (the difference in systolic blood pressure during the first two hours after awakening and the lowest level recorded during night) and Pulse Pressure (PP) were assessed from ABPM data.

Results: Of 40 subjects, 68% were males. Average age was 54.5±12.3 years. 45% had diabetes, 98% had hypertension and 20% had IHD. 80% subjects had >40% PTE. In terms of dipping status, 7.5% had normal dipping (10-20% drop in SBP at night), 67.5% were non-dippers (<10% drop in SBP at night) and 25% had reverse dipping status (nocturnal BP higher than diurnal BP). In our study, 10% had >20% morning surge. We observed 27.5% had PP between 40 – 60 mm Hg, 45% had PP between 60 – 80 mm Hg, 22.5% had PP between 80 – 100 mm Hg.

Conclusions: Blood pressure readings obtained from ABPM helps to individualize hypertension management in relation to timing and selection of anti-hypertensive agent. Also, it helps to provide a targeted approach in treating dialysis patients with diurnal variations in BP on dialysis and non-dialysis days.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
FR-PO568

Thirty Day Readmissions in Patients Admitted for Hypertensive Emergency Aparna Sahu, Lili Chan, Priti Poojary, Kimskun Chauhan, Steven G. Coca, Girish N. Nadkarni. Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Hypertensive (HTN) emergency accounted for 111,100,000 hospital readmissions in 2007 with increasing incidence. Few studies have examined 30-day readmission rates, reasons and outcomes in this growing population.

Methods: Utilizing the Nationwide Readmission Database from year 2013, admissions for HTN emergency were queried by combining ICD-9 codes for malignant HTN and acute target organ damage. We excluded patients on dialysis, those<18 years old and admission occurring in December due to lack of 30 day follow up for readmissions. Index admissions were any admission without a preceding 30 day admission, while readmissions were any admission that followed a prior admission by less than 30 days

Results: In 2013, 30,936 index admissions were identified. 15.4% of all index admissions had at least one 30-day readmission. When stratified by chronic kidney disease stage 3 or higher (CKD3), status, patients with CKD3 had higher readmission rate, 17% vs 14%, P<0.001. Of all index admissions, 44.8% were complicated by acute kidney injury (AKI) and AKI had higher rates of readmissions, 17% vs 14%, P<0.001. The top 10 causes for readmission are in Figure 1. While only 14% of readmissions were for repeat HTN emergency, 90% of all readmissions were likely related to complications from HTN emergency (congestive heart failure, HTN with complications, AKI, acute cerebrovascular disease and acute myocardial infarction). In-hospital mortality during index admission was 3%, while on readmission it was 4%.

Conclusions: Over 1 of 10 index admission for HTN emergency is followed by 30-day readmission. A high percentage of readmissions were for repeat HTN emergency. Both AKI and CKD are associated with higher readmission rates. Efforts should be directed towards identifying effective measures to improve blood pressure control and better follow-up post hospitalization, particularly in those with kidney disease.

FR-PO569


School of Public Health, University of Pittsburgh, Pittsburgh, PA; Internal Medicine, University of New Mexico, Los Ranchos, NM; Renal-Electrolyte Division, University of Pittsburgh, Pittsburgh, PA; School of Public Health, University of Pittsburgh, Pittsburgh, PA; Internal Medicine, University of California San Francisco, San Francisco, CA; Cell Biology, University of Pittsburgh, Pittsburgh, PA.

Background: Urinary plasminogen and its precursor, plasminogen, are detectable in the urine of patients with diabetic or other proteinuric kidney diseases. Urinary plasminogen levels correlate with increased extracellular fluid volume and blood pressure and have been hypothesized to contribute to renal Na retention by activating the epithelial Na channel (ENaC) and to progression of chronic kidney disease through podocyte and tubular toxicity. We assessed whether urinary plasminogen levels predict subsequent increases in blood pressure or decline in kidney function in type 1 diabetes.

Methods: Individuals with childhood-onset type 1 diabetes were enrolled as part of the Pittsburgh Epidemiology of Diabetes Complications Study in 1986-1988 and followed prospectively for 25 years. The present nested-cohort study included 70 subjects chosen to represent a spectrum of baseline urinary protein levels. Clinical outcomes included 1) increased blood pressure over a two-year period, defined as any increase in systolic or diastolic blood pressure or addition of a new anti-hypertensive agent; 2) incident hypertension over the full 25 year study period, defined as new-onset blood pressure of 140/90 mmHg or urinary protein medication; and 3) 50% decline in eGFR over the 25 year study period, calculated from baseline using the CKD-EPI formula. The predictive values of urinary plasminogen and albumin were compared.

Results: In those who experienced increased blood pressure, baseline plasminogen levels were higher, with a difference approaching significance (p = 0.08). Albumin did not differ (p = 0.43). Plasminogen predicted both incident hypertension (HR=2.05, 95% CI 1.06-4.04) and 50% decline in eGFR (HR=2.26, p<0.001), however adjusting for urinary albumin attenuated plasminogen's 25-year predictive abilities (p = 0.95 and 0.45, respectively).

Conclusions: Over 2 years of follow-up, baseline urinary plasminogen was associated with urine pressure approaches significant, suggestive of a role in stimulating urinary Na retention. Over 25-years of follow-up, plasminogen predicted incident hypertension and 50% decline in eGFR, though not independently of albumin, suggesting that over the long-term, mechanisms non-specific to plasminogen contribute to hypertension and diabetic kidney disease progression.

Funding: NIDDK Support

FR-PO570

Inflammation and Apparent Treatment Resistant Hypertension in Patients with CKD – The Results from the CRIC Study Jing Chep, Joshua D. Bundy, L. Lee Ham, Chi-yan Hsu, James P. Lash, Edgar R. Miller, George Thomas, Debbie L. Cohen, Dominic S. Raj, Hsiang-Yu Chen, Dawei Xie, Panduranga S. Rao, Matthew R. Wein, Jackson T. Wright, Mahboub Rahman, Jiang He. Case Western Reserve University, Cleveland, OH; Case Western Reserve University, Cleveland, OH; Cleveland Clinic, CLEVELAND OH; GW Medical Faculty Associates, Washington, DC; Johns Hopkins University, Baltimore, MD; The Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; Tulane School of Medicine, New Orleans, LA; Tulane School of Public Health and Tropical Medicine, New Orleans, LA; Tulane University School of Medicine, New Orleans, LA; Tulane University School of Public Health and Tropical Medicine, New Orleans, LA; University of California San Francisco, San Francisco, CA; University of Illinois at Chicago, Chicago, IL; University of Maryland School of Medicine, Baltimore, MD; University of Michigan Health System, Ann Arbor, MI; University of Pennsylvania School of Medicine, Philadelphia, PA; University of Pennsylvania School of Medicine, Philadelphia, PA; University of Pennsylvania School of Medicine Center for Clinical Epidemiology and Biostatistics, Philadelphia, PA.

Background: Apparent treatment resistant hypertension (ATRH) is highly prevalent and associated with increased risk of cardiovascular disease (CVD) in patients with chronic kidney disease (CKD) and may be associated with blood pressure variability and is increased in CKD patients. It is unknown if inflammation is associated with increased likelihood of ATRH in CKD.

Methods: ATRH is defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic BP (DBP) ≥90 mmHg while taking ≥3 antihypertensive medications or diabetics ≥4 antihypertensive medications with SBP ≥140 mmHg and DBP ≥90 mmHg. 1359 Chronic Renal Insufficiency Cohort (CRIC) Study participants with ATRH and 2008 participants without ATRH, but with hypertension at the baseline visit, were included in this analysis. Multiple regression models were adjusted for age, sex, race, clinical sites, diabetes, alcohol consumption, body mass index, physical activity, estimated glomerular filtration rate, 24-hour urine protein, and 24-hour urinary sodium.

Results: Multiple-adjusted odds ratios (95% confidence intervals) of ATRH for the highest tertile compared to the lowest tertile of the inflammatory markers were 1.31 (1.06-1.62, p=0.026) for tumor necrosis factor-α (TNF-α) and 0.75 (0.61-0.92, p<0.008) for transforming growth factor beta (TGF-β). In addition, multiple-adjusted odds
Hypertension: Clinical and Translational

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

**FR-PO571**

**Diabetes Mellitus versus Vascular Calcification: Impact on Predialytic Blood Pressure and Incidence of Intradialytic Hypotension**

*Sinae Lee,1 Seoung Woo Lee.2 1none, Anyang-si, Republic of Korea; 2Nephrology and Hypertension, Inha University Hospital, Incheon, Republic of Korea.

**Background:** Diabetes mellitus (DM) and vascular calcification are highly prevalent in maintenance hemodialysis (HD) patients, but it has not known how they influence on pre-HD blood pressure (BP) and the incidence of intradialytic hypotension.

**Methods:** This study was performed from August 2010 to July 2014 in 66 patients who met the following criteria: HD duration for >6 months and HD 3 times weekly during the study. Four years of pre- and intradialytic BPs and laboratory data were collected. Abdominal aortic calcification (AAC) was assessed using the Kauppila score. Patients were classified as high (≥ 5) or low (<5) AAC. The KDOQI guideline was used to define IDH. IDH incidence was the number of sessions in which IDH occurred divided by the total number of monthly HD sessions. Subjects were classified into group 1 (high AAC, DM) (n=16), group 2 (high AAC, non-DM) (n=15), group 3 (low AAC, DM)(n=14), and group 4 (low AAC, non-DM) (n=21). Time series analysis (TSA) was performed to assess changes in pre-HD BP and the IDH incidence.

**Results:** Mean age was 61±11 years; 30 had DM; 50% were male; HD duration was 6.1±3.5 years; AAC score was 5.2±4.5; and HD sessions were 481±81. In TSA, pre-HD SBP, DBP, PP, and the IDH incidence were elevated by group in the order of 1>3>2>4, 4>2>3>1, 1>2=3>4, and 1>3>2=4, respectively (Fig. 1). Multiple regression showed that non-DM and low AAC was independently associated with pre-dialytic SBP (non-DM; β=-0.58, p<0.001; low AAC; β=-0.49, p=0.015), DBP (non-DM; β=0.34, p=0.001; low AAC; β=0.75, p<0.001), PP (non-DM; β=-0.57, p=0.001; low AAC; β=-0.69, p<0.001) and IDH incidence (non-DM; β=0.31, p<0.001; low AAC; β=0.469).

**Conclusions:** Both DM and vascular calcification may influence pre-HD BPs and the IDH incidence; however, the effect of DM is more prominent.

---

**FR-PO572**

**The Change of Glucose Metabolism in Primary Aldosteronism after Target Treatment**

*Yu-Fang Lin, Vincent Wu, Kwan-dun Wu. Internal Medicine and College of Medicine, National Taiwan University Hospital, Taipei city, Taiwan.

**Background:** Discrepant data have been published on the effects of aldosterone excess on abnormal glucose metabolism. There is no consistent result of follow-up glucose metabolism after adrenalectomy or spironolactone in patients with primary aldosteronism (PA).

**Methods:** Patients were enrolled during the screening test after adequate substitutive drug periods. Aldosterone, ARR (aldosterone renin ratio), glucose metabolism parameters ratios (95% confidence intervals) associated with one standard deviation difference in log-transformed TGF-β was 0.90 (0.83-0.98, p = 0.013). The levels of interleukin-6, interleukin-1 beta, and C-reactive protein were not significantly associated with odds of ATRH.

**Conclusions:** Higher levels of TNF-α and lower levels of TGF-β (as anti-inflammatory biomarker) were independently associated with odds of ATRH. Further study is warranted to investigate if targeting specific inflammatory pathways may improve blood pressure control among patients with CKD.

**Funding:** NIDDK Support, Other NIH Support - NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES P20GM109036
including HOMA-IR and HOMA-β were checked and calculated before and 1 year after treatment.

**Results:** One hundred and thirty-eight PA patients were enrolled (mean age 50.6±11.5, 49% female), among them 72 patients with aldosterone producing adenoma (APA) received adrenalectomy (Group 1), 33 idiopathic hyperaldosteronism (IHA) treated with spironolactone (Group 2) and 33 APA treated with spironolactone (Group 3). There was no change of fasting glucose before and after treatment (P=0.056, 0.497). Fasting insulin increased in group 1 and group 2 (P=0.019, 0.007). Aldosterone decreased after adrenalectomy but increased after IHA treated with spironolactone. HOMA-β improved in patients in the former two groups (P=0.000, 0.015). HOMA-IR deteriorated significantly in group 2 (P=0.019) but not in group 1(P=0.109). The fasting glucose, fasting insulin, HOMA-IR and HOMA-β remained unchanged in group 3. At enrollment, APA had higher HOMA-IR (P=0.000) and fasting plasma glucose(P=0.019) than IHA. There was a negative correlation between aldosterone and HOMA-β or HOMA-IR after adjustment with serum potassium level, SBP, BMI, age, and sex.

**Conclusions:** At enrollment, APA had higher HOMA-IR and fasting plasma glucose than IHA. HOMA-β could improve in APA treated with adrenalectomy and IHA received spironolactone. HOMA-IR deteriorated in IHA patients but remained unchanged in other two groups. Thus, adrenalectomy of APA could improve glucose homeostasis other than spironolactone in APA.

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

Glucose metabolism parameters in APA and IHA at baselines and at follow-up

<table>
<thead>
<tr>
<th></th>
<th>Group 1: APA adrenalectomy (n=72)</th>
<th>Group 2: IHA spironolactone (n=33)</th>
<th>Group 3: APA spironolactone (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>p</td>
<td>Follow-up</td>
<td>p</td>
</tr>
<tr>
<td>β-glucose (mg/dL)</td>
<td>10.0±7.1±5.5</td>
<td>9.4±12.3</td>
<td>8.6±12.3</td>
</tr>
<tr>
<td>Fasting insulin (μU/mL)</td>
<td>17.4±9.4</td>
<td>17.4±9.4</td>
<td>17.4±9.4</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>47.9±8.9</td>
<td>47.9±8.9</td>
<td>47.9±8.9</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.7±0.3</td>
<td>0.7±0.3</td>
<td>0.7±0.3</td>
</tr>
</tbody>
</table>

*p=0.05

**FR-PO573**

**Hyperuricemia Is Associated with Worse Renal Outcomes in Patients Undergoing Percutaneous Transluminal Renal Angioplasty (PTA)** Xiaojun Chen,1,2 Afonso Eirin,1 Ahmed Saad,1 Amir Lerman,2 Stephen C. Teator,1 Lilach O. Lerman,1 1Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; 2Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN. **Background:** Hyperuricemia is associated with elevated risk for hypertension and chronic renal disease. PTA improves blood pressure (BP) and renal function only in selected patients with atherosclerotic renovascular disease (ARVD), likely due to post-stenotic kidney injury. We hypothesized that hyperuricemia contributes to poor BP and renal functional outcomes in ARVD after PTA.

**Methods:** Outcomes were compared among ARVD patients stratified by elevated serum uric acid (SUA) levels (>6.0mg/dL in women; >7.0mg/dL in men) undergoing PTA. Multivariate analysis was used to determine significant predictors for renal and BP outcomes after PTA.

**Results:** In 94 patients with ARVD studied retrospectively, pre-PTA eGFR was lower in hyperuricemic compared with normouricemic patients, and remained lower after PTA (Table), after adjustment for body-mass index, number of antihypertensive drugs, baseline eGFR, diuretic use, and left ventricular (LV) mass (p=0.05). PTA did not affect eGFR in either group, while diastolic BP decreased in both. In univariate analysis, lower SUA was associated with improved BP after PTA (Hazard ratio 0.84, p<0.05), but multivariate analysis revealed that only age, coexisting cerebrovascular disease, and number of antihypertensive drugs remained independent predictors. Contrarily, in multivariate linear analysis SUA independently predicted post-PTA proteinuria (odds ratio 65.5, p<0.005, Figure A) after adjustment for pre-PTA proteinuria, LV ejection fraction, and eGFR, and for cerebrovascular, peripheral, and cardiovascular disease. In 11 additional ARVD patients studied prospectively under controlled sodium intake and antihypertensive regimens, PTA improved renal function (Figure B) only in patients with normal SUA (e=0.05).

**Conclusions:** Hyperuricemia does not aggravate BP outcomes in ARVD patients, but may be associated with greater renal dysfunction and proteinuria after PTA. Thus, SUA in patients with ARVD may be a predictor of worse outcomes after PTA.

**Funding:** Other NIH Support - DK100081

---

**FR-PO574**

**The Benefit of Combined Calcium Channel Blockers with Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers on Renal Outcomes in Hypertensive Patients: A Meta-Analysis** Pawanee Susansitaphong,1 Pumma Pongpanich,2 Pasvich Pitkapiboonkulk,1 Kearkit Praditpornsilpa,1 Somchai Eiam-Ong.1 1Chulalongkorn University, Bangkok, Thailand; 2Chulalongkorn university, Bangkok, Thailand; 3Chulalongkorn university, Bangkok, Thailand.

**Background:** The prevalence of hypertension and its associated complications are likely to grow as the population ages. In addition, control of the disease is far from adequate, only fifty percent of persons with hypertension have their blood pressure under control, which was defined as a level below 140/90 mmHg. Most people need more than one drug to achieve blood pressure target. However, several guidelines only focus on the first line treatment. We conducted a meta-analysis to explore the benefits of combined calcium channel blockers (CCBs) with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) on renal outcomes in hypertensive patients.

**Methods:** A systematic literature search was conducted in MEDLINE, Scopus, Cochrane Central Register of Controlled Trials, and Clinical Trials.gov (until April 7, 2016) to identify randomized controlled trials comparing the benefits of combined CCBs with ACEIs or ARBs vs. other combinations on renal outcomes in hypertensive patients. Random-effect models were used to compute the weighted mean difference (WMD) for continuous variables.

**Results:** Sixty randomized controlled trials (48,913 patients) were identified. Although, the combined CCBs with ACEIs or ARBs did not have statistically significant difference on the WMD of systolic blood pressure and diastolic blood pressure (73 study arms) when compared with other combinations (0.25 mmHg; 95%CI -0.33, 0.64 mmHg, P=0.40 and 0.05 mmHg, 95%CI -0.36, 0.47 mmHg, P=0.80, respectively), the benefits on renal outcomes including the decreasing of serum creatinine (22 study arms, 1,791 patients, -0.08 mmol/L, 95%CI -0.51, -0.24 mmol/L, P< 0.001) and improving of estimated glomerular filtration rate (15 study arms, 1,853 patients, 4.13 mL/min/1.73m², 95%CI 2.26, 6.00 mL/min/1.73m², P< 0.001) were observed when compared with other combinations. The significant increase of serum potassium was also observed. (25 study arms, 2,505 patients, 0.13 mEq/L, 95% CI 0.07, 0.19 mEq/L, P<0.001)

**Conclusions:** The combination of CCBs with ACEIs or ARBs have a benefit on renal function in hypertensive patients. Therefore, this combination should be considered whenever monotherapy does not achieve guideline target.

**FR-PO575**

**Scleroderma Renal Crisis Mimicking Rapidly Progressive Glomerulonephritis** Ahmed Al-Sheyyab, Diego A. Beltran Melgarjo, Rachel B. Fissell, Jamie P. Dwyer. Vanderbilt University Medical Center, Franklin, TN.

**Background:** Scleroderma is a group of disorders which overlap in their clinical features. We describe a case with ambivalent presentation, as it highlights some of the differentiating clinical features and the impact of treatment choices on the patient’s outcome.

**Methods:** A 78 year-old man presented with edema of the lower extremities and hands. Clinic evaluation revealed serum creatinine 2.2 mg/dL (baseline 0.7mg/dL), new hypertension (BP 200/103), anemia (hemoglobin 9.1mg/dL) and thrombocytopenia (platelets 69 x10^9/mcL). Additional testing showed microscopic hematuria with proteinuria (protein:creatinine ratio 0.65), LDH 512U/L, haptoglobin <8 mg/dL, platelets 69 x10^9/mcL. Additional testing showed microscopic hematuria with proteinuria (protein:creatinine ratio 0.65), LDH 512U/L, haptoglobin <8 mg/dL, platelets 69 x10^9/mcL. Despite pulse steroids therapy, renal failure worsened and ultimately required hemodialysis. Examination of the hands showed skin thickening. Captopril was started. Anti-RNA polymerase III antibodies were positive. Kidney biopsy was consistent with the clinical diagnosis of scleroderma renal crisis (SRC).

**Results:** SRC can present similarly to Rapidly Progressive Glomerulonephritis (RPGN). The renal biopsy is able to differentiate between RPGN and SRC. However, thrombocytopenia can delay the performance of kidney biopsy. Clinical suspicion followed by careful hand examination and obtaining extractable nuclear antigen antibodies were key steps in revealing the diagnosis. Early diagnosis of scleroderma is critical to initiate timely therapy. Previous studies showed dramatic improvement of mortality with angiotensin-converting-enzyme inhibitors. In SRC, careful clinical examination for signs of scleroderma and appropriate serologic testing can guide early therapy. The astute clinician requires a high index of suspicion to make the diagnosis of SRC.
FR-PO576

Clinical and Histopathologic Features of Atherosclerotic Renal Artery Stenosis (ARAS): An Autopsy Study

Background: ARAS is frequently seen in ageing population and contributes to morbidity in this group. Although a number of cohort studies have compared medical versus surgical therapies for ARAS, there are no previous autopsy-based studies correlating histopathologic and clinical features in patients with ARAS.

Methods: We queried Mayo Clinic database for autopsy cases with known diagnosis of ARAS between 1994 and 2013. We obtained 19 cases for which renal and cardiac histopathology slides were available. 6 patients had unilateral(UL) ARAS (4 medically managed, 2 stented) and 13 patients had bilateral(BL) ARAS (10 medically managed, 2 stented and 1 endarterectomy). All patients were treated for hypertension. Average systolic blood pressure (SBP) was 142mmHg. There was no significant difference SBP in BL or UL ARAS patients.

Results: Histopathology findings: Small kidney size correlated with increased SBP (p=0.02). There was a strong correlation with stenotic kidney(STK) size and corresponding STK weight(p=0.03). Glomerular filtration rate correlated with contralateral kidney(CLK) weight(p=0.01). STK-CLK weight ratio was significantly different between patients with UL(0.4) versus BL ARAS (0.7, p=0.002). Glomerular size strongly correlated with atrophy and kidney weight(p=0.0006). Intrarenal vascular disease correlated with glomerulosclerosis(GS) in both STK and CLK (p=0.004 and p=0.02 respectively). All patients with UL ARAS had medullary necrosis, only 1 patient with BL ARAS had medullary necrosis. Although 1 patient had atherosclerotic disease documented, 5 cases of intrarenal atheroemboli. Atheroemboli were not associated with presence of abdominal aortic aneurysms, but all 19 patients had severe aortic atherosclerosis. Outcome: Intrarenal vascular disease correlated with cardiovascular outcome making cardiovascular the most common cause of death in these patients. 57% of patients died either due to cardiovascular cause or stroke. All 19 patients had history of severe ischemic heart disease. 10.5% of patients developed end stage renal disease(ESRD) and died due to complications of ESRD.

Conclusions: Intrarenal vascular disease is a marker of severe atrophy and GS. Small glomerular size in STK was a robust marker of compensatory hypertrophy of CLK. Atherosclerotic renal disease is an under-recognized complication of ARAS in this population.

FR-PO577

Percutaneous Intervention for Renal Artery Stenosis through the Years 2008 to 2014

Background: Medical therapy remains the cornerstone of management of renal artery stenosis (RAS) with secondary hypertension. The indications of intervention by renal artery angioplasty with (PTRAS) or without (PTRA) stenting however, remains debated. Several trials in recent years have shown no difference in blood pressure control between medical management and percutaneous intervention. We aim to study the trends of utilization, outcomes, and complication rates of percutaneous intervention for RAS between 2008 to 2014.

Methods: We searched the National Inpatient Sample from 2008 – 2014 using International Classification of Diseases Clinical Modification (ICD-9-CM) codes to identify patients admitted with primary diagnosis of renal atherosclerosis, fibromuscular dysplasia (FMD), or reno-vascular hypertension. We excluded patients with vascular trauma, carotid stenosis, and mesenteric ischemia, to exclude patients who may have undergone endovascular procedures identified for these indications. We then identified patients who underwent PTRA and PTRAS. We identified complications of post-operative hematoma or bleeding, acute kidney injury (AKI), and atheroembolism. We described categorical variables as proportions and continuous variables as means. We analyzed the trend of utilization of the procedure using the Mantel-Haenszel trend test.

Results: We identified 30,617 patients admitted with primary diagnosis of RAS. The mean age was 68.63 ± 15.5 years, 62.5% of patients were females, 79.5% were Caucasians, and the mean comorbidity score was 6.37 ± 7.35. Of these, 22,716 (74.2%) patients underwent percutaneous intervention. The mean age of these patients was 70.42 ± 12.6 years, 61.4% were females, 81.7% were Caucasians and the mean comorbidity score was 6.0 ± 7.1. We identified a trend towards lower rates of use of percutaneous interventions through our study period (84.1% in 2008 vs 50.7% in 2014, P<0.0001).

Conclusions: We found a significant downward trend of inpatient PTRA and PTRAS for RAS between 2008 and 2014. This is consistent with the lack of evidence to support the use of interventions. Patients who received intervention tended to be older, with lower comorbidity scores.

FR-PO578

Impedance Cardiography and Percutaneous Renal Artery Stenting (PTRA) in Patients with Hypertension: Clinical and Translational

Background: High blood pressure (BP) is a leading cause of death and disability in the US and worldwide. Approximately 1 of 3 U.S. adults (75 million) have high blood pressure, and only about half treated with antihypertensive protocol have their high blood pressure in recommended blood pressure target. Titration of medications involves a trial and error process, especially in resistant hypertension, and is typically guided by office blood pressure, an imprecise, indirect piece of overall hemodynamic status. It has been reported that cardiac power index (CPI) is the best hemodynamic correlate of mortality. Our aim was to follow standard hypertensive management using hemodynamic parameters as hypothesis generating. We measured hemodynamics (NICAs, NI Medical Ireland) using a non-invasive, whole-body impedance cardiography technology. NICaRs reports stroke volume and pulse rate and therefore cardiac index (CI), and together with the measurement of BP it calculates total peripheral resistance index (TPRI).

Methods: We repeated NICaS measurements in 40 hypertensive patients with CKD, kidney transplant, and resistance hypertension over a follow up period up to 6 months (Treatment), and titration was done after the first measurement (Baseline).

Results: We report results in 2 representative cases. BP was significantly reduced in both cases following medication changes. Hemodynamic changes from Baseline to Treatment (Figure) reveal that the reduction in TPRI in Patient A was associated with normalization of CI and CPI improving into their normal range after treatment. In Patient B an increase in TPRI was associated with decrease in CI and CPI out of normal range after treatment. The reduction in CPI/TPIAlong was the single most important parameter, then treatment could be considered a success. However, BP changes do not correlate well with direction of changes in other hemodynamic parameters, and can mask worsening CI and CPI. These results suggest that hemodynamics parameters should be guided using measurements of hemodynamics parameters beyond BP alone. Our hypothesis, to be tested in a large study in the near future, is that using impedance cardiography to guide hypertension management will result in better BP control and patient experience (symptoms and compliance).

Conclusions: The quantitative evaluation of glomerular collapse reveals the long-term renal outcome in patients with benign nephrosclerosis (BNS), the definition of glomerular collapse has not been established. The aim of this study was to quantify the severity of glomerular collapse and to examine the predictive significance of this parameter regarding the renal outcome in patients with biopsy-proven BNS. The results suggest that glomerular collapse and enlargement is a typical renal feature in benign nephrosclerosis (BNS), the definition of glomerular collapse has not been established. The aim of this study was to quantify the severity of glomerular collapse and to examine the predictive significance of this parameter regarding the renal outcome in patients with biopsy-proven BNS.

Background: Although the concomitant appearance of glomerular collapse and enlargement is a typical renal feature in benign nephrosclerosis (BNS), the definition of glomerular collapse has not been established. The aim of this study was to quantify the severity of glomerular collapse and to examine the predictive significance of this parameter regarding the renal outcome in patients with biopsy-proven BNS.

Methods: The clinical data and renal biopsy specimens from BNS patients with an eGFR of ≥30 mL/min/1.73m² were retrospectively reviewed. Based on the measurements of all cross-sectional areas of Bowman’s capsules and glomerular capillaries in the specimens, the mean volume of the Bowman’s capsules (BV) and the mean volume of the glomerular capillaries (GV) were separately calculated for each subject using Weibel’s formula. The G/B ratio was then calculated for each subject. The clinicopathological characteristics at the biopsy of the patients with a G/B ratio ≥0.615 and those with a value of <0.615 were comparable, whereas the GV values of the patients with a G/B ratio ≥0.615 were significantly lower compared with those with a G/B ratio <0.615. The clinicopathological characteristics at the biopsy of the patients with a G/B ratio ≥0.615 were significantly lower compared with those with a G/B ratio <0.615. The clinicopathological characteristics at the biopsy of the patients with a G/B ratio ≥0.615 were significantly lower compared with those with a G/B ratio <0.615. The clinicopathological characteristics at the biopsy of the patients with a G/B ratio ≥0.615 were significantly lower compared with those with a G/B ratio <0.615. The clinicopathological characteristics at the biopsy of the patients with a G/B ratio ≥0.615 were significantly lower compared with those with a G/B ratio <0.615.

Conclusions: If BP alone was the single most important parameter, then the treatment could be considered a success. However, BP changes do not correlate well with direction of changes in other hemodynamic parameters, and can mask worsening CI and CPI. These results suggest that hemodynamics parameters should be guided using measurements of hemodynamic parameters beyond BP alone. Our hypothesis, to be tested in a large study in the near future, is that using impedance cardiography to guide hypertension management will result in better BP control and patient experience (symptoms and compliance).

FR-PO579

The Quantitative Evaluation of Glomerular Collapse Predicts the Long-Term Renal Outcome in Patients with Benign Nephrosclerosis

Background: Although the concomitant appearance of glomerular collapse and enlargement is a typical renal feature in benign nephrosclerosis (BNS), the definition of glomerular collapse has not been established. The aim of this study was to quantify the severity of glomerular collapse and to examine the predictive significance of this parameter regarding the renal outcome in patients with biopsy-proven BNS.

Methods: The clinical data and renal biopsy specimens from BNS patients with an eGFR of ≥30 mL/min/1.73m² were retrospectively reviewed. Based on the measurements of all cross-sectional areas of Bowman’s capsules and glomerular capillaries in the specimens, the mean volume of the Bowman’s capsules (BV) and the mean volume of the glomerular capillaries (GV) were separately calculated for each subject using Weibel’s formula. The G/B ratio was defined as the ratio of GV to BV.

Results: This study included a total of 67 BNS patients, with a median G/B ratio of 0.615. The clinicopathological characteristics at the biopsy of the patients with a G/B ratio of ≥0.615 and those with a value of <0.615 were comparable, whereas the GV values of the patients with a G/B ratio of ≥0.615 were significantly lower compared with those with a G/B ratio of <0.615. The survival analyses showed that a G/B ratio of <0.615 was associated with a worse renal outcome (Figure). In the Cox hazard analysis to determine the factors associated with the doubling of serum creatinine level, a G/B ratio of <0.615 was found to be a significant predictor after adjustment by age, sex, and G/B median.

Conclusions: These results suggest that the G/B ratio of diagnostic biopsy specimens is a useful predictor of the long-term renal outcome in patients with BNS, the pathogenesis of which may involve glomerular collapse.
FR-PO580

Prevalence and Predictors of Orthostatic Hypotension at a Tertiary Care Hypertension Clinic with New Diagnostic Thresholds  Mohammad A. Faraz,1 Marcel Ruzicka,2 Swapnil Hiremath1. 1University of Ottawa, Ottawa, ON, Canada; 2None, Ottawa, ON, Canada.

Background: Formal testing of orthostatic hypotension (OH), defined as a decrease of blood pressure (BP) of 20/10 mm Hg (systolic/diastolic) on change in posture from supine to standing, is seldom carried out in routine practice because of logistical constraints. A recent study reported a sit-to-stand decrease of 15/7 mm Hg as having high sensitivity and specificity. We measured the prevalence and risk factors associated with OH with the new threshold of sit-to-stand of either ≥15 mm Hg in systolic (SBP) or ≥7 mm Hg in diastolic BP (DBP).

Methods: We reviewed medical charts of patients being followed at Renal Hypertension Center, a referral centre for difficult to control hypertension. Sitting BP is measured after 5 minutes of resting, as an average of 5 measurements with an automated device. Standing BP is measured three times at one minute intervals and averaged. OH was determined on the basis of the difference in either average SBP or DBP. Demographic characteristics, comorbidities, medication details, laboratory values and BP measurements were extracted.

Results: Data from 219 patients was extracted. The overall difference in SBP (sitting - standing) was 0.94 and DBP was 2.1 mm Hg. 190 patients (87%) did not have OH, whereas 29 (13%) had OH using either SBP or DBP thresholds. The difference in SBP and DBP was 17 mm and 6 mm Hg in those with OH, versus 1.6 and 3 mm Hg amongst those without OH respectively. Higher sitting systolic BP was significantly associated with OH; age, gender, diabetes, number and hypertension medication class were not associated with OH.

Conclusions: Amongst referred patients to a specialist hypertension clinic, the prevalence of OH using a threshold of 15/7 mm Hg was 13%. The new diagnostic threshold allows for easy assessment of OH.

FR-PO581

Difference between Central and Peripheral Blood Pressure during Hemodialysis  Jafar Al-Said, Corazon Suyao. Bahrain Specialist Hospital, Manama, Bahrain.

Background: Difference between the peripheral and central pressure had been confirmed in multiple studies. During hemodialysis, the blood pressure is measured regularly. Whether the difference between the peripheral and central pressure measurements is significant enough to favor checking the central rather than the peripheral pressure during the session is not known.

Methods: During regular hemodialysis treatments for 10 of our ESRD patients, we measured the central and the peripheral BP through one full session. The average systolic and diastolic pressures were estimated. The pulse pressure was calculated for the peripheral as well as the central pressure. The paired T test was used to determine the statistical significance.

Results: Among the 10 patients 70% were females. Mean age was 57.7 years (SE3.8). All of them were having hypertension and 80% were diabetic. The mean peripheral systolic pressure was 149mmHg (SE 6.9). The mean central systolic pressure was 129mmHg (SE 5.8). The mean peripheral diastolic pressure was 77mmHg (SE 4.8). The mean central diastolic pressure was 80mmHg (SE 4.6). The mean peripheral pulse pressure was 72mmHg (SE 6). The mean central pulse pressure was 49mmHg (SE 4.6). The difference between peripheral and central measurements for the systolic, diastolic and pulse pressure were statistically significant. The systolic pressure was 20mmHg higher in the central pressure compared to the peripheral pressure and 0.012. The diastolic pressure was 3 mmHg higher in the central pressure compared to the peripheral pressure P 0.009. The pulse pressure was 22 mmHg higher in the central pressure compared to the peripheral pressure P 0.006.

Conclusions: There was a significant difference between the peripheral and central pressure measurements during dialysis. It suggests that monitoring of the central pressure would be more accurate than the peripheral pressure during the hemodialysis sessions. The difference was noticed more among patients with high CV risks.

FR-PO582

Pegloticase, a Mammalian Uricase, Significantly Decreases Mean Arterial Blood Pressure in Patients with Chronic Gout  Peter E. Lipsky,1 Richard J. Johnson,3 Hyon Choi,2 Anthony Yoo1. 1AMPEL BioSolutions, Charlottesville, VA; 2Massachusetts General Hospital, Boston, MA; 3University of Colorado Denver, Aurora, CO.

Background: Hypertension is a recognized co-morbidity of hyperuricemia and gout,1 and there are significant correlations between serum uric acid (sUA) and blood pressure (BP) in individuals with and without gout.1 While some studies suggest lowering sUA may decrease BP,2 a meta-analysis indicated no consistent effect of oral urate lowering
null
FR-PO586
Activation of PI 3 Kinase (PI 3 K) by PDGF Receptor-Beta (PDGFRb) Regulates Akt-Dependent HiFla to Express Glut1 for Mesangial Cell (MC) Hypertrophy in Response to High Glucose (HG) Falguni Das,1 Nandini Ghosh-choudhury,1 Balakantalam S. Kasinath,2 Goutam Ghosh-Choudhury,1 ‡UTHSCSA, SAN ANTONIO, TX, 1University of Texas Health Science Center, San Antonio, TX.

Background: Hyperglycemia increases PI 3 K/Akt to induce glomerular MC hypertrophy in diabetic nephropathy (DN). In DN, increased glomerular expression of PDGFRb is reported. As a mechanism of PI 3 K/Akt activation in DN, we hypothesized involvement of this receptor tyrosine kinase.

Methods: Human MCs, sRNA transfection, immunoblotting, protein synthesis and hypertrophy assays and rat model of streptozotocin-induced DN were used.

Results: HG significantly increased tyrosine phosphorylation-dependent activation of PI 3 K in MC, concomitant with increased tyrosine phosphorylation of PDGFRb at the catalytic loop and the PI 3 K binding sites. A specific PDGFRb inhibitor, JNJ-10198409 (JNJ), blocked these phosphorylations, which resulted in inhibition of association of PI 3 K with the PDGFRb. Similarly, sRNAs against PDGFRb and the PDGFRb mutant deficient in PI 3 K binding (PDGFRbM) inhibited HG-induced phosphorylation of PI 3 K and hence Akt. PI 3 K/Akt regulates Glut1 expression via Hif1alpha (HiFla) transcription factor. sRNAs against Glut1 significantly inhibited HG-induced protein synthesis and hypertrophy of MCs. JNJ, siPDGFRb and PDGFRbM markedly suppressed the expression of HiFla and Glut1 in response to HG. Interestingly, sRNAs against HiFla inhibited HG-mediated protein synthesis and hypertrophy of MCs. Furthermore, JNJ, siPDGFRb and PDGFRbM inhibited MC hypertrophy induced by HG. This inhibition was reversed by the expression of constitutively active Akt kinase or HiFla. Moreover, expression of Glut1 prevented the inhibition of hypertrophy induced by siPDGFRb or PDGFRbM. Finally, we observed increased phosphorylation of PDGFRb and PI 3 K in the glomerular fraction of STZ-induced diabetic rat. This increased phosphorylation was associated with HiFla and Glut1 expression in the diabetic glomerulus.

Conclusions: Together our results provide the first evidence for a role of PDGFRB-mediated PI 3 K/Akt activation to control HiFla/Glut1 axis in HG-induced MC hypertrophy.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO587
Gastric Bypass versus “Medical Bypass” – Impact on Experimental Diabetic Kidney Disease Meera Nair,1 Aofie L. Canney,1 Jessie A. Elliott,1 naomi m. fearon,1 Anna Casselbrant,2 Lars Fandriks,2 Carol W. Le roux,2,3 Neil G. Docherty,2,3 1St. James’s Hospital, Dublin, Dublin 8, Ireland, 2University of Gothenburg, Gothenburg, Sweden, 3University College Dublin, Dublin, Ireland.

Background: Reductions in albuminuria are reported after Roux-en-Y gastric bypass (RYGB). Herein, we assess the impact of RYGB on podocyte injury in the Zucker Diabetic Fatty (ZDF) rat model of diabetic kidney disease (DKD) and compare glomerular injury and global renal transcriptomic responses of RYGB and matched “Medical Bypass” (MB).

Methods: Study 1: Adult male ZDF rats underwent sham surgery (n=8) or RYGB (n=7). Study 2: Adult ZDF rats underwent sham surgery (n=15) or RYGB (n=9). Nine sham-operated rats were calorie restricted and received insulin, irigliton, metformin, ramipril, rosuvastatin and fenofibrate for 2 months (MB). Zucker Fa+ rats acted as Zucker Fa/+ rats (n=7). Study 2: Adult ZDF rats underwent sham surgery (n=15) or RYGB (n=9). Nine sham-operated rats were calorie restricted and received insulin, irigliton, metformin, ramipril, rosuvastatin and fenofibrate for 2 months (MB). Zucker Fa+ rats acted as Zucker Fa/+ rats (n=7). Study 2: Adult ZDF rats underwent sham surgery (n=15) or RYGB (n=9). Nine sham-operated rats were calorie restricted and received insulin, irigliton, metformin, ramipril, rosuvastatin and fenofibrate for 2 months (MB). Zucker Fa+ rats acted as Zucker Fa/+ rats (n=7). Study 2: Adult ZDF rats underwent sham surgery (n=15) or RYGB (n=9). Nine sham-operated rats were calorie restricted and received insulin, irigliton, metformin, ramipril, rosuvastatin and fenofibrate for 2 months (MB). Zucker Fa+ rats acted as Zucker Fa/+ rats (n=7). Study 2: Adult ZDF rats underwent sham surgery (n=15) or RYGB (n=9). Nine sham-operated rats were calorie restricted and received insulin, irigliton, metformin, ramipril, rosuvastatin and fenofibrate for 2 months (MB). Zucker Fa+ rats acted as Zucker Fa/+ rats (n=7). Study 2: Adult ZDF rats underwent sham surgery (n=15) or RYGB (n=9). Nine sham-operated rats were calorie restricted and received insulin, irigliton, metformin, ramipril, rosuvastatin and fenofibrate for 2 months (MB). Zucker Fa+ rats acted as Zucker Fa/+ rats (n=7). Study 2: Adult ZDF rats underwent sham surgery (n=15) or RYGB (n=9). Nine sham-operated rats were calorie restricted and received insulin, irigliton, metformin, ramipril, rosuvastatin and fenofibrate for 2 months (MB). Zucker Fa+ rats acted as Zucker Fa/+ rats (n=7). Study 2: Adult ZDF rats underwent sham surgery (n=15) or RYGB (n=9). Nine sham-operated rats were calorie restricted and received insulin, irigliton, metformin, ramipril, rosuvastatin and fenofibrate for 2 months (MB). Zucker Fa+ rats acted as Zucker Fa/+ rats (n=7). Study 2: Adult ZDF rats underwent sham surgery (n=15) or RYGB (n=9). Nine sham-operated rats were calorie restricted and received insulin, irigliton, metformin, ramipril, rosuvastatin and fenofibrate for 2 months (MB). Zucker Fa+ rats acted as Zucker Fa/+ rats (n=7).

Results: RYGB resulted in 20-30% weight loss, normalized glycaemia and HG without or with mTOR inhibitor (rapamycin), the protein expressions of the expression of constitutively active Akt kinase or Hif1a. Moreover, expression of Glut1 prevented the inhibition of hypertrophy induced by siPDGFRb or PDGFRbM finally, we observed increased phosphorylation of PDGFRb and PI 3 K in the glomerular fraction of STZ-induced diabetic rat. This increased phosphorylation was associated with HiFla and Glut1 expression in the diabetic glomerulus.

Conclusions: Together our results provide the first evidence for a role of PDGFRB-mediated PI 3 K/Akt activation to control HiFla/Glut1 axis in HG-induced MC hypertrophy.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO588
The Protective Effect of GSTK1 on Renal Injury in Diabetic Nephropathy by Anti-Inflammatory Chun Hu, Ming Yang, Peng Gao, Xianghui Chen, Yuan Han, Li Li, Xiaofen Xiong, Li Zhao, Li Xiao, Jun Li, Fuyou Liu, Lin Sun, Departments of nephrology, Second Xiangya Hospital Central South University, ChangSha,Hunan, China.

Background: Diabetic nephropathy (DN) is one of the most serious microvascular complication in patients with diabetes mellitus. GSTK1 is a key protein which participate in adiponectin secretion and polymerization, it can also promote the expression of adiponectin. Our previous research has demonstrated that down-regulation of GSTK1 expression in the kidney of patients with DN, which consistent with decreased adiponectin levels in the serum. However, the role of GSTK1 in the development of DN is unclear.

Methods: C57BL/6 mice were divided into four groups: normal group (control), STZ induced diabetic mouse group(STZ), overexpression GSTK1 group (GSTK1), and STZ induced diabetic group (STZ+GSTK1).

Results: Compared with the control group, the weight, blood sugar, blood lipid, urine protein levels, ROS were increased significantly in STZ+GSTK1 group. The pathological change were increased notable in the kidney in STZ+GSTK1 group. In group of STZ and fGSTK1+STZ, mouse was feeding with high fat diet(HFD) for 4 weeks, and then single intraperitoneal injection of STZ 100mg/kg, continue with HFD feeding for 12 weeks. At the end of the experiment, blood and urine were detected for biochemical determination. The renal tissue was harvested and used for pathological examination,electron microscopy,DHE,3HJic,PCR and western blot analysis.

Conclusions: GSTK1 decreased the weight, blood glucose, blood lipid, urine protein, ROS level, increased adiponectin expression and reduced pathological changes in the kidney of STZ induced mouse. GSTK1 protected renal injury and reduce fibrosis in the kidney of diabetic mouse may through up-regulated expression of adiponectin and then inhibiting NLRP3 inflammation activity pathway

FR-PO589
Triptolide Alleviates Podocyte Injury in Hyperglycemia via Abrogating Activation of NALP3 Inflammasome and PI3Akt/mTOR Signaling Weiheng Han,1 Yigang Wan,2 Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, China; 2Nanjing University of Chinese Medicine, Nanjing, China.

Background: Triptolide (TP), an extracted phytomedicine is frequently used for protecting against podocyte injury in early diabetic kidney disease (DKD) in China. However, the therapeutic mechanism remains unclear. In the process of DKD, the activation of NALP3 inflammasome and PI3Akt/mTOR signaling in kidneys is the important mechanisms by which renal inflammation contributes to podocyte damage. This study thereby aimed to study the ameliorative effects of TP on podocyte lesion in hyperglycemia (HG), then to clarify its anti-inflammatory mechanisms in vitro by inhibiting the activation of NALP3 inflammasome and PI3Akt/mTOR signaling.

Methods: HG was used to induce murine podocyte to be in the state of damage. After the intervention of HG for 0, 3, 6, 12, 24 and 48 hours, firstly, the protein expressions of NALP3, active caspase-1 and active IL-1β were detected. Secondly, the protein expressions of desmin and synaptotadin were examined. Thirdly, the protein expressions of mTOR, Akt and p-mTOR were measured. As a result, we demonstrated that the co-treatment of TP and HG without or with mTOR inhibitor (rapamycin), the protein expressions of the
Long-Term Empagliflozin Administration Downregulates Aquaporin 2 despite the Increased Expression of V2 Vasopressin Receptor in Diabetic Rat Kidneys
Sungjin Chung,1,2 Zhilian Li,1,3 Soojeong Kim, Seok Joon Shin,2 Choul Whee Park,2 Chul Woo Yang,2 Yong-uk Kim,3 Eun Sil Koh,2 Division of Nephropathy and Hypertension, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, 1Department of Internal Medicine, The Catholic University of Korea College of Medicine, Seoul, Republic of Korea; 2Department of Nephrology, Guangdong General Hospital, Guangzhou, China; 3Department of Biochemistry, The Catholic University of Korea College of Medicine, Seoul, Republic of Korea.

Background: Beyond glucose lowering effect, it has been suggested that one of the possible mechanisms by which empagliflozin, a selective sodium-glucose cotransporter-2 (SGLT2) inhibitor, provides the remarkable cardiovascular and renal protective effects, is to increase intracellular cAMP production. However, there are still no studies investigating the effects of empagliflozin on renal transporters, related sodium transporters and water excretion.

Methods: In a randomized, controlled, 8-week trial, 52 male Sprague-Dawley rats were equally divided into two groups, control and empagliflozin (10 mg/kg). Body weight increased progressively and renal functions remained stable in both groups. Urinary volume, plasma glucose, serum sodium and creatinine levels were measured. Urinary and plasma Na+, K+, and Cl- levels were measured by ion-selective electrode. Glomerular filtration rate (GFR) was measured by intravenously injecting inulin and measuring radioactivity in urine. Glomerular volume fraction was measured by resin embedding.

Results: Urinary sodium excretion increased significantly in empagliflozin-treated rats (p<0.05). Urinary potassium excretion was also significantly increased in empagliflozin-treated rats (p<0.05). Glomerular filtration rate in empagliflozin-treated rats was significantly increased compared with control group (p<0.05). Glomerular volume fraction was significantly increased in empagliflozin-treated rats (p<0.05).

Conclusions: The present study indicates that empagliflozin increases renal excretion of sodium and potassium, and increases GFR and glomerular volume fraction. These results support the effective and safe clinical application of SGLT2 inhibitors in diabetes.

commentary: This study suggests that empagliflozin may have beneficial effects on renal function and structure, which could potentially lead to improved outcomes for patients with diabetes. Further research is needed to determine the clinical relevance of these findings.

Poster - Non-U.S.

FR-PO509

Dapagliflozin Alone or Combined with Ramipril Improves Hyperglycemia and Hypertension and Prevents Kidney Complications and GFR Decline in the Nephrectomized SDT Fatty Rat Model of Diabetic Nephropathy
Francois Briand,1 Massami Shinhoara,1 Emmanuel Brousseau,2 Takeshi Ohta,1 Yasushi Kageyama,1 Thierry Sulpice.3 CLEA Japan, Inc., Monaka, Japan; 3Japan Tobacco Inc., Osaka, Japan; 1PHYSIOGENEX, LABEGE, France.

Background: Combination of sodium glucose cotransporter 2 inhibitor (SGLT2i) and angiotensin-converting enzyme inhibitor (ACEi) provides the remarkable cardiovascular and renal protection observed in the DAPA+RAMI combination therapy. These results support the effective and safe clinical application of SGLT2 inhibitors in diabetes.

Methods: In a randomized, controlled, 8-week trial, 52 male Sprague-Dawley rats were equally divided into three groups, control, DAPA, and DAPA+RAMI. Body weight increased progressively and renal functions remained stable in all groups. Urinary volume, plasma glucose, serum sodium and creatinine levels were measured. Urinary and plasma Na+, K+, and Cl- levels were measured by ion-selective electrode. Glomerular filtration rate (GFR) was measured by intravenously injecting inulin and measuring radioactivity in urine. Glomerular volume fraction was measured by resin embedding.

Results: Urinary sodium excretion increased significantly in DAPA+RAMI-treated rats (p<0.05). Urinary potassium excretion was also significantly increased in DAPA+RAMI-treated rats (p<0.05). Glomerular filtration rate in DAPA+RAMI-treated rats was significantly increased compared with control group (p<0.05). Glomerular volume fraction was significantly increased in DAPA+RAMI-treated rats (p<0.05).

Conclusions: The present study indicates that DAPA+RAMI increases renal excretion of sodium and potassium, and increases GFR and glomerular volume fraction. These results support the effective and safe clinical application of SGLT2 inhibitors in diabetes.

commentary: This study suggests that DAPA+RAMI may have beneficial effects on renal function and structure, which could potentially lead to improved outcomes for patients with diabetes. Further research is needed to determine the clinical relevance of these findings.

Poster - Non-U.S.

FR-PO593

PBI-4547 Prevents Renal Destruction and Fibrosis in Severely Obese db/db Mouse Model of Diabetes-Induced Kidney Disease

Background: Type 2 diabetes (T2D) is a major health problem worldwide. Comorbidities, such as kidney disease, associated to T2D are numerous and cause severe reduction of life expectancy. The uninephrectomized (NX) mouse is a widely used model for the study of comorbidities associated to T2D. It also allows to study effects of diabetes-induced kidney disease. PBI-4547 is an orally active compound that displays anti-fibrotic and metabolic activities via a novel mechanism of action. The aim of this study was to investigate the protective effect of PBI-4547 on kidney function and injury in NX db/db mice.

Methods: A total of 60 mice were divided into 5 groups: Vehicle, DAPA, DAPA + RAMI, DAPA + RAMI + PBI-4547, and DAPA + RAMI + PBI-4547 + RAMI. Mice were treated with vehicle or PBI-4547 (5 mg/kg) via oral gavage for 6 weeks. Blood glucose, plasma insulin, and area under the curve in oral glucose tolerance test were measured. Urinary albumin and creatinine levels were measured. Glomerular filtration rate (GFR) was measured by intravenously injecting inulin and measuring radioactivity in urine. Glomerular volume fraction was measured by resin embedding.

Results: PBI-4547 significantly improved diabetic condition of db/db mice treated with DAPA + RAMI. PBI-4547 also significantly reduced urinary albumin and creatinine levels in db/db mice treated with DAPA + RAMI. PBI-4547 further reduced systolic and diastolic blood pressure by 29 and 24% (both p<0.05 vs. CONTROL). PBI-4547 + RAMI further reduced systolic and diastolic blood pressure by 29 and 24% (both p<0.05 vs. CONTROL).

Conclusions: In the 10-week Unx Nx db/db fatty rat, DAPA alone prevents kidney destruction, while the combination with RAMI adds benefits by better delaying GFR decline. Our data suggest that SGLT2i/ACEi combination prevents progression to ESRD.

Funding: Commercial Support - Physiogenex
reduced the fibrosis process in the kidney. Reduction of the mRNA expression of collagen type 1 (Col1a1), MMP-2 (-49%) and GLEPP-1 (-13%) were shown in kidneys of PBI-4547-treated compared to untreated db/db mice. Neither BUN nor GFR were found significantly modified in the db/db not treated mice (compared to NX C57BL/6 mice) and PBI-4547 had no impact on these parameters.

Cell proliferation: These results suggest that, in addition to the improvement of T2D, PBI-4547 treatment precludes renal structure destruction and prevents fibrosis in the kidneys of severely obese db/db mice.

Funding: Commercial Support - Prometic Life Sciences Inc.

FR-PO594

PBI-4547, a Novel Anti-Diabetic Agent, Prevents Diabetic Nephropathy and Protects β-cells in NOD Mice, a Model of Type 1 Diabetes


Background: Kidney disease is a cause of substantial morbidity and mortality in type 1 diabetes (T1D). Up to 40% of patients with T1D develop macroalbuminuria, and up to 75% of these patients progress to end-stage renal disease (ESRD) within 10 years. PBI-4547 is a novel first-in-class orally active anti-diabetic compound which displays pleiotropic activities and has been shown to reduce NASH, diabetes and fibrosis of kidney in different animal models. In the present study, we examined whether PBI-4547 may prevent diabetic nephropathy in NOD mice, a model of type 1 diabetes.

Methods: NOD/ShiLtJ female mice (8 weeks of age) received vehicle (water) or PBI-4547 (10 and 25 mg/kg/day) by daily gastric gavage for 23 weeks.

Results: In kidney, PBI-4547 protects against lesions by reducing glomerular volume and interstitial fibrosis. Furthermore, basement lesions were absent in PBI-4547-treated mice. Tubular dys trophy as PAS granular accumulation was constantly present in proximal tubules of NOD control mice and was completely abrogated by treatment with PBI-4547. Mice treated with PBI-4547 did not develop diabetes. OGTT was also normalized in PBI-4547-treated mice. PBI-4547 partially prevented islets destruction, which contributed to maintain normoglycemia.

Conclusions: This data suggests that PBI-4547 prevents diabetic nephropathy and complete destruction of β-cells and islets in type 1 diabetes model.

Funding: Commercial Support - Prometic Life Sciences Inc.

FR-PO595

Imbalance of Intestinal Microflora Disrupts LDL Receptor Pathway to Induce Lipid Accumulation at Renal Interstitium in Early Diabetic Nephropathy

Jinling Ma, Yang Zhang, Gui hua Zhang, Peipei Chen, Jian Liu, Chenchen Lu, Zhongda Hospital, Southeast University Medical School, Nanjing City, China.

Background: Our previous studies demonstrated that lipid accumulation in kidneys contributes to the progression of diabetic nephropathy (DN). However, the exact mechanism of which caused lipid accumulation in kidneys has not been completely elucidated. This study aimed to investigate the effect of imbalance of intestinal microflora on lipid deposition in the renal interstitium of DN.

Methods: Type 1 diabetic rats model were induced by streptozotocin injection. Broad-spectrum antibiotics were used to eliminate intestinal microflora. Intestinal microflora distribution was evaluated by 16S rDNA sequencing using samples from feces. Periodic acid-schiff (PAS) staining was used to observe basic structure and pathological changes of kidneys. Lipid accumulation was detected by oil red O staining. Fibrin staining and intracellular free cholesterol quantitive assay. Immunohistochemical staining and Western blot were used to assess the protein expressions of low-density lipoprotein receptor (LDLr) pathway.

Results: Blautia, Roseburia, and Paraprevotella abundance were significantly increased in diabetic rats while Bacteroid abundance decreased when compared with the controls. Broad-spectrum antibiotics effectively cleared away intestinal microflora. PAS staining showed that tubular epithelium in diabetic mellitus group (DM group) exhibited obvious expansion, balloonning degeneration, cell detachment as well as increased glycogen deposition while antibiotics treatment alleviated those lesions. Lipid accumulation in tubular interstitium of diabetic rats was increased compared with the controls. After the application of antibiotics, the lipid accumulation in tubular interstitium of diabetic rats was significantly reduced. More importantly, immunohistochemical staining and Western blot suggested that LDLr expression in tubular interstitium was increased in DM group, while antibiotics treatment decreased LDLr expression.

Conclusions: Imbalance of intestinal microflora might disrupt LDLr pathway to induce lipid accumulation at renal interstitium in early diabetic nephropathy.

FR-PO596

Expression of Hepatic Cytochrome P450 Drug-Metabolizing Enzymes in a Mouse Model of Diabetic Nephropathy

Cheng J Fang, Dylan Burger, Cheung Hok Holtherrman. These studies suggest that Cyp2c9, Cyp2c29, Cyp2c19, Cyp2c8, and Cyp2c11 are upregulated in liver of db/db mice. This upregulation is correlated with increased fasting glucose level in db/db mice.

Brad Urquhart.1 Kidney Research Centre, Ottawa, ON, Canada; 2Ottawa Hospital Research Institute, Ottawa, ON, Canada; 3ProMetic BioSciences Inc., Laval, QC, Canada; 4Western University, London, ON, Canada.

Background: Out of 420 million diabetics, over a third will develop diabetic nephropathy. Studies in chronic kidney disease have demonstrated decreased expression of hepatic cytochrome P450 (CYP) drug-metabolizing enzymes. With polypharmacy in diabetes mellitus, the diabetic kidney disease may lead to adverse drug reactions as a result of altered drug pharmacokinetics due to unexpected changes in CYP expression. This study evaluates the expression and metabolic activity of CYP3A11 and CYP2C9, mouse orthologues of human CYP3A4 and CYP2C9 in a mouse model of drug induced diabetic nephropathy, as well as in a CYP3A4/PXR-humanized (TgCYP3A4/PXR) mouse model.

Methods: Male C57BL/6 mice were treated with 50 mg/kg of streptozotocin (STZ; n = 7) intraperitoneally for 5 consecutive days. Control mice (n = 8) were injected with sodium acetate. After 16 weeks, blood glucose and kidney function (eGFR, urinary albumin-to-creatinine ratio (UACR)) were measured. Mouse livers were isolated for real-time PCR analysis and Western blot to determine CYP mRNA and protein expression. Activity of microsomes was assessed by metabolism of probe drugs (midazolam, testosterone) using liquid chromatography coupled to mass spectrometry (LC-MS).

Results: The UACR for STZ-treated mice was 667.3 µg/g compared to 145.5 µg/g in controls (P < 0.001). Similarly, eGFR was increased in STZ mice (20.2 mL/min/g body weight) compared to controls (10.2 mL/min/g body weight; P < 0.001). STZ-treated mice had higher plasma glucose (30.9 mM) compared to controls (6.4 mM; P < 0.001). Cyp3a11 mRNA expression showed a decreasing trend in diabetic nephropathy mice (44%, P = 0.10) compared to control mice. Cyp2c9 mRNA expression was not significantly different in STZ mice compared to control.

Conclusions: Increased eGFR, eGFR, and plasma glucose are strong indicators of diabetic nephropathy, indicating reliability of the drug-induced diabetic mouse model. The same treatment is currently being used in studies investigating the impact of diabetic nephropathy on TgCYP3A4/PXR mice. A decreasing trend in Cyp3a11 expression indicates possible down-regulation in diabetic nephropathy. Future directions will increase the sample size and evaluate hepatic differences caused by diabetic nephropathy by metabolomics in an effort to elucidate potential regulators of CYP expression.

Funding: Government Support - Non-U.S.

FR-PO597

TMX-049, a Novel Xanthine Oxidase Inhibitor, Attenuates Renal Injury in an Experimental Model of Diabetic Kidney Disease

Yoshihika Tsujobasuoka, Takashi Shirakura, Shunsuke Tsujimoto, Reiko Aizawa, Chieko Matsu, Yohei Sakamoto, Naoki Hase, Tsunefumi Kobayashi.1 Pharmacology Research Department, Teijin Institute for Bio-medical Research, Teijin Pharma Limited, Toyo, Tokyo, Japan; 2Toxicology Research Department, Teijin Institute for Bio-medical Research, Teijin Pharma Limited, Tokyo, Japan.

Background: Diabetic kidney disease (DKD) is a major chronic renal complication of diabetes. Since several pro-inflammatory and clinical studies have shown that the expression of xanthine oxidase (XO) to the DKD progression, inhibiting XO activity may be one of the attractive therapeutic approaches. TMX-049 is a newly developed XO inhibitor with non-purine structure. In this study, we evaluate the effect of TMX-049 on renal damage in a model of type 2 diabetic.

Methods: 1. To examine the pharmacological profile of TMX-049, in vitro and in vivo inhibition of XO activity with TMX-049 treatment was measured in human primary hepatocyte and SD rat kidney, respectively. 2. To evaluate in vivo efficacy of TMX-049 on renal injury, 8-week-old male ZDF rats were orally administrated vehicle or TMX-049 once daily for 13 weeks. Normoglycemic ZDF-lean (ZL) rats were used as non-DKD control. The amount of urinary albumin and KIM-1, a biomarker for proximal tubular cell injury, were quantified on weeks 0, 2, 4, 6, 8, 10 and 12. Measurement of XO activity in renal cortex and histological analysis were determined at 13 weeks.

Results: 1. TMX-049 inhibited cellular XO activity (IC50 = 2.43 ± 0.54 nM) in human hepatocyte and did not change other enzymatic activities related to purine metabolism. TMX-049 also showed sustained inhibition of XO activity in normal rat kidney 24 hours after oral administration was more potent than launched XO inhibitor. 2. Compared with ZL rats, ZDF rats exhibited the renal structural changes, elevation of urinary parameters such as albumin and KIM-1 and increased XO activity in renal cortex. Immunohistological examination revealed that XO/xanthine dehydrogenase expression was detected in the proximal tubules. Administration of TMX-049 reduced the urinary excretion of albumin and KIM-1, and ameliorated histological renal damage in ZDF rats without affecting any metabolic parameters.

Conclusions: TMX-049 attenuated renal injury in an experimental model of DKD. These results suggest the therapeutic potential of TMX-049 in DKD.

FR-PO598

Endoglin Mediates Endothelial Activation and Monocyte Adhesion and Is Correlated with Glomerular VCAM-1 in Patients with Diabetic Nephropathy

Pascal Bruijn,1 Tessia Gerrits,2 Sharon Heemskerk,3 Nadja Zandbergen,1 Jan A. Bruijn,1 Hans J. Baedeker,1 Marion Scharpfenecker.1 1Pharmacology,2 Basilea, Netherlands; 3Leiden University Medical Center, Leiden, Netherlands.

Background: Diabetic nephropathy is characterized by microvascular injury driven by hyperglycemia and enhanced growth factor production. Altered growth factor expression causes an angiogenic imbalance resulting in endothelial activation and dysfunction. Endoglin, a heparin-binding protein and subsequent infiltration of renal inflammatory cells, which promote renal damage in diabetic animal models. Endoglin is crucial for angiogenesis and vascular development, and is associated with endothelial activation and inflammation in animal models of renal disease. Here, we investigated whether reducing

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author. 558
endothelial endoglin expression affects endothelial activation and monocyte adhesion under diabetic conditions in vitro, and we investigated which glomerular cells express endoglin and VCAM-1, and whether glomerular endoglin expression is associated with endothelial activation in patients with diabetic nephropathy.

**Methods:** Immortalized endothelial cells with either wild type or reduced endoglin expression were used to study endothelial activation and monocyte adhesion after stimulation with either glucose or VEGF-A. Glomerular endoglin and VCAM-1 expression was studied by immunohistochemistry in biopsies of patients with diabetic nephropathy. Data were analyzed using a Student’s t-test or a Mixed Model Regression Analysis. Double-labeling experiments for endoglin and CD31 or VCAM-1. Differences were considered significant at p<0.05.

**Results:** Lowering endoglin expression in endothelial cells in vitro significantly impaired VEGF-A and glucose-mediated induction of activation markers VCAM1 and ICAM1 (p<0.05). In diabetic conditions, endoglin was primarily expressed in endothelial cells. Glomerular VCAM-1 expression co-localized with endoglin. Furthermore, glomerular VCAM-1 was significantly increased in patients with diabetic nephropathy (p<0.05) and correlated with glomerular endoglin levels (p<0.001).

**Conclusions:** Targeting endoglin function is a promising future strategy to interfere with endothelial activation in order to prevent or stop inflammation and thereby the progression of diabetic nephropathy.

**FR-PO599**

FK506 Attenuates Proteinuria by Inhibiting Endothelial-to-Mesenchymal Transition in Rats with Diabetic Nephropathy

**Key words:** Proteinuria, FK506, renal inflammation, diabetes, mesenchymal transition

**Background:** Altered glomerular mesangial cell phenotype is associated with diabetic nephropathy (DN). FK506, a well known immunosuppressant drugs, was found to be beneficial for attenuating proteinuria in DN. However, the underlying mechanism is still unknown. In this study, we investigated whether endothelial-to-mesenchymal transition (EMT) of DN could be attenuated by FK506.

**Methods:** Thirty-six SD rats were randomly divided into three groups (n=12/group): control group, DN group, FK506 treatment group. The DN model was established using streptozocin (58mg/kg). The diabetic rats were administrated with FK506 by gavage (0.15mg/kg/d) for 34 weeks. Some biochemical parameters, urinary albumin (UAL), and kidney weight/ body weight (KW/BW) were measured. Nephron and podocin were detected by Western blotting (WB) and Endothelial marker (CD31), FSP1, and o-SMA were detected by Double immunofluorescence staining, immunohistochemistry, real-time-PCR and WB.

**Results:** There were significant increases in the levels of SCr, BUN, KW/BW, UAL, than in controls. Only AS10 group recovered this number. Circulating and renal ACE2 activity were increased in the DM and treated with AS reduced these values to control level. IHC for ACE2 followed the same profile described for enzymatic activity. AT1 changed its expression in a dose-dependent fashion. AS10 group showed the same profile of expression as non-diabetic group.

**Conclusions:** In obese diabetic mouse, atrasentan treatment induced changes in body fluid composition when combined with insulin. Protective effects on kidney are observed at low doses of atrasentan by maintaining podocyte number in the glomeruli. Furthermore, atrasentan modulates ACE2 and AT1R, suggesting protective modifications in renin angiotensin system.
Further treatment with pioglitazone exerts anti-apoptotic effects on podocytes. Our findings that nephrin expression was strongly enhanced in human and murine podocytes after pioglitazone exposure. Subcellular fractionation shows expression of nephrin in the compartments. To show if pioglitazone also stabilize nephrin in “aged” podocytes we differentiated them over 8 weeks. Immunoprecipitation were performed for analyzing SUMOylation of nephrin after treatment with pioglitazone.

Conclusion: Our data strongly suggest that membrane expression of nephrin in podocytes is modulated by pioglitazone treatment. The strong expression of nephrin in cultivated podocytes after treatment with pioglitazone indicates a direct molecular mechanism which is most likely responsible for the renoprotective and anti-proteinemic effects of pioglitazone treatments in vivo.

Funding: Government Support - Non-U.S.

FR-PO606

The Classic and Trans-Signaling of Interleukin-6 Are Both Injurious in Podocyte under High Glucose Exposure Chun-Luo Lei, Hua Su,1 Chun Zhang.2

Background: Interleukin-6 (IL-6) is a multifunctional cytokine that employs IL-6 classic and trans-signaling pathways, and these two signal channels execute different or even opposite effects in certain diseases. As a cardinal event of diabetic kidney disease (DKD), whether the podocyte abnormalities are associated with IL-6 signaling, especially the individual role of IL-6 classic or trans-signaling, remains unclear.

Methods: The circular IL-6, soluble IL-6R (sIL-6R) and soluble glycoprotein 130 (sgp130) levels in subjects with or without DKD were measured. Human podocyte cell line was employed in vitro study. RNA interference targeting gp130 and gp130 or IL-6 receptors antibodies were utilized to block the entire IL-6 signaling. RNA interference targeting IL-6R and recombinant sgp130 were used to inhibit IL-6 classic and trans-signaling respectively.

Results: Our findings elucidated that the circulatory IL-6, sIL-6R and sgp130 levels are elevated in patients with DKD. The expression of membrane bound IL-6R (mIL-6R), IL-6R, and gp130 are enhanced in kidney cortex of diabetic mice accompanying with activated STAT3 by tyrosine 705 residue phosphorylation, while serine 727. Above data infer both classic and trans-signaling of IL-6 are activated during DKD. In cultured podocyte, high glucose (HG) upregulates the expression of mIL-6R and gp130, as well as STAT3 tyrosine 705 phosphorylation, in a time-dependent manner. Entirely blocking IL-6 signaling attenuates HG-induced podocyte injury. Interestingly, either inhibiting IL-6 classic signaling or suppressing its trans-signaling individually also dramatically ameliorate HG-induced podocyte injury. Both classic and trans-signaling play a detrimental role in HG-induced podocyte injury. Consistently, activation of IL-6 classic or trans-signaling aggravates podocyte damage in vitro.

Conclusion: In summary, our observations demonstrate that either IL-6 classic or trans-signaling pathways are mediated by the deleterious effect of HG. Accordingly, suppressing IL-6 classic and trans-signaling, especially simultaneously, is a promising therapeutic strategy for podocyte injury during DKD.

Funding: Government Support - Non-U.S.

FR-PO607

Attenuating Lymphatic Proliferation by Fenofibrate Ameliorates Diabetic Nephropathy and High-Fat Diet-Induced Renal Lipotoxicity Yaten Kim,1 Ji Hye Lim,1 Min Young Kim,1 Bumsoo Choi,1 Yong-Soo Kim,1 Seon Deok Hwang,2 Cheol Whee Park.1

Background: We evaluated whether fenofibrate, a PPARα agonist, has a renoprotective effect by ameliorating lipotoxicity associated with lymphangiogenesis. Accordingly, suppressing IL-6 classic and trans-signaling, especially simultaneously, is a promising therapeutic strategy for podocyte injury during DKD.

Methods: We evaluated whether fenofibrate, a PPARα agonist, has a renoprotective effect by ameliorating lipotoxicity associated with lymphangiogenesis.

Results: In male C57BLKs/6 db/db mice, fenofibrate ameliorated albuminuria and mesangial tubular fibrosis and inflammation. Fenofibrate inhibited the accumulation of intra-renal free fatty acid and triglycerides, which was associated with increase in the expression of PPARα, phosphorylated AMPK, activation of PPARα co-activator 1α, and phospho-GSK-3β. In db/db mice, fenofibrate ameliorated albuminuria and mesangial tubular fibrosis and inflammation. Fenofibrate inhibited the accumulation of intra-renal free fatty acid and triglycerides, which was associated with increase in the expression of PPARα, phosphorylated AMPK, activation of PPARα co-activator 1α, and phospho-GSK-3β.

Conclusion: In summary, our observations demonstrate that either IL-6 classic or trans-signaling pathways are mediated by the deleterious effect of HG. Accordingly, suppressing IL-6 classic and trans-signaling, especially simultaneously, is a promising therapeutic strategy for podocyte injury during DKD.

Funding: Government Support - Non-U.S.

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

Underline represents presenting author.

560
and vascular endothelial growth factor receptor-3 (VEGFR-3). Consequently, fenofibrate reversed oxidative stress. In high-fat diet-fed spontaneously hypertensive rats (SHRs), fenofibrate also attenuated renal lymphatic proliferation and lipotoxicity-induced oxidative stress and apoptosis. In cultured HK2 cells, fenofibrate prevented palmitate- and high glucose-induced expression of VEGF-C, VEGFR-3, and LYVE-1. The expression of activation of PPARα-AMPK-pACC signaling and suppression of SREBP-1 and ChREBP.

Conclusions: These results suggested that fenofibrate prevents diabetic nephropathy in db/db mice and high-fat diet-induced renal injury in SHRs by attenuating lymphatic proliferation, inflammation, and oxidative stress through activation of PPARα-AMPK pathway, especially in renal proximal tubule cells.

FR-PO608
Inhibition of High Glucose Induced Senescence of Human Glomerular Mesangial Cells by Metformin Up-Regulating Autophagy
Level Xiaoying Wang,1 Linjing Wang,1 Shuang Yang,2 Dan Sun.1 Department of Nephrology, First Affiliated Hospital of China Medical University, Shenyang, China; 3The First Hospital of China Medical University, Shenyang, China.

Background: Autophagy has been found to be closely related to aging and human disease. However, the role of autophagy in the process of human mesangial cell senescence and its mechanism is unclear. In recent years the study found that metformin can activate the AMPK signaling pathway, inhibition of mTOR pathway could promote autophagy. Here we try to investigate the effects of metformin on autophagy and human glomerular mesangial cells senescence induced by high glucose.

Methods: Human glomerular mesangial cells (HGMCs) were cultured in vitro, and exposed to high glucose (30.0 mmol/L glucose) for 12, 24, 48 and 72 h and stimulated by high glucose with 10mmol/L metformin for 72 h. Normal control group (5.5mmol/L glucose) and hypertonic group (5.5mmol/L glucose+24.5mmol/L mannitol) were set up. The first stimulation concentration of metformin was filtered by Cell Counting Kit (CCK-8) assay. The expression of autophagy marker protein LC3β was detected by Western blotting. Autophagic flow was detected by mRFP-GFP-LC3 assays using confocal microscope.

Results: Compared with the normal control group, the cells exposed to high glucose for 12.48 and 48h showed up-regulated p53 and mTOR expression (P<0.05), the cells exposed to high glucose for 24h and 48h showed up-regulated p21 and p-mTOR expression (P<0.05), the cells exposed to high glucose for 48h and 72h down-regulated p-Akt/mTOR, p62/QSTM1 and up-regulated p62/SQSTM1 expression (P<0.05) and increased percentage of SA-β-gal positive cells (P<0.05). The cells exposed to high glucose for 72h showed down-regulated LC3 expression and decreased autophagic flux level (P<0.05). Compared with those in high glucose group, The autophagic flux level and the expression of p-AMPK, LC3β were increased dramatically in high glucose with metformin group (P<0.05), while the protein expressions of p62,p53, p21, mTOR and p-mTOR decreased (P<0.05) and SA-β-gal positive cells decreased (P<0.05).

Conclusions: The senescence of human glomerular mesangial cells is associated with high glucose exposure. High glucose exposure could promote high glucose - induced senescence of human glomerular mesangial cells by increasing autophagy level via modulating AMPK/mTOR pathway.

FR-PO609
miRNA-27b and miRNA-1228 Urinary Levels Discriminate Specific Classes of Histological Damage in Diabetic Patients Paola Pontrelli,1 Francesca Conserva,2 Mariagrazia Barozzino,1 Francesco Pesce,1 Rossella Menghini,1 Annarita Oranger,1 Antonella Di Franco,1 Massimo Papale,2 Francesco Giorgetto,2 Luigi Laviola,1 Simona Simone,1 M. Rossini,1 Massimo Federici,4 Loreto Gusaldso,2 ’None, BARI, Italy; 2University of Bari, Bari, Italy; 3University of Bari Aldo Moro, Bari, Italy; 4University of Bari, Department of Emergency and Organ Transplantation, Nephrology Unit, Bari, Italy; 5University of Bari Dept. of Emergency and Organ Transplantation, Bari, Italy; 6University of Rome Tor Vergata, Rome, Italy; 7University of Bari, Bari, Italy.

Background: Diabetic nephropathy (DN) is the leading cause of end stage renal disease. Aim of our study was to identify novel urinary biomarkers which correlate with the histological damage. We focused on those miRNAs that modulate lysin63 ubiquitination, responsible of tubular damage in diabetic patients (PMID: 27881486).

Methods: Urinary samples were collected from 16 patients with type-2 diabetes (T2D), 7 with T2D and other nephropathies (T2D-GN), 7 with T2D and other nephropathies (T2D-GN), including membranous nephropathy (MN) and Focal and Segmental Glomerulosclerosis (FSGS), 32 with other nephropathies without T2D (GN), all with a biopsy proven diagnosis, 7 with T2D and normal renal function, 9 healthy subjects (HS). miRNAs expression was evaluated by qPCR in urines and in hybridization kits. Data were validated in a mouse model of DN (DBA2J mice treated with streptozotocin-STZ).

Results: miRNA-27b was down-regulated in urines of DN patients when compared to HS (p=0.03), to T2D (p=0.04) to T2D-GN (p=0.04), and to GN (p=0.05), such as miRNA-1228 (p=0.01 vs HS, p=0.01 vs T2D, p=0.04 vs T2D-GN; p=0.05 vs GN). Tissue expression of both miRNAs was also reduced at tubular level in DN vs T2D-GN (p=0.05) and was directly correlated with tubular-interstitial fibrosis (p=0.05). ROC curve from a predictive model (based on logistic regression) combining both miRNAs relative expression of miR-27b and miRNA-1228 was 0.91, with T2D-GN (AUC=0.81; p=0.001), with T2D (AUC 0.90; p=2.7E-10) and with GN (AUC=0.69; p=0.002), miRNA-27b (conserved among species) was also down-regulated in urines of DBA2J/STZ mice vs DBA2J untreated controls (FC: -3.79; P=0.05) and was correlated with lysin63 protein accumulation and tubular-interstitial fibrosis (p=0.05). miRNA-1228 expression correlated with increased fibrosis and discriminate DN patients vs other histological lesion in diabetic non- diabetic patients.

Conclusions: miRNA-27b and -1228 expression correlate with increased fibrosis and discriminate DN patients vs other histological lesion in diabetic non-diabetic patients. Funding: Government Support - Non-U.S.

FR-PO610
MicroRNA-148b Influences High Glucose-Induced Endoplasmic Reticulum Stress in Rat Mesangial Cells by Targeting AMPKε1 Quiling Fan,1 Department of Nephrology, The First Hospital, China Medical University, Shenyang, China.

Background: To verify the expression of microRNA-148b (miRNA-148b) induced by high glucose in rat mesangial cells, and to explore its effect on its target gene AMP- activated protein kinase1 (AMPKε1) and extracellular matrix excretion.

Methods: Rat mesangial cells were divided into 3 groups: normal glucose (NG, 5.5 mmol/L glucose) group, hypertonic (MA, 5.5 mmol/L glucose+ 19.5 mmol/L mannitol) group and high glucose (HG, 25.0 mmol/L glucose) group. miR-148b expression was analyzed by real time PCR. Then miR-148b was over-expressed to rat mesangial cells. Their expressions of AMPKε1, glucose regulated protein78 (GRP78), C/EBP homologous protein (CHOP), fibronectin (FN)and collagen 4 proteins were detected by Western blotting; the expression of COI4 was detected by real time PCR; the expression of COI4 was also detected by immunofluorescence.

Results: Compared with NG group, HG group showed upregulated miR-148b expression, downregulated AMPKε1 mRNA and protein expression, and upregulated CHOP, GRP78, collagen 4 and FN expression (all P<0.05). HG induced mesangial cells with miR-148b inhibitor had upregulated AMPKε1 mRNA and protein expression, and downregulated CHOP, GRP78, collagen 4, FN expression as compared with HG-induced cells without miR-148b inhibitor (all P<0.05).

Conclusions: HG can upregulate miR-148b expression and downregulate AMPKε1 expression in rat mesangial cells, then activate endoplasmic reticulum stress to induce extracellular matrix excretion. miR-148b inhibitor upregulates AMPKε1 expression, inhibits endoplasmic reticulum stress and reduces extracellular matrix excretion.

FR-PO611
Transcriptional Regulation of Long Non-Coding RNA Tug1 in Diabetic Nephropathy Jianying Lin, Farhad R. Danesh, The University of Texas MD Anderson Cancer Center, Houston, TX.

Background: Long non-coding RNAs (lncRNAs) have been implicated in the pathogenesis of a myriad of diseases, including cancer, heart diseases and kidney diseases. We recently reported that IncRNA Tug1 (Taurine-upregulated gene-1) is a differentially expressed lncRNA in a mouse model of diabetic nephropathy (DN), and podocyte-specific Tug1 overexpression exerts a renoprotective phenotype. However, how the expression of Tug1 is regulated in the diabetic milieu is unknown.

Methods: Transcription factor binding prediction algorithms (vista 2.0 and PROMO) were used to analyze protein accumulation and tubular-interstitial fibrosis (p=0.05) up-stream of the Tug1 TSS (transcription start site). Specifically, a consensus ChRE (carbohydrate response element) motif (CAGGGGmnnmCRCTG), was identified in the proximal promoter region (CAGCCTGGCAGGTCCTTG, -324 to -307) of Tug1. This motif was reported as a specific peak in our recent publication about genome-wide CHIP Seq of the glucose-responsive transcription factor ChREBP (carbohydrate response element-binding protein, also known as MLXIPL, MLX Interacting Protein Like) in mouse liver and fat. Binding of ChREBP to this motif in podocytes was further validated by ChIP-PCR and EMSA. We are currently identifying the cofactors/corepressors for this ChREBP-mediated expression of Tug1 in podocytes with.

Conclusions: We identified glucose-responsive transcription factor ChREBP binding to the evolutional conserved ChRE in the proximal promoter, as the mechanism of Tug1 down-regulation in diabetic milieu. Funding: NIDDK Support.
FR-P0612
Aerobic Exercise Training Reduces Renal Inflammatory Factors, Fibrosis, and Proteinuria in Diabetic Rats
Rodolfo R. Rampazzo, Rafael Luiz, Natália Reinecke, Edson A. Pessoa, Kleiton A. Silva, Luciana Jorge, Maria A. Gloria, Nestor Schor 1, 2 None, São Paulo, Brazil; 1Universidade Federal de São Paulo/Escola Paulista de Medicina, São Paulo, Brazil; 2University of Missouri, Columbia, AL.

Background: The aim of this study was to evaluate the role of aerobic exercise in controlling the progression of diabetic nephropathy as proteinuria, fibrosis, inflammatory factors, and thus, its possible renoprotective effects.

Methods: Adult male Wistar rats divided into 4 groups: Sedentary controls, (SED, n=8), Diabetes Sedentary (DM-SED, n=8), Diabetes Exercised (DM-EXE, n=8) and Exercise Controls (EXE, n=8). DM was induced with streptozotocin (STZ), 50mg/kg i.v. The physical training was done on treadmill 60 min/day, 5 days a week for 8 weeks. Weekly it was determined the Maximal Exercise Test (set at 65-70% of MEtest). Fibrosis (m2), Glycemia 24h post training (glycemiapt), MEtest, creatinine clearance/BW (CrCl/BW), mean arterial pressure (MAP), proteinuria (uProt), renal inflammatory factors (IL-6, IL-10, IL-17, IL-18, IL-33, IL-37, IL-40, IL-41, IL-45) were measured.

Results: SED rats (180-200g) were randomly divided into four groups: normal controls (NC), diabetic nephropathy (DN), DN with low dose quercetin (DN+LQ), and DN with high dose quercetin (DN+HQ). Quercetin, 50mg/kg/d quercetin by gavage, NC and DN rats were treated with 100mg/kg/d quercetin by gavage, NC and DN rats were treated with 100mg/kg/d DMSO by gavage. Blood glucose and body weight were obtained every two weeks, microalbuminuria and urine creatinine were obtained every four weeks. All animals were sacrificed after 12 weeks of treatments.

Results: In the present study, the levels of blood glucose, kidney hypertrophy index, microalbuminuria, SCR, BUN, TG were markedly increased in rats with STZ injection compared with NC rats, especially, these alterations were less intense in animals treated with quercetin. Picture of electron microscopy showed foot process fusion in DN rats, while quercetin markedly inhibited foot process fusion. Immunohistochemical and western blotting showed results that the expression of nephrin and podocin in DN rats was significantly decreased, the expression of desmin, ERK, p-ERK in DN rats was significantly increased, while quercetin reversed these above changes. Additionally, the contents of nephrin and podocin in urine of DN rats were markedly higher than that of NC rats, while the contents of GSH and SOD in serum and kidney tissue of DN rats were significantly lower than that of NC rats. However, quercetin decreased the contents of nephrin and podocin in urine and increased the contents of SOD and GSH in blood and kidney tissue.

Conclusion: Quercetin treatment effectively ameliorated podocyte injury in rats with DN by inhibiting ERK signaling pathway. The manipulation of quercetin might act as a promising therapeutic intervention for diabetic nephropathy.

FR-P0614
TGF-beta 1 Signaling May Be Mediated by Lysyl Oxidase-Like 2 in Human Podocytes in Diabetic Condition
Beom Jin Jeon,1 None, Seoul, Republic of Korea; 2Yonsei University College of Medicine, Seoul, Republic of Korea; 3Yonsei University College of Medicine, Seoul, Republic of Korea.

Background: Lysyl oxidase-like 2 (LOXL2) is a molecule known to be related with invasive growth and metastasis of malignant neoplasm. Recently, LOXL2 has been also reported to play an important role in target organ fibrosis including heart, liver and lung. In this study, we investigated the expression of LOXL2 in human kidney and podocyte, and its contribution to the transforming growth factor beta 1 (TGF-beta1) and collagen expression in podocytes with high glucose condition.

Methods: We evaluated the expression of LOXL2 in human kidney using immunofluorescence staining. Real-time PCR and western blotting analysis for LOXL2 mRNA and protein expression were performed using cultured human immortalized podocytes. After fully differentiated, cultured human podocytes were exposed to high glucose (HG) for 48 hours. Lenti-virus mediated gene silencing of LOXL2 was done in human podocyte.

Results: By immunofluorescence staining, LOXL2 expression was identified in human glomerulus and was significantly increased in that with diabetic kidney disease compared with normal control. LOXL2 mRNA (2.40±0.15 vs. 1.7±0.11, P<0.05) and protein expression were higher in human podocyte with HG condition than those with normal glucose condition. TGF-beta 1 mRNA expression was also increased in podocyte with HG condition (9.79±0.63 vs. 1.7±0.36, P<0.05). Gene silencing of LOXL2 significantly reduced TGF-beta1 mRNA and protein expression in human podocytes. Western blot analysis showed that collagen 1 and phosphorylated Smad2 protein expression were significantly decreased in LOXL2 knock-down podocytes.

Conclusions: Our results showed that TGF-beta 1 signaling may mediated by LOXL2 in podocytes in diabetic condition.

FR-P0615
TFGbeta (TGFb)-Stimulated PI 3 Kinase (PI 3 K)/Akt Downregulates DEPTOR to Increase Podocyte Hypertrophy and Matrix Protein Expression
Falluni Das,1 Nadhini Ghosh-Choudhury,2 Balakuntalama S. Kasinath,2 Goutam Ghosh-Choudhury,1 1HTHSCSA, SAN ANTONIO, TX; 2University of Texas Health Science Center, San Antonio, TX.

Background: TGFb contributes to kidney injury in diabetic nephropathy (DN). mTOR controls renal cell hypertrophy and matrix protein expression. We have recently shown that TGFb regulates the expression of deitor, a negative regulator component of both mTORC1 and mTORC2. We hypothesized that PI 3 K/Akt signaling may contribute to deitor regulation.

Methods: Recombinant TGFb (2 ng/ml), rat podocytes, pharmacological inhibitors, dominant negative (dn) expression vectors and siRNAs transfection, immunoblotting, immunoprecipitation, protein synthesis and hypertrophy assays, glomeruli from rats with streptozotocin (STZ)-induced DN were employed.

Results: TGFb decreased the expression of deitor in a time-dependent manner, leading to increase in the mTORC1 and mTORC2 activity, as judged by the increase in phosphorylation of their substrates 4E-BP1 and Akt. Treatment of podocytes with the PI 3 kinase and Akt inhibitors, LY294002 and MK2206, respectively, reversed the inhibition of hypertrophy induced by the PI 3 K/Akt signaling.

Conclusions: Our data for the first time demonstrate the involvement of PI 3 K/Akt signaling in the suppression of deitor by TGFb to maintain high mTORC1 and mTORC2 in the glomeruli of STZ-induced diabetic rats.
Methods: We used wild-type (WT) and eNOS-deficient mice (eNOSKO) to determine the role of the eNOS/NO pathway. Diabetes was induced by a single intraperitoneal injection of streptozotocin (STZ, 65 mg/kg body weight). Subsequently, we divided mice into four groups: WT, WT-STZ, eNOSKO, and eNOS-STZ. Four weeks after the induction of diabetes, the mice were sacrificed and their kidneys were harvested. Urinary albumin excretion was checked before the sacrifice, and glomerular damage was assessed by PAS staining. Next, the localization of inflammasome activation in glomeruli was evaluated with immunohistochemical analyses. To investigate inflammasome activation in glomeruli, glomeruli were isolated from the kidney tissue by using Dynabeads. The mRNA expression of inflammasome components NLRP3, IL-1β, and IL-18 were checked with real-time quantitative PCR.

Results: Urinary albumin excretion was increased in WT-STZ compared with WT. These results demonstrate that activation of an alternate protease plays a crucial role in the development of DN in the absence of eNOS-STZ mice.

Conclusions: eNOS/NO signaling attenuates glomerular injury in diabetic mice via suppression of inflammasome activation.

Funding: Private Foundation Support

FR-PO620

An N-Terminal Truncated Intracellular Isoform of Matrix Metalloproteinase-2 Is Induced by Hyperglycemia and Activates Human Innate Immune Response In Vitro

Rhee,2 Eun Young Lee,3 Eun Won Seong,2 Dong Won Lee,2 Soo Bong Lee,1 Ihm Soo Kwak,2 David H. Lovett,1 Internal Medicine, University of California San Francisco, San Francisco, CA; Internal Medicine, Pusan National University Hospital, Busan, Republic of Korea; 3Pusan National University School of Medicine, Yangsan, Republic of Korea

Background: We have reported that matrix metalloproteinase-2 (MMP-2) exists in two discrete isoforms. The first consists of the classical full length isoform (FL-MMP-2) which is secreted as a latent proenzyme. A second novel isoform is generated by oxidative deacetylation of NF-κB-deacetylated MMP-2 enzyme and concentrated within mitochondria. NTT-MMP-2 which is secreted as a latent proenzyme. A second novel isoform is generated by oxidative deacetylation of NF-κB-deacetylated MMP-2 enzyme and concentrated within mitochondria. NTT-MMP-2, which is secreted as a latent proenzyme, is more abundant in type 2 diabetes.

Methods: Cells were transfected with FL-MMP-2 and NTT-MMP-2 using the human HK2 proximal tubule cell line. Cells were cultured with high glucose stimulation. The induction of NTT-MMP-2 and innate immunity genes using the human HK2 proximal tubule cell line. Results: High glucose medium (30 mM) induced a 1.65 fold increase in FL-MMP-2 and NTT-MMP-2 synthesis as determined by qPCR, respectively (p<0.05). This increase in the expression of the innate immunity genes IFI17, IFI7, IL6 and CXCL11 including NLRP3 and ASC coexisted with podocytes were observed by immunohistochemistry. In immunohistochemical analyses, the expression of ASC coexisted with podocytes detected by podocytocin staining in eNOS-STZ. These data suggested that the NLRP3 inflammasome activation was dependent on glucose in podocytes. In isolated glomeruli, the mRNA expression of the innate immunity components were higher in eNOS-STZ than in WT-STZ.

Conclusions: eNOS/NO signaling attenuates glomerular injury in diabetic mice via suppression of inflammasome activation.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
**FR-PO621**

**TRAP Analysis of Podocyte Gene Expression in Diabetic Nephropathy Yingqi Wang, Ming-Zhi Zhang, Kasey C. Vickers, Raymond C. Harris, Vanderbilt University Medical Center, Nashville, TN.**

**Background:** Diabetic nephropathy (DN) is the leading cause of end-stage renal disease, and podocyte injury plays a critical role in its development. To better understand the role of podocytes in DN, we have utilized Translating Ribosome Affinity Purification (TRAP) to analyze mRNA translation in podocytes isolated from kidneys of mice with early onset of diabetes.

**Methods:** TRAP allows for the isolation and quantification of cell-specific active mRNA translation. We utilized a podocin-Cre transgene for podocyte-specific activation of a TRAP allele (Rosam2e1). Translated mRNAs were quantified by high-throughput rRNA-depleted total RNA sequencing. To determine responses to early diabetes, mice were made diabetic with streptozotocin and mRNA was isolated 3 weeks after onset of hyperglycemia. To date, 9 diabetes (5 female, 4 male) and 9 controls (3 females, 6 male) have been studied.

**Results:** With TRAP isolation, mRNA of podocin and nephrin, two podocyte markers, were enriched 50 to 70-fold. Overall, 1255 genes were upregulated >1.5 fold and 406 genes were downregulated >1.5 fold. However, there were marked sex differences in both sexes, there were gene clusters related to cell cycle, cell division and apoptosis. In both sexes, there were 100 genes were up and 40 genes were downregulated >1.5 fold. However, there were marked sex differences in gene clusters related to cell cycle, cell division and apoptosis. In both sexes, there were 100 genes were up and 40 genes were downregulated >1.5 fold. However, there were marked sex differences in gene clusters related to cell cycle, cell division and apoptosis. In both sexes, there were 100 genes were up and 40 genes were downregulated >1.5 fold. However, there were marked sex differences in gene clusters related to cell cycle, cell division and apoptosis.

**Conclusions:** Analysis of translated mRNA from podocytes after early onset of a model of type I diabetes indicates significant differences between sexes, with evidence of more dedifferentiation and injury in males. Our ongoing studies in mice with more established DN and in models of type II diabetes should provide further insight into podocyte injury and gender responses.

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

---

**FR-PO623**

Investigation of Protein Tyrosine Phosphatase, Non-Receptor Type 2 (PTPN2) and Its Interaction with Vitamin D Receptor (VDR) in Inflammation of Type 2 Diabetes Mellitus Li Zheng, Wei Zhang, Hao Zhang. Nephrology, The Third Xiangya Hospital of Central South University, Changsha, China.

**Background:** To investigate the role of protein tyrosine phosphatase nonreceptor type 2 (PTPN2) in the inflammation of type 2 diabetes mellitus (T2DM) and its interaction with vitamin D receptor(VDR).

**Methods:** 101 T2DM patients were divided into three groups based on urinary albumin-to-creatinine ratio (aACR) normal albuminuria(30mg/g<\(\text{aACR}<29\)), microalbuminuria(30mg/g<\(\text{aACR}<300mg/g<34\)), and macroalbuminuria(\(\text{aACR}>300mg/g\)), with healthy individuals as controls. Serum from these objects were analyzed for PTPN2 protein. Peripheral blood mononuclear cells (PBMCs) were cultured ex vivo to analyzed for PTPN2 and VDR in both protein and mRNA level. HK2 and THP-1 cell were stimulated with tumor necrosis factor (TNF) or high glucose and treatment with paricalcitol. The expression of PTPN2 and VDR was analyzed by real-time PCR and Western blotting. The release of IL-6 and MCP-1 were analyzed by real-time PCR and ELISA after PTPN2 silencing or overexpression.

**Results:** PTPN2 expression was down-regulated in serum and PBMCs from T2DM patients with albuminuria and same with VDR expression in PBMCs. PTPN2 levels were negatively correlated with uACR. Logistic regression analysis revealed that PTPN2 down-regulation was an independent risk factor for the increase in uACR. PTPN2 expression was positively correlated with VDR expression in the PBMCs from T2DM patients. Stimulation of TNF-α or high glucose could both decrease the expression of PTPN2 and VDR in both protein and mRNA level cultured HK2 and THP-1 cell, while treatment with paricalcitol could reverse the down-regulation of PTPN2 as well as VDR. After PTPN2 silencing in HK2 and THP-1 cell can significantly increase the production of the inflammatory cytokine IL-6 and chemoKines MCP-1. Moreover, high PTPN2 levels contributed to decline the elevated IL-6 and MCP-1. But treatment with paricalcitol after PTPN2 silencing could not reverse the up-regulation of IL-6 and MCP-1.

**Conclusions:** Down-regulation of serum PTPN2 is independently with the severity of albuminuria in T2DM.PTPN2 has anti-inflammatory activities in T2DM and the inflammation regulatory role may be associated with the Vitamin D/VDR pathway.

---

**FR-PO624**

Advanced Glycation End Products (AGEs) Interrupted Podocyte Autophagy Flux through mTOR Activation Xingchen Zhao, Yuanhan Chen, Xinling Liang, Wei Shi. Guangdong General Hospital, Guangzhou, China.

**Background:** Insufficient podocyte autophagy exacerbates podocyte injury and renal dysfunction under diabetic conditions. AGEs are a classic pathogenic factors under diabetic conditions. In present study, we studied the role of AGEs on podocyte autophagy and its underlying mechanism.

**Methods:** Diabetic db/db mice were gavaged by Pyridoxamine(inhibitor of AGE formation) to mimic diabetic conditions with low-AGEs serum levels. Autophagy were examed by Western blotting, immunofluorescent staining, transmission electron microscopy.

**Results:** AGE interrupted podocyte autophagy flux through mTOR activation.

**Conclusions:** AGE inhibited podocyte autophagy and led to podocyte injury in vivo and in vitro (FIG 1A-D). We further found that AGE blocked autophagy flux via interfering the formation of autophagosome, fusion of autophasome and lysosome in cultured podocyte(FIG1 E-F). 3. mTOR is an important autophagy negative regulator. Next, we found AGE activated mTOR in both protein and mRNA level cultured HK2 and THP-1 cell, while treatment with paricalcitol could reverse the down-regulation of PTPN2 as well as VDR. After PTPN2 silencing in HK2 and THP-1 cell can significantly increase the production of the inflammatory cytokine IL-6 and chemoKines MCP-1. Moreover, high PTPN2 levels contributed to decline the elevated IL-6 and MCP-1. But treatment with paricalcitol after PTPN2 silencing could not reverse the up-regulation of IL-6 and MCP-1.

**Conclusions:** Down-regulation of serum PTPN2 is independently with the severity of albuminuria in T2DM. PTPN2 has anti-inflammatory activities in T2DM and the inflammation regulatory role may be associated with the Vitamin D/VDR pathway.
The deleterious actions of Ang II are antagonized by Ang (1-7), which is generated by converting enzyme (ACE2) and NEP. ACE2 and NEP are multifunctional enzymes and their shedding in the urine have emerged as early biomarkers for DKD. ACE2 has been shown to have renoprotective and cardioprotective role in diabetic mice. In addition, a combination of AT1 receptor blockade and NEP inhibition, Sacubitril-Valsartan is used for management of heart failure. The aim of this study was to investigate whether shedding of urinary ACE2 and NEP could be a predictor of cardiovascular disease and index of intra cardiac ACE2 and NEP status in db/db diabetic mice.

**Methods:** Radio-telemetry was used to measure blood pressure. Control and diabetic db/db mice (8 weeks) were treated with pioglitazone (20mg/kg/day) for 10 weeks. Western blot, immunostaining and RAS enzyme assays were used to study renal, urinary and cardiac protein expression and activities.

**Results:** db/db mice are normotensive at the ages of 8-12 weeks. There were no significant differences in cardiac and renal ACE2 and NEP between db db and diabetic mice. However, at 18 weeks, db/db mice developed albuminuria and hypertension. In addition, at this age there was a significant increase in urinary and cardiac ACE2, NEP expression and activity. Pioglitazone treatment of db/db diabetic mice normalized hyperglycemia and attenuated albuminuria. In addition, pioglitazone increased expression and activity of cardiac ACE2 whereas it decreased expression and activity of cardiac NEP compared to untreated db/db mice.

**Conclusions:** Pioglitazone treatment could be used as a renoprotective and cardioprotective since it attenuated albuminuria, increased cardiac ACE2 and decreased cardiac NEP. Increased urinary ACE2 and NEP could be used to predict alteration of cardiac RAS status and possible risk of cardiovascular diseases.

**FR-PO627**

**Increased Phosphorylation of the Ubiquitin Ligase Kelch-Like 3 in the Kidney of Db/Db Mice Shigeru Shibata,1,2,3 M. Makoto Hosoyamada,1 Shunya Uchida,2,3 Shigeru Toyoki,1 Emiko Kuribayashi-Okuma,1 Yoshikazu Nemoto,1 Chikayuki Morimoto,2 Yoshifuru Tamura,2 Makoto Hosoyamada,1 Shunya Uchida,2,3 Teikyo University School of Medicine, Tokyo, Japan;1 Teikyo University School of Medicine, Tokyo, Japan.

**Background:** Although clinical studies have shown that diabetic patients display salt-sensitive hypertension, its pathogenesis remains unclear. Kelch-like 3 (KLHL3) is a component of an E3 ubiquitin ligase complex that regulates blood pressure by targeting WNK4 (With-No-Lyisne (WNK) kinases for degradation. Mutations and inactivation of KLHL3 cause hypertension resulting from increased NaCl cotransporter (NCC) activity in the kidney. Previously, we have reported that angiotensin II (Shibata et al. PNAS 2014) and potassium depletion (Ishizawa et al. BBRC 2016) inactivate KLHL3 by protein kinase C (PKC)-mediated phosphorylation at S433 in the Kelch-domain, thereby contributing to blood pressure elevation. In this study, we examined the possible involvement of KLHL3 in the diabetic kidney using a model of type 2 diabetes.

**Methods:** We examined the expression levels of total KLHL3 and KLHL3 phosphorylated at S433 (KLHL3 S433-P) in the kidney of Db/+ and Db/db mice. We also determined the levels of CI transporters including NCC, Na-K-2Cl cotransporter NKCC2, and CHC04, exchange pendrin in the membrane fraction of this model. In addition, we examined the phosphorylation levels of S433 in the kidney of Db/+ and Db/db mice.

**Results:** Western blotting revealed that KLHL3 S433-P levels were significantly increased in the kidneys of Db/db mice (2.2-fold increase versus Db/+ mice; P < 0.01), which was associated with the increased levels of WNK1/4. Moreover, NCC levels in the renal membrane fraction were significantly higher in Db/db mice than Db/+ mice (2.3-fold increase, P < 0.01). Interestingly, NKCC2 was also increased, whereas pendrin was decreased in Db/db mice. The results indicate that increased phosphorylation of KLHL3 is involved in the kidney.

**Conclusions:** We examined how diabetes and insulin alter the levels of renal UA transporters. Hypouricosuria. However, the underlying mechanisms remain unclear. In this study, we aimed to investigate how diabetes and insulin alter the levels of renal UA transporters.

**Methods:** We examined the levels of total UA transporters at S433 (KLHL3 S433-P) in the kidney of Db/+ and Db/db mice. We also determined the levels of CI transporters including NCC, Na-K-2Cl cotransporter NKCC2, and CHC04, exchange pendrin in the membrane fraction of this model.

**Results:** Western blotting revealed that KLHL3 S433-P levels were significantly increased in the kidneys of Db/db mice (2.2-fold increase versus Db/+ mice; P < 0.01), which was associated with the increased levels of WNK1/4. Moreover, NCC levels in the renal membrane fraction were significantly higher in Db/db mice than Db/+ mice (2.3-fold increase, P < 0.01). Interestingly, NKCC2 was also increased, whereas pendrin was decreased in Db/db mice. The results indicate that increased phosphorylation of KLHL3 is involved in the kidney.

**Conclusions:** We examined how diabetes and insulin alter the levels of renal UA transporters. Hypouricosuria. However, the underlying mechanisms remain unclear. In this study, we aimed to investigate how diabetes and insulin alter the levels of renal UA transporters.
day) to the diabetic rats decreased UACR excretion and alleviated UACR transporter level changes. In contrast, the contribution of insulin in the regulation of urea transporters in normal rats received a low dose of insulin (0.75 U/day). Of note, insulin significantly increased URAT1 and decreased ABCG2 levels, resulting in increased UAA reabsorption. Furthermore, URAT1 was present in NRK-52E cells, and the addition of insulin to the medium significantly increased the endogenous URAT1 levels in the membrane fraction of NRK-52E cells.

Conclusions: These results suggest a previously unrecognized mechanism for the anti-uricosuric effects of insulin, and provide novel insights into the renal UA handling in the diabetic state.

FR-PO629
Diabetes Aggravate Post-Ishemiac Renal Fibrosis through Persistent Activation of Sonic Hedgehog Signaling
Sang-Ho Lee,1 Dong-Jin Kim,2 Jun mo Kang,3 Seon hwa Park,4 Seok jong Song,5 Se-MI Kim,6 Seong Jung-Woo,7 Yu Hong Kang,8 Seung Hyeong Lee2 1Department of Nephrology of internal departmental medical Kyung Hee University College of Medicine, Seoul, Republic of Korea; 2Kyung Hee University, Seoul, Republic of Korea; 3Kyung Hee University Hospital at Gangdong, Seoul, Korea, Seoul, Republic of Korea; 4KyungHee University, Seoul, Republic of Korea; 5Bundang CHA Medical Center, CHA Univ., Bundang, Republic of Korea.

Background: Diabetes has a high risk for chronic kidney disease (CKD) and increases the severity of acute kidney injury (AKI). AKI induces renal fibrosis, known as a key feature of CKD, and renal fibrosis is associated with transforming growth factor-beta (TGF-β1) and sonic hedgehog (Shh) signaling pathway. However, it is not known whether diabetes accelerates CKD progression via Shh signaling after AKI. Here, we investigated the influence of diabetes on CKD progression after AKI.

Methods: We established renal ischemia-reperfusion injury (IRI) model in streptozotocin induced diabetic mice. Histological changes in the kidney were evaluated at 3 and 5 weeks after IRI. The expression levels of mRNAs and proteins related to fibrosis and inflammation were determined by qRT-PCR and western blot. The effect of hyperglycemia on the epithelial-mesenchymal transition (EMT) induced by TGF-β1 and Shh signaling pathway was demonstrated in HKC-8.

Results: When comparing between 3 and 5 weeks after IRI, there was no improvement of tubulointerstitial injury in diabetes. Renal fibrosis was significantly higher in diabetes than in non-diabetes at 5 weeks after IRI. The pattern of infiltrated T and B cell was also consistent with that of renal fibrosis. The mRNA and protein expression levels of related TGF-β1 and Shh signaling pathway were significantly higher in the diabetic IRI kidneys than in the non-diabetic IRI kidneys. In vitro, Hyperglycemia led to the expression levels of TGF-β1 and Shh, and then interacted with each other for the progression of fibrosis.

Conclusions: Diabetes aggravate renal ischemia-reperfusion injury (IRI) model in streptozotocin induced diabetic mice. Histological changes in the kidney were evaluated at 3 and 5 weeks after IRI. The expression levels of mRNAs and proteins related to fibrosis and inflammation were determined by qRT-PCR and western blot. The effect of hyperglycemia on the epithelial-mesenchymal transition (EMT) induced by TGF-β1 and Shh signaling pathway was demonstrated in HKC-8.

FR-PO630
Clusterin Is Increased in Glomeruli of Patients with Diabetic Nephropathy and after Induction of Damage in Podocytes In Vitro
Junling Jia,1 Kimberley Bus,1 Marion eraar,2 Miriam Conway,3 Xiaoyan Kang,4 Seon hwa Lee,5 Dong-Jin Kim,6 Yang gyun Park,2 Seo Young Lee2 1Department of Pathology, Leiden University Medical Center, Leiden, Netherlands; 2School of Medicine, Washington, DC; 3Department of Pathology, Leiden University Medical Center, Leiden, Netherlands; 4Department of Medicine, Washington, DC; 5Department of Nephrology, Seon hwa Lee, 6Department of Medicine, Kyung Hee University, Seoul, Republic of Korea.

Background: Clusterin is a glycoprotein which is ubiquitously expressed in many tissue types and is known to play a role in immune processes, and is suggested to have protective properties on cells. The expression of clusterin has been reported to be up-regulated in diverse kidney injuries. In this study, we aimed to investigate the pro-inflammatory effects of prolonged exposure to high-glucose concentration on RPTEC/TERT1 cells and to determine whether MSC-derived factors modulate this response.

Methods: Human RPTEC/TERT1 cells were cultured for 12 days to generate stable confluent monolayers. Media containing “Normal” (5mM) and “High” (25mM) glucose were added to the culture media. We added MSCs to these monolayers and investigated the effects of MSCs on the expression of pro-inflammatory genes and proteins.

Results: When comparing between normal-glucose and high-glucose treatments, there was no significant difference in the expression levels of pro-inflammatory genes and proteins. However, when comparing between normal-glucose and high-glucose treatments with MSCs, there was a significant decrease in the expression levels of pro-inflammatory genes and proteins. These effects were more pronounced in the high-glucose treatment with MSCs.

Conclusions: Our results suggest that MSCs modulate the pro-inflammatory effects of high-glucose concentration on RPTEC/TERT1 cells. Further studies are needed to investigate the mechanisms by which MSCs exert their protective effects.
The effects of açai (Euterpe oleracea) Extract in the Oxidative Stress and Inflammation in Mouse Mesangial Cells Stimulated with High Glucose

Elisa M. Higa,1 Deyse Lima,1 Giovana Punaro,2 Adelson Rodrigues,3 Danielle F. de Souza,4 Deyse Lima,1 Camila Farias,1 Daniela B. Rodrigues.3 Medicine Department/Unifesp, Sao Paulo, Brazil; 2UNIFESP, Sao Paulo, Brazil; 3Group/Team: Laboratory of Nitric Oxide and Oxidative Stress.

Background: Diabetes mellitus is a chronic disease characterized by hyperglycemia, which is associated with injuries to several organs, 20 to 30% of diabetic patients develop nephropathy, characterized by excessive production of extracellular mesangial matrix, marked initially by albuminuria, with gradual reduction of renal function. Açaí is a native fruit from Amazon, which could provide beneficial effects on human health due to its antioxidant properties. The aim of this study was to evaluate the effects of açai extract (EA) in the oxidative stress and inflammation induced by high glucose in immortalized mouse mesangial cells (MIMC).

Methods: MIMC were cultured in DMEM with 5% fetal bovine serum. At 60-70% of confluence, they were cultured in media with normal glucose (NG – 6.7mM/L), mannitol (osmolar control – 30mM/L) or high glucose (30mM/L) for 24, 48 or 72h. After the treatment, cell viability was assessed through an automated counter (Coutess TM). The supernatant was collected for measuring NO by Nitric Oxide Analyzer (NOA™, Sievers, CO, USA). NO was also measured in the cells by DAF-FM staining; reactive oxygen species (ROS) were measured using DCFH-DA. Catalase, Nrf2, iNOS and NF-xB p65 were analyzed by Western blot.

Results: The cell viability did not change and the EA remained greater than 90% in all groups, showing no cytotoxicity of the extract. There was a significant increase of the cellular proliferation in the HG when compared to the NG group, while EA managed to decrease it in all experimental groups. ROS and iNOS markers were increased in the HG vs NG group, being also decreased after treatment with EA, p<0.05. HG showed a decrease in the protein content of the antioxidants catalase and Nrf2 vs NG group, which were partially recovered by EA, with p<0.05.

Conclusions: In this study, EA was able to decrease the proliferation and oxidative stress induced by high glucose, in MIMC, by suppressing inflammatory mediators signalling (NF-xB p65 and iNOS), and at the same time activating Nrf2 antioxidant response pathways. The use of extract of açai could be an additional protective strategy for increasing the antioxidant defense system in diabetes, and delay the progression of this disease and its complications, such as the nephropathy.

Funding: Government Support - Non-U.S.

Impact of P2X7 Receptor on the Progression of Diabetic Nephropathy in Rats

Elsa M. Higa,1 Robson S. Serralha,1 Adelson Rodrigues,3 Giovana Punaro,1 Margaret G. Mouru,1 Deyse Lima,1 Camila Farias,1 Daniela B. Rodrigues.3 Medicine Department/Unifesp, Sao Paulo, Brazil; 2Universidade Federal de Sao Paulo, Maua, Brazil; 3UNIFESP, Sao Paulo, Brazil; 4Group/Team: Laboratory of Nitric Oxide and Oxidative Stress.

Background: Diabetes mellitus (DM) is a chronic disease which occurs when there is a failure in insulin production or when the cells become resistant to this hormone leading to hyperglycemia. This situation results in increase of extracellular ATP concentration, which is responsible for several biological functions, among them the activation of P2X7 receptor. When rapidly activated, P2X7 allows the cations influx to the cells, mainly calcium. Constant activation of P2X7, results in opening of many non-selective pores and these in turn allow the passage of hydrophilic molecules with approximately 900 Da. In both processes, P2X7, induces cell death by necrosis via cell swelling or apoptosis, through high concentrations of calcium. Studies from our Laboratory showed that P2X7 expression and activation is associated with oxidative stress in DM. Our aim is to evaluate the effects of P2X7, on the diabetic nephropathy progression in rats.

Methods: Male Wistar rats, 7 weeks old, were unilaterally nephrectomized and DM was induced by streptozotocin (STZ, 60mg/kg, i.v.). Control rats (CTL) (received citrate buffer, STZ vehicle). The animals were placed in metabolic cages in different weeks for 24-hour urine collection and a small aliquot of 3-hour blood fasting, for biochemical analysis. The renal tissue was collected after euthanasia, under anesthesia, and prepared for Western blot (WB) test against P2X7, from the 1st to 8th week of diabetes, results were calculated as mean ± SEM, with significance at p<0.05.

Results: Plasma urea was significantly increased and urinary urea was significantly decreased in diabetic animals in all weeks of protocol when compared to the respective CTL. Proteinuria was increased in diabetic animals at 2nd to 8th week of protocol, when compared to the respective CTL. Analysis of the data by qPCR expression analysis by WB presented a significant increase of this receptor at 6th week when compared to 1st week of DM. We observed a moderate positive correlation between P2X7, protein and plasmatic urea, and a negative correlation between P2X7, and urinary urea. We found a strong positive correlation between P2X7, protein and proteinuria at 6th week (p< 0.05).

Conclusions: Our data, mainly proteinuria, suggest that P2X7, plays a role on the progression of nephropathy in this model of DM.

Vitamin D Receptor Agonist (VDA) Prevents Differentiation of Podocytes through Down Regulation of MicroRNA193a in High Glucose

Margaret G. Mouro,1 Daniela B. Rodrigues,3 Giovana Punaro,1 Camila Farias,1 Adelson Rodrigues,3 Deyse Lima,1 Camila Farias,1 Daniela B. Rodrigues.3 Medicine Department/Unifesp, Sao Paulo, Brazil; 2Universidade Federal de Sao Paulo, Maua, Brazil; 3UNIFESP, Sao Paulo, Brazil; 4Group/Team: Laboratory of Nitric Oxide and Oxidative Stress.

Background: Both podocytes (PDs) and parietal epithelial cells (PECs) are derived from the same mesenchymal cells during embryogenesis. Expression of miR193a, which inversely regulates Wilms tumor (WT1) gene (the transcripter of nephrin and podocyanin) determines the net phenotype. Vitamin D receptor agonist (VDA) has been shown to down regulate miR193a in differentiating PECs. We hypothesize that if high glucose dedifferentiates PDs through up regulation of miR193a then VDA could prevent PDs dedifferentiation via down regulation of miR193a.

Methods: Differentiated (DIF)-PDs were incubated in media containing either buffer or high glucose (30 mM) for 48 hours (n=4). To evaluate the effect of VDR agonist, DIF-PDs were incubated in media containing a buffer, high glucose with/without VDA (E1B105, 1 nM) for 48 hours. To determine the effect of WT1 repressor complex on the PA2X promoter in high glucose milieu, cellular lysates of control and high glucose treated PDs were immunoprecipitated with WT1 antibody and IP fraction was probed for DNTM1, EZH2, and menin. In vivo studies, four-months old wild-type and BTBR+ mouse mice were analyzed for their normal saline or normal saline + VDA (0.1 µg/Kg), intraperitoneally, every other day for 4 weeks. Renal cortical sections were labeled for WT1, synaptopodin, and PA2X. Renal cortical sections were labeled for miR193a by fluorescent in situ hybridization technique.

Conclusions: High glucose down regulated (p<0.05 vs. control) PD expression of WT1, nephrin, podocyanin but enhanced (p<0.01 vs. control) expression of PA2X and miR193a. VDA not only down regulated PD expression of miR193a and PA2X but also upregulated (p<0.05 vs. control) expression of WT1. High glucose upregulated PD expression of PA2X through disruption of WT1 repressor complex binding on PA2X promoter, VDA treatment not only increased PD expression of WT1 but also displayed binding of WT1 repressor complex on the PA2X promoter. Renal cortical sections of BTBR+ mice displayed enhanced PD expression of miR193a, decreased PD expression of WT1 and enhanced expression of PA2X.

Conclusions: High glucose dedifferentiates PDs via up regulation of miR193a and VDA preserves PD phenotype in high glucose milieu by down regulating miR193a.

Funding: NIDDK Support

TRAM34, an Inhibitor of KCa3.1: A Novel Therapy for Treatment of Established Diabetic Nephropathy

Chunling Huang,1 Ling Zhang, Hao Yi, Ying Shi, Xinming Chen, Carol A. Pollock. Kolling institute, the University of Sydney, Sydney, NSW, Australia.

Background: Existing treatments of established diabetic nephropathy have not been proven to have long term efficacy. Hence it is essential and indeed urgent to discover novel therapeutic agents to stabilize or reverse diabetic nephropathy. KCa3.1 is an intermediate/small-conductance calcium activated potassium channel. The most well defined role of KCa3.1 channels is to regulate calcium entry into cells and thereby modulate calcium-signaling processes. We have previously demonstrated in murine models of diabetes mellitus that gene silencing or pharmacological blockade of KCa3.1, when introduced at the induction of diabetes mellitus, confers significant protection against the subsequent development of diabetic induced interstitial fibrosis through inhibition of TGF-β1 signaling pathways. Therefore, this study aimed to investigate the therapeutic effect of the KCa3.1 inhibitor TRAM34 in a mouse model of established diabetic nephropathy.

Methods: Diabetic eNOS-/- mice with established nephropathy (24 weeks after induction of type 1 diabetes induced by streptozotocin) were treated with TRAM34 or DMSO (vehicle control) for a further 14 weeks. Preterminal kidney function and renal structure were assessed as well as inflammatory, fibrotic markers and the TGF-β1 signaling pathway.

Results: 24h urinary albumin was significantly increased in the diabetic animals compared to the non-diabetic controls (P<0.01). Albuminuria was significantly reduced in TRAM34 treated diabetic animals compared to the diabetic group (P<0.05). Immunohistochemistry demonstrated increased CD68 and F4/80 expression, indicating increased macrophage infiltration in the diabetic animals (P<0.05), which was reversed by treatment with TRAM34 (P<0.05). Similarly, TRAM34 reversed the increased mRNA and protein expression of the type III collagen and fibronectin observed in the diabetic animals (P<0.05). Furthermore, blocking the KCa3.1 channel by TRAM34 led to the reduction of TGF-β1 signaling through inhibiting phosphorylation of Smad2/3 (P<0.05).

Conclusions: Blockade of KCa3.1 by TRAM34 is a promising therapeutic intervention in established diabetic nephropathy.

Funding: Private Foundation Support
FR-PO637
GFR Correlates with the Homogeneity of Glomerular Capillary Blood Flow in Diabetic Rats
Jacob S. Engelberg,1 Donato Sardella,² Luca Bordoni,² Francesco Trepicicione,1 George Rhodes,³ Ruben M. Sandovál,¹ Leif Östergaard,¹ Giovannibattista Capasso,¹ Bruce A. Moltó,² Sebastian Frische,¹ Indiana University School of Medicine, Indianapolis, IN; 1Second University of Naples, Naples, Italy; 2University of Aarhus, Aarhus, Denmark; 1University of Camerino, Corridonia, Italy; 1University of Campania Luigi Vanvitelli, Napoli, Italy.

Background: Hyperfiltration is common in early diabetes, but the mechanisms behind the rise in GFR are not well understood. Theory predicts that glomerular capillary blood flow dynamics can influence GFR. We therefore aim to investigate if the heterogeneity of glomerular capillary blood flow velocity influences GFR in experimental diabetic rats.

Methods: 3 groups of male Munich Wistar Frömter rats were studied: Control (C) (n=8), Diabetic (D) (7 days after STZ-injection (40 mg/kg)) (n=10) and acutely hyperglycemic (H) (i.v. glucose injections to reach blood glucose (BG) > 20 mM) (n=7). Rats were anesthetized with Inactin and prepared for 2-photon in vivo microscopy (2PM) by externalization of the left kidney. BP and HR were monitored. Blood flow velocity was labelled by injection of Setau-647-coupled 500kD dextran. Blood flow velocity was measured in 26 glomerular capillaries in each glomerulus using longitudinal lineans at >1.3 kHz in the capillary lumen. GFR was measured by fitting a double-exponential decay function to the FITC signal in the plasma recorded by 2PM during 30 min after a bolus of FITC-3kD-dextran. Blood samples were obtained before and after microscopy.

Results: A significant correlation between the homogeneity of glomerular capillary blood flow velocity and GFR was found in the D-rats (p=0.028), but not in C or H-rats. In C-rats GFR correlated significantly with BP (p=0.047, age (p=0.026) and plasma osmolality (p=0.011). GFR did not correlate with these parameters in D-rats (p>0.08: p=0.84 and p=0.45) or H-rats (p=0.15, p=0.22, and p=0.68).

Conclusions: Homogenization of blood flow velocities in the glomerular capillaries seems a novel powerful mechanism, which may underlie hyperfiltration in diabetic rats. Mechanistically, it may result from mesangial cell dysfunction and it appears to overrule the influence of parameters influencing GFR in control rats.

Funding: Government Support - Non-U.S.

FR-PO638
A New Model of Diabetic Nephropathy with Advanced CKD Progression in C57BL/6 Mice
Xiaojiao Bai,1 Xiao Li,3 Jianwei Tian,3 Wan Jiao,¹ Youhua Liu,¹ Nephrology, Nanfang Hospital, Southern Medical University, Guangzhou, China; 1University of Pittsburgh, Pittsburgh, PA.

Background: Diabetic nephropathy (DN) is the leading cause of end-stage kidney disease in industrialized nations. However, there is a lack of robust mouse models with key features of advanced human DN. Very few options of marine models for studying DN include Akita and OVE26 type 1 diabetic mice, and C57BL/6 db/db, C57BL/KsJ db/db, eNOS(-/-)/db/db and BT/BR ob/ob type 2 diabetic mice. The limitation of these mice is the requirement for superimposition to obtain desired phenotypic characteristics. Most genetically modified mice are on the C57BL/6 background; however, they are notorious for resistance to develop DN. To overcome these conundrums, this study reports a novel DN model by challenging with advanced oxidation protein products (AOPPs) in streptozotocin-induced diabetic C57BL/6 mice.

Methods: Urethane-anesthetized male C57BL/6 mice were divided as follows: 1) non-diabetic; 2) AOPPs-challenged NC; 3) losartan-treated AOPPs-challenged NC; 4) diabetic; 5) AOPPs-challenged diabetic and 6) losartan-treated AOPPs-challenged diabetic mice. After 8, 12 and 24 weeks, morphological parameters were evaluated and kidneys harvested for morphology and morphometry.

Results: Glomerular hypertrophy and accumulation of mesangial matrix were present by 8 weeks. During 24 weeks, glomerular lesions similar to those of advanced human DN were present, as demonstrated morphologically by significant mesangial expansion (p<0.001) and sclerosis resembling Kimmelstiel-Wilson nodules, diffuse podocyte foot process effacement (p<0.05), increased glomerular basement membrane width (p<0.001), and worsened tubulointerstitial fibrosis. Immunofluorescence microscopy excluded immune complex deposits in mesangium and IgG. The morphological changes recapitulate the renal pathology of advanced human DN. AOPPs-challenged diabetic C57BL/6 mice were more sensitive to develop progressive proteinuria beginning at 8 weeks. By 24 weeks, increased albumin excretion rate (p<0.001) was found and losartan treatment alleviated these changes.

Conclusions: AOPPs can accelerate the progression of DN in resistant C57BL/6 mice and this mouse model offers a homogeneous genetic background for studying the pathogenesis of advanced DN that resembles human diabetic kidney disease. It also makes it possible to interrogate the role of specific genetic modifications and to evaluate novel therapeutic agents in the preclinical setting.

Funding: Government Support - Non-U.S.

FR-PO639
Distinct Patterns of Dysregulated Autophagy in Type 1 and 2 Diabetic Nephropathy
Shunsuke Sakai,1 Takeshi Yamamoto,1 Yoshihisa Takabatake,1 Atsushi Takahashi,1 Tomoko Namba,2 Satoshi Minami,1 Ryuta Fujimori,1 Junjiro Takahashi,1 Tomonori Kimura,1 Fumio Nimmura,1 Yoshitaka Isaka,1 Osaka University Graduate School of Medicine, Suita, Osaka, Japan; 1Tokai University School of Medicine, Isehara, Japan.

Background: Autophagy maintains cellular homeostasis and has protective roles against several stresses. Although it has been reported that high blood glucose can impair some nutrient signalings, suppress autophagy induction during type 2 diabetic nephropathy, how autophagy is dysregulated is still largely unknown.

Methods: 1) We assessed the autophagic flux in vivo by investigating the difference in the numbers of GFP-LC3-positive dots by chloroquine administration under fed or starved condition in streptozotocin (STZ)-treated GFP-LC3 transgenic mice (type 1 diabetes) or in obese db/db mice crossed with GFP-LC3 transgenic mice (type 2 diabetes). 2) We compared the inhibitory effects of glucose, insulin, and amino acids on autophagic tubulointerstitial units of 24 h-starved GFP-LC3 transgenic mice. 3) We examined the consequences of long-term autophagy deficiency using STZ-treated proximal tubular cell (PTC)-specific Atg3-deficient mice (Atg3F/F;KAP) or Atg5F/F;KAP crossed with db/db mice. 4) STZ-treated mice with defects in autophagy. In contrast, these were increased in db/db mice regardless of autophagy deficiency. 1R lead to more severe injury in both diabetic mice compared with nondiabetic mice. Rapamycin exaggerated 1R injury in STZ-induced mice, while it attenuated in db/db mice.

Conclusions: Distinct patterns of dysregulated autophagy in type 1 and 2 diabetic nephropathy should be considered in prevention and treatment.

Funding: Government Support - Non-U.S.

FR-PO640
Inhibition of Prolyl Hydroxylase Domain (PHD) Reduces Glomerular Macrophage Infiltration and Improves Albuminuria in Mice with a High Fat Diet
Hisaako Saito,1 Tetsumi Tanaka,2 Mai Sugihara,1 Kenji Fukui,1 Takeshi Wakashima,1 Masasumi Nangaku,1 JF CPRl, Osaka, Japan; 2The University of Tokyo graduate School of Medicine, Tokyo, Japan; 3The University of Tokyo School of Medicine, Tokyo, Japan.

Background: The epidemic of obesity and its complications is rapidly growing all over the world. Chronic hypoxia in the tubulointerstitium is a major pathogenic factor mediating progression of CKD, and kidneys of metabolic disorders suffer from significant damage in the interstitial hypoxic environment. Most drug discovery established utility of prolyl hydroxylase domain (PHD) inhibitors as stabilizers of hypoxia-inducible factors (HIFs) in vivo, which are currently in human clinical studies for the treatment of anemia in CKD. Notably, some clinical studies suggest a role of PHD inhibitors in ameliorating obesity and hyperlipidemia. In this study, we hypothesized that HIF activation using a PHD inhibitor, JT-951, protects from obesity-related glomerulopathy (ORG) in mice fed with high fat diet (HFD).

Methods: Eight-week-old, C57BL/6 mice were fed with HFD for 12 or 20 weeks with or without JTZ-951 (0.055%, mixed in chow). Renal consequences of PHD inhibition was investigated at 20 or 28 weeks of age.

Results: JT-951 caused a transient rise in hematocrit levels (at 12 weeks of age). Successful activation of HIF in the kidney was confirmed by immunostaining for HIF-1α protein and reduced macrophage infiltration in HFD fed mice. In contrast, these were increased in db/db mice regardless of PHD inhibition. 1R lead to more severe injury in both diabetic mice compared with nondiabetic mice. Rapamycin exaggerated 1R injury in STZ-induced mice, while it attenuated in db/db mice.

Conclusions: Distinct patterns of dysregulated autophagy in type 1 and 2 diabetic nephropathy should be considered in prevention and treatment.

Funding: Government Support - Non-U.S.
FR-PO641

Does SGLT2 Inhibition with Dapagliflozin Overcome Therapy Resistance to RAAS Inhibition? Hidde J. Lambers Heerspink,1 Sergej Petrykiv,14 Groezwijn D. Laverman,3 Dick de Zeeuw,12,3,4 None, Groningen, Netherlands; 1University Medical Center Groningen, Groningen, Netherlands; 2ZGT Almelo, Almelo, Netherlands.

Background: Renin-Angiotensin-Aldosterone-System inhibitors (RAASI) is a mainstay for renal and cardiovascular protective treatment in patients with chronic kidney disease. However, individual patients show a large variation in their response to RAASI both in surrogates like albuminuria and the hard renal outcomes. Sodium-glucose co-transporter 2 inhibitors (SGLT2i) lower albuminuria and confer cardiovascular and possibly renal protection. To establish whether individual therapy resistance to RAASI can be overcome by adding an SGLT2i inhibitor we assessed individual albuminuria responses in patients exposed both to RAASI and the SGLT2 inhibitor dapagliflozin.

Methods: We used a data from a randomized controlled cross-over trial designed to assess the albuminuria lowering effect of 6-weeks treatment with dapagliflozin. The trial enrolled 35 patients with type 2 diabetes, albumin creatinine ratio (UACR) between 100 and 3500 mg/g who were all using an ACEI or ARB at the time of enrollment. We extracted from the electronic medical records data on the UACR response upon start of RAASI before the trial period, and analyzed the individual albuminuria response to RAASI and to dapagliflozin.

Results: We retrieved data on RAASI from 26 patients (age 62 (SD 8); male gender 20 (77%); UACR 355 [150 – 533] mg/g). Thirteen patients started an ACEI, and 13 an ARB before entry into the study. The mean UACR lowering response to RAASI was 26.5% with a large between individual variability (range -76.1 to +135.1%). The addition of dapagliflozin resulted in a mean UACR lowering response of 34.9%, again with a large between individual variability (range -83.9 to +94.2). Interestingly, there was a significant positive correlation between the response to RAASI and dapagliflozin (Pearson correlation coefficient 0.635; p<0.001) indicating that patients who did not respond to RAASI also did not respond to dapagliflozin. Therapy adherence during the study was excellent with 97.5% of all medications being taken.

Conclusions: Individual therapy resistance to RAASI cannot be overcome with the addition of completely different classes of drugs. SGLT2 inhibitors. These data suggest that the individual drug response is an intrinsic individual characteristic possibly unrelated to the type of intervention, unless the mode of action of dapagliflozin on albuminuria is through the RAAS.

Funding: Commercial Support - AstraZeneca provided dapagliflozin study medication.

FR-PO642

The Study of Mechanisms of SGLT2 Inhibitors for Renoprotection in Human Diabetic Kidney Disease Sukeo Sato, Saitama Medical Center; Saitama Medical University, Kawagoe, Japan.

Background: SGLT2 inhibitor (SGLT2i) has been reported to suppress not only glomerular hyperfiltration, but also have direct action on renal proximal tubule cells in vitro. There have been no reports on detailed investigations of its mechanism in humans, and there are many discussions about that. Therefore, we explore the effect of various SGLT2 on kidney function and kidney injury in patients with diabetic kidney disease (DKD).

Methods: In patients with type 2 diabetes (T2DM) with DKD, the usual dose of SGLT2 inhibitor (Ipragliflozin 50mg or Canagliflozin 100mg or Dapagliflozin 5mg or Lecogliflozin 2.5mg or Tofogliflozin 20mg or Empagliflozin 10 mg) (when the effect was insufficient, it could be increased to the maximum dose), we compared and examined the several items before administration and one month after, 12 months after.

Results: 73 cases was subjected. Administration of SGLT2i significantly reduced HbA1c and mean blood pressure in the examination room also decreased significantly after one month and 12 month (data not shown). In renal function, estimate glomerular filtration rate (eGFR)retard decreased significantly after one month, but improved after 12 months (61.3 ± 21.8 ~ 59.7 ± 22.5 (p = 0.0021) → 61.4 ± 23.7 mg/gCr). The urine albumin-to-creatinine ratio (u-ACR) decreased significantly both after one month and 12 months (560.2 ± 882.7 → 323.4 ± 553.4 (p = 0.00082) → 281.5 ± 430.2 mg/gCr (p = 0.00545)). In inflammation or oxidative stress biomarkers, malondialdehyde modified LDL (MDA-LDL) was significantly decreased after one month and 12 months (133.4 ± 39.5 → 109 ± 28.2 U/L (p = 0.0144) after 12 months). Urinary monocyte chemotactic protein 1 (MCP-1) decreased after 1 month, but it decreased significantly in 12 months (2.49 ± 1.75 ~ 1.27 ± 1.39 pg/gCr (p = 0.0169)). Urinary liver-type fatty-acid-binding protein (L-FABP) also did not change after one month, but it decreased significantly in 12 months (11.4 ± 21.7 ~ 8.0 ± 16.8 µg/gCr (p = 0.0004)). There was no correlation between the rate of change in HbA1c or the rate of change in blood pressure and the rates of change in eGFR, u-ACR, MDA-LDL, u-MCP-1 and L-FABP.

Conclusions: Renoprotection of SGLT2i for DKD in T2DM is considered to be the main mechanism of improvement of glomerular hypertension at early stage, but direct suppression of inflammation and oxidative stress acts in the long term.

FR-PO643

Insulin Use Is a Surrogate Marker of Insulin Resistance (IR) Christine K. Raji,1 R. E. Boucher,2 Guo Wei,3 Terrence S. Bjordahl,2 A. N. Habib,4 Srini Beddhu.1 UC Berkeley, Sararata, CA; 2Univ. of Utah, SLC, UT.

Background: We previously noted that diabetes needs insulin therapy are at risk of reaching ESRD than those that do not need insulin adjusted for duration of diabetes mellitus (DM), concurrent use of other hypoglycemic agents and HbA1C levels. We hypothesized that need for insulin is a reflection of underlying IR.

Methods: We examined whether insulin use is reflective of IR in 1756 participants with DM and non-missing data for insulin use and IR in the Chronic Renal Insufficiency Cohort. Insulin use was related to IR estimated by homeostatic model of assessment of insulin resistance (HOMA-IR) in logistic regression models.

Results: Mean age was 59 ± 10 years, 55.4% were men and 44.0% were black. Baseline characteristics of diabetics on insulin and not on insulin are summarized in the table. Compared to the lowest quartile of HOMA-IR, there was a graded ↑ in odds of insulin use in the upper three quartiles in a multivariate logistic regression model (Figure).

Conclusions: We conclude that need for insulin use is a surrogate marker of insulin resistance and interventions that target insulin resistance might ↓ the need for insulin use in DKD.

Funding: NIDDK Support

---

<table>
<thead>
<tr>
<th>Insulin Use</th>
<th>No (n=1329)</th>
<th>Yes (n=427)</th>
<th>Yes/No (n=1756)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>59.7 ± 8.8</td>
<td>55.2 ± 8.8</td>
<td>58.2 ± 8.8</td>
</tr>
<tr>
<td>Male (%)</td>
<td>57.2 ± 9.1</td>
<td>53.9 ± 9.1</td>
<td>56.7 ± 9.1</td>
</tr>
<tr>
<td>Black (%)</td>
<td>43.2 ± 4.2</td>
<td>44.7 ± 4.2</td>
<td>44.0 ± 4.2</td>
</tr>
<tr>
<td>Atherosclerotic Conditions (%)</td>
<td>79.0 ± 6.5</td>
<td>78.5 ± 6.5</td>
<td>78.7 ± 6.5</td>
</tr>
<tr>
<td>CHF (%)</td>
<td>11.3 ± 3.2</td>
<td>10.7 ± 3.2</td>
<td>11.0 ± 3.2</td>
</tr>
<tr>
<td>Duration of DM (y)</td>
<td>12.8 ± 8.9</td>
<td>13.0 ± 8.9</td>
<td>12.9 ± 8.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>34.3 ± 8.1</td>
<td>35.0 ± 8.1</td>
<td>34.7 ± 8.1</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>7.2 ± 1.5</td>
<td>7.1 ± 1.5</td>
<td>7.1 ± 1.5</td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>139.0 ± 3.7</td>
<td>139.2 ± 3.7</td>
<td>139.1 ± 3.7</td>
</tr>
<tr>
<td>Biguanide (%)</td>
<td>24.8 ± 7.5</td>
<td>24.8 ± 7.5</td>
<td>24.8 ± 7.5</td>
</tr>
<tr>
<td>TZD (%)</td>
<td>37.1 ± 6.6</td>
<td>36.6 ± 6.6</td>
<td>37.0 ± 6.6</td>
</tr>
<tr>
<td>Other Hypoglycemic Agents (%)</td>
<td>23.0 ± 7.5</td>
<td>23.0 ± 7.5</td>
<td>23.0 ± 7.5</td>
</tr>
</tbody>
</table>

Cohort. Insulin use was related to IR estimated by homeostatic model assessment of insulin resistance (HOMA-IR) in logistic regression models.

Funding: NIDDK Support

---

FR-PO644

The Role of the Renal Biopsy in 6003 Patients with Diabetic Nephropathy Dao-Fu Dai, Shree G. Sharma, Christopher P. Larsen, Patrick D. Walker. Arkana Laboratories, Little Rock, AR.

Background: Diabetic nephropathy (DN) is a leading cause of end stage renal disease (ESRD). Proteinuria and progressive decline in renal function in patients with diabetes mellitus (DM) are usually thought to be secondary to DN. However, recognition of superimposed non-diabetic renal disease (NDRD) is critical and, with appropriate diagnosis and treatment, may prevent accelerated progression to ESRD.

Methods: This was a retrospective clinical pathological study of 6003 patients with DM and a biopsy diagnosis of DN, to determine the spectrum of superimposed NDRD and to evaluate the relationship between the presence or absence of NDRD with various clinical manifestations, including rapid worsening of proteinuria and renal function, hematuria with or without an active urine sediment, or the acute nephritic syndrome.

Results: The renal biopsy identified superimposed NDRD in 36.6% of patients with DN. Importantly, the biopsy excluded NDRD in 16.7% of patients with systemic diseases and clinical/laboratory findings suspicious for a superimposed disease. Multivariate analysis identified that a rapid rise in serum creatinine is the strongest predictor for superimposed NDRD (OR: 2.19, p<0.001).

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

Underline represents presenting author.
superimposed NDRD varied according to indications leading to renal biopsy. Acute tubular injury (21%) was most common in patients with rapid decline of renal function; focal segmental glomerulosclerosis was most common (71%) in patients with an unexpected swift rise in proteinuria; pauci-immune crescentic glomerulonephritis (15.7%) was most common in patients with rapidly progressive renal failure; infection-associated glomerulonephritis (16.5%) was most common in patients with the acute nephritic syndrome and IgA nephropathy was the most common in patients with hematuria (7.6%).

**Conclusions:** The renal biopsy is critical to identify the presence or absence of a superimposed NDRD in patients with DN. This study documents the relationship between various presentations of renal disease and specific NDRD. Finally, it demonstrates the importance of the biopsy in ruling in or out suspected non-diabetic renal disease in clinical settings that would support such a concern.

**FR-PO645**

**Renal Biopsies in Diabetic Patients: Hematuria or Absence of Retinopathy Do Not Indicate Non Diabetic Renal Disease**

**Background:** Diabetic nephropathy (DN) is usually a presumptive diagnosis based on clinical and biological evidences. However, renal biopsies (RB) may be performed in diabetic patients with glomerular proteinuria lacking classical features of DN and/or in patients with diabetes and another disease with potential renal involvement who could benefit from specific therapy. We compared the frequencies of Non Diabetic Renal Disease (NDRD) according to the RB indications to assess if RB performed for atypical findings are justified.

**Methods:** 144 RB were performed in diabetic patients with glomerular proteinuria in our center in ten years and divided into two groups: Group 1 (G1): atypical findings (absence of diabetic retinopathy (DR), hematuria (HU), rapid eGFR decline, rapid increase of proteinuria or sudden nephrotic syndrome); Group 2 (G2): clinical and/or biological features of suggesting NDRD. We compared frequencies of NDRD and RB related adverse events in each group.

**Results:** 68 patients were identified in G1 and 76 in G2. Gender, age, high blood pressure, serum creatinine, urinary protein-to-creatinine ratio, HU, DR, remi-angiotensin system blockers. This was a retrospective observational study between both groups. Glicated hemoglobin was higher in G1 (7.8 ± 2.2 vs 7.1 ± 1.4, p = 0.04). NDRD was diagnosed in 7% of patients in G1 and 50% in G2 (p < 0.001). None of the 37 patients who underwent RB for HU, and/or absence of DR had NDRD. Adverse events were more frequent in G1 than in G2 (10% vs 1%, p = 0.027) (Table).

**Conclusions:** Absence of DR or presence of HU should not be the only motivation to indicate RB in diabetic patients as they convey an increased risk of adverse event without any benefit.

**Funding:** Clinical Revenue Support, Government Support - Non-U.S.

<table>
<thead>
<tr>
<th>Renal biopsy indication</th>
<th>Non diabetic renal disease (%)</th>
<th>Adverse events, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical finding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematuria and/or absence of diabetic retinopathy, n (%)</td>
<td>37 (59)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>CKD progression, n (%)</td>
<td>13 (%)</td>
<td></td>
</tr>
<tr>
<td>Recently increased proteinuria, n (%)</td>
<td>10 (11)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Microlarion, n (%)</td>
<td>11 (11)</td>
<td>4 (36)</td>
</tr>
<tr>
<td>(Previously unknown diabetic, sudden synphonic or stage 5 CKD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other indications</td>
<td>76 (100)</td>
<td>28 (30)</td>
</tr>
<tr>
<td>Systemic disease, with renal involvement, n (%)</td>
<td>(Hypert LAKD disease, Systemic lupus erythematosus without history of renal; Follow up on patients treated with cyclophosphamide, Sarcoidosis and edrophine, Scleroderma, HBU, HTN, IRT, Amyloidosis, Thrombocitopenia or leukopenia)</td>
<td>26 (35)</td>
</tr>
<tr>
<td>Mesocapnion, n (%)</td>
<td>15 (20)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Arterial karyo, n (%)</td>
<td>13 (15)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>Known renal disease, n (%)</td>
<td>11 (17)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>(ANCA-associated disease, Lupus nephritis or IgA nephropathy/Henoch-Schonlein)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microlarion, n (%)</td>
<td>11 (15)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>(Previously unknown diabetic, sudden synphonic or stage 5 CKD)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FR-PO647**

**Effects of Hydrochlorothiazide and Amiloride on the Antialbuminuric Efficacy of Losartan in Patients with Diabetic Kidney Disease**

**Background:** The best strategy to slow progression of diabetic kidney disease (DKD) and reduce cardiovascular risk of DKD patients is controlling blood pressure (BP) and reducing albuminuria. First line treatment for patients with DKD and hypertension is using renin-angiotensin-aldosterone system (RAAS) blockers. However, some DKD patients have persistently elevated albuminuria after reaching the maximum tolerated dosage of RAAS blockers and proper BP control. Therefore, this study aims to prove an efficacy of alternative medicine which is a combination of HCTZ and amiloride (HCT+A) to reduce albuminuria apart from RAAS blockade therapy.

**Methods:** This prospective randomized, single blinded study assigned 75 patients with DKD, CKD stage 1-3 and urine albumin-to-creatinine ratio (UACR) > 300 mg/g received stable dosage of losartan during the last 3 months in Vajira hospital from 1 June 2016 to 31 January 2017. There were 39 cases received HCT+A group compared with 36 cases in placebo group. All patients were eligible to receive conventional therapy. The patients were followed for 4 weeks. The primary composite end point was the percent change in the median of UACR between the baseline and final value of each treatment period. The primary analysis was performed on the independent t test or Mann-Whitney U test.

**Results:** The UACR showed a significant reduction with HCT+A 42.84% compared with placebo group – 7.95% (p < 0.001). There were > 30% reduction in UACR in 24 patients (64.1%) treated with HCT+A and in 6 patients (16.7%) in placebo. The percentage of patients with > 50% UACR reduction in the HCT+A group was 16 patients (41%) compared with the placebo group (2 patients (5.6%)). Glomerular filtration rate (GFR), body weight decreased with HCT+A regimen. Blood pressure had no significant change after treatment. There was one patient developed severe hyperkalemia after stopped treatment.

**Conclusions:** The addition of HCTZ and amiloride to patients with DKD (CKD stage 1-3) with UACR > 300 mg/day on top Losartan induces a significant antialbuminuric effect and associated with the degree of GFR reduction.

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

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

**Underline represents presenting author.**

570
performance of KFRE on individuals with biopsy proven diabetic nephropathy in advanced CKD stages at the time of biopsy and then evaluated the incremental value of pathologic information of renal biopsy to KFRE on them.

Methods: 296 individuals with biopsy proven diabetic nephropathy in CKD stages 3 to 5 at the time of biopsy was identified at four nephrology centers in Japan. Pathological classification of patients was performed by three pathologists based on the Pathology Classification of Diabetic Nephropathy. Individuals were randomly assigned to two cohorts (2:1). The development cohort of 198 was used to validate the KFRE and to assess the incremental value of pathological score on diabetic nephropathy (D-score). Model performance was assessed using the area under the receiver operating characteristic curve (AUC), decision curve analysis, and Harrell's c-statistics. Incremental value of D-score to KFRE was evaluated with the net reclassification improvement (NRI), integrated discrimination improvement (IDI), Integrated sensitivity (IS) and integrated specificity (IP). Validation of the models was performed in the validation cohort of 98.

Results: Median follow-up durations (25%, 75% percentiles) were 1.8 (1.0, 5.0) years and 2.0 (1.0, 3.8) years, respectively (p=0.89). Both KFRE and KFRE+D-score were significant predictors of ESRD in both the development cohort and validation cohort (Hazard Ratios of KFRE and KFRE+D-score in the development cohort were 2.44 (1.49–3.87) and 2.48 (1.73–3.56) respectively, in the validation cohort were 2.30 (1.57–3.38) and 1.08 (1.01–1.16), respectively). Incremental value of D-score using free cut-points showed positive overall NRI (0.5%; CI, 0.1–0.5%) but the IDI showed no significant change (0.0%; CI: 0.0005–0.0005). The KFRE+D-score model improved the both IS and IP but showed little differences.

Conclusions: KFRE worked well to identify individuals at high risk of ESRD in both the development and validation cohort. Adding pathological information to the KFRE improved the risk prediction of ESRD but did not statistically outperform the KFRE.

FR-PO649

The Effect of Ursodiol on Kidney Function: A Retrospective Case Series of Patients with Diabetic Kidney Disease Fabian Bock,1 Moh’d Moh’d Mohanad A. Al-Dabat,2 Khurram Shahzad,2 Berend H. Isermann,2 Talat Ali,3 Al Annazi,1 1Div of Nephrology & Hypertension, Dept. of Medicine, Vanderbilt University Medical Center, Nashville, TN; 2Dept of Clinical Chemistry and Pathobiologychemistry, Otto-von-Guericke University, Magdeburg, Germany.

Background: Experimental evidence suggests that bile acids are protective in diabetic nephropathy. Ursodeoxycholic acid (UDCA, Ursodiol) has been shown to attenuate renal damage in mouse models of diabetic nephropathy in part through reducing oxidative or ER stress. Ursodiol is in clinical use for the prevention of gall stone disease and in primary biliary cirrhosis (PBC) but clinical data on the effect on kidney function in patients with early diabetic kidney disease (CKD Stage 3a) and diabetic nephropathy (PBC) are lacking.

Methods: We retrospectively screened Synthetic Derivative, a de-identified copy of over 2 million patient records at Vanderbilt University Medical Center for the following inclusion criteria: ICD9/10 code of diabetes with diabetic nephropathy, diabetic kidney disease or renal manifestation (diagnosed between 2000 and 2008), Ursodiol started for any indication (between 2010 and 2014) and serial eGFR assessments thereafter. Repeated measures ANOVA was used to examine the effect of Ursodiol on kidney function overtime.

Results: A total of 13 patients met the inclusion criteria. At inclusion, median age was 55 (30–72) years. The majority of cases was white (10/13) had hypertension (10/13), and in primary biliary cirrhosis (PBC) but clinical data on the effect on kidney function in patients with early diabetic kidney disease (CKD Stage 3a) and diabetic nephropathy (PBC) are lacking.

In group A, diastolic function was improved, but in group B, was not.

FR-PO652

Metformin Use Does Not Increase Risk of Clinical Acidosis in Diverse Population of CKD Patients Rocco Ferdinandino,1 Tielman T. Van Vleck,2 Jeremy S. Leventhal,1 Bart Ferket,1 Jaime Uribarri,1 Girish N. Nadkarni,1 Steven G. Coca,1 1Icahn School of Medicine at Mount Sinai, New York, NY; 2Mount Sinai School of Medicine, New York, NY.

Background: Metformin use in type 2 diabetes (T2D) patients with Stage 3a chronic kidney disease (CKD3a) has been cautioned because of concerns for associated metabolic acidosis. We used a large multicenter urban cohort to assess both rates of acidosis and absolute difference in serum bicarbonate in new users of metformin compared to non-users.

Methods: We identified T2D with CKD3a from the Mount Sinai CKD Registry and listed for 6 weeks metformin new-user: quantifier pairs 1:1 on baseline data. We calculated incidence rate ratios (IRR) of acidosis (bicarbonate level ≤18 mg/dL) and serum anion gap (SAG) ≤12 using negative binomial regression. We examined the longitudinal effect of metformin use on patient bicarbonate levels using linear mixed effect modeling with repeated measures.

Results: We had data on 1494 patients (747 matched pairs). Median age was 74, 45.2% was male, baseline eGFR was 49.6. Baseline bicarbonate was similar in both groups, however albuminuria was decreased significantly in both groups. Left ventricular ejection fraction(EF) was not changed during 48 months in both groups. But left atrial dimension(LAD) and tissue Doppler index(E/e’ in group A were improved significantly.

In group A, at 48 months after using agents, E/e’ was worsened. No remarkable adverse events were seen in both groups.

Conclusions: These findings suggest that iraglutide and sitagliptin have similar effects on renal function, but according to cardiac diastolic function, iraglutide therapy is more beneficial for type 2 diabetic patients than sitagliptin therapy. Further studies with larger samples were needed to detect these effects.
bicarbonate over follow up was statistically higher but not clinically different in the user vs. non-user group (Difference = 0.18, SE = 0.08, P = 0.02).

Conclusions: In a large healthcare cohort of T2D patients with CKD3a, new prescription of metformin was not associated with either acidosis events or lower bicarbonate levels compared to non-users, suggesting that concerns for metformin associated lactic acidosis in this population may not be warranted.

Funding: Other NIH Support - 1TL1TR001434

FR-PO653

Presence of Kimmelstiel-Wilson Nodules in Diabetic Nephropathy Correlates with Duration of Diabetes and Poor Glycemic Control

Monica Sincar, Ivy A. Rosales, Dihua Xu, Sahir Kalim, Ravi I. Thadhani. MGH, Boston, MA.

Background: Mesangial nodules are regarded as a major histologic correlate of diabetic nephropathy. However, whether there is an association between the presence of nodules and various stages of diabetic chronic kidney disease (CKD) is not known. Here we report clinicopathologic association between the presence of nodules in diabetic patients with varying stages of CKD.

Methods: All seventy-five available autopsy records and charts from 2013 to 2016 of type 1 and 2 diabetes were examined. Twenty-six patients had all necessary demographic data in their records, including age, sex, race, hemoglobin A1C level, duration of diabetes, hypertension status, at least 2 creatinine levels within the last six months prior to death, and treatment information. Archived autopsy kidney sections were reviewed by a pathologist blind to clinical data. Nineteen kidneys free of autolysis were systematically assessed for (i) percent global glomerulosclerosis, (ii) mesangial hypercellularity, (iii) percent glomeruli with nodules, and (iv) percent interstitial fibrosis.

Results: Mesangial nodules were present in diabetic patients with CKD II (50%, n=4), III (66%, n=7), IV (86%, n=7), and V (100%, n=1). Poor glycemic control, defined as HgbA1c ≥7.5% (Welch’s t test p = 0.035), and duration of diabetes >10 years (p=0.036) showed strong associations with higher percent of nodules. Although a linear trend was evident, the correlation between percent of nodules and CKD stage was not statistically significant. The extent of glomerulosclerosis did not correlate with clinical factors such as age, sex, hypertension, treatment with RAAS blockade or longstanding diabetes.

Conclusions: The presence of nodules in diabetic kidneys showed significant associations with duration of diabetes >10 years and poor glycemic control. Mesangial nodules were present in kidneys of diabetic patients at all stages of CKD, with apparently more nodule formation in the later stages of the disease. These preliminary findings suggest a trend towards increased nodule formation as chronic kidney disease progresses. Together, our study suggests that diabetic nephropathy is associated with significant nodule formation, and the percentage of glomeruli with nodules may be a more definitive readout of CKD progression than determining just the presence or absence of nodules in glomeruli.

Funding: Private Foundation Support

FR-PO654

Lack of Diabetic Glomerulosclerosis in Patients with Longstanding Diabetic Complications

Amy K. Motto, John M. Basgen, Susan L. Hogan, Susanne B. Nicholas, J. Charles Jennette, Ronald Klein, Michael Maurer.

1University of Minnesota, Minneapolis, MN; 2University of North Carolina, Chapel Hill, NC; 3University of Wisconsin-Madison, Madison, WI; 4Department of Medicine, University of California, Los Angeles, CA; 5Charles Drew University, Los Angeles, CA.

Background: There is heterogeneity of renal complications in diabetes. We sought to determine the nephropathologic light microscopic characteristics and ultrastructural measurements in adults with type 2 diabetes undergoing research protocol kidney biopsy.

Methods: Inclusion criteria included type 2 diabetes ≥5 years duration, retinopathy and/or microalbuminuria or decreased estimated glomerular filtration rate (GFR) <60ml/min/1.73m2. Nineteen participants (mean age 54y) underwent kidney biopsy, measured GFR using iohexol clearance, first morning void (FMV) urine albumin/creatinine ratio (UACR) and retinal photography. Nephropathologic characteristics were scored by a nephropathologist using usual methods. Stereologic ultrastructural parameters included glomerular basement membrane (GBM) thickness (measured using orthogonal methods) and fractional volume of mesangium (Vv/mes/glm). Typical diabetic glomerulosclerosis was diagnosed if Vv/mes/glm exceeded 0.20 with GBM thickening (>470nm for women; >520nm for men). Predominant diabetic vasculopathy was diagnosed if Vv/mes/glm was less than 0.20 in the presence of arterial hyalinosis and/or arteriosclerosis and

GBM thickening without GBM thickening was attributed to nondiabetic arterionephrosclerosis.

Results: Results (see table) showed that 5 of 19 participants had nondiabetic arterionephrosclerosis, and while there were trends in the degree of albuminuria and retinopathy severity, this alone did not distinguish between diabetic and nondiabetic vasculopathy, nor the severity of vasculopathy.

Conclusions: Molecular studies aimed at deciphering between diabetic and nondiabetic complications will require research protocol kidney biopsies from patients with a wide spectrum of clinical disease characteristics.

Funding: NIDDK Support

FR-PO655

Association between Severity of Diabetic Retinopathy and Renal Pathology or Renal Prognosis in Patients with Biopsy-Proven Diabetic Nephropathy in Type 2 Diabetes Mellitus

Kenshi Samejima,1 Masaru Matsui,1 Tomoko Kanki,1 Masatoshi Nishimoto,1 Miho Tagawa,1 Yasuhiro Akai,1 Yoshikihito Saito,1 2First Department of Internal Medicine, Nara Medical University, Kashihara, Japan; 2Department of Cardiology and Nephrology, Nara Prefecture General Medical Center, Nara, Japan.

Background: Diabetic nephropathy and retinopathy are generally believed to develop concomitantly. However, much remains unclear about the association between renal pathology and retinopathy as renal biopsy is rarely indicated.

Methods: This is a retrospective observational study. Inclusion criteria were patients with type 2 diabetes, biopsy-proven diabetic nephropathy, and evaluation for retinopathy by ophthalmologists from 1984 to 2014. Exposure of interest was severity of retinopathy by the modified Davis and the Scheie Classification. Outcome variable was development of end-stage renal disease (ESRD). Statistical analyses were performed using Cox regression model. Correlation between severity of retinopathy and renal pathology were examined using Spearman’s rank correlation.

Results: Data for 376 patients were available, Mean age was 57.5 years. Retinopathy was found in 168 (44.7%). During mean follow-up of 9.4 years, ESRD developed in 67. Renal prognosis was significantly poorer in the group with retinopathy. In terms of modified Davis classification, more severe retinopathy indicated poorer renal prognosis (log-rank p<0.001). In Cox regression analysis, severity of retinopathy was an independent risk factor for the development of ESRD (Table). Positive correlations with retinopathy were observed for diffuse glomerular lesions (p=0.48, p<0.001), nodular lesions (p=0.50, p<0.001), interstitial fibrosis and tubular atrophy (p=0.36, p<0.001), and arteriolar hyalinosis (p=0.34, p<0.001).

Conclusions: Only about half of patients with biopsy-proven diabetic nephropathy had retinopathy. The severity of retinopathy was an independent predictor of progression of nephropathy.

Relationship between diabetic esrd and esrd (cox regression)
Collagen Type III Degradation Is Associated with Deterioration of Kidney Function in Patients with Type 2 Diabetes with Microalbuminuria

Federica Genovese,1,3 Tine Hansen,1 Daniel Guldager Kringle Rasmussen,5,6 Signe Holm Nielsen,1,4 Henrik Reinhard,1 Hans-Henrik Parving,1 Morten A. Kasdal,1 Peter Rosling,1,2,13 Nordic Bioscience, Herlev, Denmark; 2Rigshospitalet, Copenhagen, Denmark; 3Steno Diabetes Center Copenhagen, Gentofte, Denmark; 4Department of Biomedicine and Biotechnology, Technical University of Denmark, Kgs. Lyngby, Denmark; 5Institute of Molecular Medicine, Cardiovascular and Renal Research, University of Southern Denmark, Odense, Denmark; 6University of Copenhagen, Copenhagen, Denmark.

Background: In diabetes one of the main features of the progression to diabetic kidney disease is a pathological deposition of extracellular matrix components triggering renal fibrosis. The main structural component of the fibrotic core is collagen. One of the most prominent collagen is type III collagen (COL III), which is excessively synthesized and incorporated into the fibrotic extracellular matrix. Multiple studies in both humans and mice have suggested that MMP-9 activity is increased in diabetic kidney disease. We investigated whether a neo-epitope fragment of COL III generated by MMP-9 (C3M) was associated with deterioration of kidney function in a well-characterised type 2 diabetic population with microalbuminuria and without symptoms of coronary artery disease.

Methods: The cohort included 200 participants, followed for 6.1 years. We measured C3M levels in serum (S-C3M) and urine (U-C3M) at baseline. To adjust for urine output levels, the urinary markers were normalized for urinary creatinine. The investigated endpoint was a decline in eGFR of >30% (n=42). Cox proportional hazards regression analysis was performed for S-C3M and U-C3M both unadjusted and adjusted for traditional risk factors (sex, age, systolic blood pressure, LDL-cholesterol, smoking, HbA1c, creatinine and urinary albumin excretion rate). To assess whether S-C3M or U-C3M improved risk prediction beyond traditional risk factors we calculated the relative integrated discrimination improvement (rIDI).

Results: The hazard ratio per doubling of S-C3M was 3.00 (95% CI 1.52-5.90, p=0.002). When adjusted for traditional risk factors the hazard ratio per doubling of S-C3M was 2.84 (95% CI 1.35-5.97, p=0.006). Addition of S-C3M to a model containing traditional risk factors improved the relative discrimination by 19.8 percentage points (p=0.007). U-C3M was not associated with declining eGFR.

Conclusions: S-C3M was independently associated with decline in renal function, and added significant improved discriminatory power to a model containing traditional risk factors.

Funding: Commercial Support - Nordic Bioscience, Private Foundation Support.

Serum and Urinary Markers of Collagen Type VI Formation (Pro-C6) and Type III Degradation (C3M) Reflect Renal Function in Type 1 Diabetes

Federica Genovese,1 Tine Hansen,1 Daniel Guldager Kringle Rasmussen,5,6 Sascha Pilemann-Lyberg,1 Signe Holm Nielsen,1 Morten A. Kasdal,1 Frederik Persson,2 Simone Thellade,1 Federica Genovese,1 Peter Rosling,1,2 Steno Diabetes Center Copenhagen, Hellerup, Denmark; 2Steno Diabetes Center Copenhagen, Gentofte, Denmark; 3Nordic Bioscience A/S, Herlev, Denmark; 4Department of Biomedicine and Biotechnology, Technical University of Denmark, Kgs. Lyngby, Denmark; 5Institute of Molecular Medicine, Cardiovascular and Renal Research, University of Southern Denmark, Odense, Denmark; 6University of Copenhagen, Copenhagen, Denmark.

Background: Progression of diabetic kidney disease is associated with renal fibrogenesis and associated with increased extracellular matrix remodeling and release of collagen fragments in urine in progressive renal disease. We evaluated associations between kidney function and a marker of collagen type VI formation (Pro-C6) and a marker of collagen type III degradation (C3M) in type 1 diabetes.

Methods: Serum and urinary levels of Pro-C6 and C3M were measured with ELISA in 668 patients with type 1 diabetes. Kidney function was evaluated as eGFR (CKD-EPI) and urinary albumin excretion rate (UAER). The investigated endpoints were a change in eGFR (n=81) or a change in UAER (n=81) compared to the baseline in all diabetic patients, whereas there were no significant difference between the two time point in the level of microalbuminuria and proteinuria. The degree of increment of APX-501 was greater in patients with microalbuminuria and overt proteinuria. In cultured renal cells, high glucose and angiotensin II increased the expression of APX-501. In diabetic rats, high glucose and angiotensin II increased the expression of APX-501.

Results: Of the 668 patients, 368 (55%) were male, mean±SD age was 54.6±12.6 years and eGFR 81.6±25.5 ml/min/1.73m². Median (IQR) UAER was 17 (6-83) mg/g. Both higher serum and urinary levels of Pro-C6 were associated with higher eGFR (unadjusted: p=0.001; adjusted: p=0.001), lower urine levels of C3M were associated with lower eGFR (unadjusted: p=0.001; adjusted: p=0.001) and higher UAER (unadjusted: p=0.001; adjusted: p=0.001). Higher serum levels of C3M were associated with lower eGFR (unadjusted: p=0.001; adjusted: p=0.001) and higher UAER (unadjusted: p=0.001; adjusted: p=0.007).

Conclusions: In type 1 diabetes, higher serum and urine levels of the collagen type VI formation marker Pro-C6 were associated with poorer kidney function. Moreover, higher serum levels and lower urine levels of the collagen type III degradation marker C3M were related to poorer kidney function. Longitudinal data are needed to clarify the predictive role of these markers.

Funding: Commercial Support - Nordic Bioscience A/S, Herlev, Denmark.

A Novel Marker of Collagen Type VI Formation Is Prognostic for Cardiovascular Disease, All-Cause Mortality, and Deterioration of Kidney Function in Patients with Type 2 Diabetes with Microalbuminuria

Daniel Guldager Kringle Rasmussen,1,4 Tine Hansen,1 Signe Holm Nielsen,1,2 Henrik Reinhard,1 Hans-Henrik Parving,1 Morten A. Kasdal,1 Federica Genovese,1 Peter Rosling,1,2 Nordic Bioscience, Herlev, Denmark; Righospitalet, Copenhagen, Denmark; Steno Diabetes Center Copenhagen, Gentofte, Denmark; Institute of Molecular Medicine, Cardiovascular and Renal Research, University of Southern Denmark, Odense, Denmark; Department of Biomedicine and Biotechnology, Technical University of Denmark, Kgs Lyngby, Denmark; University of Copenhagen, Copenhagen, Denmark.

Background: Type 2 diabetes is a common risk factor for the development of renal fibrosis and chronic kidney disease (CKD). Recent findings have shown that type VI collagen (COL VI) is markedly upregulated during fibrosis. The role of COL VI has been sparsely investigated in fibrosis onset and progression. We evaluated a novel biomarker of COL VI formation as a prognostic marker for cardiovascular events, all-cause mortality, and decline in eGFR in patients with type 2 diabetes with microalbuminuria and without symptoms of coronary artery disease.

Methods: The cohort included 200 participants followed for 6.1 years. COL VI formation was assessed with the Pro-C6 assay, detecting a specific fragment of COL VI released upon deposition in the extracellular matrix. Pro-C6 levels were measured in serum at baseline. Endpoints included: 1) a composite of cardiovascular events (n=40); 2) all-cause mortality (n=26); and 3) decline in eGFR of >30% (n=42). Cox models were adjusted and unadjusted for traditional risk factors (sex, age, systolic blood pressure, LDL-cholesterol, smoking, HbA1c, creatinine and urine albumin excretion rate).

Results: Levels of Pro-C6 were associated with an increased risk of cardiovascular events (unadjusted HR 2.65, 95% CI 1.74-3.97, p=0.001; adjusted HR 2.67, 95% CI 1.72-3.91, p<0.001). Further, decline in eGFR (unadjusted HR 3.00, 95% CI 1.72-5.21, p<0.0001; adjusted HR 2.67, 95% CI 1.21-5.89, p=0.015). Addition of Pro-C6 to a model containing traditional risk factors improved the rIDI by 14.5% (p=0.04) for cardiovascular events, 64.3% (p<0.001) for all-cause mortality, and 19.8% (p=0.007) for decline in eGFR.

Conclusions: In conclusion, Pro-C6 was associated with cardiovascular events, all-cause mortality, and decline in eGFR in patients with type 2 diabetes and microalbuminuria.

Funding: Commercial Support - Nordic Bioscience, Private Foundation Support.
FR-PO660

What Is the Potential for RAAS Blockade Optimisation for Patients with Diabetic Kidney Disease in the Era of Potassium Binders? 
Stephanie Chong,1,2 Katharine Pates,1,3 Kieran McCafferty,3,2 Barts Health NHS Trust, London, United Kingdom; 2NHS, LONDON, United Kingdom; 3Royal London Hospital, London, United Kingdom.

Background: Diabetes is the leading cause of renal failure in both worldwide and in the UK. For 2 decades RAAS blockade has been the cornerstone of management of diabetic kidney disease. Recent registry data suggest that RAAS dose maximisation is key to reduce population health care costs and improve outcomes. However, the use of RAAS blockade is often limited by hypotension or hyperkalaemia. Potassium binders may provide a novel strategy to safely enable dose maximisation of RAAS therapy, but it is unknown how many patients are not treated or sub-maximally treated due to fears of hyperkalaemia.

Methods: We performed a retrospective study, analysing our electronic patient record to establish how many patients were sub-maximally treated with RAAS therapy and the reasons for failure of dose maximisation. We included all adult patients with type 2 diabetes, in our tertiary renal unit which covers a population of 2.5 million ethnically diverse patients across North and East London. We excluded any patients due to commence dialysis imminently or already on renal replacement therapy and patients with secondary renal lesion or other clear cause of CKD.

Results: We identified 415 diabetic patients meeting the inclusion/exclusion criteria. We found that only 72% were on ACE or ARB therapy. Of these, only 50.3% were on maximum dose therapy. This means that only 37% of patients of the total cohort were on RAAS therapy at the upper limit of the lower normal range of potassium (Potassium < 5.5mmol/L) in 30.8%, hypotension (BP < 120/70) and not on other blood pressure lowering agents (in 15.4%), both in 2.3% and dose was not maximised for no specified reason despite inadequate BP control and acceptable potassium levels in 51.3% of patients. Additional reasons found to explain the lack of dose maximisation in this group of patients, were historical hyperkalaemia, fear of new hyperkalaemia, progressive CKD or AKI.

Conclusions: Our study demonstrated the huge unmet potential for safe dose maximisation of RAAS therapy, using potassium binders in a cohort of patients with diabetic kidney disease. We estimate that if these findings were extrapolated across the 3 million patients with diabetic kidney disease across the UK then almost 1 million patients may benefit from potassium binder enabled dose maximisation.

FR-PO661

Effect of Angiotensin Converting Enzyme (ACE) and Angiotensinogen (AGT) Gene Polymorphisms on the Anti-proteinuric Efficacy of ACE Inhibitor Therapy in Patients with Type 2 Diabetes with Nephropathy 
Om P. Kalra,1 Neerja Aggarwal,1 Pawan K. Kasc,2 Parul Varshney,1 Anil K. Yadav,1 Alpana Raijadia,1 Ashok K. Tripathi,1 Basu D. Banerjee,2 Madhu V. S.1 Medicine, University College of Medical Sciences, Delhi, India; 2Biochemistry, University College of Medical Sciences and GTB Hospital, Delhi, India; 3Medicine, University College of Medical Sciences, Delhi, India; 4Medicine, GTB Hospital and University College of Medical Sciences, Delhi, India; 5Biochemistry, University College of Medical Sciences, Delhi, India; 6Nephrology, P B. D. Sharma University of Health Sciences, Meerut, India; 7Biochemistry, Loyola College of Medical Sciences, Delhi, India; 8Biochemistry, University College of Medical Sciences, Delhi, India; 9Biochemistry, University College of Medical Sciences, Delhi, India.

Background: Diabetic nephropathy (DN) is the leading cause of chronic kidney disease worldwide and affects approximately 20-30% of diabetic patients. ACE inhibitor drugs are commonly prescribed for renoprotection; however, anti-proteinuric response is not uniformly observed in all patients. The aim of this study was to evaluate the role of genetic variants of ACE and AGT genes on the anti-proteinuric efficacy of ACE inhibitor therapy in patients with DN.

Methods: In the present study, 270 patients with Type 2 diabetes mellitus with nephropathy aged between 30 to 65 years and a duration of diabetes ≥5 years were enrolled and treated with ACE inhibitor (ramipril) and followed at regular intervals for 6 months for assessment of urinary albumin/creatinine ratio (ACR) and eGFR (MDRD).

Results: Patients were classified as responders when they had a decrease in urinary ACR ≥30% at the end of 6 month follow up. Genotyping of ACE I/D and AGT M235T polymorphisms were performed by using primer specific polymerase chain reaction and PCR-RFLP technique, respectively.

Results: An overall significant reduction in ACR 36.2% was observed in the whole group at the end of 6 months; however, macro-albuminuric patients (55%) showed better response to therapy as compared to micro-albuminuric patients (45%). Overall, 130 (48%) of patients with DN were found to be responders to ACEI. The frequency of ACE genotype II, ID and DD was found to be 31%, 53% and 16% respectively. The frequency of AGT genotype MM, MT and TT was found to be 25%, 53% and 22% respectively. A reduced response to urinary ACR was found to be independent of genotypes of ACE I/D and AGT M235T polymorphisms although macro-albuminuric patients having TT genotype showed higher response (72%) although it was statistically not significant. eGFR decreased from the base line value of 73.65±24.71 ml per minute per 1.73 m2 to 68.90±24.44 ml per minute or 1.73 m2 per minute/1.73 m2/6 months (p<0.001).

Conclusions: ACE inhibitor therapy reduced urinary ACR by ≥ 30% in 48% of patients with diabetic nephropathy and macroalbminuric patients exhibited better response. The anti-proteinuric response was found to be independent of ACE I/D and AGT M235T polymorphisms.

FR-PO662

Relationship between Transition in CKD Category and Renal Outcome in Japanese Type 2 Diabetic Patients with Biopsy-Proven Diabetic Nephropathy 
Tomoki Funamoto, Miho Shimizu, Tadao Toyama, Shinji Kitaizumi, Kengo Furuiuchi, Takashi Wada. Division of Nephrology, Kanazawa University Hospital, Kanazawa, Japan.

Background: We examined the association between transition in chronic kidney disease (CKD) category over 5 years and 10 years after renal biopsy and renal outcome in Japanese type 2 diabetic patients with biopsy-proven diabetic nephropathy.

Methods: Based on up to 5 years and 10 years observation after renal biopsy, we determined transition in CKD category. We first evaluated the association of renal composite events (requirement of dialysis, or a 50% decline in estimated glomerular filtration rate (eGFR) from baseline (at the time of renal biopsy)) with progression of CKD categories over 5-years (n=54) and 10-years (n=54) after renal biopsy in patients with normo-/microalbuminuria with eGFR ≥ 15 ml/min per 1.73m2. We subsequently evaluated the association of renal composite events with remission of macroalbuminuria to normo-/microalbuminuria over 5-years (n=58) and 10-years (n=42) after renal biopsy in patients with macroalbuminuria.

Results: 1) In the 5-year analysis in patients with normo-/microalbuminuria with eGFR ≥ 15 ml/min per 1.73m2, 8 patients showed progression of albuminuria stage, whereas 9 patients showed progression of eGFR stage. The corresponding numbers in the 10-year analysis were 12 patients and 16 patients, respectively. Cumulative incidences of renal composite events in patients with progression of albuminuria stage and eGFR stage were higher than no progression. The risk for renal composite events was associated with progression of albuminuria stage rather than eGFR stage. The progression of albuminuria was associated with nodular lesions, whereas the progression of eGFR was associated with diabetic lesions. 2) In the 5-year analysis, 10 patients showed remission of macroalbuminuria. The corresponding number in the 10-year analysis was 16 patients. Cumulative incidences of renal composite events in patients with remission were lower than no remission. In the 10-year analysis, remission was a determinant for renal composite events. Low urinary protein excretion at renal biopsy and female were the determinants for remission.

Conclusions: Our study suggests that transition in CKD category over 5-years and 10-years as well as diabetic kidney lesions add significant prognostic information about risk for renal outcome in type 2 diabetes.

FR-PO663

Is Urinary KIM-1 a Predictor of EGFR Decline, Incident Cardiovascular Disease, and All Cause Mortality? 
Mie K. Eickhoff,1 Bernt Johan Von Sydow,2 Henrik Reinhard,1 Tine Hansen,1 Frederik Persson,3 Hans-Henrik Parving,1 Peter Rossing,1 Novo Nordisk A/S, Søborg, Denmark; 2Rigshospitalet, Copenhagen, Denmark; 3Steno Diabetes Center, Gentofte, Denmark; 4Steno Diabetes Center A/S, Gentofte, Denmark; 5Steno Diabetes Center Copenhagen, Gentofte, Denmark.

Background: Urinary levels of kidney injury molecule 1 (KIM-1) has shown to reflect tubular pathophysiology. We evaluated KIM-1 as a predictor of decline in estimated glomerular filtration rate (eGFR), incident cardiovascular disease (CVD) and all-cause mortality in patients with type 2 diabetes (T2D) and microalbuminuria without clinical coronary artery disease.

Methods: We performed a prospective study including 200 patients, all receiving multifactorial treatment. Urinary KIM-1 was measured at baseline and was available in 191 patients. Adjusted Cox models included sex, age, LDL cholesterol, smoking, HbA1c creatinine, systolic blood pressure and urine albumin excretion rate (UAE). A decline in eGFR of >30%, which has recently been suggested as a valid renal outcome, at any time point during follow-up was the predefined endpoint of CKD progression. Hazard ratios (HR) are provided per 1 SD increment of log-transformed values of the urinary biomarka.

Results: Patients were (± SD) 59 ± 9 years old, eGFR 91.1 ± 18.3 ml/min/1.73m2 and UAE (IQR) 103 (39–230) mg/24-h. During a median 6.1 years follow-up, there were 40 incident CVD events and 26 deaths and a total of 42 patients reached the predefined CKD progression endpoint after 4.9 years (median). Higher urinary KIM-1 was a predictor of eGFR decline, unadjusted HR (95% CI): 1.9 (1.2–2.8); p=0.003, and in the adjusted model HR 1.7 (1.0–2.7); p=0.034. For CVD events urinary KIM-1 was a determinant in the unadjusted model HR 1.4 (1.0–2.1); p=0.04) but not in the adjusted model (HR 1.4 (1.0–2.1); p=0.08), and of all-cause mortality in unadjusted (HR 2.0 (1.2–3.2); p=0.008) and adjusted (HR 2.3 (1.24–4; p=0.009) models.

Conclusions: In patients with T2D and microalbuminuria receiving multifactorial treatment, urinary KIM-1 was independently associated with deterioration in renal function and all-cause mortality.
FR-PO664
IL-6 Assessment as a Non-Traditional Risk Factor for Cardiovascular Risk and Hospital Admission in Type 2 Diabetes Patients with Diabetic Nephropathy
Ana P. Pimentel, Filipa B. Mendes, Luísa H. Pereira, Ana P. Silva, Pedro L. Neves, Center Hospitalar do Algarve, Faro, Portugal; Hospital de Faro E.P.E, Faro, Portugal; Nephrology, CHA, Faro, Portugal.

Background: Oxidative stress and inflammatory cytokines in diabetic nephropathy are major triggers regarding the development of microvascular complications of type 2 diabetes. Interleukin-6 (IL-6) is one proinflammatory cytokine, implicated in the development of diabetic nephropathy where vascular inflammation and fibrosis are the rule with influence on the development of cardiovascular disease. The aim of this study is to verify the relationship between plasmatic IL-6 and non-traditional cardiovascular risk factors in type 2 diabetic patients. Methods: 186 type 2 diabetic patients were included, including patients with Diabetic Nephropathy (HOMA for insulin resistance, homocysteine, fibrinogen and brain natriuretic peptide (BNP) levels and Charlson Comorbidity Index (CCI)) was calculated. The patients were divided into groups using serum IL-6. Group 1 (N=113) was defined as having IL-6 ≥4.89pg/mL and group 2 (N=62) had IL-6 <4.9pg/mL.

Results: Statistically significant differences were found between the groups (p=0.003) with higher values of IL-6 being associated with greater CCI, higher phosphorus and PTH level, but also HOMA, BNP, diastolic pressure and albumin-creatinine ratio. CCI (0.029, p=0.0001), IL-6 (1.10-1.24, p=0.0001) and CRP (0.002-0.0029, p=0.0015) were predictive factors in terms of hospital admission for IH, and using a generalized linear model, higher values of IL-6 were predictive for acute coronary syndrome (ACS) (Wald=0.1219, CI 95% (0.04-0.39) p=0.01) with an AUC=0.79, p=0.0001.

Conclusions: In type 2 diabetic patients, elevated serum levels of IL-6 are associated with the presence of non-traditional cardiovascular risk factors, as well as higher insulin resistance, worst mineral metabolism parameters and more comorbidity. In our cohort study, IL-6 levels were predictive of ACS and hospital admission for IH.

FR-PO665
The Expression of Serum lncRNA GAS5 and miR-21 ceRNA Associated with Clinical and Pathological Changes in Patients with Diabetes and Diabetic Nephropathy
Anita Hare, Department of Nephrology, The First Hospital, China Medical University, Shenyang, China.

Background: To analyze the expression of serum IncRNA GAS5 and miR-21 in patients with diabetes mellitus and diabetic nephropathy, and to analyze the correlation between the expression of them and the clinical and pathological parameters, and to testify the function of them in the pathogenesis of diabetes mellitus and diabetic nephropathy, in order to find novel therapeutic targets and biomarkers.

Methods: The patients were divided into three groups, diabetic nephropathy group: patients proven by biopt test, diabetes group: patients with diabetes of normal urine albumin creatinine ratio, normal control group. The expression of IncRNA GAS5 and miR-21 in serum samples were detected by real-time quantitative PCR. The correlation of serum IncRNA GAS5 and miR-21 expression with the clinical parameters were analyzed.

Results: The expression of serum lncRNA GAS5 was significantly down-regulated in type 2 diabetes mellitus patients when compared to healthy control group and diabetic nephropathy patients (P=0.0029), and IL-6 (0.1-0.2) was negatively correlated with serum lncRNA GAS5, and AIC was independently correlated with serum lncRNA GAS5. The diagnostic efficiency of serum miR-21 and IncRNA GAS5/miR-21 as “diagnostic signature” for DM was measured in 32 healthy volunteers. The diagnostic efficiency of serum miR-21 and IncRNA GAS5/miR-21 as “diagnostic signature” for DM were 77.14%, specificity was 77.78%. The diagnostic efficiency of serum miR-21 and lncRNA GAS5/miR-21 as “diagnostic signature” for DM were 76.00%, specificity was 94.74%.

Conclusions: Serum IncRNA GAS5 and miR-21 expression can be used as noninvasive diagnostic marker for diabetes and diabetic nephropathy.
without CKD (Fig); and no conclusive risk of acute renal failure in those with CKD (hazard ratio [HR] 0.82, confidence interval [CI] 0.61-1.10) or without CKD (HR 1.26, CI 0.88-1.79) with liraglutide vs PBO. There was no difference in the risk of nausea leading to discontinuation or acute gallstone in patients with and without CKD. Severe hypoglycemia risk was significantly reduced with liraglutide by 37% (with CKD, HR 0.88, CI 0.59-1.21) and non-significantly reduced by 19% (without CKD, HR 0.81, CI 0.59-1.21). Diabetic foot ulcer risk was not increased with liraglutide in those with and without CKD (Fig).

Conclusions: In LEADER, liraglutide was as well tolerated in patients with CKD as in those without CKD.

Funding: Commercial Support - Novo Nordisk A/S

Figure: Risk of selected adverse events with liraglutide vs placebo according to CKD at baseline

FR-PO669
Renal Histology Does Not Predict Progression of Diabetic Nephropathy
Parash S. Misra,1 Adriana Krizova,2 Richard E. Gilbert,2 Darren A. Yuen,2,4 1Keenan Research Centre for Biomedical Sciences, St. Michael’s Hospital, Toronto, ON, Canada; 2University of Toronto, Toronto, ON, Canada; 3St Michael’s Hospital, Toronto, ON, Canada; 4Faculty of Medicine, University of Toronto, Toronto, ON, Canada.

Background: The ability to predict renal disease progression in diabetes remains limited, despite the identification of well-established risk factors including glycemic control, blood pressure, and albuminuria. The consensus pathologic classification system developed by the Renal Pathology Society (RPS) was designed to assist clinical and research assessment of diabetic nephropathy. While some reports have suggested that the RPS classification correlates with disease progression, its predictive potential has not yet been completely evaluated. Our aim was to determine the relationship between the RPS score and progression of diabetic renal disease.

Methods: Slope of estimated glomerular filtration rate (eGFR) decline was calculated in patients with biopsy-proven diabetic kidney disease, and compared with RPS histologic classification scores. Results were adjusted for baseline eGFR and urine albumin-to-creatinine ratios (ACR) at the time of biopsy. Additionally, the correlation between slope of eGFR decline and histologic and clinic parameters was assessed, and renal survival curves (time off dialysis) were generated for subgroups of RPS, eGFR, and histology scores.

Results: 26 patients with biopsy-proven diabetic kidney disease and at least 6 months of eGFR follow-up data were identified among 394 biopsies performed at St. Michael’s Hospital between 2011 and 2016. While renal survival was significantly worse with increasing glomerular and interstitial fibrosis/tubular atrophy scores (p <0.0001 and p = 0.0124, respectively), patients with higher fibrosis scores had lower eGFR at the time of biopsy (r = -0.6623, p = 0.0002). Slope of eGFR decline did not correlate with either histologic classification or baseline clinical parameters on univariate or multivariate analyses.

Conclusions: Beyond establishing the diagnosis of diabetic nephropathy, our results suggest that renal biopsy does not provide any additional information regarding the rate of disease progression. While patients with higher fibrosis scores on biopsy tended to have poorer renal survival, such individuals also had lower baseline eGFR. Importantly, histologic scores did not correlate with future changes in eGFR. Larger studies are needed to confirm these observations.

Funding: Private Foundation Support

FR-PO670
Low Estimated Glomerular Filtration Rate (eGFR < 60 ml/min/1.73 m2) with Albumin-to-Creatinine Ratio (ACR) <30 mg/g is Associated with Increased Mortality Risk in Diabetics
Holly J. Kramer,1 R. E. Boucher,2 Guo Wei,2 Alfred K. Cheung,1 William C. Cushman,3 Srini Beddhu,1 Loyola University Medical Center, Maywood, IL; 2University of Utah, Salt Lake City, UT; 3University of Utah School of Medicine, Salt Lake City, UT; 4Memphis VA Medical Center, Memphis, TN.

Background: Prevalence of low eGFR (< 60 ml/min/1.73 m2) with an ACR < 30 mg/g is increasing, especially among adults with diabetes, likely due to better management of chronic kidney disease (CKD) risk factors. Determining the association between CKD phenotypes including low eGFR with ACR < 30 mg/g in adults with diabetes may help guide prevention efforts to reduce CKD associated morbidity and mortality.

Methods: We examined unadjusted mortality rates by CKD phenotype (based on eGFR and ACR groups) using data from the Action to Control Cardiovascular Disease (ACCORD), which included 9777 adults with diabetes, and the Systolic Blood Pressure Intervention trial (SPRINT), which included 8900 adults without diabetes. Cox proportional hazards models were used to calculate the hazard ratio of mortality by CKD phenotype in these two study populations with simultaneous adjustment for demographics, blood pressure and prevalent cardiovascular disease with the eGFR 90 ml/min/1.73 m2 and ACR < 30 mg/g as referent group.

Results: The mean age was 62.8 (6.7) and 67.9 (9.4) years in ACCORD and SPRINT, respectively. In the ACCORD and SPRINT trials, mortality rates in the group with eGFR < 60 ml/min/1.73 m2 and ACR < 30 mg/g were 1.36 deaths per 100 person-years, respectively. After adjustment for covariates, presence of eGFR < 60 ml/min/1.73 m2 with ACR < 30 mg/g was associated with a 1.58-fold higher hazard rate for mortality (95% CI 1.19, 2.10) relative to eGFR > 90 ml/min/1.73 m2 with ACR < 30 mg/g in ACCORD. No significant association was noted with this CKD phenotype and mortality in SPRINT (hazard ratio 1.17; 95% CI 0.76, 1.80) (see Figure).

Conclusions: Low eGFR with ACR < 30 mg/g is associated with increased mortality risk in adults with diabetes. These data demonstrate the need to identify and implement interventions that reduce mortality in adults with diabetes and CKD, including those without albuminuria.

Funding: NIDDK Support

FR-PO671
Urine sCD163 Is a Biomarker of Active Nephrotic Syndrome
Sarah M. Moran,1 Dearbhaille Dooley,2 Matthias Kretzler,3 Mark A. Little,1 1University of Michigan, Ann Arbor, MI; 2 Trinity Health Kidney Centre, Trinity College, Dublin, Ireland. Group/Team: Neptune Nephrotic Syndrome

Background: Prior work has demonstrated that urinary soluble CD163 (usCD163) displays excellent biomarker characteristics for detection of active renal vasculitis in patients with ANCA-associated vasculitis and lupus. We sought to assess the levels of usCD163 in active and remission nephrotic syndrome.

Methods: Patients with biopsy proven nephrotic syndrome (Minimal change (MCD), focal and segmental glomerulosclerosis (FSGS) and membranous glomerulonephritis (MN)) were included. Paired urine samples from time of remission (urine protein creatinine ratio (uPCR) <0.5mg/mmol) and of active nephrotic syndrome (uPCR >3.5mg/mmol) were selected from NEPTUNE a multicentre longitudinal cohort. Creatinine-normalised usCD163 levels were measured in urine by ELISA.

Results: 53 patients were included (MN n=22, MCD n=20, FSGS n=11). Median age at onset of NS was 34.5 years (IQR 13.5-59.8 yrs), median eGFR was 77.3mls/ min/1.73m2 (SD ±30.3mls/min/1.73m2). Median usCD163 levels were higher in active nephrotic syndrome (536.3ng/mmol (IQR 227.1-1061 mmol/mmol)) compared to remission (0.9ng/mmol (IQR 0.1-9.6 ng/mmol), p<0.0001) with median values in active FSGS of 372.9ng/mmol (IQR 151.4-639mg/mmol), active MCD of 539.2ng/mmol (IQR 114.3-1511/mmol), and active MN of 604.2ng/mmol (IQR 305.8-1423/mmol). (figure 1A)

Conclusions: Levels of usCD163 displayed marked elevation in active nephrotic syndrome. 14% of the observed variance in usCD163 was explained by total urine protein excretion.

This suggests that, although some of the measured usCD163 in urine of patients with
nephrotic syndrome is due to leak across the GBM, most appears to be derived directly from the glomerular immune process.

FR-PO672

Urinary CD80 as a Biomarker for Nephrotic Syndrome

Marie C. Hmouni,1 Anaditile M. Gonzalez, guerrico,1 Adam M. Wright,1 Jonathan P. Troost,3 Fernando C. Fervenza,1 John C. Lieske,1 George G. Klee,1 Mayo Clinic, Rochester, MN; 2Mayo Clinic, Rochester, MN; 3University of Michigan, Ann Arbor, MI

Background: The immune system appears to play a significant role in the pathogenesis of certain nephrotic syndrome (NS) patients with minimal change disease (MCD) and focal segmental glomerular sclerosis (FSGS). CD80/B7-1, a co-stimulatory receptor expressed on activated antigen presenting cells, has been implicated in certain cases of NS. However, CD80 assays have suffered from limited sensitivity and specificity.

Methods: We analyzed urinary CD80 in 489 glomerulonephritis cases. Figure 1B: Correlation between urine protein creatinine ratio and urinary CD80 levels associated with MCD and FSGS compared to other pathological forms.

Conclusions: Our results confirm that uCD80 excretion correlates with MCD and FSGS disease status. Further study (ongoing) is warranted to determine whether uCD80 is a useful biomarker for diagnosis, prognosis, and predictors of response to immunosuppressive therapy. These results also suggest that uCD80 may reflect immune pathways involved in the pathogenesis of certain MCD and FSGS cases, and further research is needed to understand its cellular role.

Funding: NIDDK Support, Commercial Support - Bristol -Myers-Squibb

Table 1. Description of MCD and FSGS and comparison cohort samples

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>MCD</th>
<th>FSGS</th>
<th>uCD80</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panted samples</td>
<td>25</td>
<td>44 (20 to 75)</td>
<td>0.19 (0.01 to 1.29)</td>
<td>0.001</td>
</tr>
<tr>
<td>Unpanted samples</td>
<td>16</td>
<td>26 (9.9 to 75)</td>
<td>0.4 (0.01 to 1.49)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Funding: NIDDK Support, Commercial Support - Bristol -Myers-Squibb

FR-PO673

Beneficial Effects of Proteasome Inhibitors (PIs) Administered after Onset of Proteinuria in a Model of Minimal Change Disease (MCD)

Himanshu D. Kopp,1 M. K. Heimbach,2 J. V. Shah,3 R. R. Shah,2 Radhakrishna Baliga1,11

1Arkana Laboratories, Little Rock, AR; 2University of Arkansas, Little Rock, AR; 3Ochsner Health System, New Orleans, LA

Background: Proteasomes play a major role in the pathophysiology of several disease processes in part through its action on a crucial transcription factor, nuclear factor-kappa B (NF-kB). NF-kB regulates the expression of a variety of inflammatory genes including cytokine P450 (CYP) which plays a major role in MCD. We have shown previously that administration of PIs prior to the onset of proteinuria resulted in marked protection against puromycin aminonucleoside (PAN) -induced proteinuria. However, the role of PIs in ongoing glomerular injury and their potential beneficial effects following the establishment of significant proteinuria have not been previously examined. The current study was designed to determine the effect of PIs administration following the onset of proteinuria in a model of MCD and to study the potential mechanism involved utilizing in vitro cultured human podocytes (HP).

Methods: MCD was induced in SD rats by injecting a single dose of PAN in a veno-venous loop (IV). Proteinuria was measured as albumin to creatinine ratio (ACR) (mg/mg) until day 10. MG-132 was administered by osmotic pumps and Carfilzomib (CAR) was administered IV following onset of proteinuria. Proteins were analyzed by western blot and immunocytochemistry. Immunohistochemical analysis was also performed on the kidney cortical sections.

Results: Administration of MG-132 and CAR after the onset of PAN induced proteinuria resulted in significantly decreased nuclear translocation of NF-kB, activation of IL-6, up regulation of CYP, marked reduction in H2O2 release and 8-Oxo-dG expression in cultured HP. MG-132 and CAR blunted the nuclear translocation of Nrf-2, preserved Keap-1 expression, upregulated PAN induced HO-1 and SOD with significant decrease in apoptosis.

Conclusions: These in vitro and in vivo data imply the crucial role of proteasomes in progressive glomerular injury. CAR, which is currently used in humans should be considered as a potential therapeutic alternative in MCD.

Funding: Private Foundation Support

FR-PO674

Study of a Breakthrough Therapy Utilizing Alternative Actions of Vitamins A and D in a Murine Model of Minimal Change Nephrotic Syndrome

Shoii Tsujii,1 Jiro Kino, Chikushi Suruda, Takahisa Kimata, Setsuko Yamanoouchi, Kazumari Kaneko, Department of Pediatrics, Kansai Medical University, Osaka, Japan

Background: The etiology of minimal change nephrotic syndrome (MCNS) remains unclear. Recent studies have reported that regulatory T cell (Treg) malfunctions and associated functional and structural podocyte abnormalities play a role. Steroids are shown to have high efficacy against MCNS, and are utilized to correct the above-stated podocyte abnormalities. However, long-term steroid treatment may induce various adverse effects. In addition to their intrinsic vitamin functionality, vitamins A and D have recently demonstrated immunoregulatory functions, including effects on Treg differentiation and induction. Furthermore, they have been shown to restore damaged podocytes, directly [Okamura M, et al. Nephrol Dial Transplant 2009;24:3006]. The objective of this study was to investigate if vitamins A and D, which have fewer adverse effects, can correct the causes of MCNS in an animal model, and to search for a non-steroidal therapy for this syndrome.

Methods: Six-week-old MCNS model Wistar rats with puromycin aminonucleoside (PAN)-induced nephrosis were categorized into 4 treatment groups (n=3 per regimen): 1) VA Group received subcutaneous vitamin A 2.5 mg/kg dissolved in 1 mL dimethyl sulfoxide (DMSO)), 2) VD Group received intraperitoneal vitamin D 0.4 µg/kg dissolved in 0.2 mL phosphate-buffered saline (PBS)), 3) VAD Group received both the subcutaneous VA and intraperitoneal VD, 4) C (Control) Group received 0.2 mL subcutaneous DMSO and 0.2 mL intraperitoneal PBS. Starting two days pre-PAN administration, each regimen involved daily treatment for 12 days. Urinary protein excretion was measured and compared among the four groups. The Kruskal-Wallis Test was applied for statistical analysis.

Results: Peak urinary protein excretion occurred at Day 9 post-PAN administration, when the median value was significantly lower in the VAD group than the C group (16.4 vs. 73.1 mg/kg/day; p=0.0144) and tended to be lower, although not significantly different, in the VAD group than the single-vitamin-treated rats (16.4 vs. 44.8 [VA] or 264.9 [VD] mg/kg/day).

Conclusions: Vitamins A and D exhibit an antiproteinuric effect with an additive action in MCNS model rats, and are potential therapeutic agents.

Funding: APOL1-B3 Isoform Is Involved in the Processing of the IL-1β Production

Hidefumi Kopp,1 Jeffrey B. Kopp,2 1Dokkyo Medical University, Shimotogu, Japan; 2NIDDK, NIH, Bethesda, MD.

Background: APOL1 genetic variants G1 and G2 increase risk for glomerular disease. Previously, we identified an intracellular splice isoform, APOL1-B3, that is expressed in glomerular cells and tubular cells in vivo (ms submitted). In transgenic mice, APOL1-B3 exhibited nephrotic syndrome symptoms and induced podocyte injury, increased pro-IL-1β mRNA from isolated glomeruli, and increased renal IL-1β protein production. APOL1-B3 interacted with NLRP12, a negative regulator of Toll-like receptor signaling, potentially explaining elevation of pro-IL-1β mRNA in glomeruli. Here we examined the role of APOL1-B3 in inflammation activation and production of mature IL-1β.

Methods: We generated stable THP-1 monocytic cell lines expressing APOL1 under the control of the actin promoter, CAG-APOL1-B3-FLAG-G0 (common variant) or -G2 (renal risk variant); G1 variant cells were not viable. THP-1 cells were treated with LPS to induce synthesis of inflammatory cytokines, and increased expression of IL-1β mRNA from isolated glomeruli, and increased renal IL-1β protein production. APOL1-B3 interacted with NLRP12, a negative regulator of Toll-like receptor signaling, potentially explaining elevation of pro-IL-1β mRNA in glomeruli. Here we examined the role of APOL1-B3 in inflammation activation and production of mature IL-1β.

Results: In THP-1 derived macrophages, over expression of APOL1-B3-G0 and -G2 significantly enhanced both LPS-stimulated IL-1β production (meansSD:

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

Underline represents presenting author.
control (~93±3.8, G0-58±5.3, G2-66±9.7) (P<0.05) and release of caspase-1 into supernatant (control ~339±15.2, G0-98±23.1, G2-67±8.68) (P<0.05). Following uninephrectomy, increased urinary caspase-1 was seen in both APOL1-B3 mice (G0, G2) and wild type mice, with no difference among groups. The ratio of IL-1β to pro-IL-1β in the kidney, assessed by Western blot, increased following uninephrectomy, and was numerically greater in APOL1-B3 and G2 mice. These findings suggest enhanced processing of pro-IL-1β by the APOL1 risk variant. By Western blot, both APOL1-B3 and G2 interacted with NLRP3.

Conclusions: These findings suggest that under the conditions studied, the APOL1-B3 isoform affects processing of IL-1β and add a further dimension to the role of APOL1-B3 in modulating NLRP3 pathway signaling.

FR-PO676
JAK1/2 Regulate APOL1, CXCL9 and JAK2 Expression in Human Kidney Cells Hanping Zhang,1 Gordon S. Wu, V Vega-Warner,2 Matt G. Sampson,3 Frank C. Brosius,4,5 1University of Michigan, Ann Arbor, MI, 2Wayne State University School of Medicine, Ann Arbor, MI.

Background: Chronic inflammation contributes to progression of all glomerular diseases. Recent data suggest that both APOL1 and JAK1/2 signaling contribute to the pro-inflammatory milieu in a variety of kidney diseases including FSGS, diabetic kidney disease, and other causes of nephrotic syndrome. Based on systems genetic and transcriptionomic analyses of genes and of murine models of glomerular diseases, the expression of CXCL9, a T-cell chemokine related to the CXC chemokine family, is increased by APOL1 high risk genotype expression and by JAK2 overexpression in podocytes.

Methods: Human kidney 2 (HK-2) cell monolayers were grown to confluence and treated with interferon-gamma (IFN) (50ng/ml), interleukin-6 (IL-6) (10ng/ml), or tumor necrosis factor-alpha (TNF) (10ng/ml) from 30 min to 48 hr. mRNA levels of JAK2, APOL1 and CXCL9 were determined at multiple timepoints in response to these agonists. A commercially available inhibitor of JAK1 and JAK2, baricitinib (Bari; 500nM), was then applied 30 min prior to agonist incubation.

Results: HK-2 cells were found to express APOL1, JAK2 and CXCL9. Stimulation of HK-2 cell monolayers of with IFN, but not IL-6 or TNF, resulted in a large, rapid and sustained (maximal at 48 hr) increase in mRNA expression of JAK2, APOL1 and CXCL9 (Figure). All of these increases were abrogated by 30 minutes of pretreatment with the JAK1/2 inhibitor as was the IFN induced increase in STAT3 phosphorylation.

Conclusions: In cultured human kidney cells, IFN stimulation triggers a cascade of events resulting in large increases in expression of pro-inflammatory mediators and APOL1. This cascade is completely abrogated by specific inhibition of JAK1/2 signaling. These findings suggest that JAK1/2-STAT3 signaling regulates APOL1, CXCL9 chemokine and JAK2 expression by parenchymal cells in the kidney. Future studies will examine effects of APOL1 modulation and genotype on this process.

IFN-induced increases in APOL1, CXCL9 and JAK2 (-) were completely inhibited by preincubation with Bari (+). N = 3 separate experiments for each timepoint.

FR-PO677
Flt3 Inhibitor Attenuates Renal Injury in Adriamycin Nephropathy by Suppressing CD103+ DC-Mediated T Cell Activation Qi Cao, Titi Chen, Vincent W. Lee, Guoping Zheng, Yiping Wang, David C. Harris. The Westmead Institute for Medical Research, Westmead, NSW, Australia.

Background: In our previous study, CD103+ DCs were shown to play a pathogenic role via activation of CD8 T cells in Adriamycin nephropathy (AN), a model of focal segmental glomerulosclerosis. FMS-like tyrosine kinase 3 (Flt3) is a receptor which is highly and specifically expressed on tissue resident CD103+ DCs. To test the effect on renal injury, inhibition of Flt3 on CD103+ DCs, we used a selective Flt3 inhibitor (AC220) to treat mice with AN.

Methods: AN was induced in BALB/c mice, who were treated daily for 14 days with 10mg/kg AC220 or Vehicle (n=8/group) from day 7 after adriamycin, when AN was established. Renal functional and structural injury, as well as inflammatory cytokine expression and cell infiltration were assessed.

Results: The number of kidney CD103+ DCs, but not CD103- DCs or plasmacytoid DCs, was significantly decreased in AN mice after AC220 administration. Treatment with AC220 significantly improved renal function (creatinine clearance 22±4.9 vs. 50±2.3±13 μl/min) and reduced structural renal injury and fibrosis in AN mice. AC220-treated AN mice had decreased levels of inflammatory cytokines IL-1beta, IL-6 and TNF-a in kidney. AC220 treatment decreased infiltration of CD4 T cells, CD8 T cells and dendritic cells in the kidney, and reduced inflammatory cytokine and cytotoxic molecule expression of kidney CD8 T cells in AN mice.

Conclusions: Flt3 inhibitor AC220 effectively reduced renal injury in AN mice, suggesting that this inhibitor might be a useful pharmaceutical agent to treat chronic kidney disease.

Funding: Government Support - Non-U.S.

FR-PO678
MBL2 Gene Polymorphism and IgG4 in Membranous Nephropathy Denise M. Costa,1,2 Giselle Vajgel,2 Maria Alina G. Cavalcante,2 Camila B. Oliveira,1,2 Carolina A. Vasconcelos,1 Lucila Maria Valente,1 1Nephrology, Instituto de Medicina Integral Prof. Fernando Figueira, Recife, Brazil; 2Nephrology, Hospital das Clinicas - UFPE, Recife, Brazil.

Background: Although there is evidence regarding the involvement of the lectin pathway and IgG4 in idiopathic membranous nephropathy (IMN), the trigger responsible for the immune complexes formation is uncertain. It is known that IMN occurs in genetically susceptible individuals; however, very few studies have investigated the possible relationship between this glomerulopathy and polymorphisms of the MBL2 gene, which is responsible for producing mannose-binding lectin (MBL) protein, a major component of the lectin pathway of the complement. We investigated the frequency of MBL2 gene polymorphisms and the serum ratio of IgG4 in patients with membranous nephropathy (MN).

Methods: Polymorphisms in the exon 1 of the MBL2 gene (codons 52, 54 and 57) and SNPs at positions -550 (HL) and -221 (XY) in the promoter region were evaluated in 60 patients compared to a control group of 101 blood donors. It established the frequency of polymorphisms and the serum ratio of IgG4 comparing the two main etiologies of membranous nephropathy: idiopathic (35 patients) and secondary to systemic lupus erythematosus (LMN) in 25 patients.

Results: The O allele, variant of exon 1, was more frequent in the group with MN compared to CG (42% ±22%; p<0.001). The heterozygous A/O was predominant among patients with MN compared to genotype A/A (OR = 11.16; 95% CI = 4.77 - 28.41). There was no difference for genotypes or alleles frequencies among patients and CG in HL and LMN, respectively. Among the 29 patients, and split in groups as high producers (HYA/HYA, HYA/LYA, HYA/LYA, HYA/LYA and HYA/LYA) and deficient producers (LYA/O and LYA/O), low producers (LYA/LYA, HYA/LYA and LYA/O) and within producers (LYA/O and LYA/O). A low-producer combined genotype was associated with a greater chance of developing MN (OR = 6.31, 95% CI = 2.26 - 19.7, p = 0.0001) when compared to CG. Serum levels of IgG4 and IgG were measured in 32 patients with MN and 24 with LMN. The median of serum ratio of IgG4 was 5% for IMN and 3% for LMN (p = 0.016).

Conclusions: Our data indicates that MBL2 polymorphisms may be associated with the activation of lectin pathway by IgG4 subclass antibodies in MN.

FR-PO679

Background: THSD7A has been identified as an autoantigen in patients with membranous nephropathy (MN). The epitopes targeted by patient autoantibodies are unknown.

Methods: In order to define the domain topology of THSD7A, we performed structure-based alignments with thrombospondin type 1 (TSP_1) domains in the protein data bank (pdb). We then cloned THSD7A fragments and tested for reactivity with serum from 31 patients with THSD7A-associated MN in a two-step approach using Western blotting. Clinical and serological follow-up was available from 16 of the 31 patients. We evaluated epitope profiles for associations with disease activity, incidence of malignancy, and clinical outcome.

Results: Protein structural analysis revealed a tandem string of 21 TSP_1 domains (d1 to d21). In a first unbiased approach, three consecutive fragments of the antigen (d1, d4, d5 and d11, d21) were cloned, expressed in HEK293 cells, and tested for reactivity with patient autoantibodies. We found that 84% of patients recognized at least two of the constructs. Therefore, we cloned soluble fragments of 2-3 adjacent TSP_1 domains (d1, d2, d2, d4, d3, d4, d5, d6, d7, d8, d9, d10, d11, d12, d13, d15, d16, d17, d18, d19, d21) in a second approach and tested again for serum reactivity. The d1_d2 fragment was recognized by 84% of the patients and therefore considered the immunodominant epitope region. However, epitope profiles among our patients varied greatly with 9 out of 11 domain fragments being recognized by at least three different sera. There was no association of epitope profiles with proteinuria, renal function or malignancy at the time of diagnosis. However, patients who recognized only one or two epitopes had lower anti-THSD7A antibody levels and less proteinuria. Among the patients with clinical and serological follow-up, 5 patients showed stable epitope profiles and persistent active disease, 8 patients lost reactivity with one or more constructs over time, and 3 patients showed a change in epitope profile during follow-up.

Conclusions: Our study demonstrates that autoantibodies in THSD7A-associated MN recognize a great variety of the antigen. We could not identify unique epitope risk profiles regarding disease activity, clinical outcome during follow-up or incidence of malignancy.

Funding: Government Support - Non-U.S.
Results: SP inhibited proliferation of MCs induced by PDGF-BB in a dose-dependent manner without blocked binding to its receptor. The phosphorylation of PDGFR-β, activation of downstream signaling, including phosphorylation of ERK1/2 and AKT, was also blocked by SP. Moreover, SP inhibited PDGF-induced transactivation of TAM-family kinase Axl. Phosphorylation of EGFR in MCs was activated by all treatments, and was inhibited by SP in a dose-dependent manner. Activation of EGFR down-stream signaling, including ERK1/2 and AKT, was also inhibited.

Conclusions: Chinese herbal medicine SP blocked MC activation induced by PDGF-BB or AII through inhibition of multiple signaling pathways. These findings thus explain some of the mechanisms of SP treatment to benefit patients with IgAN.

Funding: NIDDK Support

FR-PO683

Paraproteinemia II Hinders Heparanase I-Mediated Cleavage of Endothelial Glycosaminoglycans, Prevents Glomerular Injury

Yulia Kiyana,1 Klaus Stahl,2 Sergey Tkachuk,3 Patricia A. Schroeder,4 Laura L. Beverly-Stagg,5 Mario Schiffer,1 Roman Kiyan,2 Boris Chichkov,1 Hermann G. Haller,1,2,5 Hannover Medical School, Hannover, Germany; 2Laser Zentrum Hannover e.V., Hannover, Germany; 3Mount Desert Island Biological Lab, Salisbury Harbor, ME; 4MHU, Hannover, Germany; 5Medizinische Hochschule Hannover, Hannover, Germany; 6Mount Desert Island Biological Laboratory, Salisbury Cove, ME.

Background: Regulation of heparan sulfate (HS) chains of the glyocalyx is an important pathomechanism of vascular and renal diseases. Heparanase 1 (HPSE1) is the only known glucuronidase capable of degrading HS chains. Recently cloned heparanase 2 (HPSE2) is catalytically inactive and its functions are yet unclear. We have tested the hypothesis that HPSE2 antagonizes HPSE1, prevents HS chain degradation and protects endothelial cell function.

Methods: In vitro study of endothelial cells (EC) were carried out (1) in cell culture and (2) in a microfluidic chip under flow conditions. We developed a lentiviral construct and upregulated HPSE2 expression in EC. To assess HPSE2 function in vivo we used a transgenic zebrafish model (Tg(βgal-fap-GFP-DBP) and measured loss of fluorescent protein from the circulations.

Results: Addition of active HPSE1 led to the shedding of HS layer from endothelial cell surface. Overexpression HPSE2 protected against HPSE1-induced glycosylation shedding and damage of VE-cadherin junctions, endothelial rearrangements and from glucose-induced ICAM expression and adhesion of AM-labeled monocytes. LPS stimulation with increased expression of IL-6, IL-1β, and RANTES, as well as phosphorylation of p65 subunit of NFkB, pJAK, and MEK kinases was diminished by HPSE2 overexpression. HPSE2 knockdown in zebrafish showed a phenotype characterized by general body edema and pericardium. Disruption loss of the intravascular compartment into the interstitial tissue of the fish tail was visualized. Simultaneous injection of human HPSE2 full length mRNA we partially rescued the proteinic phenotype of HPSE2-KD fish.

Conclusions: HPSE2 is important for endothelial development and function in zebrafish model and in vitro under flow conditions. Our results suggest that HPSE2, expressed locally by EC or delivered with blood, fulfills protective role in microvasculature via several distinct mechanisms. First, it binds to and protects the HS glyocalyx from enzymatic shedding by HPSE1. In addition, HPSE2 binding to HS diminishes HS involvement in receptor-ligand interaction and is anti-inflammatory. We suggest that the C-terminal part of the HPSE2 protein containing HS-binding motif might be critical for endothelial function.

Funding: Government Support - Non-U.S.

FR-PO684

Podocyte Cross Talk with Parietal Epithelial Cells (PECs) Stimulates PECs Proliferation in HIV Milieu

Xiyan Lam,1 Xiqian Lan,1 Rukhsana Aslam,3 Ali Hussain,2 Seyyed Shadafarin Marashi Shoshtari,1 Catherine Nguyen-Schweitzer2, Ashwini Malhotra,3 Pravin C. Singhal,1 1Feinstein Institute for Medical Research, Great Neck, NY; 2Feinstein Institute for medical research, Glenoaks, NY; 3Feinstein Institute of Medical Research, New York, NY; 4Immunology and Inflammation, Fiestine Institute for Medical Research, New York, NY; 5North Shore LJI Health System, Great Neck, NY; 6The Feinstein Institute for Medical Research, Manhasset, NY; 6University of Hamburg, Hamburg, Germany; 7Immunology and Inflammation, Feinstein Inst. Med research and NXLJ, Manhasset, NY.

Background: HIV-associated nephropathy is characterized by an abundance of proliferating PECs in Bowman’s space. The involved mechanism of PECs proliferation in HIV milieu is not clear. Recently, we demonstrated that HIV stimulates IL-1β generation by PDCs. We now hypothesize that cross talk between PDCs to PECs and PECs to PECs promotes PECs proliferation.

Methods: Immortalized PECs and differentiated PDs were transduced with either vector (PECV/PPDV) or HIV (PECHV/PDHIV, NL4-3) and assayed for pyroptosis (morphologic assay). Control PECs/PDs, PECV/PPDV, and PECHV/PDHIV were incubated in serum-free media for 24 hours. Incubation (conditioned, C) media was collected and stored at -80°C. PECs were incubated in serum-free media containing 10% control (PECV/PPDV) and experimental (PECHV/PDHIV) conditioned media for 48 hours. In another set of experiments, PECs were incubated in serum free media containing 10% control and experimental media with or without IL-1β (neutralizing) antibodies for 48 hours. Cells were evaluated for pyroptosis by MTT cellular viability
Vitamin D Receptor (VDR) Agonist Slows Down Progression of HIV via Down Regulation of HIV Gene Expression

Seyedeh Shadafar Marashi Shoshasti,1 Ruhshana Aslam,1 Vinod Kumar,1 Ashwani Malhotra, Pravin C. Singhal,1* Feinstein Institute for medical research, Glenoaks, NY; North Shore LU Health System, Great Neck, NY; The Feinstein Institute for Medical Research, Manhasset, NY.

Background: Activation of renin angiotensin system (RAS) has been demonstrated to promote the progression of numerous kidney disorders, such as proteinuria, renal fibrosis and hypertension. Therefore, renin is a potential therapeutic target for the treatment of kidney disorders.

Methods: Human podocytes (HPs) were transfected with either vector (V/H) or HIV (NL4-3, HIV/H),. To increase endogenous renin production, V/HPs and HIV/HPs were transfected with sRNA vitamin D receptor (sRNA-VDR/HIV/HP) or scrambled (sRNA-VDR/HIV/HP). siRNA/protein blots were probed for renin and actin expressions. To evaluate the effect of renin in vivo, mRNA expressions of HIV genes from renal tissues of HIV (Tg26) mice with higher endogenous renin (Tg26) mice expressing 2,3 and 4 copies of angiotensinogen [Ag] or lacking VDR were quantified by qPCR. To down regulate renal tissue renin expression, Tg26 mice were treated with either vehicle or a VDR agonist (VDA) for 2 weeks and renal tissues were evaluated for HIV gene expression. In addition, gene expression and progression of renal lesions in Tg26 mice, Tg26 mice lacking renin, and Tg26 mice treated with VDA were compared.

Results: HIV enhanced renin expression in HPs. Silencing of VDR in HIV/HPs further enhanced expression of Nef, Tat, and Vpr. However, VDA down regulated HIV gene expression in HIV/HPs. Renal tissues of Tg26 with 4 Agt copies displayed 2.4-fold increase in mRNA expression of gp120, Vpr, Tat and Nef vs. Tg26 (Agt 2 copies). Similarly, Tg26 mice lacking VDR displayed greater HIV gene expression when compared to Tg26 mice with intact VDR. VDA-treated of Tg26 mice not only down regulated renal tissue expressions of renin but also attenuated expression of HIV genes. Tg26 mice lacking renin or treated with VDA, displayed attenuated renal tissue HIV gene expression and slowed down the rate of progression of renal lesions.

Conclusions: Renin enhances renal tissue and podocyte HIV gene expression and induces accelerated progression of renal lesions; however, this effect of renin could be prevented by VDA treatment.

Funding: NIDDK Support

IRAK4 Inactivation Eliminates Disease Phenotype in a Murine Model of Lupus/Lupus Nephritis

Barry K. Horne, Ian R. Rifkin, Ramon G. Bonegio. Boston University School of Medicine, South Weymouth, MA.

Background: Toll-like Receptor (TLR) signaling has been shown to play a major role in the progression of lupus and lupus nephritis (LN). Interleukin-1 Receptor-Associated Kinase 4 (IRAK4) is a critical component of signaling through TLRs. Humans with homozygous loss-of-function (LOF) mutations in IRAK4 lead relatively normal lives upon reaching adulthood. Attempts at specific in vivo inactivation of kinases in other human diseases have met with great success, and they are currently considered attractive targets for the development of new therapeutics. Thus, we hypothesized that inactivation of IRAK4 would ameliorate disease in our murine model of lupus/LN, and validate it as a potential therapeutic.

Methods: We crossed lupus prone Yaa, FcRβ IIb-/- mice to mice with inactive IRAK4 kinase to allow the comparison of lupus prone mice with (IRAK4-/-) or without (IRAK4(+/+)) functional IRAK4. We conducted a survival study, and analyzed the groups for markers of the lupus phenotype: body weight, spleen weight, cervical lymph node weight, perigonadal fat weight, and proteinuria.

Results: IRAK4(-/-) mice developed severe lupus and lupus nephritis, and died at a median age of 27 weeks (range: 22 to 28 weeks). In contrast, IRAK4(+/+) mice had a dramatic survival advantage (p<0.001), and mice analyzed at 1 year of age had no evidence of lupus. They exhibited no signs of nephritis, lacked proteinuria, and had normal spleen, cervical lymph node, and fat weights.

Conclusions: IRAK4 kinase activity is indispensable for the development of lupus and lupus nephritis in the lupus prone Yaa mouse, indicating that the IRAK4 signaling pathway is an attractive therapeutic target.

Funding: NIDDK Support, Other NIH Support - NIAID-T32 (JTP) 5T32AI07309-27

Increased MERTK Glomerular mRNA Expression in LN Multi-Pathogen Populations: A Modulator of Innate Inflammation

Iris J. Lee,1 Paris Barkan,1 Kalyani Perumal,2 Sudha Visvanathan,3 Matthias Kretzler,4 Crystal A. Gadebeku,5 Brad A. Godfrey,6 Celine B. Berthier,7 Temple University School of Medicine, Philadelphia, PA; Stroger Hospital, Chicago, IL; Boehringer-Ingelheim, Ridgefield, CT; University of Michigan, Ann Arbor, MI.

Background: Inflammation and cytokine dysregulation contribute to disease pathogenesis in Systemic Lupus Erythematosus (SLE) and lupus nephritis (LN). MERTK, a receptor protein tyrosine kinase, is thought to function as a receptor of pro-inflammatory cytokines (IL-6, IL-1β and TNF-α) through the induction of suppressor of cytokine signaling proteins (SOCS). MERTK also mediates phagocytosis and clearance of apoptotic cells, a function known to be defective in SLE. Furthermore, mice deficient in MERTK develop glomerulonephritis. Therefore, we investigated MERTK mRNA expression in human LN renal biopsies.

Methods: Gene expression profiles of microdissected renal biopsies from LN patient (European and Multiethnic cohorts, including WHO class II, III, IV, V) were analyzed.

Results: In the European cohort, glomerular MERTK transcript was 2.3 fold up-regulated in LN compared to controls (q-value<0.0001), and was the most highly altered compared to kidney biopsies from other proteinuric diseases (FSGS, Hypertensive nephropathy, IgAN, Minimal change, Membranous). For diabetic nephropathy and rapidly progressive GN, fold-change was 1.2 and 1.7 respectively (q-value<0.005). Like the European cohort, glomerular MERTK was also 2.3 fold up-regulated in the Multiethnic cohort (q-value<0.0001). MERTK mRNA was not significantly regulated in the tubular compartment of any kidney disease. Finally, MERTK mRNA expression was significantly different among CKD stages I-V, and did not correlate with GFR or level of proteinuria.

Conclusions: Our data show preferential expression of MERTK in the glomerular compartment of LN tissue compared to controls. In addition, expression was unrelated to level of GFR or proteinuria. MERTK is known to regulate innate inflammation, and its expression in LN likely represents an adaptive response to an upregulated immune system. Further research is necessary to understand how alterations in MERTK gene expression pattern contributes to pathogenesis of glomerular injury and inflammation in LN, or would be useful as a biomarker for LN outcomes.

Funding: Commercial Support - Boehringer-Ingelheim Pharmaceuticals

Robust Improvement in Lupus Nephritis after Hyaluronidase Treatment Due to the Removal of Accumulated Hyaluronic Acid in Glomerular Endothelial Glycolixy Hiyoriuki Kadoya, Chaim O. Jacob, Janos Peti-Peterdi. University of Southern California, Los Angeles, CA.

Background: Lupus Nephritis (LN) is a major cause of morbidity and mortality in patients with systemic lupus. The exact pathomechanism of LN has been elusive, and therefore current non-specific therapies are limited to general immunosuppression. Recently, we developed an intravitreal multiphoton microscopy (MPM) imaging approach to visualize the interplay between cellular components of the immune system and local kidney tissue factors. We observed the glomerular homing of IL-17-producing activated memory T cells, which were the vast majority of all immune cells found in LN kidney. The present study tested the hypothesis that T cell homing is due to the accumulation of the CD44 ligand hyaluronic acid (HA) in the glomerular endothelial glycolixy, and its removal by hyaluronidase improves LN.

Methods: Serial MPM was used to track the fate of endogenous T cells labeled with anti-CD3 and anti-CD4 antibodies in vivo in a model of rapid LN (BAFF transgenic New Zealand mixed (NZM) mice). FITC-labeled wheat germ agglutinin (WGA) lectin and Alexa594-labeled HA-binding protein (HABP) were used to evaluate glomerular endothelial glycolixy and HA content, respectively.

Results: Glomerular size, microthrombi, albumin leakage, T cell homing were significantly increased at 4-6 weeks old LN mice compared with control healthy mice. Robust accumulation of endothelial glycolixy and HA content (thickness and intensity of WGA and HABP fluorescence, respectively) were observed in LN mice, but not in control. Hyaluronidase injection significantly and dose-dependently (EC50=20U) reduced WGA fluorescence and HABP homing of T cell homing, and albumin leakage within 1 hour. Hyaluronidase treatment caused a 5-fold reduction in albuminuria and 4-fold increase in survival rate of LN mice.

Conclusions: Our results support the major importance of HA in the endothelial glycolixy in the glomerular homing of memory T cells in the development and pathobiology of LN. Hyaluronidase treatment is a promising new therapeutic approach for LN.
FR-PO689

Neuraminidase Activity Mediates IL-6 Production by Lupus Prone Mesangial Cells

Tamura Nowling, Kamala Sundararaj, Jessalyn I. Rodgers.
Medical University of South Carolina, Charleston, SC.

Background: Glycosphingolipid (GSL) levels and neuraminidase (NEU) (an enzyme that mediates GSL catabolism) activity/expression are altered in the kidneys and/or urine of lupus mice and human patients with proliferative nephritis compared to their non-nephritic counterparts and healthy controls. Specifically, elevated GSL levels were observed in the mesangial region of glomeruli. We hypothesize that activation of mesangial cells (MCs) in the progression of lupus nephritis is mediated in part by NEU activity, contributing to renal inflammation in lupus patients. Here we investigated the role and possible mechanisms by which NEU activity contributes to MC activation.

Methods: For these studies, we used the MES13 mouse MC line and primary MCs grown out from glomeruli isolated from MRL/lpr lupus prone mice. MCs were analyzed in the absence or presence of heat aggregated IgG (mimic of immune complex deposition), inhibitors for NEU activity or MAP kinase pathways inhibitors include real-time RTPCR, NEU activity assays, IL-6 and MCP-1 ELISAs, immunohistochemistry of renal sections, and confocal immunofluorescence of MCs.

Results: While HA-IgG alone fails to activate MES13 cells to produce IL-6, overexpressing NEU1 or NEU3 alone results in significant production of IL-6. HA-IgG added to MES13 cells over-expressing NEU1 or NEU3 further increased IL-6 production over NEU1 or NEU3 alone. In primary MCs, Neutrophil activity, NEU activity, and IL-6 and MCP-1 production are dose-dependently and significantly increased following addition of HA-IgG. Addition of an FDA-approved inhibitor of NEU activity significantly and dose-dependently inhibited HA-IgG-induced IL-6 while higher concentrations were required to inhibit MCP-1 production. NEU1 and NEU3 appear to co-localize with HA-IgG at the surface of the MES13 and primary MCs. JNK and p38 MAP kinase inhibitors prevented IL-6 induction in response to NEU1 or NEU3 over-expression in MES13 cells.

Conclusions: Together these results suggest that immune complex activated IL-6 production of MCs is mediated by NEU activity. This may occur at the cell surface in a complex of HA-IgG and surface receptor that recognizes HA-IgG. Furthermore, the NEU1/NEU3 mediated IL-6 production appears to involve the p38/JNK stress-activated MAPK pathways. Targeting NEU activity may reduce MC cytokine production and thus renal inflammation in lupus nephritis.

Funding: Other U.S. Government Support

FR-PO690

Effects of High Titer of Anti-Chimeric Antibodies Following Rituximab
Dario Roccato,1 Savino Sciascia,2 Roberta Fenoglio,1 1Ospedale San Giovanni Bosco, Torino, Italy; 2Center of Research on Immunopathology and Rare Diseases (CMID), Division of Clinical Immunology, Giovanni Bosco Hospital and University of Turin, Ita, Torino, Italy.

Background: Monoclonal antibodies (MoAbs) are highly successful in treating various immunological disorders. The development of anti-drug antibodies (ADA) against the therapeutic MoAb is relatively common. In recent years, knowledge of how to assess immunogenicity of biological drugs has improved. ADA are thought to form immune complexes with the MoAb, leading to accelerated MoAb clearance and low decrease in serum levels. Several reports showed an inverse relationship between MoAb concentration, efficacy, and patient-reported outcomes.

Methods: Acute infusion reactions, including anaphylaxis, develop in a close temporal relationship to MoAb infusion. Among the likely to present with infusion-related adverse effects. ADA formation is mediated by NEU activity. This may occur at the cell surface in a complex of HA-IgG and surface receptor. Together these results suggest that immune complex activated IL-6 production of MCs is mediated by NEU activity. This may occur at the cell surface in a complex of HA-IgG and surface receptor that recognizes HA-IgG. Furthermore, the NEU1/NEU3 mediated IL-6 production appears to involve the p38/JNK stress-activated MAPK pathways. Targeting NEU activity may reduce MC cytokine production and thus renal inflammation in lupus nephritis.

Results: While HA-IgG alone fails to activate MES13 cells to produce IL-6, overexpressing NEU1 or NEU3 alone results in significant production of IL-6. HA-IgG added to MES13 cells over-expressing NEU1 or NEU3 further increased IL-6 production over NEU1 or NEU3 alone. In primary MCs, Neutrophil activity, NEU activity, and IL-6 and MCP-1 production are dose-dependently and significantly increased following addition of HA-IgG. Addition of an FDA-approved inhibitor of NEU activity significantly and dose-dependently inhibited HA-IgG-induced IL-6 while higher concentrations were required to inhibit MCP-1 production. NEU1 and NEU3 appear to co-localize with HA-IgG at the surface of the MES13 and primary MCs. JNK and p38 MAP kinase inhibitors prevented IL-6 induction in response to NEU1 or NEU3 over-expression in MES13 cells.

Conclusions: Together these results suggest that immune complex activated IL-6 production of MCs is mediated by NEU activity. This may occur at the cell surface in a complex of HA-IgG and surface receptor that recognizes HA-IgG. Furthermore, the NEU1/NEU3 mediated IL-6 production appears to involve the p38/JNK stress-activated MAPK pathways. Targeting NEU activity may reduce MC cytokine production and thus renal inflammation in lupus nephritis.

Funding: Other U.S. Government Support

FR-PO691

CD11b Activation Reduces Inflammation in Lupus Nephritis by Downregulating TLR Pathways
Sanam Khan, Mohd Hafeez Faridi, Ha Won Lee, Mehmet M. Altintas, Shehryar J. Khalqidina, David J. Cimbalka, Vineet Gupta. Rush University Medical Center, Chicago, IL.

Background: Single nucleotide polymorphisms (SNPs) in the ITGAM gene, coding for CD11b subunit of the integrin CD11b/CD18, produce defective protein and confer a strong predisposition to systemic lupus erythematosus (SLE, lupus) and lupus nephritis. Elevated levels of IFN-I in circulation is a heritable risk factor for SLE and play a pathogenic role and are likely driven by a combination of genetic variations and environmental stress. Here we investigate if variations in ITGAM are linked to high IFN-I and whether pharmacological CD11b activation could be a therapeutic strategy.

Methods: To test for a direct link between ITGAM SNPs and the TLR induced IFN-I pathways, we measured serum IFN-I activity in 171 SLE patients and determined their ITGAM genotype. Since ITGAM SNPs result in functionally deficient CD11b, we tested whether partial CD11b activation with small molecule agonist, leukaedrin-1 (LA1) can suppress IFN-I pathways and determined TLR signaling components that are regulated by CD11b activation. To test the efficacy of LA1 in a lupus model, we used the MRL/lpr mice that develop IFN-I dependent multi-organ lupus similar to human lupus with renal inflammation.

Results: We report that SLE subjects carrying ITGAM SNPs have significantly elevated serum IFN-I activity indicating a direct link between reduced CD11b activity and elevated inflammation in patients. LA1 treatment reduced IFN-I responses and protected lupus-prone MRL/lpr mice from kidney injury. LA1-treated mice had reduced glomerular injury, proteinuria, and IgG renal immune complex deposition as compared to vehicle-treated controls. CD11b agonist LA1 suppressed proinflammatory cytokine secretion by TLR-activated leukocytes and suppressed IFN-I signaling. An AKT-FOXO3-IRF7 pathway. TLR-stimulated macrophages from CD11b SNP carriers showed increased expression of IFR7 and IFNB, as well as increased nuclear exclusion of FOXO3, which was reversed by LA1.

Conclusions: LA1 suppresses TLR-induced cytokine production that has been directly linked to exacerbation of lupus nephritis. Hence pharmacological CD11b activation is a promising potential novel therapeutic target, particularly in patients identified as carriers of ITGAM variants.

Funding: NIDDDK Support

FR-PO692

Exogenous Hepcidin Mitigates and Delays Onset of Lupus Nephritis
Yogesh M. Scindia,1 Ewa U. Mandziak,2 Valentina Loi,1 Saleh Mohammad,1 Sundaramaran Swaminathan,1 ’AO Brotsu Cagliari, Cagliari, Italy; 2University of Virginia, Charlottesville, VA; 3University of Virginia, Charlottesville, VA.

Background: Lupus nephritis (LN) is an end-organ manifestation of systemic lupus erythematosus (SLE) with a strong gender bias and affects mostly pre-menopausal women. Current interventions are imprecise and broadly immunosuppressive and hence there is a constant need for identifying new therapeutic targets. Recent human studies have identified Hepcidin (Hamp), the master regulator of iron metabolism as a biomarker of LN, and renal flares are associated with low Hamp levels. So far there are no mechanistic studies examining the role of hepcidin in the pathogenesis of SLE. We therefore hypothesized that Hamp treatment would mitigate SLE-induced kidney disease.

Methods: 7-week-old female MRL/lpr mice (a spontaneous model of SLE, n = 4-5) were treated bi-weekly with saline or 50 µg of hepcidin (i.p) for 10 weeks, following which outcomes like microalbuminuria, histopathology, circulating autoantibody levels and other markers of inflammation were examined.

Results: Saline treated mice developed severe LN by 17 weeks of age as indicated by high microalbuminuria, collagen deposition, renal IL-6, CXCL-1 and M-CSF transcripts, and an infiltration of CD45 cells, F4/80+ve macrophages and T cells. There was a concomitant increase in circulating autoantibodies and serum MCP-1, IL-6, GM-CSF and TNFa. Hamp treatment significantly reduced all Theses manifestations of LN (Microalbuminuria; PBS, 914.6 ± 64.6 mg/gm vs Hamp 314.2 ± 111.2 mg/gm). Hamp treatment was associated with a systemic decrease in Cox-2, a mediator of inflammation. There was an increase in renal H-ferritin and a concomitant decrease in iron dependent enzymes, Rrm-1 and Rrm-2, both of which are required for DNA synthesis.

Conclusions: This is the first study to demonstrate therapeutic benefit of Hamp in LN. Our results indicate that Hamp protects against LN by decreasing Cox-2 and reducing inflammation as well as by reducing cell proliferation through the induction of cytoprotective H-ferritin. Further studies are required to investigate whether Hamp mediated protection leads to end-organ resistance to LN or through to modulation of immune responses.

Funding: NIDDK Support

Table 1

<table>
<thead>
<tr>
<th>Gene</th>
<th>% of CD11b-positive CD14+</th>
<th>% of CD11b-positive CD16+</th>
<th>% of CD11b-positive CD16+CD14+</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD11b</td>
<td>85</td>
<td>65</td>
<td>10</td>
</tr>
<tr>
<td>CD14</td>
<td>75</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>CD16</td>
<td>65</td>
<td>45</td>
<td>10</td>
</tr>
</tbody>
</table>

Abbreviations: %: not determined. * Patient with severe hypersensitivity reaction

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
**FR-PO069**

Antirenal CD4+ T Cells Arise in Lupus Nephritis, Are Mainly of the Th1 Phenotype, Are Only Partially Controlled by Their Regulatory Counterparts, and Invade the Inflamed Kidneys

**Philipp Enghard,1 Sebastian Tesch,2 Dimas Abdairama,3 Gabriela Riemekasten.4 1Charité, Berlin, Germany; 2Charité Universitätsmedizin Berlin, Berlin, Germany; 3University Lübeck, Lübeck, Germany.

**Background:** Lupus nephritis (LN) is associated with local MHC II upregulation and a T cell-rich infiltration, suggesting an antigen-specific immune response. However, up to date no renal target antigens are known in LN. Here we report the identification of a set of target autoantigens and characterize the respective CD4+ T cell response.

**Methods:** Peripheral blood T cells from 57 SLE patients and 11 healthy controls (HC) were analyzed. In an initial cohort T cells were stimulated with kidney lysates from healthy kidneys. Subsequently five candidate autoantigens were identified based on the assumption that a corresponding autoantibody is present and that the respective antigen is upregulated in the inflamed kidney in LN. Enrichment via CD4+ expression was performed and intracellular cytokine production was measured with flow cytometry (ARTE method). Regulatory T cells were assessed via CD137 enrichment. Urinary T cells from six patients with active LN were isolated and probed for the presence of autoreactive T cells.

**Results:** Only marginal T cell reactivity was detectable when stimulating peripheral blood T cells with kidney lysates. In subsequent experiments, a pool of renal candidate autoantigens was used and autoreactive CD4+ T cells were detected in patients with SLE and healthy controls. These cells were mainly IFN-g producing Th1 T cells and were significantly expanded in patients with active LN, compared to inactive SLE patients and HC. IL-4, IL-10 and IL-17 producing antirenal CD4+ T cells were present in lower frequencies, albeit also expanded in patients with active LN. Upon stimulation with renal autoregents, CD137 expressing Tregs were also detected, and the ratio of IFN-g+ T cells to CD137+ Treg cells was significantly higher in active LN patients and correlated with disease activity. Using T cell libraries we identified Vimentin and Annexin A2 as the main, but not exclusive targets of the antirenal T cell response. Finally, we were able to also detect antirenal T cells in the urine of patients with active LN, indicating renal invasion of these cells.

**Conclusions:** An antirenal CD4+ T cell response arises in LN. These cells are mainly of the Th1 phenotype, invade the inflamed renal tissue and are only partly controlled by their regulatory counterparts.

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

---

**FR-PO0695**

Synergetic B-Cell Immunomodulation with Rituximab and Belimumab Combination Treatment in Severe, Refractory SLE: The SynBiose Proof-of-Concept Study

**Tineke Kraaij,1 Sylvia Kamerling,1 Esther de Rooij,2 Paul L. Van daele,3 Edwin Bredeveld,4 Jaap A. Bakker,5 Ingeborg M. Bajema,6 Hans Ulrich Scherer,7 Rene Toes,8 Tom Huizinga,9 Ton J. Rabelink,6 Cees van Kooten10,11 Yoe Kie Onno Teng.1 1Nephrology, Leiden University Medical Center, Leiden, Netherlands; 2Clinical Immunology, Erasmus MC, Rotterdam, Netherlands; 3Clinical Chemistry, Leiden University Medical Center, Leiden, Netherlands; 4Pathology, Leiden University Medical Center, Leiden, Netherlands; 5Rheumatology, Leiden University Medical Center, Leiden, Netherlands.

**Background:** Neutrophil extracellular traps (NETs) are auto-antigenic DNA strands and could give rise to SLE-specific autoantibodies that can deposit in glomeruli. It has been shown that autoantibodies can induce NETs, contributing to a vicious circle of immune activation in SLE. We hypothesized that eliminating autoantibodies can lead to decreased NET induction and thereby ameliorating disease in SLE. We designed a proof-of-concept study to eliminate autoantibodies and NET formation through synergetic B-cell immunomodulation with rituximab and belimumab (RTX+BLM) in severe refractory SLE.

**Methods:** We treated patients with severe, refractory SLE in a phase 2 study with RTX+BLM. The primary endpoint assessed reduction of pathogenic autoantibodies and NET induction at week 24. Anti-dsDNA autoantibodies were measured and high sensitivity FACS was performed to assess B-cell subsets. NET induction was measured with 3D confocal microscopy.

**Results:** We included 14 patients with severe, refractory SLE of whom 11 had a renal flare. At 24 weeks we observed significant reductions in anti-dsDNA autoantibodies (p=0.0015). CD19+ B-cells were depleted throughout the study (p=0.0005) while plasma cells (PCs) temporarily decreased but returned at week 24 despite persistent depletion of transitional B-cells. Taken together with reductions of autoantibodies and stable total IgG, there is no reconstitution of autoreactive PCs. We observed significant decrease in NET production (p=0.0017). In vitro studies elucidated this resulted in reduction of immune complexes by RTX+BLM. Importantly, beneficial immunological effects translated to amelioration of clinical disease activity: SLEDAI decreased from a median of 18 to 2 (p=0.0002). Ten out of 11 LN patients showed a response (4 complete renal responders). The response was achieved while tapering immunosuppressive drugs. Treatment was well-tolerated.

**Conclusions:** The SynBiose study is the first to demonstrate that RTX+BLM ameliorated disease in severe SLE in association with the reduction of pathogenic autoantibodies and immune complex-mediated NET induction. Therefore, RTX+BLM represents a novel treatment concept in SLE. ClinicalTrials.gov NCT02284984

---

**FR-PO0696**

Erythropoietin (EPO) Ameliorates Lupus Nephritis by Inhibiting TFH and Increasing Treg

**Andrea Angeletti,1 Chiara Donadelli,2 Vivette D. A’agari,3 Arun Cumpelik,2 Joaquin Manrique,2 Miguel L. Fribourg,2 Gaetano La Manna,4 Peter S. Heeger,2 Paolo Cravidi,2 Colombia University College of Physicians and Surgeons, New York, NY; 3Icahn School of Medicine at Mount Sinai, New York, NY; 4Complejo Hospital de Navarra, Pamplona, Spain; 5Nephrology, DIMES, Bologna, Italy.

**Background:** Systemic lupus erythematosus (SLE) is characterized by impaired immune regulation and enhanced follicular helper T cell (Th17)-dependent B cell activation, autoantibody production and tissue deposition/injury. Building upon evidence that EPO inhibits effector T cells (Teff) while promoting regulatory T cells (Treg) (JASN 2017), we tested the effects of EPO in murine lupus.

**Methods:** We treated MRL/lpr mice with rEPO (5,000IU/ml, 3/week mo 4-6) or vehicle, serially measured proteinuria and at 6 mo quantified anti-dsDNA, glomerular Ig deposition and splenic Treg/Tfh. We also administered EPO or vehicle to (bxd) F1 mice given B6 spleen cells and quantified splenic Tfh, Treg and germinal center (GC) B cells 2 weeks later.

**Results:** In MRL/lpr mice, rEPO increased Treg (20.1±3.3 vs. 11.5±4.2%, p=0.05) and reduced proteinuria, autoantibodies, glomerular IgM deposition, and histological score (is that right?) (Fig 1A). In the parent to F1 model, EPO inhibited Tfh and GC B cells formation (Fig 1B-C), while it increased Treg vs. vehicle (1.4±0.3 vs. 0.4±0.2%, p<0.05).

**Conclusions:** EPO administration inhibits Tfh and GC B cell formation while promoting Treg, together reducing the clinical and histological expression of murine lupus nephritis. Together with our published evidence that EPO promotes human Treg, the data support safety/efficacy testing of EPO as an immunomodulating agent in lupus patients.
FR-PO697

Relationship between B Cell Signatures and Disease Flare in Lupus Nephritis Patients

Background: Nephritic flares in patients with lupus nephritis (LN) reduce renal survival but factors contributing to flares remain elusive. Perturbations of B cell subsets have been implicated in the pathogenesis of LN, but the relationship between B cell signatures and relapse has not been investigated.

Methods: We compared circulating B cell subsets and signatures (miRNA148a, BACH1, BACH2 and PAX5) in the serum and plasma cells during disease quiescence between Class III/IVaV LN patients who are multiple relapsers (MR, defined as ≥3 relapses within 36 months unrelated to non-compliance) or non-relapsers (NR, defined as no relapse after the presenting episode).

Results: 33 patients were included (MR n=20; NR n=13). MR showed lower percentage of circulating naïve and memory B cells (0.48%, IQR 0.24%-3.15% vs. 4.52%, IQR 3.18%-8.25%; and 0.51%, IQR 0.26%-0.67% vs. 0.96%, IQR 0.86%-1.91%; p=0.014 and 0.014 respectively) and higher plasma cell-to-naïve B cell ratio (1.52±2.19 vs. 0.21±0.33, p=0.011) compared with NR. MR had higher miRNA148a in serum and plasma cells compared with NR (relative expression (RQ) 4.25±2.86 vs. 0.71±0.55 and 3.53±1.56 vs. 1.38±1.17, p=0.002 and 0.128) (Figure 1A). MR also showed lower BACH2 expression in circulating plasma cells [RQ 12.86±3.10 vs. 28.10±1.56 vs. 2.86 vs. 0.71 ±2.19 vs. 0.55 and 2.86 vs. 0.71 ±2.19 vs. 0.55 and 2.86 vs. 0.71, p<0.0001]. However, there was no difference in BACH1 and PAX5, and the percentage of circulating naïve and memory B cells (0.48%, IQR 0.24%-3.15% vs. 0.51%, IQR 0.26%-0.67% vs. 0.96%, IQR 0.86%-1.91%; p>0.05 for both) (Figure 1B).

Conclusions: Elevated serum and plasma cell miRNA148a might be related to BACH2 downregulation in plasma cells and altered circulating B cell subsets, thereby increasing risk of LN relapse.

FR-PO698

Serum VCAM-1 Level in Patients with Lupus Nephritis and Its Clinical Associations

Background: Cardiovascular disease is more common in patients with lupus nephritis. Endothelial cell activation or injury is associated with shedding of adhesion molecules into the circulation. We investigated circulating VCAM-1 level in lupus nephritis patients and its clinical associations.

Methods: Archived paired serum samples, one during flare and the other during clinical remission, from 29 patients with biopsy-proven Class III/IV lupus nephritis were included. Serial samples obtained at intervals of 3-4 months over two years in 27 stable patients were included for longitudinal studies. Smokers and patients with serum creatinine above 450µmol/l or eGFR below 15ml/min were excluded. Age- and sex-matched patients with non-lupus glomerular diseases and healthy subjects (n=25 for each group) were included as controls. Serum VCAM-1 level was measured by ELISA.

Results: 482 serum samples from lupus nephritis patients (20 females and 9 males; age 39.0±10.2 years; disease duration 7.6±8.6 years) were studied. Only one patient had clinically evident vascular disease. Serum VCAM-1 level was significantly higher during active lupus nephritis, compared to remission samples, patients with non-lupus renal diseases or healthy subjects (P<0.001, for all). VCAM-1 level correlated with SLEDAI and the level of anti-dsDNA antibody, serum creatinine, urine albumins-to-creatinine ratio, and prevailing prednisolone daily dose, and inversely correlated with serum C3 and albumin levels. VCAM-1 level was not associated with lipid parameters. Longitudinal studies showed that increased circulating VCAM-1 level preceded clinically evident renal flare by 4.6±3.4 months, and persisted for 11.7±8.8 months after clinical disease quiescence. Analysis with ROC curve showed that serum VCAM-1 level distinguished patients with active lupus nephritis from healthy subjects with sensitivity and specificity rates of 96.5% and 96.0% respectively (P<0.0001), and from patients with non-lupus renal diseases with sensitivity and specificity rates of 89.6% and 82.6% respectively (P<0.0001).

Conclusions: Active lupus nephritis was associated with elevated VCAM-1 level in serum, which persisted for many months despite renal response after treatment. The findings suggest prolonged subclinical vascular endothelial injury and could have implications on the pathogenesis of cardiovascular complications.

Funding: Government Support - Non-U.S.
C4d Deposits in FSGS before the Development of Sclerosis

Pathologic Findings in Monoclonal Glomerulopathy with Features of Cryoglobulinemic Nephropathy in the Kidneys of a Vk*MYC Transgenic Model of Multiple Myeloma Ping L. Zhang,1 Guillermo A. Herrera,2 Karen L. Lewinski,1 Bei Liu,1 Anatomic Pathology; Beaumont Health System, Royal Oak, MI; 2Immunology, Medical University of South Carolina, Charleston, SC. 1St. Petersburg, University, LSU School of Medicine, Dept.Pathology, Leiden, Netherlands; 2Charite- University Medical Center, Dept.Pathology, Leiden, Netherlands; 3Pathology, Louisiana State University Health Sciences Center, Shreveport, LA.

Background: There are only a few animal models of monoclonal light chain-associated renal diseases and no animal models of monoclonal cryoglobulinemic nephropathy (CN) that can be used to evaluate treatment modalities. The Vk*MYC transgenic model in 50-70 weeks old mice with renal involvement has been reported before (Chesi et al., 2008) but detailed renal pathologic changes have not been well documented. This study fully investigates pathologic changes in these kidneys.

Methods: The kidneys of 6 wild type and 12 Vk*MYC transgenic mice were investigated using routine light microscopy (LM), immunofluorescence stains for light chains (IF), and electron microscopy (EM). The EM score system developed to evaluate findings is as follows: 0 – no deposits, 1+ minimal electron dense deposits, 2+ moderate deposits and 3+ - moderate to prominent deposits with subendothelial deposits.

Results: By LM, wild-type kidneys were unremarkable. However, the kidneys from transgenic mice showed either mesangial segmental expansion, some with associated hypercellularity and / or thrombotic obstruction of glomerular capillaries. By IF, the glomeruli of wild-type mice showed minimal or no staining for both kappa and lambda. In the transgenic mice, lambda was 2+, stronger than kappa 1+ staining in glomeruli as a result of kappa light chain deposits. In the aging transgenic mice, minimal electron dense deposits can be seen in the mesangial areas by EM. Notably, in transgenic mice, 6 out of 12 kidneys showed mild mesangial deposits (1+). The other 6 kidneys from the transgenic mice showed 2-3+ electron dense deposits. The deposits were located in glomerular capillary lumina in 3 cases. Large luminal and subendothelial deposits were characterized by randomly disposed microtubular structures measuring up to 16 nm in diameter, with overall features consistent with findings CN. Segmental fusion of foot processes were seen, but no mesangial interposition was noted.

Conclusions: Our pathologic evaluation suggests that 50% (6/12) of kidneys from the Vk*MYC model of MM had significant EM deposits with features of CN in 3 of them (most likely lambda dominant). This transgenic model of monoclonal-associated glomerulopathy may be useful to evaluate treatment of neoplastic B cell clones with renal manifestations.

Funding: Other NIH Support - NC1

FR-PO702

Proteomic Analysis of Glomerular Extracellular Matrix Demonstrates Differences between FSGS Variants

Michael Merchant,1 Dawn J. Caster,2 Daniel W. Wilkey,2 Michelle T. Barati,3 Kenneth R. McLeish,2 Department of Medicine, Division of Nephrology & Hypertension, University of Louisville, Louisville, KY; 2Rohley Rex VA Medical Center, Louisville, KY.

Background: Abnormal remodeling of glomerular extracellular matrix (ECM) is a prominent feature of focal segmental glomerulosclerosis (FSGS). Changes in ECM that accompany FSGS have not been defined in humans. We postulated that FSGS is characterized by specific changes in ECM composition. The current study used laser capture microdissection (LCMD) of glomeruli from human biopsy specimens and mass spectrometry (MS) and immunohistochemical (IHC) methods to compare -ECM composition among patients with FSGS-NOS, collapsing FSGS (CFSGS), and normal subjects.

Methods: Glomerular sections were obtained by LCMD from de-identified FFPE tissue from FSGS-NOS (n=6), CFSGS (n=7), and from 2 kidneys retrieved, but not used, for transplantation. Samples were analyzed as recently published (Hokeba L., et al. Characterization of glomerular extracellular matrix by proteomic analysis of laser-captured microdissected glomeruli. Kidney Int. 2017 91:501-511). Abundance data were filtered by GO annotation and matrixione recommendation for confirmatory IHC studies using Human Proteome Atlas validated antibodies and an expanded disease/normal- control renal biopsy panel.

Results: HIC was performed on 7 of 25 ECM proteins unique to CFSGS, 3 of 6 unique to FSGS-NOS, and 2 of 20 present in both subtypes of FSGS but not normal. All ECM proteins identified from normal were present in FSGS glomeruli. Annexin 3, marker of podocyte foot processes, and CD68, a marker of podocyte phagocytosis, were induced by exposure to FSGS sera that disrupted podocyte FACs and that could be reversed by TNFalpha blockade, but not by sera from healthy controls or rheumatoid arthritis patients.

Conclusions: Sera from a subset of primary FSGS patients cause striking dispersion of podocyte FACs. This activity is unrelated to serum TNFalpha level but may be due to the effect of FSGS serum on activation of endogenous podocyte TNFalpha pathway signaling. Our assay may be useful in identifying patients at high risk for recurrence of FSGS in the renal allograft and who may potentially benefit from TNFalpha blockade to attenuate podocyte injury.

Funding: Government Support - Non-U.S.
FR-PO703

Role of Monocyte Interleukin (IL)-27 in Minimal Change Nephrotic Syndrome (MCNS) Chang-Yien Chan,1,2 Wee Song Yeo,1,3 Jimiao Chen,1,3 Henry H. Yang,1 Hui Kim Yap,1,2,4 Cancer Science Institute of Singapore, National University of Singapore, Singapore, Singapore; 1Paediatrics, National University of Singapore, Singapore, Singapore; 2Singapore Immunology Network (SIgN), (BMBF 4STAR), Singapore, Singapore; 4KTP-National University Children’s Medical Institute, National University Hospital, Singapore, Singapore.

Background: We have previously shown upregulation of lymphocyte IL-13 gene expression during nephrotic relapses in MCNS patients, associated with downregulation of pro-inflammatory cytokines, IL-8 and tumor necrosis factor (TNF)-α in lipopolysaccharide (LPS)-stimulated monocytes, and decreased monocyte CD14 expression, suggestive of an IL-13-induced anti-inflammatory effect. This study aimed to identify the monocyte 'gene signature' in MCNS patients and subsequently to validate the findings in human podocytes.

Methods: Monocyte RNA from 5 patients in relapse and remission were analysed using Illumina Human Ref8 chips. Subsequently plasma IL-27 levels were measured on 14 MCNS patients in relapse and remission and 20 healthy controls. The role of IL-27 in human podocytes was studied using cell migration assay (collutex). Podocyte RhoA/Rac1 activity were measured using ELISA and STAT1/3 levels were studied using Western blot. Statistical analysis was done using Mann-Whitney test and Wilcoxon signed rank test for paired data.

Results: MetacoreTM analysis on the monocyte transcriptome of MCNS patients in relapse compared to remission revealed involvement of genes in IL-1 signaling, regulation of actin cytoskeleton and receptor tyrosine kinase signaling. Treatment with RheGTPases, tol-liko-receptor inhibitor (TRI)-domain-containing-adapter-inducing-interferon-β (TRIF) and IFN-induction (IRF4, IRF7, IFI6, IFIT2, IFI15, IFI44, SERPING1, OAS1, OAS2, OAS3, CXCL9, CXCL10, DDX58) pathways. Of note gene expression of IL27 was 2.7 times upregulated in MCNS patients in relapse. Consistent with the microarray results, plasma IL-27 levels were significantly higher in MCNS patients in relapse (1.56±0.13 pg/ml) compared to remission (0.95±0.14 pg/ml) (p ≤0.05) and controls (0.89±0.14 pg/ml (p=0.01). IL-27 stimulation in human podocytes resulted in phosphorylation of both STAT1 and STAT3. RhoA activity in IL-27 stimulated podocytes remained largely unchanged whereas activated Rac1 levels in podocytes were 1.56-fold higher compared with unstimulated podocytes at 20 minutes. Moreover, IL-27 induced 6.53% podocytes migration, comparable to the 6.96% podocytes migration observed in LPS-stimulated podocytes.

Conclusions: Monocytes may play a role in the pathogenesis of MCNS relapses via induction of IL-27 and subsequent activation of STAT1, STAT3 and Rac1 as well as induction of cell migration in human podocytes. Funding: Government Support - Non-U.S.

FR-PO704

Loss of Mif Aggravates PAN Induced Proteinuria in Zebrafish Philipp Niggemann,1 Patricia A. Schroder,2 Patricia Bolanos-Palmieri,1 Janina Müller-Deile,1 Heiko J. Schenk,1 Laura L. Beverly-Stagg,2 Beina Teng,1 Hermann G. Haller,3 Mario Schiffer,1 Hanover Medical School, Freiburg, Germany; 1Mount Desert Island Biological Laboratory, Salisbury Cove, ME.

Background: We developed a standardized proteinuria model in zebrafish using pancreatectomized (PANC) fish through treatment with the toxicant. We observed that fish with the nacre mutation show a significantly higher susceptibility to PAN than AB fish upon exposure to the same dosage of PAN. (AB is a standard wild-type line) Nacre is the name of a mutation yielding a truncated version of Microphthalmia-associated transcription factor (Mif) in zebrafish. Mif is an evolutionarily conserved transcription factor that controls pigment cell fate in vertebrates. It is well known that a mutation in mif1 leads to missing neural-crest-derived melanophores and results in a pigment-less phenotype, making this mutation a commonly used fish line to study organ development.

Results: In this study, we crossed GFP-DiP zebrafish that were backcrossed onto AB or nacre background and were exposed to PAN in the water at varying timepoints from 4 hours post fertilization (hpf) to 50 hpf. Loss of high molecular weight proteins from the circulation was measured at 96 hpf as a surrogate marker for proteinuria. In addition, we performed mif1 knockdown experiments in AB zebrafish using morpholinos. Moreover, cultured human podocytes were examined after silencing of mif in vitro.

Results: Zebrafish homozygous for the nacre mutation and AB zebrafish after knockdown of mif exhibited stronger proteinuria after PAN treatment compared to control animals. Moreover, a treatment with PAN at 46 hpf yielded the strongest proteinuria. Treatments at later timepoints were less effective in proteinuria induction. Silencing of MIF in human podocytes led to a disrupted cytoskeletal organization after PAN treatment. At the same time the expression of MIFT downstream partners like IFN2 was changed, indicating that MIFT plays an important role for cytoskeleton recovery in podocytes.

Conclusions: We present the first reproducible PAN-nephrosis model in zebrafish, which could serve as a suitable setting for drug testing in zebrafish. Furthermore, we can demonstrate that a mutation in mif leads to a higher susceptibility for disruption of the glomerular filtration barrier upon PAN treatment, which results in stronger proteinuria.

FR-PO705

Heterogeneous Nuclear Ribonucleoprotein F Deficiency Aggravates Podocyte Loss via Down-Regulation of Sirtuin-1 Expression in Adriamycin-Induced Nephropathy in Mice Chao-Sheng Lu,1 Isabelle Chenier,2 Janos G. Filep,3 Julie R. Ingelfinger,4 Shia-Ling Zhang,5 John S. Chan,1 CHUM-Hotel Dieu Hosp, Montreal, QC, Canada; 2CRCHUM, University of Montreal, Montreal, QC, Canada; 3Maisonneuve-Rosemont Hosp, Montreal, QC, Canada; 4Research Center of Centre Hospitalier de l Universite de Montreal (CRCHUM), Montreal, QC, Canada; 5The New England Journal of Medicine, Boston, MA.

Background: We reported that overexpression of heterogeneous nuclear ribonucleoprotein F (hnRNPF) enhances sirtuin-1 expression and attenuates apoptosis in renal proximal tubular cells in db/db InfRNP F- transgenic mice (Diabetes 2017). In the present study, we investigated whether hnRNPF deficiency in podocytes would aggravate podocyte injury in adriamycin (ADR)-induced nephropathy in mice.

Methods: Podocyte-specific hnRNPF knockout (KO) mice were generated by crossing breeding podocin (Pod)-Cre mice with floxed hnRNPF F mice on a C57BL/6 background. Male adult non-KO littermates (controls) and Pod-hnRNPF KO mice were studied at age 10 to 20 weeks. Body weight (BW) and urinary albumin/creatinine ratio (ACR) were monitored bi-weekly. To induce nephropathy, male controls and Pod-hnRNPF KO mice were administered ADR (doxorubicin) (18 mg/kg BW) via tail vein at the age of 10 weeks. Urinary ACR were assessed 7 and 11 days post-ADR. Mice were euthanized on day 12. Kidneys were processed for histology. Freshly isolated glomeruli were assessed for mRNA and protein expression by real time-qPCR and Western blotting, respectively. In addition, primary podocytes isolated from controls and Pod-hnRNPF KO mice were cultured in vitro and were studied in ADR.

Results: Pod-hnRNPF KO mice were phenotypically normal with a slight increase in ACR at week 20. Glomeruli isolated from Pod-hnRNPF F KO mice exhibited significantly lower mRNA and protein levels of sirtuin-1 and podocyte markers including nephrin, WT1 and synaptopodin that compared to controls. Administration of ADR significantly increased urinary ACR and apoptotic podocytes in both groups. However, these changes were more pronounced in Pod-hnRNPF F KO mice, parallel with significant decreases in sirtuin-1, nephrin, WT1 and synaptopodin expression. Finally, in vitro studies confirmed that podocytes from hnRNPF KO mice exhibited lower sirtuin-1 expression and higher acetylated p53 expression and apoptotic podocytes after ADR treatment.

Conclusions: HnRNPF F deficiency aggravates podocyte apoptosis in ADR-induced nephropathy in mice, indicating a protective role for hnRNPF F against podocyte injury. Funding: Government Support - Non-U.S.
**FR-PO707**

**Title:** Treatment of IgA Nephropathy—A Case Study in a Grouped ddY Mouse

**Affiliation:** Affiliated Hospital of Dalian Medical University, Dalian, China

**Abstract:** Antigen-based targeting of APRIL as a therapeutic strategy in the FR-PO709

**Background:** APRIL is a member of the TNF/CD40L cytokine family that is implicated in B-cell survival and plasma cell differentiation. Previous studies have shown that APRIL is involved in the pathogenesis of IgA nephropathy (IgAN). However, the role of APRIL in the pathogenesis of IgAN remains unclear. In this study, we aimed to investigate the role of APRIL in the pathogenesis of IgAN using a mouse model.

**Methods:** We used a mouse model of IgAN and treated the mice with an anti-APRIL monoclonal antibody. The effect of APRIL targeting on the histopathology of the kidneys was evaluated.

**Results:** Treatment with the anti-APRIL monoclonal antibody led to a significant improvement in the histopathology of the kidneys, as evidenced by a decrease in the number of mesangial cells and mesangial matrix.

**Conclusions:** Our results suggest that targeting APRIL may be a potential therapeutic strategy for the treatment of IgAN.

**FR-PO708**

**Title:** Inhibition of p53 Desumoylation by SENP1 Exacerbates Purumycin Aminonucleoside-Induced Apoptosis in Podocytes

**Affiliation:** Lingyu Wang, the First Affiliated Hospital of Dalian Medical University, Dalian, China

**Background:** p53 is a tumor suppressor protein that regulates cell cycle arrest and apoptosis. Desumoylation refers to the removal of SUMO (small ubiquitin-like modifier) proteins from proteins. Podocyte apoptosis is a major cause of reduced podocyte numbers, which leads to proteinuria and/or glomerulosclerosis. In this study, we investigated the role of p53 desumoylation in podocyte apoptosis.

**Methods:** We used wild type (WT), p53−/−, and dB2 (a p53 heterozygous mouse) mice to study the effect of p53 desumoylation on podocyte apoptosis.

**Results:** Our results showed that SENP1 deficiency significantly increases PAN-induced podocyte apoptosis. Moreover, SENP1 knockdown results in the accumulation of SUMOylated p53 in podocytes, which is associated with increased p53 protein levels and decreased podocyte viability.

**Conclusions:** p53 desumoylation is a novel strategy for the treatment of glomerular disorders that involve podocyte apoptosis.

**FR-PO709**

**Title:** Antibody-Based Targeting of APRIL as a Therapeutic Strategy in the Treatment of IgA Nephropathy—A Case Study in a Grouped ddY Mouse

**Affiliation:** Jairynn Myette,1 Toshiki Kano,1 William E. Smoyer,1 2CCTR, The Research Institute at Nationwide Children’s Hospital, Columbus, OH; 2Pediatrics, The Ohio State University, Columbus, OH

**Background:** IgA nephropathy (IgAN) is a chronic autoimmune glomerular disease of unknown etiology. The cytokine APRIL (TNFSF13) is emerging as a key player in disease onset and progression, based on a recent convergence of biological and translational data. The pathogenic role of APRIL in IgAN has been previously published in grouped ddY (gddY) mice, an early-onset disease model which recapitulates many of the clinical hallmarks of IgAN pathophysiology and progression.

**Methods:** We used a mouse model of IgAN (IgAN) and treated the mice with an anti-APRIL monoclonal antibody. The effect of APRIL targeting on the histopathology of the kidneys was evaluated.

**Results:** Treatment with the anti-APRIL monoclonal antibody led to a significant improvement in the histopathology of the kidneys, as evidenced by a decrease in the number of mesangial cells and mesangial matrix.

**Conclusions:** Our results suggest that targeting APRIL may be a potential therapeutic strategy for the treatment of IgAN.

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

Underline represents presenting author.
synthesis and hypertrophy of mesangial cells. Similarly, anti-miR-181a attenuated TGFB-stimulated mesangial fibrotic expansion.

Conclusions: Our results provide the first evidence for the mechanism of dector downregulation by TGFB, involving miR-181a. Furthermore, we demonstrate for the first time that miR-181a contributes to TGFB-induced mesangial cell hypertrophy and matrix protein expression. Use of anti-miR-181a may be beneficial in TGFB-mediated fibrotic kidney disease. 

Funding: NIDDK Support, Veterans Affairs Support

FR-PO712

Exosomes from High Glucose-Treated Human Mesangial Cells Activate Renin Angiotensin System in Healthy Mesangial Cells
Antonio S. Novacs,1,2 Fernanda T. Borges,1 Mirian A. Boim,1 1Federal University of São Paulo, São Paulo, Brazil; 2UNIFESP, São Paulo, Brazil.

Background: High glucose (HG) induced-intracellular angiotsin II (Ang II) accumulation is correlated with upregulation of Ang II target genes, such as pro-fibrotic cytokines. This effect can be propagated via microRNAs and peptides transferred to other cells via exosomes (Ex), which play a key role in cellular communication under physiological and pathological conditions.

Methods: To verify whether exosomal signaling initiated in HG stimulated human mesangial cells (HCM) would affect control cells function, HMC were cultured under standard (5 mM) or HG (30 mM) concentrations for 24 hr. Ex secreted to culture medium were purified by ultracentrifugation and analyzed by electron microscopy. The vesicles size/concentration ratio was determined by the particle tracking using a nanoparticles analyzer and the Ex were characterized by the presence of CD63 and CD81 by western blot. In addition, we observed Ang II stimulated-HG (Ex) (HG stimulated-HG (Ex)) were labeled with PKH67 and added in normal HMC. The Ex internalization was evaluated by confocal microscopy (CM). The presence angiotensinogen (AGT), renin and ACE in the Ex was analyzed by western blot. The bioactivity of the Ex was examined in Chinese Hamster Ovary cells (CHO-K1), which do not express components of RAS, and in CHO-K1 transfected ECA (ECA-CHO) in the presence of C-Ex or HG-Ex. The synthesis of Ang II in ECA-CHO was analyzed by CM. Expressions of fibronectin, AGT, renin, AT1, AT2 receptors and proliferation were used to assess the cellular response to signal transferred through the Ex in control HMC exposed to C-Ex or HG-Ex.

Results: HG stimulated induced a change in the amount, but not in the size of Ex. HG-Ex are internalized by normal HMC. C-Ex contained AGT and renin proteins, whose expressions were increased in cells exposed to HG-Ex. ACE was not detected in C-Ex and HG-Ex. The exposure of HG-Ex to ECA-CHO resulted in Ang II formation in these cells. The expression levels of fibronectin, AGT, renin, AT1 and AT2 were higher in control HMC treated with HG-Ex compared with those treated with C-Ex, indicating that HG-Ex can modify the function of target control HMC.

Conclusions: These results suggest that the intercellular communication through the exosomes may have pathophysiologic implications in the diabetic kidney.

Funding: Government Support - Non-U.S.

FR-PO713

Connective Tissue Growth Factor (CTGF, CCN2) Is Sufficient to Drive Expression of Collagen IV, Fibronectin and Mesangial Expansion
Yongxin Gao,1,2 Charles W. Hellig,1,2 Leighton R. James,1,2 1Medicine, University of Florida, Jacksonville, FL; 2Diabetes Institute, University of Florida, Gainesville, FL.

Background: CTGF has been linked to organ fibrosis. Using an animal model we hypothesized that CTGF directly influences expression of extracellular matrix protein (ECM) proteins. Accordingly, we evaluated CTGF has been linked to organ fibrosis. Using an animal model we hypothesized that CTGF directly influences expression of extracellular matrix protein.

Methods: To test this hypothesis we measured urine flow rate, urine albumin (Alb), creatinine (Cr), and microprotein (MP) levels in 129Sv, C57B1/6J, WT (n=6) and the kidney of mice with HT (n=6). The levels of MP were assessed by ELISA.

Results: Baseline levels were not different between the two groups. Renal mass reduction induced albuminuria in both groups at 2 weeks; however, 24h albumin excretion (UAlbV) was markedly higher for the KO compared to the WT mice at both 2 weeks (p<0.001) and 4 weeks (p<0.001). UAlbV was 11 (6–21), 161 (57–497) and 169 (42–500) µg/24h for baseline, 2 and 4 weeks respectively for the WT and the APAKO mice, respectively. Similar findings were observed when albumin levels were expressed as albumin/creatinine ratio (UACR). UACRs were 277 (113–745) vs 1856 (842–2539) at 2 weeks (p<0.001) and 242 (116–1781) vs 1837 (618–3845) at 4 weeks (p<0.001) for the WT and APAKO respectively. Concomitant with the reduction in renal mass was a decrease in the generation of total urinary MP (MP/Cr) that was similar in both groups. Further, the formation of protein associated podocyte-derived MP also decreased in both groups. For WT, the generation of (ps)MP at baseline and 2 weeks was 2.2x10^6 ± 1.4x10^5 and at 4 weeks 2.6x10^6 ± 1.0x10^6 psMP/mg (p<0.01) and at 4 weeks 2.4x10^6 ± 1.2x10^6 psMP/mg (p<0.01). For the APAKO mice psMP at baseline and 2 weeks was 2.2x10^6 ± 1.4x10^6 ± 4.8x10^5 psMP/mg (p<0.01) and at 4 weeks it was 2.4x10^6 ± 2.8x10^6 psMP/mg (p<0.01). Our findings support a role for APA in ameliorating glomerular injury following 5/6 renal ablation. The finding that the formation of (ps)MP was not different between the 2 groups 2 weeks after renal injury, suggests that the chronic renoprotective role of APA may not be associated with attenuation of podocyte MP formation.

Funding: Private Foundation Support
FR-PO716

**3D Analysis of Optically Cleared Kidney Slices Reveals Focal Podocyte Loss in Crescentic Nephritis**

Victor G. Puelles,1,2 David Fleck,3 Michael Vogt,1 Stella Papadouri,1 Thiago Strieder,1 Turgay Saritas,1 David J. Nikolic-Paterson,2 Marc Scher,2 Marcus J. Moeller.1

**Background:** Podocyte depletion is a common feature of glomerulosclerosis (FGS), but its role in crescentic nephritis remains unclear. This study combined genetic tagging of podocytes with three different optical clearing techniques to determine podocyte depletion in whole glomeruli from mice with crescentic nephritis.

**Methods:** Podocyte nuclei were labeled by GFP-histone in adult male Pod-rtTA/ H2B-GFP mice by oral doxycycline, followed by a 7-day wash out period, and a single intra-peritoneal injection of neprotoxic serum (NTS; 5mg/g). Experimental mice were killed 10 days after NTS injection, and compared to age-matched controls. Kidney slices were optically cleared with SCALE-A4, CLARITY and Ethyl Cinnamate (EC). High-resolution serial optical images were obtained by confocal and two-photon microscopy.

**Results:** Mean podocyte number per mouse showed very low variability within controls (1-5% variability, P=0.05) and within NTS-Injected mice (1-9% variability, P=0.05) independent of the clearing technique. In NTS-injected mice, a similar degree of average podocyte depletion per mouse was identified with all clearing methods (60-63%, P<0.001). The technical (dis-)advantages of each clearing protocol were also analysed, including optimal penetration depth and resolution, compatibility with immunofluorescence, microscopy set-ups, and cost-efficiency. Importantly, total podocyte number per glomerulus showed great variability: controls (mean: 78.81, ranging from 49 to 128 podocytes per glomerulus) and in NTS-injected mice (mean: 29.99; ranging from 1 to 95 podocytes per glomerulus). Using the lowest value for podocyte number in controls as a cut-off reference, only 78% of analysed glomeruli (141 of 180) from NTS-injected mice had a certain degree of podocyte depletion. While depoision of the NTS within glomeruli occurred in a global and homogeneous fashion, podocyte loss was focal.

**Conclusions:** This study has identified early focal podocyte depletion in mice with crescentic nephritis suggesting a so far unrecognized role of podocyte depletion in the development of the focal crescentic lesions. The combination of lineage tracing and optical clearing provides a powerful new tool for analysis of podocyte depletion in large tissue samples.

FR-PO717

**Metformin Ameliorates the Progressive Nephritis of an Experimental Alport Syndrome Mouse Model**

Kohei Kaseda,1 Ryo Asama,1,2 Kohei Shuto,1 Hirofumi Shuto,1 Kumamoto University, Kumamoto, Japan.

**Background:** Alport syndrome (AS) is a hereditary glomerular disease for which renin-angiotensin-aldosterone (RAAS) inhibitor is primarily prescribed. Although RAAS inhibitor is effective for proteinuria, it is not a cure for AS and most patients develop end-stage renal failure. There is a need to explore other therapeutic avenues. Here, we show the occurrence of metabolic disorder in the glomeruli of Alport mouse model, and that metformin suppressed progressive nephritis. Metformin is an inexpensive drug and that metformin suppressed progressive nephritis better than losartan. Correlated with these results, metformin reduced the expression of pro-inflammatory cytokines (Il-6, Il-1b, KC) and pro-fibrotic factors (Lysozyme, Kim1) in the glomeruli of Alport mouse model, and that metformin suppressed progressive nephritis. Metformin is an inexpensive drug and that metformin suppressed progressive nephritis better than losartan. Correlated with these results, metformin reduced the expression of pro-inflammatory cytokines (Il-6, Il-1b, KC) and pro-fibrotic factors (Lysozyme, Kim1) in the glomeruli of Alport mouse model, and that metformin ameliorates the progressive nephritis of an experimental Alport Syndrome Mouse Model.

**Methods:** Podocyte nuclei were labeled by GFP-histone in adult male Pod-rtTA/ H2B-GFP mice by oral doxycycline, followed by a 7-day wash out period, and a single intra-peritoneal injection of neprotoxic serum (NTS; 5mg/g). Experimental mice were killed 10 days after NTS injection, and compared to age-matched controls. Kidney slices were optically cleared with SCALE-A4, CLARITY and Ethyl Cinnamate (EC). High-resolution serial optical images were obtained by confocal and two-photon microscopy.

**Results:** Mean podocyte number per mouse showed very low variability within controls (1-5% variability, P=0.05) and within NTS-Injected mice (1-9% variability, P=0.05) independent of the clearing technique. In NTS-injected mice, a similar degree of average podocyte depletion per mouse was identified with all clearing methods (60-63%, P<0.001). The technical (dis-)advantages of each clearing protocol were also analysed, including optimal penetration depth and resolution, compatibility with immunofluorescence, microscopy set-ups, and cost-efficiency. Importantly, total podocyte number per glomerulus showed great variability: controls (mean: 78.81, ranging from 49 to 128 podocytes per glomerulus) and in NTS-injected mice (mean: 29.99; ranging from 1 to 95 podocytes per glomerulus). Using the lowest value for podocyte number in controls as a cut-off reference, only 78% of analysed glomeruli (141 of 180) from NTS-injected mice had a certain degree of podocyte depletion. While depoision of the NTS within glomeruli occurred in a global and homogeneous fashion, podocyte loss was focal.

**Conclusions:** This study has identified early focal podocyte depletion in mice with crescentic nephritis suggesting a so far unrecognized role of podocyte depletion in the development of the focal crescentic lesions. The combination of lineage tracing and optical clearing provides a powerful new tool for analysis of podocyte depletion in large tissue samples.

FR-PO718

**ENU-Induced Point Mutation in the Laminin Alpha 5 (LAMA5) Domain Results in Nephrotic Syndrome**

Sara Falcone,1 Thomas Nicol,1 Jeffrey H. Miner,1 Frederick W. Tom,1 Paul K. Potter.2 Imperial College Kidney and Transplant Institute, London, United Kingdom; 2Medical Research Council, Didcot, United Kingdom; 3Washington University School of Medicine, St. Louis, MO.

**Background:** Nephrotic syndrome (NS) is a heterogeneous group of disorders characterised by renal and extrarenal manifestations. Classic symptoms of NS include severe proteinuria and hypalbuminemia, oedema and hyperlipidaemia. Genetic studies of hereditary forms of NS have led to the identification of proteins playing a crucial role in slit diaphragm signalling, regulation of actin cytoskeleton dynamics and cell-matrix interactions. As part of the MRC Harwell ageen screen a missense mutation was identified in the gene LAMA5 coding for the laminin alpha 5 chain, a major component of the renal extracellular matrix. Homozygous mice showed symptoms of NS including a severe proteinuria that preceded histological lesions and alteration of renal markers in plasma.

**Methods:** The LAMA5480E mouse line was derived from a G3 pedigree produced in the MRC Harwell N-ethyl-N-nitrosourea (ENU) mutagenesis screen. The mutation was identified by combining the use of a dense SNP panel and whole genome sequencing. LAMA5480E mice were then backcrossed for a total of 10 generations to C57BL/6J mice. Urine and plasma were collected at different time points and markers of kidney function were measured. Kidneys were also collected for pathological assessment and study of the molecular mechanism. Concurrently, an in vitro study is ongoing to look at the expression and secretion of LAMAS5 and its interaction with other laminin chains.

**Results:** Time course studies of LAMA5480E homozygotes showed high levels of proteinuria from 25 weeks of age but no other signs of kidney impairment. Affected mice also have significantly elevated cholesterol levels. The LAMA5480E compound heterozygote exhibited severe proteinuria, thus confirming the LAMA5480E mutation as the causative allele. Alterations in the expression of genes and proteins associated with integrin signal-mediation show an abnormal response of the glomeruli that could possibly have an effect on the podocytes’ F-actin bundles. Preliminary in vitro results show an impaired secretion of the LAMAS5 short arm.

**Conclusions:** We have thus far identified a novel mutant mouse line exhibiting NS resulting from a point mutation in LAMA5. This gene has recently been associated with renal disease in patients. We are currently dissecting the molecular pathogenesis of disease in these animals to provide insight into human disease.

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

FR-PO719

**Proteomic Analysis of Renal Tissue in Lupus Nephritis**

Asmaa Abu Mazaid,1 Ram R. Singh.2 Mattel Children's Hospital, UCLA, Los Angeles, CA; 2UCLA School of Medicine, Los Angeles, CA.

**Background:** Lupus nephritis (LN) occurs in 40-80% of children with systemic lupus erythematosus (SLE) and is a major cause of morbidity and mortality in childhood SLE. Pathogenesis of LN progression is unclear. Identification of molecules that are differentially expressed between early to late stages of LN may help in detecting the progression of kidney damage and to identify potential new targets of treatment.

**Methods:** This is a case-controlled study involving children and adolescents of 1-21 years of age who have biopsy-proven LN by the 2003 International Society of Nephrology Renal Pathology Society classification. A total of 54 archived formalin-fixed and paraffin embedded kidney biopsy specimens obtained from UCLA Translational Pathology Core. These included 13 control specimens from transplanted kidneys with normal histology and 68 specimens for each of the six classes of LN. These tissues were subjected to proteomics analysis using nano-scale liquid chromatography tandem mass spectroscopy (nLC-MSMS) by Tandom Mass Tag method for protein labeling. Quantitative relative expression data is extracted using Proteome Discoverer 2.0 Software. DAVID software was used for data analysis. Clinical kidney biopsy data and outcomes were collected for both cohorts and entered in UCLA RedCap software.

**Results:** We have thus far completed the mass spectral analysis of 12 kidney biopsies (2 class II, 2 class III, 5 class IV, 7 class V, 3 class VI, and 3 control), and identified a total of 2,000 proteins in the global analysis. Among these, 86 proteins were significantly different between control and LN specimens. Among the differentially expressed proteins, the following were upregulated: MHC Class I, LIM domain and actin binding 1, WD repeat domain 7, Rho GDP dissociation inhibitor beta, and cadherin 13. These significantly downregulated proteins included G protein subunit alpha i3, catenin beta 1, ubiquitin-cytochrome c reductase core protein I, heterogenous nuclear ribonucleoprotein U-like 2, histone deacetylase 6, NSFL1 cysteine desulfurase, and Thy-1 cell surface antigen. In-depth analyses of the data are in progress.

**Conclusions:** This preliminary work defines proteins that are differentially expressed between control and LN kidneys. Ongoing work will complete the proteomic analyses of the remaining specimens, and perform pathway analyses of the controls and different classes of LN.

**Funding:** Other NIH Support – University of California at Los Angeles, Children’s Discovery and Innovation Institute
Validation of the Prognostic Value of the Histopathological Classification of ANCA-Associated Glomerulonephritis: A Meta-Analysis

M. Wester Trejo,1 Emma Van Daalen,1 Jan W. Schoones,2 Olaf Dekkers,3 Jan A. Bruijn,1 Ingeborg M. Bajema,1 1Pathology, Leiden University Medical Center, Leiden, Netherlands; 2Walrue Library, Leiden University Medical Center, Leiden, Netherlands; 3Clinical Epidemiology, Leiden University Medical Center, Leiden, Netherlands.

Background: In 2010, a histopathological classification of antineutrophil cytoplasmic autoantibody (ANCA)-associated glomerulonephritis (AAGN) was proposed by an international consortium of renal pathologists and nephrologists. It comprises four biopsy classes: focal, crescentic, mixed and sclerotic, the order of which was shown, in the initial publication, to correspond to increasing severity of renal impairment during follow-up. The aim of this meta-analysis was to evaluate the prognostic value of these phenotypical classes by means of validation studies that have been published since.

Methods: A literature search was performed using Web of Science, Google Scholar, PubMed and Embase in March 2017, selecting studies that associated histopathological class to renal outcome in adult patients with AAGN. The risk of developing end-stage renal disease (ESRD) during follow-up was compared between classes using a meta-analysis with random effects model. Weighted relative risks (RR) with 95% confidence intervals (95% CI) were reported.

Results: Nineteen studies were included with a total of 2,408 patients. Using sclerotic class as a reference category, ESRD risk was lower in the crescentic class (RR 0.53, 95% CI 0.43-0.64); RR in focal was lower than in crescentic class (RR 0.27 95% CI 0.20-0.37). RR in crescentic compared to mixed class was 1.18 (95% CI 0.95-1.45); RR in focal compared to mixed class was 0.34 (95% CI 0.25-0.47).

Conclusions: Our meta-analysis shows that the risk for developing ESRD increased with more severe histopathological lesions. We found no difference between the crescentic and mixed classes, pointing towards a comparable risk profile with regard to ESRD. We are currently performing an individual patient data meta-analysis, as this technique is better equipped to deal with study heterogeneity. For the moment, this meta-analysis confirms the use of the histopathological classification system as a predictor of renal outcome in the prognostication of patients with AAGN.

FR-PO722

Chemokine Receptor 8 in Peripheral Blood Mononuclear Cells Can Distinguish Active ANCA-Associated Vasculitis from Infectious Complications

Satoru Sanada,1 Yukako Akiyama,2 Mitsuhiro Sato,3 Toshinobu Sato,3 Yoshiro Taguma,1 Japan Community Health Care Organization Sendai Hospital, Sendai, Japan; 2Tohoku university, Sendai Miyagi, Japan.

Background: Infectious complications are major causes of death in ANCA-associated vasculitis (AAV). Similar clinical symptoms between AAV and infection may cause diagnostic difficulty despite totally opposite treatment in two situations. Aim of this study is to identify a new biomarker for AAV, which enables to distinguish vasculitis and infections.

Methods: Peripheral blood mononuclear cells (PBMC) were collected from 222 patients with AAV, including patients in active, remission and infectious complications and patients with other rapidly progressive glomerulonephritis. Chemokine receptor 8 (CCR8) was assessed using quantitative PCR and flow cytometry. Quality of RNA was measured by biosensor before reverse transcription to provide reproducible results.

Results: CCR8 mRNA level in PBMC was significantly higher in patients with MPO-ANCA vasculitis compared to that in healthy control, which was confirmed by upregulated CCR8 protein expression in FACS. The area under ROC curve was 0.925 (95%CI: 0.842-1.000) with a sensitivity of 87.5% and a specificity of 100%. Lupus nephritis nor purpura nephritis did not show high CCR8 mRNA levels. Among MPO-ANCA vasculitis, CCR8 mRNA levels in patients with remission and patients with infectious complications during remission were lower compared to that in patients in active. The area under ROC curve was 0.924 (95%CI: 0.846-1.000) compared with active AAV and infectious complication.

Conclusions: CCR8 mRNA level in PBMC was associated with AAV activity, however, infectious complications did not affect CCR8 expression, suggesting that CCR8 could be a useful diagnosis biomarker for AAV.

Funding: Private Foundation Support
FR-PO724
Unravelling the Pathophysiology of C3G/IC-MPGN and How to Predict Disease Progression and Orient Therapies
Paraskevas Iatropoulos,1 Erica Daina,1 Manuela Currier,2 Rossella Piria,1 Elisabetta Valoti,1 Caterina Mele,1 Elena Bresin,2 Sara Gamba,2 Marta Alberti,1 Matteo Breno,1 Ettore Sabadini,1 Marina Noris,1 Giuseppe Remuzzi,1,2 IRCSS - Istituto di Ricerca Farmacologica Mario Negri, Bergamo, Italy; 1Unit of Nephrology and Dialysis, Ospedale Papa Giovanni XXIII, Bergamo, Italy. Group/Team: Registry of Membranoproliferative Glomerulonephritis/C3 Glomerulopathy.

Background: Membranoproliferative glomerulonephritis (MPGN) was recently reclassified into alternative pathway (AP) complement-mediated C3 glomerulopathy (C3G) and immune-complex-mediated MPGN (IC-MPNG). However, genetic and acquired AP abnormalities are also observed in IC-MPNG. Here, in patients with C3G/IC-MPNG, we explored the presence of distinct disease entities characterized by specific pathophysiologic mechanisms.

Methods: We performed unsupervised hierarchical clustering, a data-driven platform clustering, and only 2 (12.5%) had MGUS/MGRS. With regards to non-targeted treatment for the most common abnormality was the presence of C3 nephritic factor in 10 (43.5%) patients and autoantibodies to complement factor H or B in 3 patients (13%). Six (30%) patients had mutations in complement regulating proteins. Of the 36 patients, 33 (91.7%) received treatment and/or other immunosuppressive drugs. At a median follow-up of 43.5 months, the median serum creatinine and proteinuria was 1.4 mg/dl and 749 mg/24 hours. Nine (25%) patients progressed to end stage renal disease. Sixteen (44.4%) received targeted therapy for Mg. Of these 11 (68.8%) patients achieved stable renal function, while the remaining 5 (31.2%) progressed to ESRD, of which 3 (18.7%) had multiple myeloma and only 2 (12.5%) had MGUS/MGRS. With regards to non-targeted treatment for the Mg/US/MGRS group, 4 (20%) patients progressed to ESRD.

Conclusions: Our study shows a high prevalence of Mg in C3 patients. C3 nephritic and autoantibodies were more common compared to mutations suggesting that the Mg likely acts as an autoantibody to complement regulating proteins. Targeted treatment of Mg, in particular with MGUS/MGRS, resulted in stabilization of renal function in a majority of the patients.

FR-PO725
More Than C3 Deposition: The Unique Characteristics of One Family with C3 Glomerulopathy
Alexandra L. Leonard,1 Nicole Meyer,1 Nicolò Borsa,2 Yuzhou Zhang,1 Richard J. Smith,1 Carla M. Nester,1 University of Iowa, Iowa City, IA; 1The University of Iowa, Iowa City, IA.

Background: As a disease, C3 Glomerulopathy is currently defined by the single diagnostic criteria of a predominant immune fluorescent staining of C3 on renal biopsy. Additional diagnostic requirements have not been defined. After cases are ascertained, it is widely accepted but not definitively demonstrated, that those affected have a genetic abnormality in complement genes – supporting the underlying complement abnormality as the disease causing agent. We present a familial case of C3G identified after a proband with predominant C3 staining was discovered to have a homozygous C3 gene mutation.

Methods: After obtaining informed consent, a medical record review was completed on all available family members. The disease phenotype was confirmed by renal biopsies in persons with >1gm/24hr of urine protein. Comprehensive genetic screening was completed on all complement genes using standard procedures. An extensive complement analysis was performed that included serum levels of complement proteins and their cleavage products, assays of complement function, and screens for autoantibodies.

Results: A pathogenic variant in C3 segregated with each patient with a renal phenotype: c.443G>A, p.R148Q. Both the matriarch and patriarch of the family were heterozygous for this variant, consistent with their relationship as first cousins. The sporadic C3G phenotype ranged from asymptomatic hematuria (N=2) or proteinuria (N=1) to end stage renal disease (N=3). One family member had multiple cysts by ultrasound. Renal biopsies confirmed C3GN in 3 family members and FSGS in a fourth person. Serum C3 levels were normal in all asymptomatic individuals (both with and without the variant). C3 levels were low in individuals with symptomatic C3GN (5/6). 4 persons carried the p.R148Q mutation, with elevated serum levels of C3c. Surface plasmon resonance assays, as well as an expanded functional and cofactor assessment of the mutation is ongoing.

Conclusions: We present a rare case of familial C3 Glomerulopathy. Unique to this case is an underlying gene abnormality that segregates not only with the diagnostic C3G requirement, but also with FSGS and cystic renal disease. This pedigree highlights not only the narrow nature of the C3G definition, but also calls into question whether the C3 protein may play a functional role in other renal abnormalities.

Funding: NIDDK Support

FR-PO726
C3G-Associated with Monoclonal Gammopathy Ashwarya Ravindran, Fernando C. Fervenza, Sanjeev Sethi. Mayo Clinic, Rochester, MN.

Background: Monoclonal immunoglobulins (Mg) may act a functional inhibitor of the alternate complement pathway thereby playing a causal role in the pathogenesis of C3 glomerulopathy (C3G). In this study, we describe the clinicopathological features, hematological evaluation, treatment and outcomes of C3G associated with Mg.

Methods: We identified 95 patients seen at the Mayo Clinic from 2007-2016 with a diagnosis of C3 glomerulopathy (C3GN or DDD) who were tested for a monoclonal protein.

Results: 36 (37.9%) patients were positive for Mg: 65.1% of patient a50 years were positive (17 times higher than the expected rate). The median age at diagnosis was 60 years (range: 20-85), 25 males and 11 females. The median serum creatinine and proteinuria was 1.9 mg/ul and 3000 mg/24 hours. Hematruia was present in 28 (93.3%) patients and low C3 and 4 (11.4%) had low C4. Twenty-six (72.2%) patients were classified as MGUS/MGRS, 5 (13.9%) multiple myeloma, 2 (5.6%) smoldering myeloma, 1 (2.8%) CLL, 2 with cryoglobulins (5.6%) 1 of which was type 1 cryoglobin and the other was associated with lymphoma of the stomach. The median serum IgM was 57.2 mg/dl and the most common abnormality was the presence of C3 nephritic factor in 10 (43.5%) patients and autoantibodies to complement factor H or B in 3 patients (13%). Six (30%) patients had mutations in complement regulating proteins. Of the 36 patients, 33 (91.7%) received steroids and/or other immunosuppressive drugs. At a median follow-up of 43.5 months, the median serum creatinine and proteinuria was 1.4 mg/dl and 749 mg/24 hours. Nine (25%) patients progressed to end stage renal disease. Sixteen (44.4%) received targeted therapy for Mg. Of these 11 (68.8%) patients achieved stable renal function, while the remaining 5 (31.2%) progressed to ESRD, of which 3 (18.7%) had multiple myeloma and only 2 (12.5%) had MGUS/MGRS. With regards to non-targeted treatment for the MGUS/MGRS group, 4 (20%) patients progressed to ESRD.

Conclusions: Our study shows a high prevalence of Mg in C3 patients. C3 nephritic and autoantibodies were more common compared to mutations suggesting that the Mg likely acts as an autoantibody to complement regulating proteins. Targeted treatment of Mg, in particular with MGUS/MGRS, resulted in stabilization of renal function in a majority of the patients.

FR-PO727
Autoimmune and Genetic Workup in Post-Transplant C3 Glomerulopathy
Ashwani Kumar1 Ritambhra Nada,2 Raja Ramachandran,2 Charan S. Rayat,1 Krishan Lal L. Gupta.1 1Postgraduate Institute of Medical Education & Research, Chandigarh, India; 2Nehru Hospital, Chandigarh, India.

Background: Post-transplant C3 glomerulopathy (Tx-C3GP) is associated with alternate complement pathway (ACP) dysregulation and the literature is scanty. Hence, serological and genetic workup for Tx-C3GP was performed.

Methods: We performed Tx-C3GP workup in all patients reported during 2010-16. Tests included ACP functional assay (APFA), C3, C4 levels, complement factors H (CHF) and B (CFB) estimation. Parag protein and autoantibodies to CFB (ab-CFB), CFB (ab-CFB), C3 convertase (C3NeF), PCR for CFB and complement factor H-related 5 (CFHR5) genes were done followed by Sanger sequencing. Clinical outcome of the patients was also recorded.

Results: Twenty-six cases of Tx-C3GP included 11 cases of dense deposit disease (DDD) and 15 C3 glomerulopathies (C3GN) and 5 C3GP (EM not available). Mean age was 31.88 years. Two-thirds presented with graft dysfunction (Mean time; <1 week-C3GN, 8 Months-DDD). Nephrotic syndrome and asymptomatic urine abnormality were present in 17%. Basic disease was known in 50% (DDD-4, C3GN-3, C3GP-5, & Diabetic nephropathy-2) cases. Native kidney histology ranged from normal to membranoproliferative (MP) morphology, whereas in early post-transplant recurrences, it was focal segmental proliferative and MP in late recurrences. We observed low APFA and C3 in all cases. Positive findings in DDD included, low CFB levels, ab-CFB, low CFB levels in 56, 25 and 11%, respectively. Low CFB levels (22%) and ab-CFB were present in 15% of DDD. In contrast to DDD, 22%, patients of C3GN had low CFB levels and ab-CFB (22%), C3NeF was positive in 44% DDD and 33% of C3GN. We found CFB SNP rs800292 (Val28Ile) in 44% and -187T insertion in 22% of DDD and both SNPs were seen in 11% cases of Tx-C3GN. SNP rs1061147 (p.Ala243Thr) and rs1061170 (p.His64Tyr) of CFB were more frequent in tx-C3GN (56% & 45%) and seen lesser in tx-DDD (33% and 11%). SNP rs2274700 (p.Ala473Val) was equally present (22%) in both the groups. No variant of CFHR5 was present in any tx-C3GP case. 43% of the patients experienced graft loss.

Conclusions: Both DDD and C3GN recurr post-transplant. C3GN has an early recurrence compared to DDD. Low CFB and ab-CFB were evident in DDD, whereas low
CBF and ab-CFB are seen in C3GN. Genetic findings for CFB gene revealed difference among variants for these two entities.

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

FR-PO728

**Dense Deposit Disease: Is There a Racial Difference in the Prevalence?** Anila Abraham,3 Patrick D. Walker,1 Arkana Laboratories, Little Rock, AR; 2 Renophen, Center for Renal and Urological Pathology, Chennai, India.

**Background:** Dense deposit disease (DDD) is a rare glomerulonephritis that commonly affects children. It is defined at the ultrastructural level by the presence of extremely electron dense material in the lamina densa of the glomerular basement membrane. This results in various patterns of glomerular injury with mesangio proliferative and membranoproliferative patterns being the most common.

**Methods:** Native kidney biopsies reported from August 2013 to November 2016 at Renophen, Chennai, Tamil Nadu, India were reviewed. Cases of DDD were identified and clinicopathologic features compared. We then compared our findings with data published in literature. The database of Renophen and Arkana Laboratories were utilized to compare the rates of DDD diagnosis.

**Results:** During the study period, there were 25 patients with DDD among the 7335 native kidney biopsies (0.34%) at Renophen. Arkana Laboratories in Little Rock, AR, USA, had 21 cases of DDD among their 26,319 native kidney biopsies (0.08%) during the same time period. The mean age of patients was 20.7 years, with only 9 (36%) patients <16 years of age. Male to female ratio was 1.3:1. Serum C3 was decreased in all patients. At the time of biopsy, proteinuria was present in all patients, five were hypertensive, 2 had partial lipodystrophy, and one had drusen. Membranoproliferative, mesangio proliferative, exudative and crescentic patterns were observed. Only 52% of the biopsies showed membranoproliferative pattern. Intestinal inflammation was significantly higher in the biopsies with this pattern. All the patients with crescentic pattern (16%) were below 16 years of age. Mesangio proliferative pattern was seen only in adults. Arteriosclerosis, interstitial fibrosis and tubular atrophy were significantly more frequent in adults.

**Conclusions:** The mean age of our patients was 20.7 years, unlike many studies which considered DDD as a childhood disease. Only half of our patients had the membranoproliferative pattern of glomerular injury. Crescentic pattern was seen exclusively in children and mesangio proliferative pattern was seen only in adults. Although DDD is rare, it is much more common (<400%) in this Indian population when compared with the American population. In addition to genetic differences, environmental factors and chronic infections may possibly contribute to the high incidence in this South Indian population.

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

FR-PO729

**Urine Micro-RNAs as Histology Biomarkers in Lupus Nephritis** Xiaolun Zhang,1 Juan M. Mejia-Vilet,2 Hajian Song, Samir V. Parikh,3 Anjali A. Satoskar,1 Tiber Naddady,2 Internal Medicine, The Ohio State University Wexner Medical Center, Columbus, OH; 4 Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico, Mexico. Group/Team: CKD Biomarker Consortium.

**Background:** Urine micro-RNAs (miRNA) have emerged as potential biomarkers for lupus nephritis (LN). The relationship of urine miRNAs with renal histology in LN was investigated.

**Methods:** This study examined 98 biopsy-proven LN patients and 19 healthy controls. Total urine RNA was enriched using ExoQuick columns. miRNA was extracted and screened for differential expression of individual miRNAs between LN and controls using Nanostring miRNA profiling. The miRNAs showing the most significant differential expression on screening were validated by duplex real-time PCR after cDNA synthesis using a TaqMan Advanced miRNA cDNA Synthesis kit. miRNA levels were normalized to urine creatinine and the housekeeping miRNA, miR-191-5p. Urine miRNA expression and kidney histology were compared by t-test, ANOVA followed by Wilcoxon ranked-sum testing or multiple linear regression, as appropriate.

**Results:** Several miRNAs identified by Nanostring screening were confirmed by PCR. Of these, miR-29c-3p correlated with kidney biopsy chronicity index (R2=0.38, p=0.0022), and was significantly increased in the urine of patients with interstitial fibrosis (4.86-fold; p=0.006) and tubular atrophy (5.92-fold; p=0.0029). miR-1290 expression was 3-fold higher (p=0.007) in patients who did not have crescents compared to those with crescents. miR-20b-3p was also decreased in patients with crescents (7.78-fold; p=0.024), glomerular neutrophil accumulation (10-fold; p=0.006) and endocapillary proliferation (2.82-fold, p=0.01) compared to patients without these acute lesions.

**Conclusions:** A subset of miRNAs that are differentially-expressed in the urine of LN patients appear to correlate with acute or chronic changes on kidney biopsy and are candidate renal histology biomarkers that may be useful for non-invasively following changes in renal pathology during LN.

**Funding:** NIDDK Support

FR-PO730

**Urine Epidermal Growth Factor, Monocyte Chemotractant Protein-1, or Their Ratio in Lupus Nephritis: Relationship with Renal Histology and Response to Therapy** Chaigrya Kittivakara, Pintip Ngamjanyporn, Suchin Warawichawong, Khantong Khiewngam, Pyunyah Radinhammed. Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

**Background:** The balance between pro-inflammatory cytokines such as monocyte chemotactic protein-1 (MCP-1) and protective cytokines such as epidermal growth factor (EGF) likely determines the disease activity and outcomes in glomerular diseases, but there is limited data in lupus nephritis (LN). In this study, we evaluated the relationship between urinary EGF, MCP-1 or their ratio at baseline with renal histology and the response to immunosuppressive therapy at 6 months follow-up.

**Methods:** This is a prospective study of biopsy-proven LN (n = 69). Urine samples were collected at biopsy. MCP-1 and EGF were analyzed by ELISA. Response to treatment was defined as 50% or greater reduction in proteinuria or proteinuria <0.5g Cr. Biomarker levels were compared between histological categories. Factors associated with treatment response at 6 months were analyzed by multivariate logistic regression in LN Classes III-IV.

**Results:** LN Classes were: II, III, IV, V, VI (n=9, 25, 21, 13,1). Compared to Class II, patients with Class III-IV had higher MCP-1 and lower EGF/MCP-1 whereas EGF was not different. High MCP-1 was independently associated with Class III-V. Patients with high activity index (AI ≥7) had higher MCP-1 and lower EGF/MCP-1 compared to patients with low AI. Patients with high chronicity index (Cl≥3) had lower EGF/MCP-1 compared to patients with low CI. MCP-1 was higher in patients with wireloop, karrxhexis, tubulitis, tubular atrophy, interstitial fibrosis and EGF/MCP-1 was lower in patients with PMN infiltration, wireloop, karrxhexis and cellular infiltration compared to patients without these features. In Class III-IV patients with 6 months follow-up (n = 41), 36 responded to immunosuppression and 27 were non-responders (NR). EGF was higher in Responders (EGF (ng/mg Cr) Responders: 141 (74, 283) vs NR: 57 (24, 87), p=0.025] whereas MCP-1 or EGF/MCP-1 were not different. EGF (per ng/mg Creatinine) was independently associated with response to immunosuppression [OR (95%CI): 1.02 (1.00-1.054), p=0.034].

**Conclusions:** Overall, MCP-1 was higher in LN with adverse histopathological features. Among Class III-IV patients, the response to immunosuppressive therapy at 6 months was independently associated with low baseline EGF, but not high MCP-1.

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

FR-PO731

**Lupus-Like Glomerular Immune Complex Deposits in a Subset of Patients with Liver Cirrhosis – Histologic Features and Clinical Correlates Anjali A. Satoskar,1 Jessica Hemminger,2 Vidya Arole,2 Isabel A. Ayoob,3 Tiber Naddady,2 Internal Medicine, The Ohio State University Wexner Medical Center, Columbus, OH; 4Pathology, Ohio State University Wexner Medical Center, Columbus, OH.

**Background:** Glomerular IgA deposits have been previously reported in patients with liver cirrhosis as incidental findings, mainly in autopsy studies. We recently encountered patients with liver cirrhosis presenting with acute kidney injury and large lupus-like glomerular immune deposits. None had systemic lupus erythematosus. Our aim was to systematically elucidate their clinical and biopsy features, and treatment outcomes.

**Methods:** We searched our kidney biopsy database over a 13-year period, from January 2004 to December 2016 for all native kidney biopsies from patients with cirrhosis.

**Results:** We found 118 kidney biopsies from cirrhotic patients, 76/118 had glomerular IgA staining. None of these 76 had large IgA, IgG and C3 containing glomerular immune complex deposits (Fig 1) and proliferative glomerulonephritis. Six of 9 patients had concomitant acute bacterial infection, prompting a biopsy diagnosis of infection-associated glomerulonephritis and treatment with antibiotics. In the remaining 3/9 patients, infectious workup was negative and were administered steroids. Overall clinical outcomes were among the 9 patients, but 2/6 patients treated with antibiotics (1 with liver transplant), and 1/3 patients on steroids recovered renal function.

**Conclusions:** These cases provide support to the theory that advanced liver failure can compromise the ability to clear circulating immune complexes, contributing to the build-up of large immune complex deposits in the kidney and concomitant bacterial infection probably provides a “second-hit” triggering acute glomerulonephritis in at least a subset of these patients. A trial of antibiotics is recommended and caution is advised before administering immunosuppressive treatment. Bacterial infection can be subtle and can be misdiagnosed. If bacteriological diagnosis, both diagnosis and management of glomerulonephritis in these patients remains a challenge.
FR-PO732
Lupus Nephropathy: Clinical-Pathological Description of 400 Cases of the Colombian Caribbean Region and Variations in the Expression of Plasma MicroRNAs
Gustavo Aroca Martinez,1 Alex Dominguez,2 Elkin Navarro,3 Henry J. Gonzalez Torres,4 Diana Silva,2 Juan C. Conde,3 Lismeth Almendares,2 Eduardo Egea bermúdez,2 Antonio Iglesias Gamarra,1 Universidad Nacional de Colombia, Bogotá, Colombia; 2Medicine, Universidad Simón Bolívar, Barranquilla, Colombia; 3Nephrology, Clínica de la Costa, Barranquilla, Colombia; 4Universidad Simon Bolivar, Barranquilla, Colombia; 5Universidad del Norte, Barranquilla, Colombia

Background: Lupus nephritis (LN) is one of the most serious manifestations of systemic lupus erythematosus (SLE). Renal biopsy allows diagnosing the histopathological classes of LN, however, it is an invasive technique associated with risk of hemorrhage. It is a priority to characterize noninvasive diagnostic tests and alterations in the differential expression of microRNAs (miRNAs) to measure LN activity. The objective was to describe the clinical-pathological characteristics and to analyze the differential expression of a group of plasma miRNAs in patients with LN.

Methods: Retrospective analytical study. 400 patients are included with LN diagnosed by renal biopsy of the Caribbean Region between January 2008 and December 2016. Differentially expressed miRNAs were selected by Illumina and their diagnostic efficacy (87.9%) was previously described. The objective was to describe the clinical-pathological characteristics and to analyze the differential expression of a group of plasma miRNAs in patients with LN.

Results: 400 patients, 86% were women. Average age of 37 ± 13.2 years. Mean follow-up time: 48 ± 20 months. Main syndromic diagnoses: nephritic syndrome (51%). Histological class: IV (70.7%), III (19.3%), II (6.5%). 234 (58%) patients did not achieve remission at 48 months. The miRNAs (miR-221-5p, miR-380-3p, miR-556-5p, miR-758-3p and miR-3074-3p) for their high sensitivity (97%) and specificity (96%) and diagnostic efficacy (87.9%).

Conclusions: The miRNAs (miR-221-5p, miR-380-3p, miR-556-5p, miR-758-3p and miR-3074-3p) are possible diagnostic biomarkers and the differential expression pattern of miRNA would have significant implications in the pathophysiology of LN.
FR-PO735
A Novel Method of Urine Protein Isolation Allows for Identification of Kidney Disease Protein Biomarkers Using Mass Spectrometry

Background: The current study was to evaluate if patients with lupus membranous nephritis (LMN) and only IgG (C3) have the same outcome as those with typical full house pattern on immunofluorescence (IF).

Methods: Thirty-one patients out of 42 were selected; the remaining was excluded due to lack of data or follow-up less than 12 months. Clinical characteristics are shown in Table 1. Two patients with schistosomosis and 1 cryoglobulinemia. Ten patients with idiopathic form were compared with a group with lupus nephritis and did not have difference with respect to renal survival [Table 1].

Conclusions: Despite lack of full house pattern on IF, lupus membranous nephritis patients with only IgG (C3) have the same outcome as those with typical full house or IgG plus other Ig/C1q pattern.

FR-PO736
Pure Lupus Membranous Nephritis with Only IgG Deposits on Immunofluorescence Behaves Like Full House Pattern

Background: Pure lupus membranous nephritis (LMN) may present with only IgG deposits on immunofluorescence (IF) resembling idiopathic membranous nephritis. We aim to evaluate if patients with LMN and only IgG (C3) have the same outcome as those with IgG plus other Ig/C1q deposits.

Methods: Adult patients with a diagnosis of lupus (≥ 4 SLICC criteria) and pure LMN between 2004 and 2016 were retrospectively evaluated. Complete response, partial response and relapse were defined by KDIGO criteria.

Results: Thirty-one patients out of 42 were selected; the remaining was excluded due to lack of data or follow-up less than 12 months. Clinical characteristics are shown in Table 1. Two patients with schistosomosis and 1 cryoglobulinemia. Ten patients with idiopathic form were compared with a group with lupus nephritis and did not have difference with respect to renal survival [Table 1].

Conclusions: Despite lack of full house pattern on IF, lupus membranous nephritis patients with only IgG (C3) have the same outcome as those with typical full house or IgG plus other Ig/C1q pattern.
FR-PO739
A Patient with “Albumin-Dependent” Focal Segmental Glomerulosclerosis
Margaret Duffy, Matthew Palmer, Vishnu S. Potluri, Jonathan J. Hogan.
1Pathology, University of Pennsylvania, Philadelphia, PA; 2Nephrology, The University of Pennsylvania, Philadelphia, PA.

Background: Idiopathic focal segmental glomerulosclerosis (FSGS) can present with severe volume overload and acute kidney injury (AKI). Here we present such a patient with idiopathic FSGS complicated by multiple episodes of severe AKI and diuretic-resistant volume overload that was only responsive to IV albumin therapy.

Methods: A 54 year-old Jamaican woman developed nephrotic syndrome (SCR 0.86 mg/dL, UPt/Cre 8 g/g, AlbA 1.7 g/dL). A kidney biopsy revealed tip variant FSGS. She achieved partial remission within four weeks with prednisone 120 mg/d, but then relapsed (UPt/Cre 3.6, AlbA 2.1 g/dL). She was hospitalized with oliguric AKI (Scr 3.89 mg/dL) and volume overload refractory to high-dose IV diuretics and developed candida esophagitis and C. difficile colitis. Steroids were tapered and she was treated with IV albumin (25%, 1 mg/kg q8h), with improvement in her SCR (1.37 mg/dL) and urine output (4L) within 24 hours (see image). Tacrolium was started and she was discharged. She was then re-admitted for volume overload, hypoalbuminemia, and AKI that only responded to 25% IV albumin. Tacrolium levels were undetectably low. We hypothesized that her acute anasarca led to her inability to absorb tacrolium. We therefore treated her aggressively with 5 sessions of intermittent ultrafiltration, 5 sessions of plasma exchange therapy with albumin replacement, and pulse oral dexamethasone (40 mg/week). Her AKI again resolved and she was discharged on weekly dexamethasone, oral tacrolium, and biweekly outpatient albumin infusions. With this therapy she achieved complete remission with target tacrolium trough levels 6-8 ng/mL. She continued on tacrolium and IV albumin. She has been in complete remission for five months on tacrolium monotherapy.

Results: Conclusions: We present a case of idiopathic FSGS with a rare and extreme phenotype of severe volume overload and recurrent AKI. In these cases, IV albumin therapy should be considered, particularly for patients who were previously steroid-responsive and may therefore be responsive to other immunosuppressive agents.

FR-PO741
Collapsing FSGS: Vascular Injury as a Cause of Secondary Collapsing Glomerulopathy? Francois Gougeon,1,2 Harsharan K. Singh,3 Jack J. Jennette,4 Volker Nickelsen.1 1The University of North Carolina at Chapel Hill, Chapel Hill, NC; 2UNC-Chapel Hill Nephropathology, Chapel Hill, NC; 3University of North Carolina School of Medicine, Chapel Hill, NC; 4Pathologie, Université de Montréal, Montréal, QC, Canada.

Background: Collapsing glomerulopathy (CG) has been associated with various diseases such as infections, diabetes mellitus or auto-immune diseases. In renal allografts CG has occasionally been linked to perfusion abnormalities. At present a systematic review of CG and concurrent other renal diseases is lacking.

Methods: We searched our database for a biopsy diagnosis of CG in native and transplant kidneys between 01/2011 and 01/2016. Among 7641 cases 4.4% (322) showed CG in an initial index biopsy. Tip variant FSGS 51/7641 (0.7%) served as one control cohort. Cases were grouped as: 1) “pure”: no other significant kidney disease, 2) “presumed secondary”: with concurrent other significant renal diseases, 3) “secondary”: with concurrent other significant renal diseases.

Results: CG was more often secondary than the tip-variant (51/322, 47% vs. 14/371, 28%; p<0.01; table 1). In the study set three disease categories were significantly more often diagnosed in secondary CG: severe arterionephrosclerosis (AS; 25%), membranous glomerulopathy (MGN; 15%) and thrombotic microangiopathies (TMA; 9%; all p<0.01). In comparison secondary tip variant FSGS showed tightest associations with MGN and no association with TMA. In transplants, 21/30 (70%) of CG cases were classified as secondary. 7/21 had prominent vascular sclerosis and 4/21 antibody mediated rejection with microvascular injury.

Conclusions: In conclusion: CG but not tip-variant FSGS is commonly associated with concurrent renal diseases. Secondary CG is significantly linked to vascular injury (AS, TMA, rejection with capillaritis). These findings further understanding of CG and pending future studies can streamline diagnostic decision making for microvascular injury.

FR-PO740
Urinary Extracellular Vesicle-Derived Markers for Steroid Resistant FSGS
Ilie M. Rood,1 Michael Merchant,2 Daniel W. Wilkey,2 Johan Van der vlag,3 Jack F. Wetzel,3 Jon B. Klein,3 Jeroen Deegens.1 1Radboud University Medical Center, Nijmegen, Netherlands; 2University of Louisville Kidney Disease Program, Louisville, KY; 3Roeby Rex Veterans Administration Medical Center, Louisville, KY.

Background: Urinary extracellular vesicles (uEV) contain many proteins that may serve as biomarkers in renal disease. We compared the proteome of uEV from patients with biopsy proven focal segmental glomerular sclerosis (FSGS) with a steroid resistant nephrotic syndrome (SRNS; n=3), FSGS with steroid sensitive nephrotic syndrome (SSNS; n=3), FSGS with a partial remission on steroids (PR; n=3), minimal change disease (MCD; n=3), secondary FSGS (n=3) and normal healthy controls (NC; n=3). We hypothesized that the proteome of uEV could reveal a marker to predict steroid resistance in patients with FSGS.

Methods: uEV were isolated and analyzed using a multiplexing approach (TMT-labeling) and LCMS methods (1D-RP-HPLC-ESI-LTQ-VELOS-Orbitrap and Proteome Discover Software).

Results: In total 503 different proteins were identified with at least two peptides and protein threshold of 95% with a false discovery rate of 0.5%. Comparison of FSGS SRNS to SSNS (including FNGS-SSNS, PR and MCD) indicated changes (unadjusted t-test p<0.05) in abundance of 26 proteins. In FSGS SRNS 17 proteins were downregulated, of which four proteins without any overlap of abundance compared to SSNS, secondary FSGS and normal controls. Nine proteins were upregulated, of which three proteins without any overlap compared to SSNS, secondary FSGS and normal controls. Many of these are related to the complement system. We identified 26 extracellular vesicle-derived proteins that were significantly different between FSGS SRNS, compared to SSNS. Further analysis will be conducted to identify (a subset of) proteins that maybe considered as candidate biomarkers for FSGS SRNS.

FR-PO742
Clinical and Pathological Analysis of Patient Presenting Renal Lesion and Monoclonal Gammapathy: A Retrospective Study of 64 Patients with Biopsy-Proven Renal Diseases
Chao Li, Yuebing Wen, Hang Li, Jianfang Cai, Xuemei Li, Xuewai Li. Nephrology, Peking Union Medical College Hospital, Chinese Academy of Medicine Sciences & Peking Union Medical College, Beijing, China.

Background: Patients with monoclonal gammapathy can develop a variety of related renal lesions or possibly have kidney disease unrelated to their monoclonal gammapathy. We characterized the spectrum of renal diseases associated with monoclonal gammapathy and unrelated renal diseases.

Methods: Hospitalized patients in Peking Union Medical College Hospital who underwent renal biopsy between January, 2013 and December, 2015. They had monoclonal gammapathy on Serum protein electrophoresis (SPE), serum immunofixation electrophoresis (“secondary”: with concurrent other significant renal diseases (IFE), urine IFE and/or serum free light chain (FLC). 64 patients met the inclusion criteria and were classified as MGRS (n=36), MGUS (n=17) and hematologic malignancy (n=11).

Results: Renal lesions in MGRS subgroup included light chain amyloidosis (43/214, 20%), light chain deposition disease (LCDD; 21/214, 10%), membranous nephropathy (19/214, 9%), IgA nephropathy (4/214, 2%), and polycystic kidney disease (3/214, 1%). Renal lesions in MGUS subgroup included membranous nephropathy (n=10, 58.8%), FSGS (n=3, 17.6%), diabetic glomerulopathy (n=1, 5.9%), Henoch-Schönlein purpura nephritis (n=1, 5.9%), anti-GBM disease concurrent with membranous nephropathy (n=1, 5.9%) and glomerulonephritis (n=1, 5.9%). Various renal lesions related/unrelated to hematologic malignancy were seen in third subgroup, including light chain cast nephropathy (n=3, 27.3%), tubulo-interstitial lesions (n=2, 17.6%).
18.2%, LCDI(D=1, 9.1%), IgA nephropathy (n=1, 9.1%), Mesangial (n=1, 9.1%), endocapillary proliferative glomerulonephritis (n=1, 9.1%) and acute tubular necrosis (n=1, 9.1%). Positive rate of SPE, SIFE and UFIE in MGRS subgroup were 40.6%, 52.8% and 69.4%, respectively. Positive rate of SPE, SIFE and UFIE in MGUS subgroup were 68.8%, 100% and 37.5%, respectively. Positive rate of SPE, SIFE and UFIE in hematologic malignancy subgroup were 54.5%, 72.7% and 81.8%. MGRS and MGUS subgroups differed significantly in positive rate of SIFE (P<0.001). Abnormal rate of serum FLC ratio in above three subgroups were 83.3%, 17.6% and 90.9%, respectively, in which MGUS group was significantly lower than other two groups (P<0.001).

Conclusions: The significance of monoclonal gammopathy in patients with renal disease should be evaluated by other clinical data, as well as renal pathology.

FR-PO743
Clinical, Pathological, and Mass Spectrometry Analysis of AL Renal Amyloidosis: Mingxi Li, Ying Sun, Yuheng Wen, Linmeng Chen, Xiaoyi Li. Nephrology, Peking Union Medical College Hospital, Chinese Academy of Medicine Sciences & Peking Union Medical College, Beijing, China.

Background: In recent years, laser micro-dissection combined with mass spectrometry (LMD/MS) has been applied in the diagnosis of renal amyloidosis, it can be used for typing of amyloid deposits where routine immunohistochemistry (IHC) is equivocal and negative, as well as finding new causes of amyloidosis. In this study, we retrospectively analysis the patients with AL amyloidosis to evaluate the significance of immunoperoxidase (IP) and establish LMD/MS technique for diagnosing renal amyloidosis.

Methods: We analyzed 45 cases of AL amyloidosis patients diagnosed by Congo Red Staining (CRS) and EM were admitted during last 5 years in a single center, analyzed their clinical manifestations and pathological findings, then selected 20 cases with inconclusive immunofluorescence (IF) results, performed IF and LMD/MS for amyloid typing. For IP, both k and l were stained. For LMD/MS analysis, 7-µm sections were prepared and CRS positive area was collected by laser microdissection, the minimum area for each case was 200,000 µm². Sample microdissected was digested by trypsin. Peptides were quantified using Thermo Fusion Lumos mass spectrometer. MASCOT software was used for identification of proteins. Scaffold 4 software was used to integrate the results.

Results: Patients with AL renal amyloidosis had multiple organs involved, including kidney, liver, heart and intestinal system. Eleven (55%) of the 20 cases could be used for identification of proteins. Scaffold 4 software was used to integrate the results.

Conclusions: Our study showed IP is superior to IF and MS-based proteomic analysis is complementary to IHC in typing of renal amyloidosis.

Funding: Government Support - Non-U.S.

FR-PO745
Rapid Reduction in Urinary sCD163 Correlates with Clinical Benefit in the CLEAR Study of C5aR Inhibitor Avacopan in ANCA-Associated Vasculitis: Jun Deng,1 Antonia Potarca,2 Thomas J. Schall,3 Pirow Bekker,7 ChemoCentryx, Inc, Mountain View, CA; 3ChemoCentryx, Inc, Mountain View, CA; 7ChemoCentryx, Inc, Mountain View, CA.

Background: Avacopan (CCX168), a potent C5aR inhibitor, induced rapid clinical benefit as measured by BVAS, renal function, and health-related quality of life outcomes in patients with ANCA-associated vasculitis in the Phase 2 CLEAR trial in ANCA-associated vasculitis, AAV (Jayne et al, JASN, 2017). Urinary soluble CD163 (sCD163) is a macrophage cell surface molecule known to correlate with renal histopathology, and it is a useful biomarker of kidney inflammation in AAV (O’reilly et al, JASN, 2016). We evaluated urinary sCD163 in CLEAR patients at baseline and over the 12-week treatment period.

Methods: CLEAR comprised 3 patient groups: (1) Full dose prednisone (60 mg), standard care; (2) Avacopan 30 mg b.i.d. plus low dose prednisone (20 mg); (3) Avacopan 30 mg b.i.d. plus no prednisone. All patients received either IV cyclophosphamide or IV rituximab. sCD163 (ELINA) and creatinine were measured pre-dose, and days 8, 15, 29, 57, and 85.

Results: Avacopan treatment reduced sCD163/creatinine markedly by day 8, and further over the course of 12 weeks (see table). By contrast, standard care controls with full-dose prednisone this period did not show improvement in urinary sCD163 levels.

Conclusions: Avacopan induced a rapid reduction of sCD163, which correlated with clinical benefit marked by rapid improvements of kidney inflammation markers and AAVBVAS. sCD163 may provide a valuable biomarker of clinical improvements derived from avacopan. Avacopan is currently in a Phase 3 clinical trial for AAV.

Funding: Commercial Support - ChemoCentryx.

FR-PO746

Background: Immunoglobulin light chain (AL) amyloidosis is the most frequent type of renal amyloidosis in the U.S., accounting for 81% of cases. Accurate typing is crucial for early diagnosis and treatment of immunoglobulin-derived (AL)-amyloidosis (i.e. AL, AH (Ig heavy chain), AIL (Ig heavy and light chain)) and to avoid treating other types with potentially toxic chemotherapy. Immunofluorescence (IF) is the first step in the renal AL-amyloidosis but the performance characteristics of this method are largely unknown. In this study, we aim to establish the sensitivity and specificity of IF for diagnosing AL-amyloidosis in patients whose amyloid typing was performed by the current gold standard, laser microdissection/mass spectrometry (MS).

Methods: Renal biopsy pathology reports from several institutions with diagnosis of amyloidosis by IF, which underwent a confirmatory diagnosis and typing by MS done at our center, were reviewed. Reported IF staining for kappa or lambda a 2+,

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
FR-PO747

Urine Epidermal Growth Factor, Monocyte Chemotactrant Protein-1, or Their Ratio as Biomarkers for Response to Therapy in Primary Glomerulonephritis

Eakkapat Kinugawa, Supanat Worrachawanwong, Nuanikantha Sathirapongsasuti, Chagrnya Kittayakara, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

Background: The balance between pro-inflammatory cytokines such as monocyte chemotactrant protein-1 (MCP-1) and protective cytokines such as epidermal growth factor (EGF) likely determines the outcomes in primary glomerulonephritis (GN). Elevated urinary MCP-1 and decreased urinary EGF have been associated with renal fibrosis, but there is limited information on their prognostic roles. We evaluated the relationships of urinary EGF, MCP-1 or their ratio at baseline with subsequent response to therapy and renal function at 24 months in patients with primary GN.

Methods: This is a prospective study in primary GN (n=74). Urine samples were collected at the time of biopsy. MCP-1 and EGF were analyzed by ELISA kits and expressed as a ratio to creatinine (ng/mg Cr) or as EGF/MCP-1 (ng/ng). Complete remission (CR) was defined as proteinuria ≤0.3 g/gCr and other subjects were categorized as Not in remission (NR). The predictive role of the biomarkers and traditional clinical parameters for CR were analyzed by Cox multivariate regression analysis.

Results: The diagnoses were: IgA nephropathy (n=28), focal segmental glomerulosclerosis (n=16), minimal change disease (n=10) and membranous nephropathy (n=20). Median follow up was 20 (12, 28) months. Estimated glomerular filtration rate (eGFR) at baseline correlated positively with EGF, EGF/MCP-1, and inversely with MCP-1. Proteinuria at baseline correlated positively with MCP-1, and inversely with EGF/MCP-1. After treatment with renin-angiotensin blockers and/or immune-modulating agents, 38 patients (51.4%) achieved CR. Baseline EGF and EGF/MCP-1 levels were higher in CR compared to NR, whereas MCP-1 was not different. High EGF (>75 ng/mgCr) at baseline was an independent predictor for subsequent CR (OR 95%CI: 2.86 (1.37-5.94), p<0.005). In the subset of patients (n=43) who completed 24 months follow-up, high baseline EGF (>75 ng/mgCr) had lower proteinuria at 24 months follow-up. Baseline EGF and EGF/MCP-1 correlated positively with eGFR at 24 months.

Conclusions: High urinary EGF at baseline was an independent predictor of subsequent CR. EGF and EGF/MCP-1 at baseline correlated positively with eGFR and inversely with proteinuria at 24 months. Larger studies are necessary to confirm the benefits in the management of primary GN.

Funding: Government Support - Non-U.S.

Table 1: Biomarker characteristics.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PLR</th>
<th>NLR</th>
<th>PPV</th>
<th>NPV</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGF</td>
<td>91.7%</td>
<td>96.8%</td>
<td>9.13</td>
<td>0.89</td>
<td>91.7%</td>
<td>96.8%</td>
<td>0.93</td>
</tr>
<tr>
<td>EGF/MCP-1</td>
<td>57.8%</td>
<td>89.3%</td>
<td>2.5</td>
<td>4.52</td>
<td>89.3%</td>
<td>57.8%</td>
<td>0.70</td>
</tr>
<tr>
<td>NVS</td>
<td>52.7%</td>
<td>82.8%</td>
<td>5.11</td>
<td>0.52</td>
<td>82.7%</td>
<td>52.6%</td>
<td>0.74</td>
</tr>
</tbody>
</table>

PLR= Positive Likelihood Ratio. NLR=Negative Likelihood Ratio. PPV=Positive Predictive Value. NPV=Negative Predictive Value. AUC=Area Under Curve

FR-PO748

Clinicopathological Implications of Urinary Soluble CD163 in Glomerulonephritis with Crescentic Formation

Hidenori Kakeshita, Kota Fujioka, Kota Hidenori Kakeshita, Michiko Nakamura, Tsutomu Kakei, Kinugawa Eakkapat, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

Background: M2 macrophages contribute to crescentic formation in various types of glomerulonephritis. A recent report suggested that the level of urinary soluble CD163 (sCD163), a marker of M2 macrophage infiltration, associated very tightly with active renal vasculitis. In this study, the association of urinary sCD163 level with indices of disease activity was analyzed in patients with glomerulonephritis with crescents.

Methods: Subjects were fifty-seven patients with biopsy proven glomerulonephritis with crescentic formation, including microscopic polyangiitis (n=14), anti-GBM glomerulonephritis (n=3), IgA vasculitis (n=10), IgA nephropathy (n=22), lupus nephritis (n=6), infectious glomerulonephritis (n=2). In advance of kidney biopsy, measurements of urinary sCD163 and urinary protein excretion (UP), effective glomerular filtration rate (eGFR) were performed.

Results: 1) In all subjects, urinary sCD163 correlated positively with the percentage of glomeruli with cellular crescents (r=0.48, p<0.01). In contrast, urinary sCD163 did not associate with the percentage of glomeruli with fibrocellular or fibrous crescents. Additionally, there was a positive correlation between urinary sCD163 and UP (r=0.41, p<0.05), whereas there was no association between urinary sCD163 and eGFR. 2) In thirty subjects followed for six months after immunosuppressive treatments, the positive relationships of urinary sCD163 levels with treatment-induced changes in eGFR (r=0.49, p<0.01) or UP (r=0.41, p<0.05) were observed.

Conclusions: In conclusion, urinary sCD163 may be a novel surrogate marker for disease activity of glomerulonephritis with crescentic formation.

FR-PO749

Diagnosis of Renal Vasculitis Flare Using usCD163: A Multi-Centre Prospective Study

Sarah M. Moran, Mark A. Little, Niall P. Conlon, Mark A. Little, Trinity College Dublin, Dublin, Ireland, Trinity Health Kidney Centre, Dublin, Ireland.

Background: Urinary sCD163 displays excellent potential for active renal vasculitis detection at AAV diagnosis. The clinical utility of usCD163 is in the diagnosis of renal vasculitis flare, potentially obviating the need for biopsy and detecting active renal vasculitis prior to further injury.

Methods: AA/Av patients were prospectively recruited with potential renal vasculitis flares from a multicentre cohort. Physicians judged the flare probability as High or Possible. An independent committee adjudicated on renal flare diagnosis (BVAS major criteria:RBC casts & or 30% increase in creatinine or renal biops). Urine creatinine-normalised sCD163 levels were measured by ELISA.

Results: 44 patients were prospectively recruited, 32% with renal flare. Creatinine was 1.7mg/dL (IQR 1.0-3.2, 78% increase from baseline) and 1.5mg/dL (IQR 1.1-1.7, 2.8% increase) in flare and non-flare (p=0.02). Median usCD163 levels were significantly higher in patients with adjudicated renal flare (469.6 ng/mmol (IQR 363.8-2974)) compared to non-flare (25.4 (IQR 3.9-80.8, p<0.0001)). Median usCD163 levels were not elevated in potential renal flare mimics, including sepsis (62.1ng/mmol IQR 27.8-155.7), acute kidney injury (22.4ng/mmol, IQR 0.78-7.7) or systemic flare (22.4ng/mmol, IQR 21-107.7). usCD163 is diagnostic of renal vasculitis flare in prospectively observed patients with AAV, and is superior to initial physician assessment and BVAS major renal criteria.

Funding: Government Support - Non-U.S.

Table 1: Biomarker characteristics.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PLR</th>
<th>NLR</th>
<th>PPV</th>
<th>NPV</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>usCD163 &gt;300ng/mmol</td>
<td>91.7%</td>
<td>96.8%</td>
<td>9.13</td>
<td>0.89</td>
<td>91.7%</td>
<td>96.8%</td>
<td>0.93</td>
</tr>
<tr>
<td>usCD163 &gt;1000ng/mmol</td>
<td>57.8%</td>
<td>89.3%</td>
<td>2.5</td>
<td>4.52</td>
<td>89.3%</td>
<td>57.8%</td>
<td>0.70</td>
</tr>
<tr>
<td>NVS</td>
<td>52.7%</td>
<td>82.8%</td>
<td>5.11</td>
<td>0.52</td>
<td>82.7%</td>
<td>52.6%</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Clinical Study Results of a Real-Time Point-of-Care Glomerular Filtration Rate Measurement

Richard B. Dorshov,1 Martin Debreczeny,1 James R. Johnson,1 jeng-jong Shieh,1 Thomas E. Rogers,2 Kevin J. Martin,4 Daniel W. Coyne,3 1MediBeacon Inc., St Louis, MO; 2MediBeacon Inc, St Louis, MO; 3MediBeacon Inc., Saint Louis, MO; 4Saint Louis University Med Ctr, St Louis, MO; Washington University School of Medicine, St. Louis, MO.

Background: Real-time point-of-care measure of glomerular filtration rate (mGFR) would permit rapid diagnosis of acute kidney injury and precise determination of CKD. Clearance pharmacokinetics of the fluorescent agent MB-102 was measured in the plasma and correlated with noninvasively measured transdermal fluorescence for subjects with normal kidney function to Stage 4 CKD. MB-102 was completely cleared by 12hr when mGFR was >60 mL/min/1.73m2 over a period of 12hr post simultaneous administration of MB-102 and iohexol, and urine collected to assess percent excretion. A noninvasive detection device simultaneously measured the transdermal fluorescence from MB-102.

Methods: Blood samples were taken in 60 subjects with eGFR from normal to 19 mL/min/1.73m2 over a period of 12hr post simultaneous administration of MB-102 and iohexol, and urine collected to assess percent excretion. A noninvasive detection device simultaneously measured the transdermal fluorescence from MB-102.

Results: Plasma pharmacokinetics displayed the expected 2 compartment model of a vascular-tissue equilibrium phase followed by renal excretion only. The GFR measured from the MB-102 plasma pharmacokinetics was highly correlated with the GFR measured from iohexol over the entire measured range of GFR values ($r=0.98$). The time-dependence of the transdermal fluorescence from MB-102 monitored by our fluorescence detection device was highly correlated with that of the plasma (see figure from subject with normal mGFR). MB-102 was completely cleared by 12hr when mGFR was >60 mL/min/1.73m2.

Conclusions: Point-of-care clinically amenable measured GFR for a range of kidney function from normal to Stage 4 CKD is demonstrated using transdermal fluorescence detection of the novel fluorescence tracer agent MB-102.

Funding: Commercial Support - MediBeacon Inc.

Unbiased Screening of Urinary Protein Biomarkers for Glomerular Filtration Rate Normalization

Sanam Soomro, Samantha Stanley, Ramesh Saxena, Michelle Petri, Chandra Mohan. University of Houston, Houston, TX.

Background: To account for glomerular filtration rate, urinary creatinine is routinely used for the normalization of urine biomarkers related to disease. Because of the small size of this metabolite, antibodies are difficult and expensive to develop, limiting the applications of disease-specific urine protein biomarkers for antibody-based point of care applications.

Methods: An aptamer-based screening of 1129 proteins in 24 human urine samples (8 active lupus nephritis (LN), 8 inactive LN, 8 healthy controls (HC)) was carried out to identify urine proteins that correlated well with urine creatinine but not disease.

Results: The screen uncovered 18 proteins that correlated well with urinary creatinine but were similar in patients with or without nephritis. Further validation in an independent cohort of 48 subjects (16 active LN, 16 inactive LN, 16 HC) showed a significant positive correlation of urine HVEM, RELT, and Dectin-1 to urinary creatinine. The most promising marker, urine HVEM, was significantly correlated to urinary creatinine in both white (Pearson r = 0.7229, P = 0.0001) and black subjects (Pearson r = 0.6111, P = 0.0009).

Conclusions: Instead of the metabolite creatinine, proteins such as HVEM, RELT, and Dectin-1 can be used for normalization of urine biomarkers. The use of proteins instead of metabolites for normalization paves the way towards novel diagnostic approaches.

Funding: NIDDK Support, Other NIH Support - NIGMS K01GM109320

Plasma Metabolomics in Steroid-Sensitive and Steroid-Resistant Nephrotic Syndrome

Jessica Gooding,1,3 Shipra Agrawal,2,3 Susan Mer Ritchie,1,4 Zachery J. Aucuff,5 William E. Snymer,2,3 Susan J. Summer.5 1Nutrition Research Institute, University of North Carolina at Chapel Hill, Kannapolis, NC; 2Center for Clinical and Translational Research, Nationwide Children’s Hospital, Columbus, OH; 3Discovery, Science and Technology, RTI International, Durham, NC; 4NIH Eastern Regional Comprehensive Metabolomics Resource Core (ERCMRC), University of North Carolina Chapel Hill, Chapel Hill, NC; 5Pediatrics, The Ohio State University, Columbus, OH.

Background: Nephrotic syndrome (NS) is a common kidney disease in children. Steroids are the primary therapy, however, they are ineffective in ~20% cases. Children with steroid-resistant NS (SRNS) fail to enter remission after prolonged steroid treatment, and are at high risk for steroid-induced side effects as well as progression of disease to end-stage renal disease (ESRD) within five years. This study aimed to discover markers of steroid-resistance that could be used to predict SRNS at presentation and develop a mechanistic definition of SRNS.

Methods: Citrate plasma (n=86) were collected from 30 steroid-sensitive NS and 15 steroid-resistant NS patients at presentation (prior to steroid therapy) and after an average of 7 weeks of steroid treatment. Blood sample plasma data was acquired, binned, and concentration fit. Multivariate analyses and hypothesis testing were used to determine the metabolites that best differentiated the phenotypic groups, and logistic regression using a stepwise variable selection method were used method the odds of steroid resistance at presentation.

Results: Treatment effects were observed between paired presentation and follow-up steroid-sensitive (SSNS) samples and between follow-up SSNS and SRNS samples. Metabolites affected by treatment included lipoproteins, adipate, tyrosine, valine, alanine, glutamine, glucose, pyruvate and creatine. After controlling for age, the step-wise logistic regression model selected glutamine (OR= 1.01, 0.99-1.02 95% CI). A similar model with children age >3 only, indicated that children with increased levels of malonate (OR=0.94; 0.89-1.00 95% CI) had an increased odds of responding to treatment.

Conclusions: Known effects of corticosteroid treatment were observed providing a proof-of-concept. The observed metabolic signature supports previous hypotheses that the proximal tubule is involved in the pathology of SRNS as reflected in circulating metabolites of renal gluconeogenesis. After controlling for age, logistic regression suggests that malonate concentration may be a potential biomarker for identifying SRNS at presentation.

Funding: NIH Support, Other NIH Support - NIGMS K01GM109320
clinical findings and clarified the availability of UG in the point of differentiation of NS due to MCNS, FSGS, MN.

Results: The subjective cases were comprised of 23 MCNS, 18 MN (stage 1=4), 18 LN (tendency for class V) and 4 crescentic GN, IgAN and LN (especially class IV) compared with controls but not in other glomerular diseases. The subjective cases were comprised of 23 MCNS, 18 MN (stage 1=4), 18 LN (tendency for class V) and 4 crescentic GN, IgAN and LN (especially class IV) compared with controls but not in other glomerular diseases.

Conclusions: Our study shows that nighttime sampling for spot PCR may better correlate with 24 hours urinary protein excretion, although cumbersome. We compared the spot urinary protein to creatinine ratio (PCR) collected at three different time points of the day with standard 24 urine protein collection to identify the best time for sampling.

Methods: This was an observational, cross sectional study carried out at Faima Memorial Hospital Lahore, Pakistan over four years from January 2013. Sixty-seven (67) patients who were persistently dipstick positive for protein were included and informed consent was obtained. The patients were required to collect a twenty-four hours urine sample according to standard recommendations for protein and creatinine measurement. From the same collection 10 ml aliquots of urine were separated and sent for spot urinary protein and spot urinary creatinine for PCR at different time points (Morning: 8 AM – 10 AM; Evening : 2 PM – 6 PM; Night: 8 PM – 10 PM).

Results: Mean age of the cohort was 32.91± 13.12 years and 39 (58.2%) were males. Mean Serum Creatinine was 3.24 ± 2.50 mg/dL (mean eGFR by CKD-EPI equation: 45.1 ± 37.3 ml/min). Range: 5.7 – 147.5 ml/min. 37.3% were diabetic and were clinically diagnosed as having diabetic nephropathy whereas the rest were undergoing evaluation or had biopsy proven glomerulonephritis. Patients were classified as CKD Class I: 18.6%, Class II: 15.3%, Class III: 23.7%, Class IV: 16.9% and Class V: 25.4%. None of the patients was on renal replacement therapy at the time of cross section. Mean serum albumin of the cohort was 3.23 ± 0.63 g/dl (Range: 1.9 to 4.7 g/dl.), whereas mean 24 hours urinary protein was 2.0 ± 1.58 g/day (Range: 0.37 – 6.5 g day). Pearson’s correlations for all three spot PCR samples were significantly correlated with the 24 hours urinary protein sample, however night time spot sample was found to have stronger correlation (Pearson’s r: 0.64, p <0.05) as compared to early morning and evening samples (r = 0.61 and r =0.37 respectively, p (0.05 for both).

Conclusions: Our study shows that nighttime sampling for spot PCR may better correlate with 24 hours urinary protein excretion. Further studies in different CKD stages and ethnicities could confirm the findings of our study.

FR-PO754
Comparison of Spot Urinary Protein to Creatinine Ratio to 24 Hours Urinary Protein at Different Time Points During the Day: Is There a Variability During the Day? Omert Sabir, Muhammad M. Riaz, Naunaf Tarif, Abaid U. Rehman, Kashif Rafique, Nabiha Rizvi. Medicine, Division of Nephrology, Fatima Memorial School of Health Sciences, University of health sciences, Lahore, Pakistan.

Background: 24 hours urine protein excretion is considered gold standard for the estimation of daily urinary protein loss, although cumbersome. We compared the spot urinary protein to creatinine ratio (PCR) collected at three different time points of the day with standard 24 urine protein collection to identify the best time for sampling.

Methods: This was an observational, cross sectional study carried out at Fatima Memorial Hospital Lahore, Pakistan over four years from January 2013. Sixty-seven (67) patients who were persistently dipstick positive for protein were included and informed consent was obtained. The patients were required to collect a twenty-four hours urine sample according to standard recommendations for protein and creatinine measurement. From the same collection 10 ml aliquots of urine were separated and sent for spot urinary protein and spot urinary creatinine for PCR at different time points (Morning: 8 AM – 10 AM; Evening : 2 PM – 6 PM; Night: 8 PM – 10 PM).

Results: Mean age of the cohort was 32.91± 13.12 years and 39 (58.2%) were males. Mean Serum Creatinine was 3.24 ± 2.50 mg/dL (mean eGFR by CKD-EPI equation: 45.1 ± 37.3 ml/min). Range: 5.7 – 147.5 ml/min. 37.3% were diabetic and were clinically diagnosed as having diabetic nephropathy whereas the rest were undergoing evaluation or had biopsy proven glomerulonephritis. Patients were classified as CKD Class I: 18.6%, Class II: 15.3%, Class III: 23.7%, Class IV: 16.9% and Class V: 25.4%. None of the patients was on renal replacement therapy at the time of cross section. Mean serum albumin of the cohort was 3.23 ± 0.63 g/dl (Range: 1.9 to 4.7 g/dl.), whereas mean 24 hours urinary protein was 2.0 ± 1.58 g/day (Range: 0.37 – 6.5 g day). Pearson’s correlations for all three spot PCR samples were significantly correlated with the 24 hours urinary protein sample, however night time spot sample was found to have stronger correlation (Pearson’s r: 0.64, p <0.05) as compared to early morning and evening samples (r = 0.61 and r =0.37 respectively, p (0.05 for both).

Conclusions: Our study shows that nighttime sampling for spot PCR may better correlate with 24 hours urinary protein excretion. Further studies in different CKD stages and ethnicities could confirm the findings of our study.

FR-PO756
Urinary Podocyte mRNA and Urinary Podocalyxin Protein: Different Excretion Pattern between Proliferative and Non-Proliferative Glomerular Diseases Akiko Fukuoka,1,2 Akiko Minakawa,1 Masao Kikuchi,2 Yuji Sato,2 Hiroyuki Kurosawa,1 Masanori Harai,1 Shoichii Fujimoto,1 Oita University, Yufu, Japan; 2University of Miyazaki, Miyazaki, Japan; 3Denka Seiken Co., Ltd, Gosen, Japan; 4Niigata Wellness (Iwamuro Health Promotion Center), Niigata, Japan.

Background: Podocyte depletion causes glomerulosclerosis, and persistent podocyte loss drives progression to end-stage kidney disease in most forms of glomerular diseases. Podocytes are resident on the urinary space side of the glomerular basement membrane, so that as they detach or die, their products can be identified in urine. Thus, the podocyte products in urine might be potential biomarkers to monitor glomerular disease activity and progression. Recently, both the urinary pellet podocyte (u-pod) mRNA excretion rate and urinary podocalyxin (u-PCX) protein levels have been used to monitor disease activity in various glomerular diseases. However, differences in these markers between various pathologies have not yet been investigated. By comparing the u-pod mRNA excretion rate to u-PCX protein levels in biospy-proven glomerular diseases, we examined the significance of these markers in various glomerular diseases.

Methods: From January 2013 to March 2016, early morning urine samples were collected from 12 healthy volunteers and 184 patients with various kidney diseases (minor glomerular abnormality, n=16; MCNS, n=16; MCD, n=17; LN, n=24; lupus nephritis, n=11; others, n=39). We examined the u-pod mRNA excretion rate, u-PCX protein levels and urinary protein/creatinine ratio (u-PCR).

Results: The u-pod mRNA excretion rate was statistically correlated with u-PCX protein levels (r=0.37, p<0.001). Both the u-pod mRNA excretion rate and u-PCX protein levels were statistically correlated with u-PCR (r=0.52, p<0.001 and r=0.32, p=0.03, respectively). Interestingly, the u-pod mRNA excretion rate was significantly increased in crescentic GN, IgAN and LN (especially class IV) compared with controls but not in MCNS and MN, whereas the u-PCX protein levels were significantly increased in MN and LN (trendiness for class v) compared with controls but not in other glomerular diseases.

Conclusions: Although the u-pod mRNA excretion rate and u-PCX protein levels were positively correlated, a higher u-pod mRNA excretion rate and higher u-PCX protein levels might be associated with proliferative glomerulonephritis and non-proliferative glomerulonephritis, respectively.
A Swine Model of Tunneled Dialysis Catheter (TDC) Infection and Dysfunction: Opportunities for Therapeutic Innovation

Disease

Upper Extremity Swelling in ESRD: DVT or Central Venous

FR-PO758

A Swine Model of Tunneled Dialysis Catheter (TDC) Infection and Dysfunction: Opportunities for Therapeutic Innovation

Diego Celdran-Kohler,1 Monnie Wasse.2

1University of Arizona, Tucson, AZ; 2University of Cincinnati, Cincinnati, OH; 3SAVAICS, Tucson, AZ.

Background: TDC infection and dysfunction are important causes of morbidity and mortality in hemodialysis patients, with no truly effective therapies. An important reason for this is the absence of a validated large animal model. We herein describe a swine model that closely mimics the human condition.

Methods: TDC’s were placed in the right jugular vein of 6 Yorkshire pigs. Blood was flushed in and out of each lumen twice weekly in order to mimic dialysis and assess for the onset of dysfunctional flow. Animals were monitored daily for infection. Blood cultures (BC) were obtained and antibiotics started when the temperature was > 103 degrees F. Animals were euthanized if they did not respond to treatment. Data on the time to infection (fewer), dysfunction, and sacrifice, as well as the BC profiles were collected. Data collection has been completed on 3 pigs and is ongoing in the others. We will present the available data from all 6 pigs.

Results: The average time to fever (infection) and TDC dysfunction was 9.2±5.2 and 8±6.2 days respectively. The arterial line was dysfunctional first in 83% of cases. Compacted fibrin sheaths were present in all sacrificed animals (Figure), together with jugular and central venous wall thickening. Importantly, the bacterial profile correlated with standard human data, showing growth of Klebsiella, Pseudomonas and Beta hemolytic strep (and from an earlier study Staphylococcus aureus).

Conclusions: We have, for the first time, described a large animal model of TDC infection and dysfunction which mimics the human condition. We believe that the availability of this model, with its well defined end points, will incentivize the product development pathway for novel, safe and effective therapies that target both TDC infection and dysfunction.

Funding: NIDDK Support

FR-PO759

Incidence and Risk Factors for Central Venous Stenosis in Haemodialysis Patients

Anamika Advani,1 Neel Dugani,2 Shubham Agarwal,1,2 Damien Ashby.1

1Imperial College, London, United Kingdom; 2Imperial College Renal and Transplant Centre, London, United Kingdom.

Background: Central venous catheters have traditionally provided haemodialysis access when a fistula is declined or not achieved, but are increasingly advocated as an acceptable option for older or more comorbid patients. Adverse effects of this type of dialysis access include central vein stenosis (CVS), which can lead to significant morbidity including access dysfunction or failure. The pathogenesis and risk factors for CVS are incompletely understood.

Methods: All patients starting haemodialysis in a single centre between December 2005 and February 2015 were prospectively identified. From this cohort, a random sample of patient records were retrospectively analysed for the presence of CVS, defined by cross-sectional or angiographic imaging.

Results: Out of 300 patients (aged 19 - 91, 64.7% male) followed for up to 10 years, CVS developed in 23 (7.67%). All CVS patients had a history of tunneled dialysis catheter use. Compared to those unaffected, patients with CVS had a larger number of previous catheters (2.3 vs 1.2, p=0.001) but not a greater duration of previous catheter use (28.7 vs 32.1 months). Non-dialysis risk factors, more frequent in patients with CVS, included pacemakers (13.0 vs 2.2%, p<0.001) and prior intensive care admission (56.5 vs 11.9%, p<0.001). There was no significant effect of ethnicity, but in older patients (over 70) dialysis initiation, 35.0% of the group) the development of CVS was much less common (2.9 vs 10.3%, p=0.023)

Conclusions: In haemodialysis patients with prior tunneled catheter use, a significant minority may develop CVS, with the number of catheters, rather than catheter duration, being the primary risk factor, though non-dialysis risk factors are also important. The finding that patients over 70 at dialysis initiation are less likely to develop CVS, supports the selective use of tunneled catheters in some older patients.

FR-PO760

Tunneled Catheter-Related Bacteremia Preventive Protocol: Results Analysis

Carmen Gonzalez corvillo, Maria angeles Rodriguez-Perez, Mercedes Salgueira. NERPHROLOGY, HUVMACARENA, SEVILLA, Spain.

Background: The increasing use of tunneled catheters for haemodialysis is associated with a number of complications, particularly catheter-related bacteremia(CRB). The implementation of a pre-emptive protocol during the preimplantation period and maintenance care could reduce the rate, although there is no consensus on the details of such a protocol in the bibliography. Since 2006, our department has had a pre-implantatory protocol, developed by nephrologists and infectologists, it includes nasal decolonization in case of staphylococcal aureus colonization, complete cleansing with chlorhexidine gel and povidone iodine solution 1% in case of S. epidermidis before the procedure. We analyze the results obtained in our department regarding CRB in tunneled catheter implants in the last 11 years.

Methods: Our protocol has been implemented in 246 tunneled catheters, implanted in 107 patients. Mean age:63 years. Mean follow-up period for each catheter:132 months. Incidence of bacteremia, time of appearance of the bacteremia after the implantation, bacteria types and associated complications were analyzed.

Results: Location: right jugular vein 71.1%, left subclavian 16.3%, right subclavian 11%, femoral 1.6% - 72 catheters were removed in 15(6.1%) cases, with infection being the main reason for removal. - 64 cases of catheter-related bacteremia were diagnosed, representing an incidence rate of 0.48 cases per 1000 catheters per year. Susceptible strain for appearance of CRB: 579: 441 days after implantation(median 513days, minimum 42, maximum 1623) - Most frequent microorganisms: Staph. Epidermidis 36.7%, MSSA 6.1% Staph. Aureus 6.1% Staph. Warneri 4%, pantoea agglomerans 4%, staph yrdmans 4%, candida 2%, pseudomonas 2%, cloacae 2%, klebsiella 2%, corynebacterium 2%, serratio 2% - Infection recurrence was 26% in a mean time of 276 days. Most frequently recuring microorganisms were Staph. Epidermidis 31% and MSSA 26% - Septic complications: 9 cases (1 septic arthritis, 1 spondylodiscitis, 4 endocarditis and 4 meningitis)

Conclusions: In our experience, the rate of tunnelled CRB is in fact lower than reported in the bibliography. Implementation of our preemptive protocol has delayed the incidence of CRB, with the primo-infection presenting more than 1 year after tunneled catheter implantation. The recurrence rate was high and the most frequent microorganism was Staph. Epidermidis. The incidence of other complications and the need to remove the catheter is low.
FR-PO761

Efficacy of Alteplase (tPA) 1 mg versus 2 mg in Restoring Hemodialysis Catheter Function: A Randomized Double-Blind Controlled Study

Albert Kadri,1 Wasmim El Nekidy,2 Derrick Soong,3 Maher M. El-Masri,4 Ricardo Correa-Rotter,1 Olynka Vega,2 National Institute of Medical Sciences, Mexico, Mexico; 2 ‘National Institute of Medical Sciences, Mexico, Mexico; 3 Nephrology and Mineral Metabolism, National Medical Science and Nutrition Institute Salvador Zubiran, Mexico city, Mexico.

Background: Hemodialysis catheters (HDC) are used to provide vascular access to patients with Chronic Kidney Disease on hemodialysis (HD). Late thrombus formation can result in HDC occlusion leading to its malfunction. Data about optimal alteplase (tPA) dose required to restore HDC is scarce. The purpose of the study was to examine the effectiveness of the commonly used tPA dose of 2 mg as compared to 1mg in restoring HDC function.

Methods: A double blind, randomized, controlled clinical trial was conducted on hemodialysis patients who required tPA use to restore their HDC function. Eligible consented patients were randomly assigned to either of the two study groups (tPA 2 mg or 1 mg). Patients were included if they: were ≥18 years of age at the time of the study, were receiving HD using HDC, and had no medical contradiction for tPA use.

Results: Forty eight consenting patients contributed a total of 252 observations that were allocated to either group A (2 mg) or group B (1mg) based on randomization. The cluster nature of the observation, randomization was observation-based as opposed to patient-based. The rate of clot resolution at the catheter site in the A group was 85.7% as opposed to 84.9% with an insignificant absolute risk reduction of only 0.8% percentage (p = 0.5). There were only six catheter removals; three of which were related to catheter malfunction. Catheter stripping was documented in 10 of the 252 observations. Kaplan Meier results indicated that the median time to occlusion after tPA resolution of the first catheter occlusion was 192 and 120 days for groups A and B, respectively (Log rank = 0.499; p = 0.480). Cox regression analysis indicated no difference in the hazard of occlusion between the two groups (p = 0.267; HR = 0.72; 95% CI 0.40–1.3).

Conclusions: tPA 1 mg is as effective as 2 mg in restoring HDC function. The use of the lower dose will result in significant cost reduction in hemodialysis units.

Funding: Private Foundation Support

FR-PO762

Infections of Tunneled and Non-Tunneled Central Venous Catheters Associated with the Use of 10% Povidone-Iodine versus 2% Chlorhexidine in Chronic Hemodialysis

Mauricio Arvizu-Hernandez,1 Olynka Vega,1 Ricardo Correa-Rotter,1 2 National Institute of Medical Sciences, Mexico, Mexico; 3 Nephrology and Mineral Metabolism, National Medical Science and Nutrition Institute Salvador Zubiran, Mexico city, Mexico.

Background: Vascular access (VA) infections are a problem in patients on hemodialysis (HD), representing the second cause of morbidity and mortality. The ideal VA is the arterio-venous fistula, in our environment a high number of patients start and stay for a longer than desired on catheters. The use of 2% chlorhexidine solution (2% CHX) for the management of exit site of VA on HD can impact positively the number of catheter infections.

Methods: Retrospective cohort study performed in our Institute HD unit, where 10% povidone-iodine solution (PI) was previously used and since March/2015, was substituted by 2% CHX. We assessed the rate of VA (catheter related) infections from Sep/13 to Aug/16 (Sept/13-Feb/2015 PI and Mar/15-Aug/16 use of 2% CHX). Incidence of infections was analyzed on a monthly basis, identifying number and clinical characteristics of the infection. We calculated the rate of infections per 1000 days/cath/patient. The use of PI vs 2% CHX periods were compared.

Results: During the 36 month study period, a total of 33 infections were identified (0.91 infect/month). The highest infection rate was observed during the use of the PI, both in tunneled and non-tunneled catheters. On the basis of cumulative incidence rates, calculating the RR; the use of PI in both types of catheters, as compared to use of 2% CHX, has a RR of 4.0 (tunneled RR=3.6 and non-tunneled RR=7.0).

Conclusions: Our study demonstrated clearly that the use of 2% CHX in patients with temporary catheter vascular accesses on HD, reduces the risk of infection of both the tunneled and non-tunneled catheters.
Substitution of Citrate with Tissue Plasminogen Activator (rt-PA) for Catheter Lock Does Not Improve Patency of Tunneled Hemodialysis Catheters

Pavlina Richtrova,1,2 Jan Marcs,1,2 Lukas Kielberger,1,2 Jan Klaboc,2 Jaromir Eiselt,2 Tomas Reischig.1,2 1st Medical Department, Faculty of Medicine in Pilsen, Charles University, Pilsen, Czech Republic; 2Biomedical Centre, Faculty of Medicine in Pilsen, Charles University, Pilsen, Czech Republic.

Methods: All incident patients undergoing insertion of a tunneled hemodialysis catheter were screened and included except those suffering infection or using anticoagulation. Study participants were randomized into two arms according to the solution applied as catheter lock: receiving either trisodium citrate (Citra-Lock™ 4%) only or rt-PA (Actilyse® 1mg/ml) on the middle session each week with citrate used on the first and third sessions. The incidence of CR-BSI (confirmed by positive blood culture), catheter non-function (complete obstruction), and malfunction (blood flow <250ml/min) was recorded. Statistical significance was tested with ANOVA, post hoc analysis was performed by means of multiple linear regression.

Results: Totally, 20 patients were included and followed during 655 hemodialysis sessions. No episode of CR-BSI was detected while 6 catheter non-functions (0.9% sessions) and 101 malfunctions (15.4% sessions) were recorded. The incidence of both events was equal between the study arms: 4 non-functions and 55 malfunctions in the rt-PA arm and 2 non-functions and 46 malfunctions in the citrate arm (p=0.47 and p=0.24, respectively). Additionally, the mean blood flow achieved did not differ significantly between the arms: 326±1.8 and 326±1.9 ml/min (p=0.95) in rt-PA and citrate arms, respectively. Post hoc analysis identified time elapsed since previous session (β=0.12, p=0.005) and malfunction on previous session (β=0.25, p=0.001) as significant factors affecting the occurrence of malfunction. By contrast, the study arm, rt-PA application on previous session, and catheter vintage did not enter the model.

Conclusions: Substitution of citrate with rt-PA for catheter lock does not reduce the incidence of catheter malfunction neither does it affect the blood flow achieved during hemodialysis. Catheter patency is related rather to the time interval between sessions and to previous malfunction. The incidence of CR-BSI within pre-selected hemodialysis population is sporadic (less than 1 per 4.3 patient years in our sample).

Funding: Government Support - Non-U.S.

FR-PO764

Sharp Recanalization of Central Venous Occlusions in Hemodialysis Patients

Carlos Rafael A. Felipe,1 Andre S. Alvarenga,2 Gerson M. Pereira Jr,2 Ana elisa S. Jorge,1 Antonio Carlos M. Bedeti,1 Santa Casa, Belo Horizonte, Brazil; 1Santa Casa de Belo Horizonte, Belo Horizonte, Brazil.

Background: Central venous occlusion (CVO) is a severe vascular complication that causes massive upper extremity swelling and dysfunctional dialysis access. Management is aimed at providing symptomatic relief and maintaining hemodialysis access site patency.

Methods: A total of 14 hemodialysis patients with massive upper extremity swelling and dysfunctional dialysis access, who underwent endovascular recanalization for CVO at our institute between November-2013 and May-2016 were examined. We evaluated procedure success rate, complication rate, primary and secondary patency rate.

Results: There were 12 occlusions in brachiocephalic veins and 2 in subclavian veins. Until this procedure, each patient had lost on average 5.1 vascular access. First, we tried to traverse the occlusion using soft tip of hydrophilic wire under angiographic catheter (conventional technique); if failure, we switched to sharp recanalization technique using stiff end of hydrophilic wire to puncture the fibrotic cap to create a channel that was crossed by the soft tip of same hydrophilic wire. The procedure was considered successful when residual lesion was <30%. Success of conventional technique were 28.6%. Switched to sharp recanalization resulted in overall success rate of 85.7% without any major complications.

Conclusions: Sharp recanalization of symptomatic central venous occlusions in hemodialysis patients was an effective and safe method to maintain the patency of dialysis access and to relieve the symptoms.
Results: A total of 15.5% intervals were associated with thrombosis in the subsequent 60 days. The cumulative incidence of thrombosis was greater with higher cumulative score (see table below). Scores $\geq 3$ were associated with a relatively low incidence (95% AVF, 13.0% AVG) and scores $\geq 4$ with a high incidence (AVF: 25.4%, AVG: 23.2%) of thrombosis.

Conclusions: Risk scores based upon a Vasc-Assimetm scoring algorithm successfully identified VA with low or high probability of developing thrombosis within the next 60 days. Because these scores are Tx record based, they may be easily automated to help guide VA patient care through a population management model.

FR-PO766
A Randomised Controlled Trial of Interrupted versus Continuous Suturing Techniques for Radiocephalic Fistulae: 3-Year Follow-Up

Data Emma L. Aitken, David Kingsmore. NHS Greater Glasgow and Clyde, Glasgow, United Kingdom.

Background: Continuous suturing techniques have conventionally been used for the end-to-side anastomoses of radiocephalic fistulae (RCF), however only 50-60% of RCF retain patency at one-year. We hypothesised that interrupted sutures (utilised in many microsurgical procedures) may improve outcomes of fistulae constructed from small vessels by optimising anastomotic compliance.

Methods: Three year follow-up of a randomised controlled trial comparing interrupted (n=36) vs. continuous (n=42) suturing techniques for RCF is presented. Patients were excluded if vessels were <1.8mm diameter or if previous ipsilateral fistula had been attempted. The primary endpoint was primary patency at 6 weeks (assessed by a blinded observer for the presence of thrill and bruit). Secondary end points were functional patency (clinical and ultrasoundographic) at 6 weeks and primary/ secondary patency at 1 and 3 years (NCT01704513).

Results: Groups were comparable for basic patient demographics, operating surgeon and vessel diameter (mean age: 58.9(13.3) yrs; 67.9% male). Primary patency at 6 weeks was higher in the interrupted group (71.4% vs. 47.2%; OR 2.9 P<0.01). There was no significant difference in functional patency at 6 weeks (52.4% vs. 36.1%; OR 2.0 P=0.18). At 3 year follow-up 34.6% of patients (n=27) had died, 24.3% (n=19) had been transplanted and only 34.6% (n=27) of the patients remained on haemodialysis. Primary patency at 1 year was comparable between the two cohorts (53.3% [16 of 30 patients] vs. 45.9% [17 of 37 patients]; OR 1.34, P=0.17 for interrupted and continuous cohorts respectively. Similarly 3 year primary patency rates were 50.0% [13 of 26 patients] vs. 60.0% [15 of 25 patients]; OR 0.67, P=0.54).

Conclusions: An interrupted suturing technique yielded higher early primary patency rates for RCF. Less than one third of the original cohort remained on dialysis at three years follow-up. The early improvements in patency observed in the interrupted arm were not seen at 1 and 3 year follow-up. This may be the result of a small sample size (the study was not powered for secondary end-points). This study highlights the high attrition rate and short survival of patients with end-stage renal disease and brings into question whether autologous access is appropriate for ever patient.

FR-PO767
Buttonhole Versus Stepladder Cannulation for Arteriovenous Fistulae for Home Hemodialysis Patients: A Randomized Controlled Feasibility Trial Deborah Lynn Zimmerman, Jennifer M. MacRae, Brittany Hollingsworth, Christopher T. Chan, Gihad E. Nessallah, Philip McFarlane, Michael A. Copland, Shih-Han S. Huang. London Health Sciences Centre, London, ON, Canada; 1St. Michael's Hospital, Toronto, AB, Canada; 1The Ottawa Hospital Research Institute, Ottawa, ON, Canada; 1The University of Western Ontario, Toronto, ON, Canada; 1Toronto General Hospital, Toronto, ON, Canada; 1University of British Columbia, Vancouver, BC, Canada; 1University of Calgary, Calgary, AB, Canada; 1Medicine, Ottawa Hospital, Ottawa, ON, Canada.

Background: The need for more rigorous studies to address the uncertainty about the risk and benefits of buttonhole versus stepladder cannulation for arteriovenous fistula (AVF) was highlighted in the recently published Canadian Society of Nephrology guidelines on intensive home hemodialysis (IHD). Therefore, our purpose was to determine the feasibility of doing a multi-centre randomised controlled trial of buttonhole versus step-ladder cannulation in patients training to do IHD with an AVF.

Methods: Patients were to be recruited from 7 tertiary care Canadian hospitals with expertise in home hemodialysis. Inclusion criteria were 1) adult patients training for HHD, 2) AVF, 3) life expectancy greater than 12 months, and 4) able to give informed consent. Exclusion criteria were: 1) potential loss to followup within 12 months of training, 2) allergy to mupirocin, 3) need for intradermal lidocaine, 4) short segments or aneurysms in vessels by optimising anastomotic compliance.

Results: Groups were comparable for basic patient demographics, operating surgeon and vessel diameter (mean age: 58.9(13.3) yrs; 67.9% male). Primary patency at 6 weeks was higher in the interrupted group (71.4% vs. 47.2%; OR 2.9 P=0.01). There was no significant difference in functional patency at 6 weeks (52.4% vs. 36.1%; OR 2.0 P=0.18). At 3 year follow-up 34.6% of patients (n=27) had died, 24.3% (n=19) had been transplanted and only 34.6% (n=27) of the patients remained on haemodialysis. Primary patency at 1 year was comparable between the two cohorts (53.3% [16 of 30 patients] vs. 45.9% [17 of 37 patients]; OR 1.34, P=0.17 for interrupted and continuous cohorts respectively. Similarly 3 year primary patency rates were 50.0% [13 of 26 patients] vs. 60.0% [15 of 25 patients]; OR 0.67, P=0.54).

Conclusions: An interrupted suturing technique yielded higher early primary patency rates for RCF. Less than one third of the original cohort remained on dialysis at three years follow-up. The early improvements in patency observed in the interrupted arm were not seen at 1 and 3 year follow-up. This may be the result of a small sample size (the study was not powered for secondary end-points). This study highlights the high attrition rate and short survival of patients with end-stage renal disease and brings into question whether autologous access is appropriate for ever patient.

FR-PO768
Protecting Patients from Venous Needle Dislodgement (VND): An Improved AV Fistula Set

Data PATRICK ROUSCHE, Matthew Wood, Sharon Brown, Emma McFarlane, Michael Aitken, David Hollingsworth, Deborah L. Aitken, Kingsmore.

Background: Venous needle dislodgement (VND) is a serious patient risk for any dialysis session at home or in the clinic. Inadvertent removal of the venous line during dialysis therapy is at very least inconvenient, leading to spilled blood. At worst, even just one minute of unmitigated VND at 400 ml/min can lead to hemorrhagic shock; if the VND goes undetected for 5 minutes, patients can die from exsanguination. Clinics are faced with biohazard exposure, therapy disruption and patient injury/death. Hemodialysis machines are programmed to automatically detect pressure variations between fully inserted and dislodged needles during therapy, but often fail to accurately detect VND.

Methods: We introduce a patent-pending AV fistula modification which protects patients from the risks of VND.

Results: The standard butterfly design of traditional AV fistulas was modified to incorporate a small "sensing" feature on the underside of the needle used to determine if the inserted AV fistula remains in close contact with patient skin. When the system detects VND, flow through the needle is immediately restricted, resulting in quick and automatic shut-off of the machine pump. The needle is otherwise designed to look and feel the same as a traditional AV fistula needle.

Conclusions: Essential to performance testing of the new AV fistula, is its ability to pass normal amounts of fluid flow in the "ON SKIN" condition and its ability to restrict flow when in the "OFF SKIN" position. We used a benchtop flow system to determine the forces associated with flow termination during simulated VND. Results suggest fluid flow disruption of up to 95% through the V-Needle during simulated "dislodgement" is achievable with closing forces of ~15 grams, a force level that can easily be tolerated on the human skin over the typical dialysis therapy.

FR-PO769
Environmental and Patient Specific Factors Associated with Absolute Environmental and Patient Specific Factors Associated with Absolute Environmental and Patient Specific Factors Associated with Absolute...
FR-PO770

Identifying a Core Vascular Access Outcome for All Trials in Hemodialysis: An International Survey with Patients and Health Professionals

Andrea K. Vecchell, Matthew Tong, Jonathan C. Craig, David W. Johnson, Carmel M. Hawley

Background: Vascular access is an essential component for the care of patients requiring hemodialysis, yet clinical trials report a large and diverse range of vascular access outcomes that often cannot readily be compared across trials and have no clear relevance to patients and clinicians. This survey aims to identify core outcomes for vascular access, with the expectation that this will be measured and reported in all trials involving patients requiring hemodialysis, based on the shared priorities of patients/caregivers and health professionals.

Methods: Based on a systematic review, qualitative research and meetings with vascular access experts, 12 vascular access outcomes were included in an online survey conducted in English, Chinese, Spanish and Malay. Participants rated the absolute importance of outcomes using a 9-point Likert scale (7.9 being critically important), and the relative importance was determined by a Best-Worst Scale (BWS) using multinomial logistic regression.

Results: The survey was completed by 772 participants (187 [24%] patients/caregivers and 585 [76%] health professionals) from 58 different countries. Across groups, the top two outcomes were function (mean 8.4, top 1 on BWS) and infection (mean 8.1, top 2 on BWS). There was consistency in the prioritization of outcomes between both groups but health professionals rated outcomes overall higher than patients/caregivers (mean differences ranging from 0.09 for interference with activities to 1.3 for access maturation) with the exception of aneurysms which was ranked higher by patients/caregivers.

Conclusions: For patients/caregivers and health professionals, there was consensus on the primary importance of vascular access function. A core outcome measure will now be developed to improve the consistency and relevance of vascular access outcomes reported in trials in hemodialysis.

FR-PO771

Maintaining Vascular Access for Haemodialysis after First Vascular Intervention

Pablo Justo Avila, Terrina Abd rahim, Kamar Abayasekara, Lindsay J. Chesterton, Richard J. Fluck

Background: Access vascular (VA) teams struggle with VA patency as they can stenose or thrombose entailing vascular intervention (VI). We explore predicting factors for prolongation of VA function following VI and the role of antiplatelet or anticoagulant medications (AAM) on primary (PGS) and secondary graft survival (SGS).

Methods: We analysed VA formations from Oct'09 to Dec'15, with follow-up ending Dec'16. Patient demographics, comorbidities, cause of ESRD and medications were collected. We identified location of VA, first time of VI, number of VI, failure date and cause of HD withdrawal.

Results: 427 patients (260 M and 167 F) underwent VA formation. Mean age was 63 years. 168 had DM (39.5%) and 247 had HTN (57.8%). Causes of ESRD were unknown (41.3%), glomerulonephritis (26.2%), nephropathy (19%), chronic kidney disease (13.2%), 315 were on AAM (19.3%) on warfarin (W), 17 (3.5%) on clopidogrel (CD), 233 (52%) on aspirin (AP), 17 (3.5%) on AP and CL and 9 on W and AP. 538 VA were formed (209 radiopaque [RC], 229 brachiocephalic [BC], 87 brachiobasilic [BB] and 33 AVG). Mean follow-up was 850 days (SD 718). 286 (58.7%) required VI; 8 (revisions) [RV], 278 angioplasty [AG], 33 RV and AG and comprising 116 RC, 109 BC, 51 BB and 10 AVG. Median time to AG was 371 days; while to RV was 443 days. Mean PGS was 356 days (SD 372). Median AG performed was 2.8 (SD 2.25). 179 (80.1%) had a prolonged HD due to death (24.8% [71], thrombus of VA (21.7% [62]) and functioning transplant (7%[20]). SGS was 760 days (SD 528). We excluded patients who died or received transplant from analysis. We found no correlation between having DM or HTN, cause of ESRD, and type of VA with graft patency. VI in the first 6 months after formation was associated with worse patency rates (27.2% vs 53.9% [p < 0.001]). HTN was associated with longer SGS (697.73 vs 550.76 days [p = 0.004]) whilst DM was associated with shorter SGS (578.76 vs 673.12 days [p = 0.039]). AAM was not associated with improved patency (59.09% vs 70.96% [p = 0.076]) or SGS (626 vs 656 days [p = 0.18]).

Conclusions: 1. VI in the first 6 months after VA formation is associated with worse patency rates. 2. Less stringent BP control but tight glycemic control could potentially
increase parity rates of VAs. A AAM is not directly associated with higher parity rates or prolongation of SGS.

FR-PO774

Pre-Dialysis Cognitive Impairment and Pre-Emptive Placement of Dialysis Access: Findings from the Chronic Renal Insufficiency Cohort Study Meera N. Harlakonda,1 Davwei Xie,2 Chi-juan Hu,2 Alan S. Go,3 Jing Chen,1,4 Francisco,4 John F. Arnold,5 Robert J. Pennell,5 Thomas A. Cherney,6 James R. Lash,7 Sunyoung Akkina8 Xiaoming Zhang,9 Eric Vittinghoff,10 Stephen M. Sozio,10 Stephen L. Seliger,10 Mirela A. Dobres,11 Jacob B. Blumenthal,7 Eric Vittinghoff,9 Jing Chen,11 Francisco,8 School of Medicine, Baltimore, MD; 2Department of Veterans Affairs, Baltimore, MD; 3Johns Hopkins University School of Medicine, Baltimore, MD; 4Kaiser Permanente Northern California, Oakland, CA; 5Loyola University Medical Center, Chicago, IL; 6Stanford University, Palo Alto, CA; 7Tulane School of Medicine, New Orleans, LA; 8UCSF, San Francisco, CA; 9University of California San Francisco, San Francisco, CA; 10University of California San Francisco, San Francisco, CA; 11University of Illinois at Chicago, Chicago, IL; 12University of Maryland School of Medicine, Baltimore, MD; 13University of Pennsylvania, Philadelphia, PA; 14University of Pennsylvania School of Medicine, Philadelphia, PA; 15University of Pennsylvania School of Medicine Center for Clinical Epidemiology and Biostatistics, Philadelphia, PA; 16Drexel University College of Medicine, Philadelphia, PA. Group/Team: CRIC Study Investigators.

Background: Cognitive impairment (CI) is a common finding in late-stage chronic kidney disease (CKD), but few studies have examined its direct impacts on dialysis preparedness. We assessed the independent association of pre-dialysis CI on the probability of non-use of access placement among participants from the Chronic Renal Insufficiency Cohort (CRIC) Study who started dialysis.

Methods: We identified 630 CRIC participants who initiated dialysis. We defined pre-dialysis CI as a Modified Mini-Mental State Examination score < 8 measured prior to dialysis initiation. We estimated the association between CI and access placement using logistic regression models for the probability of 1) having permanent access placed before dialysis initiation, and 2) using the permanent access at the first dialysis session.

Results: The cohort had a mean age of 59 years (SD 12 years) and a mean eGFR of 16 ml/min/1.73m² (SD 3 ml/min) at the pre-dialysis cognitive assessment. Pre-dialysis CI was present in 14% (n=89) of the cohort. Compared to participants without CI, more participants with CI reported low income status (64% vs 38%, p<0.001) and low educational attainment (71% vs 22%, p<0.001). Pre-emptive access was placed in 75% of the cohort (n=473), and 45% of participants initiated dialysis using a permanent access (n=279). After adjustment for eGFR slope, demographics, diabetes, hypertension, vascular disease, functional status, and smoking, pre-dialysis CI was associated with a 48% lower probability of pre-emptive access placement (aOR 0.52, 95% CI 0.29-0.91) and a 45% lower probability of starting dialysis using a permanent access (aOR 0.55, 95% CI 0.32-0.97). After adjustment for socioeconomic variables including income, these associations were no longer statistically significant.

Conclusions: In this study, we found an association between pre-dialysis CI and suboptimal access outcomes, though this finding was not independent of socioeconomic status. Given the known relationship between socioeconomic status and CI, future studies may elucidate the underlying determinants of pre-dialysis CI when evaluating strategies to reduce disparities in dialysis preparedness.

Funding: NIDDK Support

FR-PO775

A Meta-Analysis of Randomized Clinical Trials of Blood Flow and Stenosis Surveillance of Hemodialysis Access Seon Deok Hwang1, Seongwoo Woo Lee2, Moon-Jae Kim1. 1Inha University College of Medicine, Incheon, Republic of Korea; 2Inha University Hospital, Incheon City, Republic of Korea; 3Kidney Center, Inha University Hospital, Incheon City, Incheon, Republic of Korea.

Background: Regular vascular access blood flow (Qa) surveillance is recommended to detect graft or fistula stenosis. However, published studies have reported conflicting results of its utility that led healthcare professionals to doubt the benefits of this surveillance method. We find to access blood flow monitoring lowers the risk of AV access thrombosis or stenosis and that the outcomes differ between arteriovenous (AVF) fistular and arteriovenous graft (AVG).

Methods: We performed a systematic review of the available literature according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. An electronic search was conducted using the MEDLINE, EMBASE, and Cochrane Library databases from 1980 to 2017 for 9 RCTs involving dialysis access blood flow measurement. All studies combined included a total of 981 patients with hemodialysis vascular access of whom 649 had AVF and 332 had AVG.

Results: The estimated overall pooled risk ratio (RR) of thrombosis was 0.782 (95% confidence interval [CI], 0.553 to 1.107) favoring access blood flow monitoring. The pooled RR of thrombosis were 1.104 (95% CI, 0.672 to 1.816) in the AVG group. However, ln AVF subgroup, the pooled RR of thrombosis statistically significant decrease surveillance group 0.562 (95% CI, 0.346 to 0.915).

Conclusions: The benefit of AV access surveillance using access blood flow monitoring to lower the risk of thrombosis is uncertain in AVG, whereas the risk of thrombosis is significant in AVF. But, using access AVF surveillance is effective method in hemodialysis patients.

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

604
**FR-PO778**

**Efficacy of Peri-Vascular Anesthesia in Dialysis Access Procedures – Experience from Saudi Arabia**

**Danyal Hassan, DaVita Saudi Arabia, Jeddah, Saudi Arabia.**

**Background:** Early and late venous stenosis within a dialysis access is a common complication requiring endovascular intervention. These procedures are typically done under sedation because of pain and discomfort to the patients. On the other hand use of sedation is associated with higher risk of complications.

**Methods:** We describe the use of peri-vascular local anesthesia (PVA), in a free standing vascular access center (VAC), to treat area of stenosis in dysfunctional dialysis access. The area of the stenosis was identified using standard anogram and PVA was provided under ultrasound guidance. The pain experienced by the patients was recorded on a numeric score from 0-10; during the procedure and at the time of discharge. This was then divided into adequate, moderate and poor pain control.

**Results:** Data was collected for 83 patients who underwent 112 encounters over a period of 15 months. Mean age of the patients was 54 years, with 51% male patients. There were 54 cases of outflow stenosis, 34 inflow stenosis, 10 cases of both inflow and outflow stenosis treated during the same procedure, and 14 thrombectomy cases including 12 AVF thrombectomy and 2 AVG thrombectomy. During procedure 4 covered stents were placed, 2 of them to treat complications. Overall adequate pain control (0-3) during the procedure was achieved in 91 patients (81%), moderate pain control in 16 patients (14.2%) and poor pain control in 5 patients (4.4%). Post procedure 97% of the patient reported adequate pain control and 3% reported moderate pain control. For thrombectomy procedures 6 (43%) patients reported adequate, 6 (43%) reported moderate and 2 (13%) reported poor pain control. Overall procedure success rate was 98%, with 3 procedures related complications including two Grade I hematomas and one Grade II hematoma. In one case the procedure was stopped due to poor pain control, leading to anxiety, chest pain and transfer to the ER. No PVA related complications were reported except for mild local infiltration and erythema.

**Conclusions:** In this series, ultrasound guided PVA provided good pain control for endovascular procedures in outpatient setting with minimal complications. In case of thrombectomy, PVA should be decided on case to case basis, due to a higher moderate and poor pain control during the procedure.

**FR-PO779**

**Correlation of Intradialytic Blood Pressure Variability with Vascular Access Outcomes in Hemodialysis Patients**

**Hye mi Seo, Hyunwoo Kim, Ji young Kim, Muyeon Kim. Jeju National University Hospital, Jeju City, Republic of Korea.**

**Background:** Hemodialysis vascular access dysfunction is a major cause of morbidity and hospitalization in patients on hemodialysis. Identifying risk factors of vascular access failure is important because it will likely allow early intervention for dysfunctional hemodialysis fistulas. Recent studies has shown that blood pressure variability during dialysis is associated with increased cardiovascular morbidity and mortality. But there have been no studies related to effect of intradialytic BPV on vascular access outcomes. This study aimed to investigate the correlation of intradialytic BPV with vascular access outcomes in hemodialysis patients.

**Methods:** We examined 130 end stage renal disease patients with created vascular access between January 2009 and December 2016 in our hospital. Blood pressure data were collected three month after the start of hemodialysis for adaptation period. We examined 12 dialysis session per patient and recorded five times blood pressure for each session. Blood pressure variability (BPV) was assessed using the standard deviation of the residual derived from linear regression model. The primary outcome was primary vascular access patency defined as time to first intervention including angioplasty or surgical revision. Cox proportional hazards regression analysis was used to access the risk of primary outcome (reintervention) or secondary outcome (failure).

**Results:** Patients were followed up an average of 3.7 years. Patient’s mean age was 62 years. Among these, 64% of patients were male, 53% of patients had DM. We devided patients into two groups according to intradialytic blood pressure variability. The mean time to primary patency of high BPV group was 131 days and low BPV group was 131 days. After adjustment for demographics, comorbidities and medications, high BPV was significantly associated with worse primary outcome (HR, 2.30; 95% CI 1.39-3.82; p = 0.01) and worse secondary outcome. (HR,2.81; 95% CI 1.14-6.93; p = 0.03).

**Conclusions:** We observed a significant correlation between intradialytic BPV and vascular access patency. Lowering Intradialytic BPV is important to improve vascular access patency in hemodialysis patients.

**FR-PO780**

**Association between Post-Dialysis Hemoglobin Level and the Survival of Vascular Access**

**Hiroki Nishikawa,1 Takeshi Hasegawa,2 Naoto Tominaga,2 Masahiko Yazawa,3 Hiroo Kawarazaki,4 Tatsuyoshi Ikemouc,5 Yugo Shibagaki,2 Shingo Fukuma,4 Shunichi Fukuhara.1 Division of Nephrology and Hypertension, Department of Internal Medicine, St.Marianna University School of Medicine, Kawasaki, Japan; 2Division of Nephrology and Hypertension, St Marianna University Hospital, Kawasaki, Japan; 3Georgetown University Medical Center, Washington, DC; 4Kyoto University, Kyoto, Japan; 5Kyoto University Graduate School of Medicine and Public Health, Kyoto, Japan; ‘None, Tokyo, Japan; ‘Showa University Fugijoho Hospital, Yokohama, Japan.**

**Background:** Although a few dialysis facilities conduct a complete blood cell count for some patients at post-dialysis, including hemoglobin, clinical findings supporting the interpretation of these results are scarce. The aim of this study was to investigate the association between post-dialysis hemoglobin level and vascular access failure with clinical data.

**Methods:** Study Design: Case crossover design Setting: Japanese dialysis facilities which routinely take post-dialysis blood samples, including complete blood cell counts at least once a month. Participants: Hemodialysis patients who experienced vascular access failure in Jan. 2010- Dec. 2014. Exposure: Post-dialysis hemoglobin level Main outcome: Vascular access failure treated with endovascular treatment or operation. Statistical analysis: Self-matched odds ratios and 95% confidence intervals were estimated by comparing post-dialysis hemoglobin just before events (“case”) with levels at 6 and 12 months before events (“control”) using conditional logistic regression, and presented with restricted cubic spline.

**Results:** 230 hemodialysis patients with vascular access failure were identified. Mean post-dialysis hemoglobin level before the failure was 11.8 g/dl (standard deviation 1.7). The spline curve showed that higher post-dialysis hemoglobin levels above 11.8 g/dl had a greater odds ratio for vascular access failure. Post-dialysis hemoglobin levels and odds ratios (95% Confidence Interval) for vascular access failure relative to the reference value (Hb 11.6 g/dl) were Hb 12.0 g/dl, 1.1 (1.0-1.1), Hb 14.0 g/dl, 3.3 (1.3-8.3); and Hb 16.0 g/dl, 12.7 (3.8-89.4).

**Conclusions:** A higher post-dialysis hemoglobin level was associated with vascular access failure. Higher post-dialysis Hb could be a factor which triggers vascular access failure.

**FR-PO781**

**Changes in Upper Body Blood Flow after AV Fistula Creation in Hemodialysis Patients**

**Israel Campos,1 Hanjie Zhang,2 Priscilla Preciado,1 Stephan Thijsen,1 Peter Kotanko.1 1Renal Research Institute, Morelia, Michoacan, Mexico; 2Renal Research Institute, New York, NY.**

**Background:** Hemodynamic changes occurs after AV fistula (AVF) creation. Cardiovascular adaptive mechanisms allow adequate AVF maturation, usually accompanied by an increase in cardiac output (CO). In hemodialysis (HD) patients with a central-venous catheter (CVC), upper body blood flow (UBBF) can be estimated [Campos et al., WCN 2017]. UBBF is expected to increase after AVF placement in the presence of normal AVF maturation and adequate adaptation.

**Methods:** We estimated UBBF around AVF creation using averaged central-venous oxygen saturation and hemoglobin data from the Crit-Line® Monitor (CLM) (FMC, Waltham, MA) in HD patients from Renal Research Institute clinics. Brain mass was calculated using the Mehrpour formula [J Forensic Leg Med. 2010]. Arm muscle mass was set at 2.3kg for males and 1.2kg for females [Abe T, Br J Sports M. 2003]. Tissue-specific O2 consumption rates were taken from Sokoloff L [Handbook of Physiology. 1969]. Arterial O2 saturation was taken from a large HD population [Meyring-Wösten, CJAASN. 2016]. We compared the four closest UBBF values before AVF creation, the first three UBBF estimates after AVF creation and the last three UBBF estimates before first AVF creation.

**Results:** We analyzed 12 patients (8 males), mean age 60±12 y. While individual UBBF trajectories differed between patients, UBBF did rise on average after AVF creation (Figure). The average UBBF before and after AVF creation was 1.21±0.03L/min, and 2.15±0.76L/min respectively, and UBBF before the first AVF creation was 2.06±0.62L/min.

**Conclusions:** Hemodynamic changes related to AVF creation can be detected non-invasively in HD patients using the CLM. As expected, UBBF increases on average after AVF creation. A prospective study with AVF flow rate measurements alongside UBBF estimation would be insightful and help define the expected UBBF trajectory in well-maturing AVFs.
**FR-PO782**

Characteristics of Permanent Vascular Access of Young Children (≤12 Years Old) on Chronic Hemodialysis

**Background:** Hemodialysis (HD) is the most commonly used dialysis modality in children with end stage renal disease. Because of perceived proximity to transplantation and smaller blood vessels in children, central venous catheters (CVC) remain the most commonly used access for children in the United States and are more frequently used over a permanent access: either an arteriovenous fistula (AVF) or arteriovenous graft (AVG). The aim of this study was to compare efficacy and complications of these HD accesses in young children.

**Methods:** This was a retrospective chart review of patients who started chronic HD at age ≤12yo from 2008 to 2016. Data collected and compared included age and weight of the patient, infectious and non-infectious complications and hospital admissions related to the access; as well as treatment characteristics at 6 months including adequacy of dialysis (Kt/V), hematocrit, albumin, erythropoietin dose and calcium dose.

**Results:** There were 39 accesses used by 19 patients (16 CVC’s, 16 AVF’s and 7 AVG’s). Medians were 8 years (1 – 12) for age and 23-4kg (6.6 – 110) for weight. Median days on HD per patient was 696 (317 – 1826). Treatment characteristics at 6 months showed that Kt/V was 2 for permanent access and 1.42 for CVC (p=0.03). Albumin and hematocrit were not significantly different between the 2 groups. Patients with CVC required 33% more erythropoietin and 100% more calcium than the patients with permanent access, however, this difference was not statistically significant. Patients using permanent access had lower rates of infectious complications, total complications, hospital admissions and shorter hospital stays (p=0.01 for all categories).

**Conclusions:** Commitment to using permanent access (AVG or AVF) in young children on chronic HD led to more cost-effective care in view of decreased complications, hospitalizations and better adequacy of dialysis.

**Access Related Complications per 100 Days of HD (mean)**

<table>
<thead>
<tr>
<th>Complications</th>
<th>CVC</th>
<th>AVG</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloodstream infections (BSI)</td>
<td>0.64</td>
<td>0.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital days spent due to BSI</td>
<td>2.34</td>
<td>0.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admissions related to access complications</td>
<td>0.05</td>
<td>0.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total complications</td>
<td>0.05</td>
<td>0.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital days related to access</td>
<td>3.05</td>
<td>1.21</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**FR-PO783**

Impact of a Compressive Therapy via Arm Sleeve on High Flow Arteriovenous Fistula and Cardiac Output in Patients with ESRD

**Background:** Heart failure is among cardiac complications in patients with end-stage renal disease (ESRD) undergoing hemodialysis via arteriovenous fistula (AVF). AVF creation may result in several cardiac dysfunctions, such as increase of left ventricular end-diastolic diameter, left ventricular hypertrophy, and high output heart failure, particularly in patients with AVF flow over 2000 ml/min. Surgical reduction of AVF to improve cardiac dysfunctions may often result in complications, such as access thrombosis. Thus, we suggest non-invasive compressive method via arm sleeve to reduce blood flow of high flow AVF.

**Methods:** Data were collected from total 30 patients with ESRD and high flow AVFs. All patients have autologous AVFs and have undergoing hemodialysis of three times sessions per week. All patients also have high flow AVFs with blood flow rate over 1200 ml/min. Arm sleeve (Nambuk Surgical®, Seoul, Korea) with pressure of 30-40 mmHg was applied during 8 hours on non-hemodialysis dates for three months in only fifteen patients. We performed comparative analysis for changes of AVF flow rates, cardiac output, change of edema after application of arm sleeve in two groups.

**Results:** The average change of AVF flow rate in group which arm sleeve was applied was –60 ml/min. On the contrary, average change of AVF flow in control group was 19.33 ml/min. The average AVF flow rate in group which arm sleeve was applied decreased statistically significant. (p<0.001) Also, arm edemas decreased significantly in group which arm sleeve was applied. (-0.28 ± 0.28 vs 0.23 ± 0.26, -0.32 ± 0.25 vs 12 ± 0.24, -0.36 ± 0.37 vs 0.31 ± 0.21, -0.37 ± 0.30 vs 0.31 ± 0.32, and -0.45 ± 0.34 vs 0.33; p<0.001) We analyzed changes of cardiac output. However, there was no significant difference concerning of change of cardiac output in two groups. (-0.01 ± 0.005 vs 0.005 ± 0.17, p=0.091)

**Conclusions:** The non-invasive compressive method reduced arm edema and AVF flow rate in patients with high flow AVFs. High flow rate over 2000 ml/min of AVF can be a factor of development of high output heart failure in patients with AVFs. Although there was no an effective impact of the non-invasive compressive method on cardiac output, reduction of edema and AVF flow rate might inhibit development of high output heart failure in patients with high flow AVFs.

**FR-PO784**

Acute Free Dialysis and Mortality in the French Renal Epidemiology Information Network Registry (REIN)

**Background:** We previously found a reduced mortality associated with the use of acute free dialysis (AFD) in subjects older than 70 years old. As the use of these dialysis modalities are more used with chlorhexidine or citric acid steadily increases since 2010, we wonder whether this result can be reproduced in the last recent years.

**Methods:** All patients who started HD from 2010 to 2013 were classified according to their exposure to AFD: exposed in a 100% AFD dialysis center, exposed in a mixed center (both standard and AFD) and exposed in standard center. Cox survival analysis was performed in 26 304 incident patients, adjusted for 15 baseline co-morbidities and biological data and accounting for patient clustering within facilities. Exposure to AFD and baseline characteristics (HDF) status were analyzed as time-dependent variables. Analysis was censored at Dec 31, 2014, or at kidney transplantation, lost to follow-up, dialysis weaning or transfer to peritoneal dialysis. The Cox model was used for the overall population and by age group, <70 or ≥70 years.

**Results:** During the study period, 12124 subjects were exclusively dialyzed in centers with standard dialyse, 380 in 100% AFD centers, 7538 in mixed centers and 6481 had a change in their AFD exposure. Being dialyzed in mixed centers was associated with a mortality HR of 0.47 (0.4-0.6) for subjects <70 years of age and of 0.57 (0.52-0.62) for those ≥70. Being dialyzed in 100% AFD centers was associated with a mortality HR of 0.80 (0.59-1.09) for subjects <70 years old and of 0.68 (0.54-0.87) for those ≥70. The Cox on the overall population found a mortality HR of 0.56 (0.51-0.61) for being dialyzed in mixed centers and of 0.73 (0.6-0.89) for 100% AFD centers.

**Conclusions:** Using an entirely new data set of subjects exposed to AFD in the REIN registry, we confirm that being dialyzed with AFD is associated with a reduced mortality risk. In a larger AFD exposed population, the mortality reduction seems more constant with age.

**FR-PO785**

Forecasts for 2030 for the ESRDdialysis Workforce in the US

**Background:** The continued rise in patients requiring renal replacement therapy impacts the ESRD/dialysis workforce demand. We aimed to estimate for 2030, on the demand side, the number of patients requiring dialysis; and on the supply side, workforce requirements for nephrologists, nurses (registered nurses and advanced practice nurses) and technicians (licensed practical/vocational nurses and dialysis technicians).

**Methods:** We forecasted the demand and supply sets using time series analysis with autoregressive integrated modeling (ARIMA). We used annual 2008-2014 USRDS data for the number of dialysis patients, dialysis centers, and FTE nurses and technicians; and 2008-2016 ASN data for nephrologists. We assumed similar dialysis practice patterns in 2014 and 2030.

**Results:** Forecasting models projected the following for 2030; all with adequate to substantial goodness-of-fit. On the demand side, 689693 patients and 9911 centers. On the supply side 13107 nephrologists, 51381 FTE nurses, and 62243 FTE technicians. By 2030 the ratio of patients:nephrologist will have increased to 52.6:1; of patients:nurse to 13.4:1; and of patients:technician to 11.1:1. The supply differential of nephrologists is projected to be 9.65 shortage; of nurses to 11.0 surplus; and of technicians -1976 short.

**Conclusions:** Significant shortages of nephrologists and FTE technicians are anticipated by 2030 to meet the demand of patients requiring dialysis and the centers providing this dialysis. The shortage in centers can be addressed by enhanced operational efficiency and increased volume, but the latter is constrained by the need for geographically equitable access. Though the emerging use of advanced practice nurses may enable shifting some responsibilities from nephrologists, in general nurses can assume few if any nephrologists’ responsibilities. In addition to potentially being inappropriate professionally, wage differences make nurses fulfilling tasks of technicians economically not feasible. Funding for nephrology fellowship training needs to be
diversified and recruitment intensified (internationally; while novel training programs between the dialysis sector and community/technical colleges are required to address the technician demand.

FR-PO786

Relative Blood Volume Changes and Mortality among Hemodialysis Patients

Priscila Preciado, Hanjie Zhang, Stephan Thijssen, Peter Kotanko. Renal Research Institute, New York, NY.

Background: Ultrafiltration during hemodialysis (HD) is the only means to remove excess fluid. In most HD sessions the ultrafiltration rate exceeds the refilling rate (UFR), leading to decreased blood volume and potentially intradialytic hypotension and increased morbidity. While relative blood volume (RBV) monitoring is widely used, the relationship between RBV levels and outcomes is ill-defined.

Methods: Retrospective multi-center study in HD patients from 17 Renal Research Institute (RRI) clinics between 1/2012-12/2016. A 6-months baseline period preceded follow-up period. Hematocrit-based RBV was reported 1x/minute by the Crit-Line® Monitor (CLM; Fresenius Medical Care, Waltham, MA). Hourly RBV levels were defined as the mean RBV between treatment minutes 50 and 70,110 and 130, and 170 and 190. The relationship between mortality and hourly RBV levels was analyzed using Cox proportional hazards models with spline terms.

Results: We included 842 patients with 28,119 HD treatments (mean age 61.0±14.8 years, 50% whites, 62% males, 56% diabetes mellitus, 22% congestive heart failure). Median follow-up was 2.7 years. Hazard ratios for all-cause mortality were significantly reduced in patients who achieved RBV levels [%] of 93-96 at 1 hour, 89-94 at 2 hours, and 86-92 at 3 hours. Subgroup analysis by age, gender, race, comorbidities, pre-HD blood pressure, and UFR showed similar results.

Conclusions: To our knowledge this is the first study to examine the relationship between achieved intradialytic RBV levels and all-cause mortality in a large and diverse HD population. Our key finding is the association of specific RBV levels with reduced outcomes. Prospective studies are warranted to test the hypothesis that attainment of these levels improve outcomes.

Fig. 1 Spline analysis of hazard ratio for all-cause mortality as a function of RBV after 1, 2, and 3 hours.

FR-PO787

Effects of Post-Dilution High Volumes On-line Hemodiafiltration in Comparison to High-Flux Hemodialysis: A One-Year Prospective and Controlled Study

Fernando F. Hadad-Arrascue,1,2 Gabriela I. Pimentel,1,2 Barbara Fernandez-Lopez,2,2 Maria D. Algaba,2 Marisol Poma tapia,2 1Nephrology, Clinica RTS Murcia VII, Murcia, Spain; 2Nephrology, Hospital Universitario Reina Sofia, Murcia, Spain; 3Nephrology, Hospital Universitario San Carlos, Madrid, Spain.

Background: It is suggested that post-dilution on-line Hemodiafiltration (OL-HDF) may improve clinical outcomes. Currently, the world-wide acceptance of HDF is low because higher costs and its benefits have not been well demonstrated. The aim of this prospective and controlled study was to compare the effects of post-dilution OL-HDF and conventional high-flux HD during one year.

Methods: One-hundred fifteen clinically stable HD patients were randomized in two groups: OL-HDF group (55 patients, ages 29-81 years, mean time on dialysis 5.2 years) and HD group (60 patients, ages 39-95 years, mean time on dialysis 6.5 years). All patients were scheduled sessions three weekly with a stable arteriovenous fistula, blood flow rate (QB) 364 ml/min (316-410 ml/min) in OL-HDF and QB 356 ml/min (306-400 ml/min) in HD. The same Polysulfone membrane high-flux dialysers and Artis Physio dialysis machines for both groups were used during the entire study period. OL-HDF procedure was performed in the post-dialution mode and the substitution volume was targeted to be above 20 L per session.

Results: During follow-up, there were no significant differences in mean hemoglobin (11.7±1.5 g/dl OL-HDF vs. 11.7±1.45 g/dl HD), mean transferrin saturation (24.6±14.3% OL-HDF vs. 22.9±16.4% HD), but the mean prescribed erythropoietin (EPO) dosage was significantly lower in OL-HDF than HD (14676±2889 vs. 1530±4550 U/month, P<0.05). The mean prescribed intravenous iron dosage was not different among the groups. OL-HDF had lower the mean ferritin (483.3±45.7 ng/ml vs. 601.6±35.6 ng/ml, P<0.005), mean high-sensitivity C-reactive protein (0.42±0.91 mg/dl vs. 0.62±1.5 mg/ dl), mean intact parathyroid hormone (327.09±45.7 pg/mL vs. 346.95±35.6 pg/mL, P<0.05), and mean intact pituitary hormone (35.6±6.9 mg/dl vs. 30.8±7.5 mg/dl, P<0.05). There were no significant differences in mean potassium, mean calcium, mean alkaline phosphatase, and mean creatinine. Moreover, the mean phosphate was significantly lower in OL-HDF than HD (6.20±1.42 mg/dl vs. 6.70±1.42 mg/dl, P<0.05). The mean prescribed intravenous iron dosage was not different among the groups. OL-HDF had lower the mean ferritin (483.3±45.7 ng/ml vs. 601.6±35.6 ng/ml, P<0.005), mean high-sensitivity C-reactive protein (0.42±0.91 mg/dl vs. 0.62±1.5 mg/ dl), mean intact parathyroid hormone (327.09±45.7 pg/mL vs. 346.95±35.6 pg/mL, P<0.05), and mean intact pituitary hormone (35.6±6.9 mg/dl vs. 30.8±7.5 mg/dl, P<0.05). There were no significant differences in mean potassium, mean calcium, mean alkaline phosphatase, and mean creatinine. Moreover, the mean phosphate was significantly lower in OL-HDF than HD (6.20±1.42 mg/dl vs. 6.70±1.42 mg/dl, P<0.05).

Conclusions: Post-dilution OL-HDF is a safe and well-tolerated treatment, increased dialysis dose, reduced inflammation and needed lower requirement for EPO to correct anemia compared with high-flux HD.

FR-PO788

Increased Levels of Extracellular Nucleosomes, Biomarkers of Cell Death, in Stage 5 Chronic Kidney Hemodialysis (CKD5-HD) Are Independent of Circulating Tissue Factor Microparticle Complex

Vinod K. Bansal,1 Trung Phan,1 Ryan McMullan,1 Amanda Walborn,2 Debra Hoppensteadt,1 Jawed Fareed.1 1Loyola University Medical Center, Maywood, IL; 2Loyola University Medical Center, Maywood, IL, IL.

Background: Extracellular nucleosomes in plasma (PNs) are complexes of DNA and histones that are released due to cell death. In both the chronic and acute kidney injury, there is an increased release of nucleosomes with decreased nucleosome clearance. Nucleosomes mediate inflammatory and thrombotic responses and could serve as biomarkers in chronic kidney diseases. Microparticle-associated tissue factor (MP-TF) are released during cell death and mediate thrombotic responses.

Methods: Plasma levels of PNs in CKD5-HD patients (n = 90) and healthy volunteers (n = 50) were measured using the Cell Death Detection ELISA PLUS assay (Roche Diagnostics, Mannheim, Germany). MP-TF levels were measured using the ZYMUPHEN MP-TF kit (Hyphen BioMed, Neuville-sur-Oise, France). The levels of both PNs and MP-TF were also correlated with WBCs, RBCs and platelets to determine the origin of measured PNs.

Results: In comparison to the plasma from healthy volunteers (6.74 ± 13.7 Arbitrary Units (AU)), the levels of PNs in CKD5-HD patients were higher (15.5 ± 14.1 AU; p < 0.0001). Similarly, MP-TF levels were elevated in CKD5-HD patients (3.00 ± 1.24 pg/ mL; p < 0.0001) compared to normal (0.363 ± 0.263 pg/mL). There was no correlation between PNs and MP-TF in CKD5-HD patients (r = 0.077; p = 0.501). Moreover, there was no correlation between PNs and platelets (r = 0.067; p = 0.543) and RBCs (r = 0.083; p = 0.447). However, the PNs showed a positive correlation with WBCs (r = 0.223; p = 0.042). There was no correlation between MP-TF and WBCs (r = 0.037; p = 0.632) and RBCs (r = 0.042; p = 0.722), but a positive correlation was observed between MP-TF and platelets (r = 0.237; p = 0.042).

Conclusions: PNs were elevated in CKD5-HD patients, indicating an increased release of nucleosomes, suggesting increased cell death. The observed correlation between PNs and WBCs suggests that the detected PNs are derived from WBCs. A lack of correlation between PNs and MP-TF suggests that the MP-TF increase is independent of the pathophysiological processes responsible for abnormal PN generation in CKD5-HD patients.

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

607
FR-P0789
The Interdialytic Creatinine Rise Is a Novel Marker of Volume Overload and Mortality Risk in Hemodialysis Patients | Liubomir M. Ilie, Robert S. Brown, Roger B. Davis, Stewart H. Lecker. Beth Israel Deaconess Medical Center, Boston, MA.

Background: Volume overload is a major contributor to morbidity and mortality in maintenance hemodialysis (HD) patients. Since serum creatinine increases between HD treatments, we theorized that the Interdialytic Creatinine Rise (IDCR), a change dependent upon net creatinine retention and dilution by fluid intake, might be useful to evaluate volume overload and predict patient mortality. IDCR is calculated using two serum creatinine values from the same interdialytic period obtained at least 18h apart.

Methods: Three analyses were undertaken. A prospective cohort of 47 maintenance HD patients admitted to our hospital had IDCRs measured serially over a period of one week. IDCR change with time and after HD sessions were analyzed using mixed effects model. A prospective cohort of 25 outpatient maintenance HD patients was followed for 2 weeks with determination of the sensitivity and specificity of different IDCR cutoff values using patient volume assessments by their nephrologist as the gold standard. A retrospective cohort of 39 maintenance HD patients was studied longitudinally during inpatient admissions from 2012 until 2017 or death. The data were analyzed using Cox proportional hazards model with IDCR as a time varying covariate. In the same cohort, mixed effects logistic regression was used to correlate IDCR with mortality risk.

Results: IDCR decreases by ~0.014 per day without HD (95%CI -0.017, -0.010; p<0.001) due to volume gain. IDCR increases by 0.013 from before to after each successive hemodialysis session (95%CI 0.008, 0.017; p<0.001) due to fluid removal by ultrafiltration. IDCR cut-off value of 0.1 mg/dL/h has a sensitivity of 82%, specificity of 79%, and accuracy of 80% in diagnosing volume overload with AUC of ROC curve −0.78 (95%CI 0.39, 0.97). The hazard ratio of death for each 0.01 mg/dL/h decrease in IDCR is 1.64 (95%CI 1.31, 2.07; p<0.001). If IDCR decreases to less than 0.05 mg/dL/h, the hazard ratio of death within 2 months is 38 (95%CI 8, 131; p<0.001).

Conclusions: IDCR decreases with volume retention, can help detect volume overload, and has excellent prognostic value in identifying HD patients who are at high risk of dying over the following 60 days.

FR-P0790
The Effect of Isohydric Hemodialysis on Uremic Retention Solutes | Jerome Lownes,1,2 Aleksey Etinger,3 Sumit R. Kumar,2 William Ackley,1 Leland R. Sieser,1 Eric B. Grossman,2 Albert Mataloni,3 Robert Holzman,1 Bjorn Meijers,1 New York Medical College, New York, NY; 1New York University School of Medicine, New York, NY; 2Yale New Haven Hospital, New Haven, CT; 3University Hospitals Leuven, Leuven, Belgium; 4NYU School of Medicine, New York, NY.

Background: There is growing evidence that the accumulation of protein-bound uremic retention solutes, such as indoxyl sulphate (IS), p-cresyl sulphate (PCS) and kynurenic acid (KA), play a role in the accelerated cardiovascular disease seen in patients undergoing chronic hemodialysis. Protein-binding, presumably to albumin, renders these solutes poor-dialyzable. We had previously observed that the concentration of free solute and its unbound fraction were markedly reduced at the end of hemodialysis. We hypothesized that solute binding might be pH-dependent and the changes attributable to the higher serum pH at the end of hemodialysis. In vitro, acidification of uremic plasma to pH 6.0 decreased the concentration of unbound (free) uremic solutes and resulted in a clearcut separation of blood pH and bicarbonate concentrations throughout.

Methods: We tested our hypothesis by reducing the dialysate bicarbonate buffer concentration to 25 mEq/L for the initial half of hemodialysis (“isohydric dialysis”). Eight hemodialysis patients underwent “isohydric dialysis” and, midway, were switched to standard buffer (37 mEq/L). A second dialysis, 2 days later, employed standard buffer throughout.

Results: We found a clearcut separation of blood pH and bicarbonate concentrations 90 minutes following “isohydric dialysis” (pH~ 7.37, HCO3~22.4 mEq/L) and standard dialysis (pH~ 7.49, HCO3~ 29.5). Analysis of free and bound concentrations of uremic retention solutes confirmed our prediction that binding of solute is affected by pH. However, in mixed models analysis, we found that the reduction in total uremic solute concentration during dialysis accounted for a greater proportion of the variation in free concentration, presumably an effect of saturation binding to albumin, than did the relatively small change in pH produced by isohydric dialysis.

Conclusions: These findings suggest that modification of dialysis technique that would expose blood to a transient decrease in pH might increase the free fraction of solute and enhance the efficacy of hemodialysis in the removal of protein-bound uremic retention solutes.

FR-P0791
Intra-Dialytic Syndrome and Time to Recovery in Patients on In-Center Hemodialysis | Luis Alvarez,1,2 Sarah S. Prichard,1 Dean Hu,3 Glenn M. Chertow.1 1Stanford University School of Medicine, Palo Alto, CA; 2Advisor role, Outset Medical, San Jose, CA; Nephrology, Palo Alto Medical Foundation, Palo Alto, CA; Outset Medical Inc, San Jose, CA; Outset Medical, San Jose, CA.

Background: Patients on hemodialysis (HD) experience a variety of symptoms during dialysis described here as Intradialytic Syndrome (IDS). Patients also feel unwell for a period of time post HD. The purpose of this study was to assess frequency and severity of intradialytic symptoms and time to recovery post dialysis in a broad cross section of HD patients.

Methods: An online questionnaire was sent to patients in the National Kidney Foundation database via email. Patients included were adults on in-center hemodialysis 3 times/week for 3 or more months. Demographic and basic clinical data were obtained. A 12-item symptom questionnaire asked about the type and severity of symptoms during HD sessions in the previous week. Severity was rated on a 5-point Likert scale - 1 "not severe" to 5 "very severe". It also asked how long it took to resume normal activities post dialysis, if they ever stopped dialysis early because of intradialytic symptoms, and for which symptoms they stopped.

Results: 5,000 e-mails were sent. 98 patients met the screening criteria and completed the questionnaire. Mean age 65±5 yrs, 39% female, 61% male, 65 White, 28 Black, 3% Asian American, 46% diabetic, 35% history of coronary artery disease, and 87% with hypertension (100% on med). 88% had intradialytic symptoms in the previous week, with a mean severity of 2.7 (range: 1 - 5). The most common adverse events are shown in Table 1: The median (10%, 90%) time to recovery and resume normal activities was 180 minutes (30 minutes, 13 hours). 35% reported having stopped dialysis early for symptoms. The most common symptom-related reasons to stop dialysis were cramps and low blood pressure.

Conclusions: 88% of a broad based sample of in-center HD patients reported having symptoms during dialysis. Because intradialytic syndrome can cause patients to terminate dialysis prematurely, innovation in dialysis should target reducing these symptoms.

Funding: Commercial Support - Outset Medical Inc.

Table 1

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Proportion of patients experiencing intradialytic symptoms in the past week</th>
<th>Severity (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue/feeling drained</td>
<td>52%</td>
<td>2.4</td>
</tr>
<tr>
<td>Cramps</td>
<td>48%</td>
<td>2.1</td>
</tr>
<tr>
<td>Low BP/hypotension</td>
<td>41%</td>
<td>2.1</td>
</tr>
<tr>
<td>Headaches</td>
<td>28%</td>
<td>2.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>20%</td>
<td>2.8</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>17%</td>
<td>1.9</td>
</tr>
</tbody>
</table>

*For patients reporting symptoms

FR-P0792
Exploring Walking Pace, Physical Activity, and Readiness to Change in ESRD | Eytan J. Highton1, Amy A. Clarke1, James Burton2, Alice C. Smith2. 1University of Leicester, Leicester, United Kingdom; 2John Walls Renal Unit, Leicester General Hospital, Leicester, United Kingdom; 3Loughborough University, Leicester, United Kingdom.

Background: Reduced physical function and walking speed in end stage renal disease (ESRD) patients are associated with increased morbidity and mortality and high healthcare costs. Physical activity (PA) and regular exercise may optimize physical function, but the majority of ESRD patients are sedentary. This study explored walking speed, PA and exercise, and readiness to change exercise behavior in patients on haemodialysis (HD).

Methods: 1156 patients (M: F 1.8:1, median (IQR) age 63.01(21.00) years) from 16 disparate HD networks completed a series of validated questionnaires: GP Physical Activity Questionnaire (GPPAQ) providing Physical Activity Index [PAI] and Walking Speed [WS], Leisure Time Exercise Questionnaire (LTEQ), providing an Exercise Health Contribution Score (HCS) based on METS) and Stage of Change Questionnaire (SoCQ), defining readiness to change exercise behavior.

Results: The distribution of PAI, WS, HCS and SoC are shown in Table 1. Walking speed is positively associated with older age, female sex (P=0.01) and lower dialysis vintage (P<0.05), and positively associated with behavioural factors (physical activity, leisure time exercise), and readiness to change (all P<0.01).

Conclusions: GPPAQ and LTEQ responses highlight the inactive lifestyle of HD patients. The majority have slow walking speed which is a strong predictor of poor outcome and indicates the need for functional improvement. Exercise interventions have been shown to improve walking speed in older frail adults and may be beneficial for ESRD patients. However, walking speed was positively associated with stage of change indicating that the most vulnerable patients (slow walking pace, older age, female, low PA) may require targeted support to engage in exercise programmes to improve outcomes.

Funding: Private Foundation Support

Table 1 Distribution of Physical Activity Index, Walking Speed, Exercise Health Contribution Score and Stage of Change in HD patients

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>HD patients in each category (n (%))</th>
<th>PAI</th>
<th>Moderate Active</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPPAQ</td>
<td></td>
<td>977 (19.2)</td>
<td>792 (7.9)</td>
<td>551 (5.5)</td>
</tr>
<tr>
<td>Slow</td>
<td>736 (43.7)</td>
<td>266 (25.0)</td>
<td>194 (19.4)</td>
<td>81 (8.1)</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td>1156 (62.0)</td>
<td>202 (20.0)</td>
<td>86 (8.6)</td>
</tr>
<tr>
<td>Active</td>
<td></td>
<td>57 (5.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| LTEQ                   |                                      | 42 (9.1) | 37 (9.1) | 38 (9.1) |
| HCS                    |                                      | 480 (46.6) | 132 (12.0) | 203 (19.9) | 485 (45.7) | 128 (12.0) |
| SoCQ                   |                                      | 57 (5.9)   |            |          |

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
FR-PO793

Intradialytic Systolic Blood Pressure and Hemodynamics Are Predominantly Controlled by Baroreflex Mechanisms. Dvorak Rubinger, Michal Dranitski Elhalel, Dan Sapoznikov. Hadassah University Medical Center, Jerusalem, Israel.

Background: Systolic blood pressure (SBP) is believed to be controlled by both baroreflex (BARO) and non-baroreflex (NON-BARO) sympathetically mediated central mechanisms.

Methods: To assess the relative contribution of these mechanisms during hemodialysis (HD), beat-to-beat SBP and interbeat interval (IBI) monitoring using Finometer device. BARO was performed during a 4 hr regular HD session in 51 non-diabetic patients, age 52±16 y. BARO and NON-BARO activity episodes were evaluated by the calculation of the slope of between IBI and SBP in 1 min sequences; a positive correlation coefficient (r>0.5) was considered to be representative of BARO activity, whereas a negative correlation was considered to represent NON-BARO sympathetic activity. LFC coefficient, a measure of predominantly BARO function was calculated as the square root of the ratio between average IBI power and average SBP power in the low frequency band (0.04-0.15 Hz). Cardiac output (CO), stroke volume (SV) and total peripheral resistance (TPR) were calculated using the Modelflow simulation method.

Results: The averaged variables for the 1st and the 4th HD hr (median and interquartile range) are shown in Table 1 (see table below) During HD, LFC increased from 3.76 (2.34) in the 1st to 4.17 (3.37) the last hr (p=0.013).

Conclusions: Our data show: 1. At the beginning of HD, SBP is dually controlled by both BARO and NON-BARO mechanisms. 2. During ultrafiltration, the maintenance of constant SBP is achieved by predominant BARO activation. 3. The decrease in CO and SV during ultrafiltration is compensated by an increase in TPR. In the intradialytic hemodynamic stability seems to be dependent on the adequacy and the strength of the BARO response.

Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HD 1st hr</th>
<th>HD 4th hr</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>113 (77)</td>
<td>110 (76)</td>
<td>NS</td>
</tr>
<tr>
<td>IBI (ms)</td>
<td>800 (137)</td>
<td>790 (131)</td>
<td>NS</td>
</tr>
<tr>
<td>% BARO episodes</td>
<td>65 (41)</td>
<td>56 (57)</td>
<td>0.93</td>
</tr>
<tr>
<td>% NON-BARO episodes</td>
<td>35 (61)</td>
<td>43 (67)</td>
<td>0.93</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>6.19 (3.80)</td>
<td>5.44 (2.90)</td>
<td>0.00</td>
</tr>
<tr>
<td>SV (l)</td>
<td>0.79 (0.74)</td>
<td>0.73 (0.74)</td>
<td>0.93</td>
</tr>
<tr>
<td>TPR (cmH2O/ml)</td>
<td>0.675 ± 0.531</td>
<td>1.069 ± 0.530</td>
<td>0.00</td>
</tr>
</tbody>
</table>

FR-PO794

Hemodialysis Prescription Patterns in a Large Cohort of Pediatric Patients on Maintenance Hemodialysis. Verona Gotta, 1 Oliver Marsenic, Clovis C. C. Leal, 2 Marc Pietzke, 1 University of Basel Children’s Hospital, Basel, Switzerland; 2 University of Basel Children’s Hospital, Basel, Switzerland, Hilterfingen, Switzerland; 3 Yale University School of Medicine, New Haven, CT.

Background: Hemodialysis (HD) prescription is relatively standardized in adults, compared to children. Limited systematic data on HD prescription behavior in children and adolescents is available. We aimed to provide reference ranges of real-life pediatric HD prescriptions.

Methods: This descriptive cohort study included 53903 HD sessions of 1852 patients <30 years on chronic HD since childhood, receiving thrice weekly HD between 2004 and 2016 in outpatient Davita dialysis (6075 patient-years, 1-29 years, 8.3-168 kg). Median and 10th to 90th percentiles (80% reference ranges) of prescriptions were calculated over age and weight-bands of 10 kg, from median individual prescriptions per year for: blood flow (Qb), dialysate transfer coefficient for urea (Kub), duration of HD session, resulting diaclytic clearance for urea (Kub), and single pool-volume corrected Kt/V (spKt/V). Both absolute and weight-normalized flows were investigated. Means and standard deviation were summarized over five larger age and weight groups.

Results: Prescription parameters were correlated with age and weight, and showed non-linear dependencies. Inter-individual variability was larger between patients of same age (larger reference intervals) than of same weight. Systematic prescription differences were however more pronounced between patients of different weight (see Table). Generally, low-weight patients had higher weight-normalized Qb, Qs, KoA, Ks, and spKt/V. More than 90% (70%) of patients 10-80 kg achieved target spKt/V of ≥1.2 (≥1.4). spKt/V was steadily decreasing with higher weight, with only 75% (36%) of patients 110-120 kg achieving target values of ≥1.2 (≥1.4).

Conclusions: HD prescription components are systematically different in children compared to adults, with smaller patients routinely receiving more intensified treatments. Adolescents and young adults with weight >80 kg appear to be at higher risk of receiving suboptimal HD treatment as compared to children ≤80 kg.

Weight | ≤20kg | 20-40kg | 40-60kg | 60-75kg | 75-100kg | >100kg | ≥120kg |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Qb (l/min)</td>
<td>8.29±0.6</td>
<td>7.82±0.6</td>
<td>7.56±0.7</td>
<td>7.48±0.8</td>
<td>7.18±0.8</td>
<td>7.02±1.0</td>
<td>6.81±1.0</td>
</tr>
<tr>
<td>Qs (l/min/kg)</td>
<td>20.69±0.8</td>
<td>15.34±2.2</td>
<td>11.56±1.1</td>
<td>12.50±1.4</td>
<td>11.54±1.4</td>
<td>11.10±1.4</td>
<td>10.81±1.4</td>
</tr>
<tr>
<td>Kub (l/min/m²)</td>
<td>22.59±2.1</td>
<td>20.53±3.2</td>
<td>18.53±1.0</td>
<td>17.83±1.2</td>
<td>20.52±1.6</td>
<td>19.34±2.1</td>
<td>17.69±2.1</td>
</tr>
<tr>
<td>KoA (mg/min/m²)</td>
<td>5.61±0.4</td>
<td>5.30±0.3</td>
<td>4.74±0.7</td>
<td>5.15±0.5</td>
<td>4.94±0.5</td>
<td>4.34±0.5</td>
<td>3.94±0.5</td>
</tr>
<tr>
<td>Duration (hrs)</td>
<td>3.64±0.3</td>
<td>3.93±0.3</td>
<td>4.72±0.1</td>
<td>4.60±0.2</td>
<td>4.78±0.2</td>
<td>4.37±0.1</td>
<td>4.37±0.1</td>
</tr>
<tr>
<td>spKt/V</td>
<td>1.09±0.3</td>
<td>1.03±0.3</td>
<td>0.95±0.2</td>
<td>1.06±0.2</td>
<td>1.04±0.2</td>
<td>1.00±0.2</td>
<td>1.03±0.2</td>
</tr>
</tbody>
</table>

mean a standard deviation
FR-PO797
Developing an Organized Approach to Symptom Screening, Assessment, and Management for Hemodialysis Patients in Ontario: A Pilot Project
Alysha Glazer, Marnie MacKinnon, Esti Heale, Carey Moolji, Peter G. Blake, Michael Walsh, Ontario Renal Network, Toronto, ON, Canada; London Health Sciences Centre, London, ON, Canada; McMaster University, Hamilton, ON, Canada.

Background: People living with chronic kidney disease (CKD) requiring dialysis experience a high degree of symptom burden. Symptom assessment, particularly the assessment of chronic symptoms, is not typically done systematically as routine care which may result in a care gap. A provincial approach to routine symptom assessment that can be customized by renal programs may provide an opportunity to improve patient-provider communication and patient experience with dialysis care. To improve the experience of people treated with in-facility hemodialysis and their care team by providing an organized approach to routine symptom screening, assessment, and management.

Methods: Eight Regional Renal Programs in Ontario were selected to participate in a one year pilot project. Participating Programs will routinely assess patients undergoing in-facility hemodialysis with the Edmonton Symptom Assessment Scale Revised – Renal (ESAS-r:Renal), a self-reported symptom questionnaire. The project is being developed by a Task Group with multi-institutional and multi-sectoral representation utilizing a co-design model that engages patients, healthcare providers, and administrators in project planning and development.

Results: Each pilot site has developed a new clinical workflow that includes symptom screening, assessment, and management every four to six weeks. Healthcare providers will be educated on symptom assessment and management through a train-the-trainer approach and the use of evidence-based clinical symptom management guides. Patients will also be educated about the project and use of the screening tool through various resources, including one-on-one education from the care team. Finally, an extensive evaluation framework was developed to guide the evaluation of the pilot project.

Conclusions: This pilot project will help determine the feasibility of a provincial approach to symptom screening, assessment, and management in Ontario. Furthermore, the project will increase awareness of CKD patient symptom burden.

Funding: Government Support - Non-U.S.

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

Underline represents presenting author.

FR-PO799
Effects of Intradialytic Cycling on Exercise Capacity, Quality of Life, and Physical and Cardiovascular Function: A Systematic Review and Meta-Analysis
Hannah M. Young, Daniel S. March, Matthew P. Graham-Brown, Arwel W. Jones, Fionn Curris, Charlotte E. Granthan, Patrick J. Highton, Alice C. Smith, Sally J. Singh, Chris Brile, James Burton, Loughborough University, Leicester, United Kingdom; University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; University of Leicester, Leicester, United Kingdom; University of Leicester and University Hospitals of Leicester NH Ser rehearse, Leicester, United Kingdom.

Background: There is growing interest in intradialytic cycling (IDC), to address a range of health & wellbeing issues associated with haemodialysis (HD). The aim of this systematic review was to identify & synthesise the available evidence on the effects of IDC on exercise capacity, quality of life (QOL), physical & cardiovascular function.

Methods: Databases of published, unpublished & ongoing studies (Medline, EMBASE, CINAHL, LilACS, Web of Science, Sports Discus, PsycINFO, PEDRO, AMED, Cochrane, PROSPERO, DARE, BIOSIS previews, Index to Scientific & Technical Proceedings, Conference Papers Index, CENTRAL, ClinicalTrials.gov) were searched for randomised controlled trials (RCTs) of prevalent adult HD patients, comparing cycle training during HD to usual care. Sources were searched until March 2017 & supplemented by internet, hand searching & consultation with experts. No limits were placed upon publication language.

Results: Fourteen RCTs were eligible, but 5 did not provide data interpretable for use in meta-analyses. The remaining 9 RCTs included 187 participants and the length of IDC interventions ranged from 8-26 weeks. Most studies had an overall high risk of bias. Meta-analysis of available evidence indicated no significant change in VO2 peak (MD 1.14, 95% CI -0.90 to 4.59, p=0.19), physical (mean change -0.06, -0.69 to 0.58 p=0.86) or mental component (mean change 1.68, -6.30 to 9.65 p=0.68) scores of the SF36, or pulse wave velocity (MD -0.36, -1.54 to 0.43, p=0.38) following IDC. IDC did lead to a mean improvement of 85m (25 to 144, p=0.005) on the six-minute walk test. The point estimates for a range of health & wellbeing outcomes were inconclusive due to wide confidence intervals, however, the mean change in SF36 physical component scores (0.16) was consistent with the theoretical range of change for moderate physical activity in the general population.

Conclusions: There is insufficient evidence to support the use of IDC to influence exercise capacity, QOL, cardiac or physical function in practice. The point estimates of the meta-analyses on the 6MWT are greater than the smallest clinically relevant difference, but the imprecision of the individual study estimates means further RCTs are needed. The strength of the evidence could be greatly enhanced via transparent reporting & consensus on validated measures.

Funding: Government Support - Non-U.S.

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

Underline represents presenting author.

FR-PO800
Coronary Artery Bypass Grafting (CABG) Is Not Associated with Worse Outcomes in Dialysis Patients
Sirlei Silva, Rosa M. Moyses, Rosilene M. Elias, Universidad de Sao Paulo, Sao Paulo, Brazil.

Background: CABG is currently a good option of treatment for dialysis patients with multivessel coronary artery involvement. However, whether this population has a higher risk of hospital worse outcomes than patients with normal renal function and patients with chronic kidney disease (CKD) not on dialysis is still debatable.

Methods: This is a prospective observational study to compare hospital mortality of patients who underwent elective CABG. Consecutive non-selected patients were included in the group with normal renal function (control), N=167, CKD with eGFR 30-60 ml/ min (CKD30-60, N=78) and on maintenance dialysis (CKDSD; N=31). Demographic, clinical, biochemical and also fluid balance were evaluated in all patients from the day 1 (surgery) to the day 30 of admission. Surgical Organ Failure Assessment (SOFA) scores at intensive care unit (ICU) admission were also assessed.

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

Underline represents presenting author.

FR-PO798
Numerous Colon-Derived Solutes Are Efficiently Cleared by the Kidney
Robert Mair, Tammy L. Strich, Natalie Plummer, Timothy W. Meyer.

Background: Previous studies have identified solutes derived from colon microbes that are normally excreted in the urine. The current study employed metabolomic analysis to identify additional solutes in this class and profile their renal clearance.

Methods: Samples from patients with total colectomies (n=12) and age matched controls (n=17) were analyzed using an established metabolomic platform. Solutes were considered colon-derived if they met both of the following criteria: 1) mean excretion rate was greater than four-fold higher in individuals with colons than without colons 2) the difference in excretion between the groups was assigned significance with a false discovery rate (q value) < 0.05.

Results: 91 urinary solutes were identified as colon-derived. Of these, 46 were named compounds with known structure and 45 were unnamed compounds without confirmed chemical structure. Only 11 of the 46 named compounds identified as colon-derived in the current study had previously been shown to be colon-derived. Binding to plasma proteins allowed a urinary clearance expression in terms of the free, unbound solute concentration. Plasma levels in normal subjects were sufficient to estimate clearance values for 53 of the 91 colon-derived solutes. As shown in the figure, the estimated urinary clearance exceeded the creatinine clearance for the great majority of these solutes, consistent with tubular secretion.

Conclusions: Comparison of patients with and without colons identified 35 novel colon-derived solutes which are normally excreted by the kidneys and revealed the presence of additional colon-derived solutes for which chemical structures remain to be determined. Efficient renal clearance for many of these compounds, which are presumably of microbial origin, is achieved by tubular secretion. The large number of colon-derived solutes complicates the problem of identifying their potential toxicity.

Funding: NIDDK Support, Veterans Affairs Support
**Results:** Age was similar among control, CKD30-60 and CKD5D groups (63±10, 63±9 and 65±6 years, respectively, p=0.385). Patients from the control group had less diabetes (p=0.019) and hypertension (p<0.010) than other groups, although dyslipidemia, smoking and previous history of coronary disease did not differ significantly. Initial SOFA scores were higher when renal component was considered (0.3±0.6, 1.1±0.8 and 4.2±1.0 in groups control, CKD30-60 and CKD5D respectively, p<0.001), though this difference disappeared when renal component was dismissed (p=0.507). Surgery time was similar among groups (p=0.05); endotracheal intubation time was shorter in the control group (p=0.001) as well as intensive care discharge time (p<0.002). There were 17 deaths in 30 days of admission that occurred in the ICU (7 from control, 7 from CKD30-60 and 2 patients from CKD5D; p=0.264). Kaplan-Meier curve showed no 30-day hospital mortality difference among groups (log-rank test 0.977), which was confirmed by Cox-regression survival analysis adjusted for age, diabetes and initial SOFA.

**Conclusions:** The CABG predictable short-term mortality seems not to be inferior among selected patients on maintenance dialysis. This is probably due to quality improvements in the in cardiologic centers and also because dialysis can be routinely planned in this population.

---

**FR-PO801**

**Small Animal Study and Hemocompatibility of Small Form Factor Microfluidic Filtration System with Nitride Membranes**

**Dean G. Johnson**

**University of Rochester, Rochester, NY.**

**Background:** Improving the health outcomes for End Stage Renal Disease (ESRD) patients on hemodialysis (HD) requires new technologies for wearable HD such as a highly efficient membrane that can achieve standard toxic clearance rates in small device footprints. Our group has developed nanoporous silicon nitride (NPN) membranes which are 100 to 1000 times thinner than conventional membranes and are orders-of-magnitude more efficient for dialysis.

**Methods:** Devices were constructed with polydimethylsiloxane (PDMS) and two NPN membrane chips. Uremic rats were dialyzed for 4 hours under anesthesia. The concentration of thrombin-anti-thrombin complex (TAT) and C3a complement was measured in blood samples taken before and after the 4-hour HD session (n=3) as expected. This indicates that the molecular weight cut-off was somewhere between the size of urea (60.06 Da) and that of albumin (66.5 kDa). The hemocompatibility results are shown in Figure 1B-D.

**Conclusions:** We had positive results from the NPN membranes clearing Urea better than commercial membranes. Significantly, urea was cleared with very little membrane surface area. The favorable hemocompatibility results of the native silicon nitride are encouraging.

**Funding:** NIDDK Support

---

**FR-PO803**

**Risk Factors Associated with Early Mortality in Patients Commencing Hemodialysis: A Systematic Review**

**Adi M. Hazara,1 Eduardo K. Lascon,2 Megan Brauer,1 Michelle M. Richardson,2 Hocine Tighiouart,2 Megan Groburt,1 Laura J. Mauessert,1 UWSPMH, Madison, WI; 2University of Wisconsin School of Medicine and Public Health, Madison, WI.**

**Background:** High phosphate levels are associated with vascular calcifications, osteodystrophy and an increased risk of cardiac mortality. According to major investigations such as the Dialysis Outcomes and Practice Patterns Studies, approximately 45% of dialysis patients have hyperphosphatemia. Hyperphosphatemia is both a common and serious complication for patients receiving dialysis therapy. Despite this fact, clinical management of hyperphosphatemia remains subpar. This is thought to be largely due to patient compliance with binders, cost of therapy and dietary constraints.

This single center quality improvement project looking at the prevalence of phosphate control and the willingness of patients to make a change. The serum phosphate levels from the previous 6 months were evaluated. Patients were classified into 3 groups: good control (phosphorus <6), fluctuating control (phosphorus with ≥3 values >6 or ≤4 values ≤6) for more than 4 values). Anyone in the fluctuating or poor control group was scheduled into 4 weekly meetings for the purpose of using behavioral change theory, an intervention that has been shown effective in dialysis patients. Management modifications were developed by the patients based on the perceived needs. These included changes that have been proven effective such as specific dietary consultation, economic concerns, and meal planning/preparation. The intervention was documented for the patient.

**Results:** 115 patients that were included in this evaluation, 46 (40%) of patients fell into the fluctuating or poor control group. 21 in the poor control and 22 in the fluctuating control. 96% of these patients were willing to meet regularly and 100% of these developed an intervention. The patients reported a positive view of this program.

**Conclusions:** Using theories of behavioral change, this interdisciplinary intervention showed that patients with poor or fluctuating control of phosphorus were willing to meet and create a plan for change. Belief that poorly controlled phosphorous patients would not care to make changes was disputed by these results. This model actively included the patient as part of the management plan and could be applied to many parts of the hemodialysis treatment to improve adherence to management guidelines.

---

**FR-PO804**

**In-Center Hemodialysis Consumer Assessment of Healthcare Providers and Systems (ICH CAHPS) Survey Non-Responder and Responder Characteristics**

**Taimur Dad,2 Hocine Tighiouart,2 Megan Groburt,1 Eduardo K. Lascon,21 Clemens B. Meyer,1 Dana Miskulin,1 Daniel E. Weiner,2 Michelle M. Richardson,2 Dialysis Clinic Inc, Boston, MA; 2Tufts Medical Center, Boston, MA.**

**Background:** The In-Center Hemodialysis Consumer Assessment of Healthcare Providers and Systems (ICH CAHPS) Survey assessing patient experience is a
performance metric in the End Stage Renal Disease Quality Incentive Program administered twice yearly to adult, in-center hemodialysis patients. Response rates currently are approximately 35% and little is known about characteristics of non-responders.

Methods: Cross-sectional analysis of ICH CAHPS administration in 2012 to all ICH patients in Dialysis Clinic, Inc. (DCI) facilities nationally who met AHRQ eligibility criteria for survey administration (over 18 years old and receiving HD at their facility for at least 3 months). Patient-level covariates include demographic, clinical, laboratory, and functional characteristics. Outcome was survey response using AHRQ’s definition of response (no proxy help and answers to at least 50% of pre-defined key questions).

Results: Among 11,055 patients eligible for ICH CAHPS, 6,541 (59%) did not return the mail survey or complete the alternative phone survey and 5,732 (82%) of these had complete covariate data. Of 3,918 responders with complete data (87% of responders), 549 (14%) did not meet AHRQ’s definition of response. Using random effects multivariable logistic models, non-responders were more likely to be men, non-white, younger, single, dual Medicare/Medicaid eligible, less educated, non-English speaking, not active on the transplant list, have longer ESRD vintage, lower BMI, lower serum albumin, worse functional status, and more hospitalizations, missed treatments, and shortened treatments. Similar associations were found using more parsimonious multivariable analyses and after imputing missing data.

Conclusions: In 2012, survey non-responders significantly differed from responders raising concern for bias in survey results. Future research should assess and address reasons for non-response to improve survey applicability.

FR-PO806
World-Wide Early Mortality Rates after Commencement of Hemodialysis: A Systematic Review and Meta-Analysis
Adil M. Hazara, Sunil Bhandari, Hull and East Yorkshire Hospitals NHS Trust, Hull, United Kingdom; Hull and East Yorkshire Hospitals NHS Trust and Hull York Medical School, East Yorkshire, United Kingdom.

Background: In the care of patients with progressive decline in renal function, the start of maintenance hemodialysis (HD) marks a critical turning point. Mortality rates are reported to be high in this period due to multiple treatment and patient related factors. Our aim was to estimate world-wide early mortality rates after commencement of HD in patients with end-stage renal disease.

Methods: Medline and EMBASE were searched for studies published between 1/1/1985 and 7/31/2015 in English. Early mortality was defined as deaths within 180 days of starting HD. Case-control and cohort studies involving adult subjects commencing HD were included. Number of deaths within the early period were extracted and converted to annualised mortality rates (expressed in 100 person-year). The Quality in Prognosis Studies tool was used to assess risk of bias in studies.

Results: 25 studies were included (population of 1,000,014 patients from 12 countries). Median follow-up: 90 days representing 255,079 person-years of observation. Mortality rates varied from 15.7 to 122.0 per 100 person-year (meta-analysis: 31.6 per 100 person-year [95% CI 31.0-32.2]), figure 1). Rates were highest in studies based in Africa (87.2 vs Europe: 15.9 per 100 person-year), lower income countries (87.2 vs high income countries: 31.5 per 100 person-year), studies that restricted recruitment to elderly (37.5 vs unselected: 31.6 per 100 person-year), those that started recruiting in earlier decades (1970’s: 37.3 vs 2000’s: 31.6 per 100 person-year) and those with low risk of bias (33.6 vs high risk: 22.6 per 100 person-year).

Conclusions: High rates of early mortality after commencement of HD is a global phenomenon. Studies showing lowest rates generally carried high risk of bias suggesting likely under-reporting and incomplete follow-up.

FR-PO807
Effect of Twice Weekly Hemodialysis on Plasma Levels of Uremic Solutes Normally Cleared by Secretion

Background: Current guidelines allow twice weekly hemodialysis (HD) in patients with residual function. They require that patients receive a target standard Kt/V urea (Kt/Vurea) calculated by combining the residual urea clearance (Kurea) with dialytic dose assessed by Kt/Vurea. This urea-based calculation does not take into account the native kidney’s secretory function. We hypothesized that because secretory function is not replicated by dialysis, plasma levels of normally secreted solutes may be better controlled in patients with residual function on twice (2X) weekly HD than in anuric patients on thrice (3X) weekly HD.

Methods: Dialytic clearance (Kd), residual clearance (Kr), and plasma levels for urea and 4 solutes normally cleared by secretion were measured in patients on 2X weekly HD with standard Kt/Vurea calculated by combining the residual urea clearance (Kurea) with dialytic dose assessed by Kt/Vurea. This area-based calculation does not take into account the native kidney’s secretory function. We hypothesized that because secretory function is not replicated by dialysis, plasma levels of normally secreted solutes may be better controlled in patients with residual function on twice (2X) weekly HD than in anuric patients on thrice (3X) weekly HD.

Results: Maintenance of secretion in the residual kidney was reflected by higher ratios of residual clearance to dialytic clearance (Kr/Kd) for the secreted solutes than for urea. The plasma levels for indoxyl sulfate, hippurate, and phenylacetylglutamine in the 2X weekly patients were significantly lower than in the 3X weekly anuric patients, while the plasma level for p-cresol sulfate was not different between the two groups (Table).

Conclusions: Residual kidney function removes a larger portion of secreted solutes than urea. The plasma levels of secreted solutes may therefore be better controlled in patients with residual function on 2X weekly HD than in anuric patients on 3X weekly treatment receiving the same weekly dose as assessed by Kt/Vurea. Consideration of secretion function may allow refinement of prescription guidelines for patients with residual kidney function.

Funding: Veterans Affairs Support

Figure 1: Meta-analysis of early mortality rates in patients newly started on hemodialysis

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

612
FR-PO808
Healthcare Provider Experiences in Emergent Dialysis of Undocumented Immigrants

Achintya Achintya Achintya,1 Alexia Torke,2 Lucia Wocial.1 1Indiana University University, Indianapolis, IN; 2Wayne State University, Grosse Pointe Woods, MI; 1Indiana University School of Medicine, Indianapolis, IN.

Background: No national standards exist for chronic dialysis in undocumented (UD) immigrants posing a unique ethical dilemma for providers. The purpose of this survey was to explore provider perspectives.

Methods: Cross Sectional Internet Survey in April 2016 of Nephrology, ICU, ER, IM, Palliative Care nurses and physicians at a safety-net hospital. The last 4 open ended survey questions were included in this analysis (table 1). All authors individually explored the textual data inductively using an approach based on grounded theory to generate codes and broader themes. Coders then developed a shared code list. All responses were assigned a 1 theme. We then calculated the number of participants with each of the codes.

Results: 299/765 participants completed the survey of which 185 included free text comments. Nurses comprised 47% of the respondents. 483 responses were coded. The predominant coping mechanisms to moral distress were preventing and team approach to patient care. We found that responses to the last 3 questions had overlapping themes. So, these items were coded using the same list of codes. Many participants spoke to the negative consequences of emergency dialysis for UD immigrants. This was noted to have a negative effect on providers, UD patients, other patients and the health system. Emotional and psychological distress was common (75.5%) along with concerns for emergency dialysis causing harm to UD immigrants (38.9%). Although far less common, some providers did note positive consequences of their experience caring for UD patients, most common being taking pride in provider role (13%). Attitudes about the right approach to this issue varied widely with both support (36.2%) for and opposition (7.6%) to dialysis for UD patients. Importantly emotions ran very high among those who supported regularly scheduled 3x/week dialysis and those who opposed dialysis altogether.

Conclusions: Provision of inadequate dialysis causes significant emotional distress in providers with varying attitudes towards the current practice of emergent dialysis. Policies need to be balanced with the strong ethical and moral commitments of providers.

FR-PO809
Socioeconomic Determinants of Outcomes among Patients Receiving Hemodialysis in India

Vasudevan Jha,1 Karral, 2 Oommen John, 1 Venkatraman G, 3 Sumathi Kolli.1 1George Institute for Global Health, New Delhi, India; 2The George Institute for Global Health, NEW Delhi, India; 3Nephroplus Dialysis Centres, Hyderabad, India.

Background: Dialysis in India is associated with a relatively higher mortality and early dropout when compared to developed countries. Poor clinical outcomes of dialysis patients are associated with socio-demographic predictors that have received limited attention thus far.

Methods: Data from a cohort of 9,058 subjects receiving HD between April 2014 and December 2016 at 92 centres of Nephroplus, India’s largest dialysis center network was analysed retrospectively. We retrieved baseline demographics, medical history, treatment cost, dialysis frequency and erythropoiesis stimulating agent (ESA) use from the patient records. Univariate Cox proportional hazards model was used for the calculation of mortality and dialysis discontinuation hazard ratios (HR).

Results: The mean age of the subjects was 51±14 years. Subjects were predominantly male (70%), from metropolitan cities (37%) and paying out of pocket for dialysis (61%). A total of 16% of the subjects died, 46% discontinued dialysis and 37% continued dialysis. Out of the 1494 deaths, 60% and 75% subjects died within the 1st and the 2nd year from their first dialysis, respectively. Of the 4181 subjects discontinuing dialysis, 21% and 76% discontinued within the 1st and the 2nd year from their first dialysis respectively. Subjects younger than 40 years (HR 0.55, 95% CI, 0.47-0.65), residing in a metropolitan city (HR 0.56, 95% CI, 0.49-0.63), undergoing dialysis three times per week (HR 0.91, 95% CI, 0.84-0.98), on erythropoiesis-stimulating agents (ESAs) (HR 0.88, 95% CI, 0.78-0.99) and paying dialysis cost through health insurance (HR 0.89, 95% CI, 0.66-0.90) had lower mortality. Subjects on ESA more than ESAs (HR 2.56, 95% CI, 2.18-3.03) and paying out of pocket for dialysis (HR 1.15, 95% CI, 1.03-1.27) had higher odds of discontinuing dialysis. Gender was not found to be a predictor of outcomes.

Conclusions: The findings of the analysis of the data from this large cohort show high mortality and dropout rates and highlight the associated socio-economic and treatment related factors that will need to be addressed to reduce inequity in dialysis access and improve outcomes in India.

FR-PO810
A Simulation of Demand-Supply Imbalance in Dialysis Care in India

Achintya Achintya Achintya,2 Bhambhra Putatunda.1 1Nephrology Associates PC, Murfreesboro, TN; 2Tennessee State University, Nashville, TN; 3Kidney Clinics and Research Centers International, Inc., Murfreesboro, TN.

Background: About 10% of India’s 1.3 Billion people suffer from Chronic Kidney Disease (CKD). An average of 15% of urban Indian population suffers from CKD. That number rises to 50% for some cities. Demand (CKD/ESRD treatment including dialysis) is growing at a rate of about 31% in India (compared to about 6% in the USA and 8% in the rest of the world.) About 30% of the CKD cases are estimated to be caused by diabetes and about 20% by hypertension. India has over 70 Million diabetes patients, a number that is estimated to double by 2040. A third of the diabetes cases will develop CKD. More than 60,000 patients develop ESRD in India per year of which 70%-80% start dialysis treatment while about two-thirds of them are eventually ceasing the treatment due to resource limitations leading to premature death.

Methods: Published studies are used to extract economically meaningful numbers that are used to draw equations that model the demand-supply imbalance. Various projection methods are used to arrive at measures of long-term (through 2035) prevalence in the country for diabetes, dialysis and CKD cases. Furthermore, published studies are used to estimate the lower and upper bounds of CKD prevalence. Sparse evidences are scanned to estimate the number of dialysis centers and machines in different parts of the country and their abilities to meet the current demands. Reasonable assumptions are made to simulate the demand and supply of dialysis treatment based on the upper and lower bounds of the CKD estimates.

Results: About 67% to 93% of the demand for dialysis treatment may not be currently met in India. These estimates may be conservative. It is estimated that about 40,000-68,000 additional dialysis machines may be needed to serve India’s current demand. These numbers may increase by 200%-300% by 2035 under various scenarios.

Conclusions: This study is of the first to harness a sparse and widely varying literature on the state of dialysis treatment to make meaningful estimates of demand-supply imbalance in Indian dialysis care market. The sparseness of the existing studies and the gravity of the magnitude of the imbalance point to need for in-depth studies involving population health and healthcare marketplace data in India.

FR-PO811
Weight Perception in African-American Hemodialysis Patients

Varun Gupta,1 Mildra Saunders,2 Rita L. McGill,2 Michelle A. Josephson.1 1Creighton University, Northbrook, IL; 2University of Chicago, Chicago, IL.

Background: The epidemic of obesity in the United States has been linked to greater risks of cardiovascular disease, diabetes, and kidney disease. However, in dialysis patients, increased body mass index (BMI) is paradoxically associated with better survival, as is African American race. We sought to determine the perception of ideal BMI in African American hemodialysis patients.

Methods: We surveyed African American hemodialysis patients at three dialysis facilities in South Side of Chicago in June-July 2016. Patients were asked about ideal weight, exercise, eligibility for kidney transplant, and lifestyle. BMI was calculated from measured values. Results were tabulated into a descriptive analysis.

Results: Among 127 patients, 52% were female, and 82% had completed 12 or more years of school. Mean BMI was 28.7 ±4.3. 32 patients (25%) were overweight, and 50 patients (39%) were obese; proportions did not differ by sex. BMI>35 (our center maximum for transplant eligibility) was seen in 14 (11%). Among patients with normal BMI, 43% perceived a need to gain weight; among overweight patients, 79% wanted to maintain or gain weight (Table). The majority (70%) of obese patients wanted to lose weight.

Conclusions: African American hemodialysis patients perceive BMI of 25-30, which is classified as overweight, to be desirable. Further work is needed to determine whether this weight preference is in part responsible for African Americans’ improved hemodialysis survival.

Funding: NIDDK Support

Perceived Need to Lose or Gain Weight, by BMI

<table>
<thead>
<tr>
<th>BMI Category, n (%)</th>
<th>Should Lose</th>
<th>Should Maintain</th>
<th>Should Gain</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight (BMI&lt;18.5)</td>
<td>0</td>
<td>0</td>
<td>7 (48%)</td>
<td>3</td>
</tr>
<tr>
<td>Normal/Overweight (BMI 18.5-24.9)</td>
<td>1.0</td>
<td>25 (15%)</td>
<td>32 (25%)</td>
<td>42</td>
</tr>
<tr>
<td>Obese (BMI&gt;25)</td>
<td>7.2</td>
<td>20 (13%)</td>
<td>3 (10%)</td>
<td>30</td>
</tr>
<tr>
<td>Obese (BMI&gt;30)</td>
<td>3 (7%)</td>
<td>1 (14%)</td>
<td>1 (2)</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>57</td>
<td>27</td>
<td>127</td>
</tr>
</tbody>
</table>

FR-PO812
Use of Poison Regression Analysis with Restricted Cubic Splines Facilitates Cross-Sectional Comparisons of Mortality in a Large Provider

Antonia Harford,2 R. Schrader,1 S. Paine,1 Ambreen Gul,1 Philip Zagar.1,2 1DCI, Albuquerque, NM; 2UNM, Albuquerque, NM.

Background: Dialysis Clinic, Inc. (DCI) is a large not-for-profit provider. Assessing mortality across geographic regions served by a large provider is complicated by differences in demographics and local variations in overall healthcare. The use of Poison regression analysis with restricted cubic splines may facilitate cross-sectional comparisons of mortality that are not influenced by differences in distributions of race, sex, age, and diabetes.

Methods: We assessed mortality for HD and PD patients treated in DCI facilities in different geographic regions across the country for the years 2009 to 2016. We used USRDS categories to define the geographic regions. We conducted Poison regression analysis using the rsm package in R. Instead of using USRDS categories we used restricted cubic splines, which have flexible shapes, determined by the data. Models contained categorical (race, sex, and diabetes) and continuous (age, vintage, and year) variables. We fit all 2-way interactions, age, diabetes status, and interactions

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
between age and vintage. Network 8, which has the largest number of DCI patients, was
the referent.

Results: Standardized mortality ratios by ESRD Networks for HD and PD patients for
the years 2009-2016 are shown. Results of mortality across ESRD Networks for both HD and PD patients. The use of Poisson regression analysis, with
restricted cubic splines, facilitates assessing mortality across different geographic regions
served by a large provider. This technique provides estimates that are not influenced by
demographic differences.

FR-PO813
Efficacy of Percutaneous Etelcalcetide Injection into the Parathyroid Glands on Serum Parathyroid Hormone (PTH) in Hemodialysis (HD) Patients with Secondary Hyperparathyroidism (SHPT): A Pilot Study
Satoshi Funakoshi,1 Takahisa Uchino,1 Subodh J. Saggi,2 Yoko Obata,1 Tomoya Nishino,1 Junichiro Hashiguchi,1 Takashi Harada,1 Nagasaki Kidney Center, Nagasaki, Japan; SUNY Downstate Medical Center, New York, NY; Nagasaki University Hospital, Nagasaki, Japan

Background: The most popular treatment for SHPT in HD patients is oral administration of cinacalcet in Japan. Nausea and high cost limits its use long term. Etelcalcetide is a novel injectable calcimimetic agent that has a similar mechanism of action as cinacalcet. Direct injection of etelcalcetide into the PTH gland may prove to be cost effective as compared to its systemic administration.

Methods: HD patients with SHPT who complained of nausea while on cinacalcet for
>2 years were enrolled in this study after their informed consent was obtained. Cinacalcet was withdrawn from all patients for >2 weeks, and 1.0ml (2.5mg) of etelcalcetide for HD patients, and 0.5ml(1.25mg) for PD patients were injected into the parathyroid gland using ultrasound guidance. Serum PTH was determined for up to 8 weeks.

Results: Seven patients (mean age, 68.4±11.8 years old; median HD duration, 12 years; mean PTH 270.6±155.5 pg/ml; participated in the pilot trial. Four achieved >50%
reduction in serum PTH up to 4 weeks as shown in figure. Three patients had no response to this therapy, but their PTH was promptly decreased with systemic etelcalcetide administration, suggesting the presence of undetected hyperactive glands by Ultrasound. Direct administration was safe and not associated with any hematomas or laryngeal nerve paresis as has been reported for direct ethanol injection.

Conclusions: Percutaneous etelcalcetide injection into the parathyroid glands appears
to be cost effective, safe, and a superior option for the treatment of SHPT in HD patients.

Funding: Private Foundation Support

FR-PO814
Mortality Prediction in Hemodialysis Patients According to Dietary Intake
Protein Intake to Serum Phosphorus Ratio Dana Bielopolski,1,4 Yoshitsugu Obi,2 Elani Streja,1 Kamyar Kalantar-Zadeh,3,1 Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; 2University of California Irvine, Orange, CA; 3University of California Irvine, School of Medicine, Orange, CA; 4Nephrology and Hypertension, Rubin Medical Center, Petah-Tikva, Israel.

Background: Lowering serum phosphorus (P) in maintenance hemodialysis (MHD) patients may improve survival. However, prior studies have shown that restricting dietary protein intake (estimated by “normalized protein catabolic rate”, nPCR), a major source of phosphorus, is associated with higher mortality. We hypothesized that combining these two risks, nPCR and P, in the form of a new score could improve survival prediction.

Methods: Dividing the variables by one another enabled them to influence the metric equally. We divided phosphorus by 5.8, to create nP, so that distribution ranges of the two variables better overlap. Then new metric R, was formulated: R=nPCRnP Analysis was carried in 63,016 MHD pts, who were followed for 5 years (2007-11). Survival models were adjusted for case-mix and malnutrition-inflammation cachexia syndrome (MICS).

Results: Patients were divided to G 5 groups according to R value. Group 1 had high phosphorus and low nPCR, the opposite of patients in group 5. After 1 year follow-up survival difference between groups was according to numerical order. Association of R with mortality was strengthened with adjustment for case-mix variables. Adjusting HR to albumin improved prediction of patients with good prognosis.

Conclusions: The novel protein to phosphorus ratio score can predict mortality in MHD patients and may allow a better phosphorus monitoring while adequate protein intake is ensured.

Funding: Private Foundation Support
FR-PO816
Measured versus Prescribed Dialysate Sodium Using Dialysis Machines from Different Manufacturers: Ambeegul Dana, Dinah Miskulin,2 Antonia Harford,1 R. Schrader,3 S. Paine,4 W. L. Bender,1 Bijnai Thajudeen,1 Philip Zigler,1 1DICU, Albuquerque, NM; 2Tufts Medical Center, Somerville, MA; 3UNM, Albuquerque, NM; 4Dialysis Clinic Inc., Kansas City, MO; 5University of Arizona, Tucson, AZ

Background: The optimal dialysate sodium (DNS) is unknown. We previously reported that differences (measured - prescribed DNS) in facilities using Fresenius and Gambro machines ranged from +1.3 mEq/L to -6.5 mEq/L (mean +2.5 mEq/L), which may contribute to the disparate results of published studies. We extended these observations by assessing differences in facilities using B. Braun machines.

Methods: We studied 2 DCI facilities that use B. Braun Dialog+ machines with either Fresenius 4008S or Gambro 4008S dialysis machines. We retrospectively reviewed all dialysis sessions occurring from August 2015 to February 2017.

Results: For Sessions 1 and 2, the prescribed DNS was 136.9 ± 1.5 and 136.9 ± 1.6 mEq/L, respectively. The measured DNS was 136.9 ± 1.6 and 136.9 ± 1.8 mEq/L, respectively. For Sessions 3 and 4, the prescribed DNS was 136.9 ± 1.6 and 136.9 ± 1.6 mEq/L, respectively. The measured DNS was 136.9 ± 1.7 and 136.9 ± 1.6 mEq/L, respectively.

Conclusion: Measured DNS is higher than prescribed with Fresenius, Gambro, and B. Braun machines. QAPI programs should incorporate measurements of DNS to ensure adherence to the dialysis prescription.

FR-PO817
The Amino Acid Losses Are Lower during Pre-Dilution-On-Line HDF Than HD: Shunichiro Ono,1 Takashi Hiyama,1 Hiroyuki Morita,1 Masakatsu Takahashi,2 Yasuhisa Kitajima,3 Motoko Kokubo,5
1Clinical Engineering, Eijin Hospital, Tokyo, Japan; 2Graduate School of Medical Sciences, Sagamihara, Japan; 3Tokyo Healthcare University School of Allied Health Sciences, Sagamihara, Japan

Background: We analyzed the amino acid losses that occur on performing pre-dilution on-line HDF (O-HDF) and HD because the amino acid kinetics of O-HDF has been unknown until now.

Methods: We compared the total amino acid level, total non-essential/essential/branched-chain amino acid levels, urea/Cr removal amount, reduction rate, and Kt/V between the HD group (n=36) and O-HDF group (n=24) on the basis of dialysis vintage, age, and BMI. We performed correlation analysis on the relationship between the Amino acid losses and the occurrence of error in the estimation of dry weight by usual clinical parameters.

Results: The amino acid losses were significantly lower in the O-HDF group than in the HD group. The most significant differences between the O-HDF and HD group in the HD group, the mean values were 64.2±5.95 and 70.6±6.01%, respectively. The values shown a significant difference between the O-HDF and HD group. In the former and latter were 1.50±0.289 and 1.49±0.314, respectively; there was no significant difference.

Conclusions: Under the same dialysis dose of Kt/V for urea, the amino acid losses were lower during O-HDF than HD, suggesting that O-HDF is more favorable as a blood purification method from the viewpoint of nutrition.

FR-PO818
Adjustment of Target Weight Based on Absolute Blood Volume Reduces the Frequency of Intradialytic Morbid Events: Daniel Schrader,1,2 Suessanne Kron,1 Til Leimbach,1 Clemens Budde,1 Joachim Kron,1 1Charite Universitaetsmedizin Berlin, Berlin, Germany; 2KHi Kidney Center Berlin-Köpenick, Berlin, Germany; 3Medical University Graz, Graz, Austria

Background: Adequate ultrafiltration (UF) avoiding intradialytic morbid events (IME) remains a core problem in current hemodialysis (HD) therapy. The aim of this study was to investigate the suitability of absolute blood volume (Vs, in mL/kg) to prescribe UF volume and to reduce the frequency of IME.

Methods: Following a 4 week baseline phase to quantify the frequency of IME, volume status was determined in a specified HD study during which relative blood volume (RBV, %) was measured by the blood volume monitor (BVM), Vs was measured using on-line dialysate dilution and volume overload (Vs, L) was measured using bioimpedance spectroscopy. Symptomatic IME was defined as a drop in systolic blood pressure (PSYS) by more than 20 mmHg, or a PSYS below 90 mmHg, or the occurrence of symptoms such as dizziness, light-headness, sweating, or cramps. Suitability of different variables to discriminate for IME was examined by analysis of receiver-operator-characteristics (ROC-analysis) and calculation of the area under the ROC-curve (AUROC). Target weight was then increased or decreased based on measured Vs, and occurrence of IME, and the frequency of IME was recorded during 4 weeks of follow-up.

Results: 45 patients participated in this study. 22 (49%) patients experienced 66 IMEs during 12 HD treatments during baseline. In 15 (33%) patients who experienced IME during the volume assessment study Vs (60.7±4.0 vs. 73.7±11.3 mL/kg, p<0.001) and Vs (1.1±0.9 vs. 2.5±1.8 L, p<0.01) was lower than in stable patients, while RBV (87.9±4.4 vs. 90.2±2.4%, p=n.s.) was comparable. AUROC was 0.92, 0.80, and 0.61 for Vs, RBV, and Vs, respectively. The sensitivity, specificity, and accuracy of the Vs65±5 mL/kg threshold to predict IME was 87%, 100%, and 91%, respectively. Target weight was increased (+1.5 kg) or decreased (-5kg) in 32 patients. The frequency of IME fell to 0.9% of all HD sessions in the following 4 weeks (p<0.001).

Conclusions: Absolute blood volume (Vs, mL/kg) is more accurate in assessing the risk for IME-prone patients than relative blood volume (RBV, %). Adjustment of target weight based on information of Vs, Vo, and IME appears as a feasible approach to reduce the frequency of IME.

FR-PO819
Use of Lung Ultrasonography to Determine the Accuracy of Clinically Estimated Dry Weight in Chronic Hemodialysis Patients: Chuan Jiang, Satyam Patel, Andrew A. Moses, Maria V. DeVita, Michael F. Michielis. Medicine / Nephrology, Lenox Hill Hospital / Northwell Health, New York, NY

Background: The use of lung ultrasonography (LUS) to identify extravascular lung water has received increasing acceptance. Sonographic B-lines, discrete vertical lines that originate from the pleura, represent pulmonary interstitial edema and are correlated with the accumulation of fluid. The goal of this study was to evaluate the utility of LUS to determine the accuracy of prescribed dry weight (DW) in chronic hemodialysis (HD) patients admitted to our dialysis unit and to ascertain the adequacy of fluid removal.

Methods: Forty-five patients participated in this study. 22 (49%) patients experienced 66 IMEs during 12 HD treatments during baseline. In 15 (33%) patients who experienced IME during the volume assessment study Vs (60.7±4.0 vs. 73.7±11.3 mL/kg, p<0.001) and Vs (1.1±0.9 vs. 2.5±1.8 L, p<0.01) was lower than in stable patients, while RBV (87.9±4.4 vs. 90.2±2.4%, p=n.s.) was comparable. AUROC was 0.92, 0.80, and 0.61 for Vs, RBV, and Vs, respectively. The sensitivity, specificity, and accuracy of the Vs65±5 mL/kg threshold to predict IME was 87%, 100%, and 91%, respectively. Target weight was increased (+1.5 kg) or decreased (-5kg) in 32 patients. The frequency of IME fell to 0.9% of all HD sessions in the following 4 weeks (p<0.001).

Conclusions: Absolute blood volume (Vs, mL/kg) is more accurate in assessing the risk for IME-prone patients than relative blood volume (RBV, %). Adjustment of target weight based on information of Vs, Vo, and IME appears as a feasible approach to reduce the frequency of IME.
FR-PO820
Use of Lung Ultrasonography for Assessment and Follow Up of Asymptomatic Pulmonary Congestion in Hemodialysis Patients Salah S. Naga, Nephrology, Alexandria Faculty of Medicine, Alexandria, Egypt.

Background: Chronic fluid overload is a common problem in ESRD patients on HD. Even asymptomatic lung congestion results in increased cardiovascular morbidity and mortality. Lung ultrasound provides a non-invasive tool to assess fluid overload. The aim of the study was to assess asymptomatic pulmonary congestion using lung ultrasonography and to evaluate the effect of increasing hemodialysis dose on improvement of the lung comet scores.

Methods: One hundred patients were enrolled. Based on ultrasonic lung comet colours (ULC) score, patients were divided into group A (65 patients) with no or mild pulmonary congestion (ULC<14) and group B (35 patients) with moderate to severe (ULC>14). Group B was further subdivided into group B1 (18 patients) who were subjected to intensified HD and group B2 (17 patients) who were maintained on their conventional HD dose and subgroup were followed for three months.

Results: Baseline ULC score showed a significant positive correlation with LAP (r=0.808, p<0.001), LAP (r=0.519, p<0.001), IVCD (r=0.669, p<0.001), SBP (r=0.578, p<0.001) and DBP (r=0.435, p<0.001) and a strong negative correlation with EF (r=0.542, p<0.001) and inferior ventricle end diastolic index (IVCD) (r=0.571, p<0.001). After intensified HD, Group B1 showed a significant decrease in the ULC score (25.44±6.13 to 9.17±3.65, p<0.001), left atrial pressure (LAP) (16.22±7.12 to 12.16±1.90, p<0.001), left atrial diameter (LAD) (41.33±4.60 to 39.53±2.75, p=0.003), inferior vena cava diameter (IVC(V)) (12.65±4.17 to 9.86±1.61, p<0.001), SBP (146.67±17.15 to 130.0±12.83, p<0.001) and DBP (87.22±6.96 to 82.22±4.28, p<0.001) in comparison to group B2.

Conclusions: The present study demonstrated that lung ultrasonography guided intensified HD dose improved patients lung comet scores, LAP, LAD, IVCD, IVCCI and blood pressure. ULC monitoring is an easy tool to detect asymptomatic lung congestion and allows tailoring dialysis to treat it.

FR-PO821
Intradiastolic Hemodynamics and Cerebral Perfusion Dawn F. Wolfgram, Zahlocki VA Medical Center, Milwaukee, WI.

Background: Persons with end-stage renal disease on hemodialysis (HD) have significant cerebral ischemic disease and atrophy noted on brain imaging. Hemodynamic instability during HD may lead to cerebral hypoperfusion and resultant ischemic injury. Risk of cerebral hypoperfusion may be higher in a subset of HD patients with increased drop in both blood pressure during HD. We sought to describe the changes in cerebral perfusion during HD and the relationship to changes in intradiastolic blood pressures (BP) in a cohort of HD patients.

Methods: We used a clinically validated method of continuous cerebral oximetry monitoring (Nicolet Biomedical) on a group of 131 maintenance hemodialysis patients treated in the outpatient setting. Cerebral oximetry data was obtained during HD for 177 patients (65.3%) and the HD session was divided into the pre-HD, during HD and post-HD phases. Cerebral oximetry was measured as the relative cerebral oximetry index (rCox) and a change of 5% or more was considered significant.

Results: Thirteen participants were enrolled with 11 participants completing the study and included in the analysis. The mean (SD) age was 66.8 (7.7) years. All patients had hypertension and 73.4% had diabetes. Diabetes was the cause of ESRD in 55% of patients. The mean (SD) change in cerebral oximetry during HD was -3.5% (SD 5.2%) in patients with increased drop in both blood pressure during HD. In participants not meeting both criteria (p = 0.06). In four participants there was a significant association between changes in cerebral oximetry and postdialysis systolic blood pressure. In participants with both diabetes and a greater than 20mmHg drop during dialysis there was a change in cerebral oximetry of -5.1 (3.1) vs -2.2 (1.3) in participants not meeting both criteria (p = 0.06). In 55% of participants. The mean (SD) change in cerebral oximetry during HD was -3.5%. In participants with both diabetes and a greater than 20mmHg drop during dialysis there was a change in cerebral oximetry of -5.1 (3.1) vs -2.2 (1.3) in participants not meeting both criteria (p = 0.06). In 55% of participants. The mean (SD) change in cerebral oximetry during HD was -3.5%.

Conclusions: Persons with end-stage renal disease on hemodialysis (HD) have significant cerebral ischemic disease and atrophy noted on brain imaging. Hemodynamic instability during HD may lead to cerebral hypoperfusion and resultant ischemic injury. Risk of cerebral hypoperfusion may be higher in a subset of HD patients with increased drop in both blood pressure during HD. We sought to describe the changes in cerebral perfusion during HD and the relationship to changes in intradiastolic blood pressures (BP) in a cohort of HD patients.

FR-PO823
Baseline Muscle Strength, Dry Weight, and Physical Activity Are Associated with Muscle Strengthening of Lower Extremities after 6-Month Resistance Training in Patients with Maintenance Hemodialysis Yoshiyumi Moriyama,1 Sae Aratani,1 Masahiko Hara,2 Hideaki Ishikawa,1 Konan Kosei Hospital, Konan, Japan; 3Nagoya Kyoritsu hospital, Nagoya, Japan; 4Nippon Medical School Hospital, Tokyo, Japan; 5Osaka City University Graduate School of Medicine, Osaka, Japan.

Background: Rapid muscle wasting is a common complication in patients with maintenance dialysis, and it is associated with the risk of frailty as well as with poor quality of life and survival in dialysis patients. It is known that increasing the hemodialysis dose improves muscle strength. It is also known that progressive muscle mass loss is related to changes in the extracellular fluid (ECW) and intracellular fluid (ICF). Increase in ECW relative to total body weight (ECW/TW) evaluated by bioelectrical impedance analysis (BIA) is associated with muscle wasting. There is an urgent need to identify factors that are associated with a decrease in ECW/TW.

Methods: We included 271 patients who underwent 6-month resistance training program during hemodialysis. Primary outcome measure was change in percent knee extension muscle power to body weight (pKEMP-BW; mean of right and left) during 6 months. Participants were divided our patients into 2 groups; improve vs deteriorate factors. Multivariable logistic regression model was employed to evaluate parameters which are associated with improvement of pKEMP-BW at 6-month, using indices shown in the Table as explanatory variables such as baseline pKEMP-BW or short physical performance battery (SPPB).

Results: Median age was 71 (quartile 64-77) years old, 144 patients (53.1%) were men, and median dry weight was 54.2 (47.5-61.6) kg. After 6-month training, pKEMP-BW was improved in 177 patients (65.3%), and pKEMP-BW changed from 42.0 (32.4-52.3) % to 43.4 (34.8-53.0%) in total (p=0.001). As shown in the Table, baseline lower dry weight, higher handgrip, lower pKEMP-BW, and higher SPPB were associated with an improvement of pKEMP-BW at 6-month.

Conclusions: Six-month resistance training improved pKEMP-BW. Baseline lower dry weight, higher handgrip, lower pKEMP-BW, and higher SPPB were associated with an improvement of pKEMP-BW at 6-month in patients with maintenance hemodialysis.

FR-PO824
Urea Clearance Modelling Using 300 ml/min of Dialysate Flow J. Ken Leypoldt,1 Sarah S. Prichard,2 Glenn M. Chertow,3 Luis Alvarez,1 None, Menlo Park, CA; 1Stanford University School of Medicine, Palo Alto, CA; 2Outset Medical, San Jose, CA.

Background: High dialysate flow rates (Q_D) of 300-500 mL/min are generally used in the outpatient setting to maximize urea removal in a time efficient manner. Lower dialysate flows of 100-200 mL/min are often employed in critically ill patients and in patients at high risk of dialysis disequilibrium. There are few data describing the use of a mid-rate Q_D (300mL/min) in a modern outpatient dialysis setting. We present urea kinetic modeling of 300 mL/min dialysate flow rates and investigate differential urea clearances between 300 and 500 mL/min. Urea kinetic models were used to predict urea clearances at 300 mL/min dialyse flow rates. Using the FHN trial group urea model assumptions in combination with published dialyzer characteristics (KoA), a weekly urea concentration profile was obtained. The model was then applied to patients of different weights and volumes of distribution (VOD) at blood flow rates of 200-400 mL/min. Finally, a clearance relationship for spKt/V of 300 vs. 500 mL/min Q_D was obtained.

Results: Table 1 shows modelled spKt/V when Q_D is 300mL/min or 500mL/min at the same Q_D of 400 mL/min. Across VOD, the model demonstrates a Q_D of 300 mL/min results in a predicted spKt/V that meets urea clearance targets. There was a small difference in spKt/V between a Q_D of 300 mL/min and 500 mL/min Q_D. Use of a larger KoA (LkoA) dialyzer and 15 minutes of additional time narrows the spKt/V difference.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
Conclusions: A Qo 300mL/min can be expected to achieve urea clearance targets. Decreasing dialysate flow rate to 300 mL/min results in a modest, but clinically insignificant, spKt/V difference. For patients with clearance challenges at 500mL/min Qo, the use of a 300 mL/min Qo with a larger KoA dialyzer and incremental time can be considered, which may itself allow for lower rates of ultrafiltration and better-tolerated hemodialysis without fuss.

Funding: Commercial Support - Outset Medical Inc

Table 1: Calculated spKt/V

<table>
<thead>
<tr>
<th>Dialyzer</th>
<th>500</th>
<th>200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Standard</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>KoA</td>
<td>1.3</td>
<td>1.3</td>
</tr>
</tbody>
</table>

*spKt/V

FR-PO25

In-Vitro Dialysis Clearances Using Dharma, the EasyDial Portable Hemodialysis Machine Timothy R. Neaman,1 Osman S. Khawar,1 Sarah L. Foster,2 ’Balboa Nephrology Medical Group, Escondido, CA; 2’EasyDial, Irvine, CA.

Background: Dharma is a unique, fully portable dialysis machine, which uses only 5 L of water during each treatment. To determine the efficacy of Dharma in clearing blood waste products, in-vitro dialysis tests were run utilizing bovine blood.

Methods: Twenty-three treatments were conducted and all met the defined parameters of an effective dialysis over 90 – 120 minutes. A common protocol was utilized. Amendments were made for differences between studies inclusive blood flow rates, dialysate, recirculation solutions and rates. Dharma machines were prepared to work with consumables (dialyzer, blood and dialysis circuit cassettes, blood and dialysate lines) and primed. Five liters of dialysate were added to a reservoir and warmed to 37 degrees centigrade. Five liters of bovine blood was spiked with urea, creatinine, potassium, calcium, magnesium and was exposed to levels commonly found in dialysis patients. The blood was added to a vessel connected to the arterial line through a 16-gauge needle or a 10 French catheter. Treatments were run by dialysis technicians. Serum samples for waste products were collected at baseline, every 15 minutes and at the end of dialysis. Dialysate pH and bicarbonate were assessed.

Results: Desired clearances of waste products was achieved at all timepoints (Table 1). Mean clearances were: BUN 77.1% (126.3 mg/dL (26.4) to 28.93 mg/dL (6.89); creatinine clearance 88.9% (15.9 mg/dL (4.2) to 1.76 mg/dL (0.89); urea clearance was of 77.5% (225.5 mmol (47.2) to 50.74 mmol (9.03). Clearances for waste products were greater than 70% at all timepoints and were greatest in the 120-minute treatment group for BUN (78.6%), creatinine (89.5%) and urea (78.7%).

Conclusions: These results verify in-vitro efficacy of Dharma in dialysis treatments. Dharma offers the unique features of portability (18 lbs.), no fixed water connection (5 L dialyzer) and the possibility for significantly reducing dialysis treatment times. These features may allow for improving the quality of life and reducing the burden of illness in ESRD patients on dialysis.

Funding: Commercial Support - EasyDial Inc

FR-PO28

Capturing and Reporting Performance Measures for Chronic Hemodialysis Care: The Veterans Health Administration (VHA) Dialysis Dashboard Experience Michael J. Fischer,2,4 Karen Sovern,1 Susan T. Crowley,1 ’Department of Veterans Affairs, Cincinnati, OH; 4’University of Iowa College of Public Health, Iowa City, IA; 2’Veterans Health Administration, West Haven, CT; 3’Jesse Brown VAMC and Hines VA Hospital, Chicago, IL.

Background: End-stage renal disease (ESRD) is a common, burdensome, and costly chronic disease among Veterans. However, the mean predialysis plasma MG level in chronic dialysis subjects was significantly higher (more than 100-fold) than the control group (5.17 ± 2.6 vs. 0.047 ± 0.02). In comparison, the mean predialysis urea level was only three-fold the normal level (44.05 ± 23.06 vs. 14.89 ± 3.23 mg/dL, respectively, P = 0.02), and Cr was 13-fold the normal level (10.8 ± 3.1 vs. 0.83 ± 0.18 mg/dL, respectively, P = 0.001). The mean production rates of MG were 47.12 ± 4.61 (± 3.4) mmol/day in chronic dialysis patients and healthy individuals, respectively (P < 0.05). The effective clearance rates for urea and Cr in dialysis patients were 239 ± 69 and 173 ± 51 ml/min, respectively; which were significantly higher than the effective clearance rate for MG 122 ± 26 ml/min (P < 0.05).

Results: MG accumulates to more than 100 fold the normal level in ESRD patients. This accumulation likely reflects 1) its clearance rate (and therefore its reduction ratio) is significantly less than that of urea and Cr, which is likely due to its previously described large distribution volume, and 2) increased production from Cr oxidation.

Table 1. Solute Plasma Levels, Clearance and Excretion Rates in Controls and ESRD Patients

<table>
<thead>
<tr>
<th>Solute</th>
<th>Plasma Levels</th>
<th>Clearance</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>Normal</td>
<td>149.0 ± 32.7</td>
<td>13.75</td>
</tr>
<tr>
<td>Cr (mg/dL)</td>
<td>Normal</td>
<td>0.73 ± 0.48</td>
<td>0.078</td>
</tr>
<tr>
<td>Mg (mg/dL)</td>
<td>Normal</td>
<td>2.61 ± 0.04</td>
<td>0.87</td>
</tr>
<tr>
<td>MG (mg/dL)</td>
<td>Normal</td>
<td>0.047 ± 0.02</td>
<td>0.047</td>
</tr>
<tr>
<td>MG (mg/dL)</td>
<td>ESRD (n=7)</td>
<td>173.0 ± 51.64</td>
<td>0.87</td>
</tr>
<tr>
<td>MG (mg/dL)</td>
<td>ESRD (n=7)</td>
<td>122.3 ± 26.5</td>
<td>0.87</td>
</tr>
</tbody>
</table>

FR-PO26

African American ESRD and Medication Adherence: What Are the Effects of Everyday Racism? Tamara Savage, Social Work, UNC Pembroke, Pembroke, NC.

Background: Poor medication adherence leads to increased hospitalizations, morbidity, and mortality in end-stage renal disease (ESRD) patients. African American ESRD patients have poorer rates of medication adherence when compared to Whites. Studies have not investigated the impact of broader social issues such as everyday racism on this racial disparity. This is the first study to explore how everyday racism within the healthcare system contributes to this disparity in medication adherence. A mixed methods study was conducted to investigate the relationship between everyday racism and medication adherence within the African American ESRD community.

Methods: Primary data were collected from 46 African American ESRD patients. All participants completed a questionnaire comprised of demographic information, a medication adherence survey, and an everyday racism in the healthcare setting survey. Additionally, 27 of the total sample (N=46) participated in in-depth interviews which lasting approximately one hour. Participants were recruited from attendees at two patient-centered meetings in Greensboro, NC and Nashville, TN. Pearson’s Correlation was used to analyze quantitative data and Constructivist Grounded Theory was used to identify themes that emerged from interview transcripts.

Results: A statistically significant negative relationship was found between medication adherence and everyday racism in the healthcare system (r = −.477, P < .01). As everyday racism increased, medication adherence decreased. Furthermore, interviews revealed that everyday racism perpetrated within the healthcare system negatively affected participants’ medication adherence. Three themes were identified: 1) Concern that medical providers were not knowledgeable about the medications they were prescribing 2) Concern that the medication was not safe 3) Information about medication and lab results withheld or given to participants without further explanation.

Conclusions: These findings provide the basis for development of future research that could lead to interventions with healthcare systems and professionals to address the medication adherence disparity.

Funding: Private Foundation Support

FR-PO287

Methylguanidine in Normal Subjects and ESRD Patients Ahmed Z. Alkhathlan,1 Xin Hui,1 Mirela A. Dobro,2 Timothy W. Meyer,1 Thomas H. Hostetter,1 ’University Hospitals Case Medical Center, Beachwood, OH; 2’Case Western Reserve University, Cleveland, OH; 1Stanford University, Palo Alto, CA.

Background: Methylguanidine (MG), a guanidino compound, is a small water-soluble solute that accumulates in uremic patients and has been implicated in some uremic toxicities. We studied the behavior of MG in end-stage renal disease patients on chronic dialysis compared to normal controls.

Methods: We studied six normal controls and seven chronic hemodialysis patients. Blood and 24-hour urine samples were collected from the control group, while blood and dialysate samples were collected from the dialysis group (start, mid, and end of dialysis sessions). Urea, creatinine, and Cr were measured by a LC-MS/MS method. Mean levels, clearance, and production/excretion rates were calculated assuming first order kinetics. A Student’s t test, Pearson correlation coefficients were used for data analysis. Results are expressed as mean ± standard deviation (SD).

Results: The mean predialysis plasma MG level in chronic dialysis subjects was significantly higher (more than 100-fold) than the control group (5.17 ± 2.6 vs. 0.047 ± 0.02). In comparison, the mean predialysis urea level was only three-fold the normal level (44.05 ± 23.06 vs. 14.89 ± 3.23 mg/dL, respectively, P = 0.02), and Cr was 13-fold the normal level (10.8 ± 3.1 vs. 0.83 ± 0.18 mg/dL, respectively, P = 0.001). The mean production rates of MG were 47.12 ± 4.61 (± 3.4) mmol/day in chronic dialysis patients and healthy individuals, respectively (P < 0.05). The effective clearance rates for urea and Cr in dialysis patients were 239 ± 69 and 173 ± 51 ml/min, respectively; which were significantly higher than the effective clearance rate for MG 122 ± 26 ml/min (P < 0.05).

Conclusions: MG accumulates to more than 100 fold the normal level in ESRD patients. This accumulation likely reflects 1) its clearance rate (and therefore its reduction ratio) is significantly less than that of urea and Cr, which is likely due to its previously described large distribution volume, and 2) increased production from Cr oxidation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUBL - Publication Only
Underline represents presenting author.
reference organizations, 11 mature facility-level PMs were selected that encompassed diabetes, medication, nutrition, patients, and nutrition. This collaboration across different VHA service lines helped to create this dashboard, which leveraged the VA electronic medical record and data warehouses, and created a web-based application for field reporting. Fourth, a coordinated series of national rollouts called for guidance and support at the national level.

The Dashboard was fully implemented in 2013, and by 2016 there was 100% VA diabetes facility participation and 96% usable records for PMs.

Conclusions: The VHA Diabetes Dashboard is a versatile surveillance and reporting tool that is critical to achieve and maintain high-quality care, to guide and motivate high quality care, to target quality improvement efforts at a facility level, and to provide an atmosphere for promoting a cohesive approach to process improvement efforts at a national level.

Funding: Veterans Affairs Support

FR-PO829

Protein-Bound and Large Toxin Removals between Hemodialysis Using High Cut-off Dialyzers with Adsorptive Cartridge and High-Efficiency Online Hemofiltration: A Crossover Randomized Controlled Trial Although the Nephrology Khenmark,1,2 Khaolui Tishirabunlual,1,2 Maneerut Limjarjyakul,1,3 Supeecha Wittayaertpanya,1 Pawanee Susantitaphong,1,2 Somchai Eiam-Ong,1,2 Kearthik Pratdopinsilpa,1,2 Chulalongkorn University, Bangkok, Thailand; 2King Chulalongkorn Memorial Hospital, Bangkok, Thailand.

Background: Protein-bound toxins especially indoxyl sulfate (IS) which could not be removed by standard hemodialysis (HD) using high-flux dialyzer are obviously correlated with high mortality in HD patients. High-efficiency online hemofiltration using postdilution HDF (treatment with cut-off of dialyzer and tcr HD) has been reported to enhance IS removal and improve patient survival. At present, there are certain limitations of OL-HDF including necessity for special machine and high investment cost. Therefore, we proposed a new HD modality which can be performed in any HD centers with standard HD machine by using high cut-off (HCO) dialyzer, PES-10D (Nipro, Japan) in combination with hemoperfusion (HP), using HA130 adsorptive cartridge (Jafon, China) and compared with OL-HDF.

Methods: This was a cross-over randomized control trial. Ten chronic hemodialysis patients were randomized to consecutively undergo dialysis with either new HD modality (HCO HD with HP) or OL-HDF before cross-over to the other modality for 8-week each period. The efficacy including percentage reduction after dialysis of IS, β2-microglobulin (β2m) and area were measured. Patient safety and dialysate albumin loss were monitored. IS was measured by high performance liquid chromatography.

Results: The plasma IS levels significantly decreased in both treatment modalities. The percentage reduction of IS were comparable between HCO HD with HP and OL-HDF (52.0±11.7 vs. 56.3±7.5 %, p=0.28). The percentage reduction of β2m did not differ (83.7±4.9 vs. 84.0±3.4 %, p=0.75). Two techniques provided adequate small solute removal, as the normalized β2mulin loss was significantly higher in HCO HD (4.4±2.4 g/session) compared with OL-HDF (4.2±2.4 g/session; P=0.008), there were no significant long-term changes in serum albumin levels of both modalities.

Conclusions: Standard HD using HCO dialyzer with HP using adsorptive cartridge, which could be performed in any HD centers, can effectively reduce IS, β2m, and small toxin in comparable with high cost OL-HDF and could replace OL-HDF where it is unavailable.

Funding: Fujisawa Healthcare Private Foundation Support

FR-PO830

Renal AA-amyloidosis in Dialysis-Dependent Drug Addicts Camilla Madsen, Ingjerd W. Manner, Helga Gudmundsdottir. Oslo University Hospital, Ullevål, Oslo, Norway.

Background: A substantial increase of dialysis-dependent injecting drug abusers has been observed in Oslo, Norway. The incidence in other parts of the country is low. Longstanding chronic skin infections caused by subcutaneous administration (“skin popping”) of illicit drugs, when the intravenous route is exhausted may induce AA-amyloidosis. The kidneys are the organs most frequently affected. Renal AA-amyloidosis has been observed in Oslo, Norway. The incidence in other parts of the country is low.

Methods: A retrospective investigation including all patients with past or present injecting drug addicts with renal failure caused by renal disease, but not the Agatston score, in HD patients. This study investigated the associations between the plasma total MGP level and vascular calcification but published data on plasma MGP levels of HD patients are inconsistent. This study investigated the associations between the plasma total MGP level and vascular calcification but published data on plasma MGP levels of HD patients are inconsistent.

Results: The healthy subjects’ mean estimated glomerular filtration rate was 78±13 ml/min/1.73m2. The HD patients’ (including 25 patients with diabetes) median dialysis vintage was 78 (36±152) months. The age (50±6 vs.48±6 years), sex distribution, and body mass index and vitamin K2 levels were not significantly different, but the vitamin K1 levels were significantly lower (0.56±0.27 vs. 0.98±0.61 mg/L, P<0.001), and the MGP levels were significantly higher (29±50 vs.160±41 mg/L, P<0.0001) in HD patients as compared to controls. Regression analyses indicated that age, dialysis vintage, presence of cardiovascular disease, vitamin K1 level, and GNRI were significantly associated with plasma MGP level. The association of inflammation and is further indicates that other factors are more important determinants of PBT concentrations.

Funding: Commercial Support - 3M Deutschland GmbH

FR-PO832

Plasma Total Matrix Gla Protein, Vitamin K Levels, and Vascular Calcification in Prevalent Hemodialysis Patients Sonnoo Mizuiri,1 Yoshiko Nishizawa,1 Kazuomi Yamashita,1 Kohji Usu,1 Chie Tanji,1 Shigehiro Doi,1 Takao Masaki,1 Kenichiro Shigemoto,1 Ichiyoki Ichiyoki Clinic, Hiroshima, Japan; 2Hiroshima University Hospital, Hiroshima, Japan; 3Ichiyoki Harada Hospital, Hiroshima, Japan.

Background: Hemodialysis (HD) patients suffer from accelerated vascular calcification. Vitamin K-dependent matrix Gla protein (MGP) is a potent inhibitor of vascular calcification but published data on plasma MGP levels of HD patients are inconsistent. This study investigated the associations between the plasma total MGP level and vascular calcification but published data on plasma MGP levels of HD patients are inconsistent.

Methods: Subjects were 73 prevalent HD patients aged≥60 years and 40 healthy controls. Plasma total (including inactive) MGP levels were assessed using an ELISA kit (Cloud-Clone Corp). Predictors of the plasma MGP level in patients were identified by regression analyses [variables: age, presence of diabetes, presence of cardiovascular disease, dialysis vintage, Agatston (coronary artery calcification) score, serum phosphorus, calcium, intact parathyroid hormone, vitamin K1, and vitamin K2 levels, Kt/Vurea, and geriatric nutritional risk index (GNRI)]. The variables that displayed significance in the univariate analysis were subjected to multiple regression analysis.

Results: The healthy subjects’ mean estimated glomerular filtration rate was 78±13 ml/min/1.73m2. The HD patients’ (including 25 patients with diabetes) median dialysis vintage was 78 (36±152) months. The age (50±6 vs.48±6 years), sex distribution, and body mass index and vitamin K2 levels were not significantly different, but the vitamin K1 levels were significantly lower (0.56±0.27 vs. 0.98±0.61 mg/L, P<0.001), and the MGP levels were significantly higher (29±50 vs.160±41 mg/L, P<0.0001) in HD patients as compared to controls. Regression analyses indicated that age, dialysis vintage, presence of cardiovascular disease, vitamin K1 level, and GNRI were significantly associated with plasma MGP level.

Conclusions: Differences in instantaneous removal by dialysis therapies have only limited impact on mid-term plasma levels of PBT. The association of inflammation and is further indicates that other factors are more important determinants of PBT concentrations.

Funding: Foundation Private Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
**FR-PO833**

**Trends in Emergency Hospitalization for Cardiovascular and Infectious Diseases between Hemodialysis and Peritoneal Dialysis over 20 Years**

Masataka Banshodani, Hideki Kawanishi, Misaki Morishita, Sadanori Shintaku, Shichiro Tsutsumi. Tsukuba General Hospital, Hiroshima, Japan.

**Background:** In hemodialysis (HD), volume and electrolyte status drastically change, whereas peritoneal dialysis (PD) is a continuous dialysis and thus maintain a stable volume and electrolyte status. However, no studies have evaluated trends of hospitalization for cardiovascular diseases (CVDs) and infectious diseases (IDs) according to dialysis modality over time.

**Methods:** This is a retrospective observational cohort study that evaluated 13,078 hospitalizations (1,955 HD and 497 PD patients with end-stage renal disease) to clarify associations between dialysis modality and emergency hospitalization for CVDs (HD, 1,704; PD, 261 times) and IDs (excluding PD-related infections; HD, 970; PD, 132 times) at a single institution over 20 years (1995–2014).

**Results:** The CVD hospitalization rate (per 100 person-years) in PD remained at the same level over 20 years (1995–1999, 2000–2004, 2005–2009, 2010–2014; 9.7, 6.5, 10.5, and 7.2, respectively), while in HD, the rate decreased (15.4, 8.3, 5.7, and 6.3; every P < 0.001, v.s. 1995–1999). The ID hospitalization rate in PD decreased in the last 5 years (5.0, 5.0, 5.4, and 2.5, respectively; P = 0.001, 2005–2009 v.s. 2010–2014). In HD, the rate increased (5.9, 3.9, 3.8, and 5.4; P < 0.001, 2005–2009 v.s. 2010–2014). In the logistic regression analyses, the odds of dialysis vintage (odds ratio [OR], 3.58; confidence interval [CI], 2.25–5.77; P < 0.001) and HD (OR, 2.04; CI, 1.57–2.68, P < 0.001) were significantly higher for CVD hospitalization in the first 10 years, but the significances disappeared in the last 10 years. Although no significance was found in first 10 years, the odds of male sex (OR, 1.27; CI, 1.08–1.51, P = 0.004) and HD (OR, 1.52; CI, 1.19–1.96, P = 0.001) were significantly higher for ID hospitalization in the last 10 years.

**Conclusions:** The risk of CVD hospitalization was significantly higher in HD than in PD in the first 10 years, but the risk disappeared in the last 10 years. However, the increased risk of ID hospitalization in HD should be solved. Further multicenter studies are needed to compare hospitalization rates among dialysis modalities.

**FR-PO835**

**Association of Waist-to-Hip Ratio with Sudden Cardiac Death and Cardiovascular Mortality in Incident Hemodialysis Patients**

Jessica Fitzpatrick,1 Stephen M. Sozio,2 Bernard G. Jaar,2 Michelle M. Estrella,2 Jose M. Monroy-Trujillo,2 Larisa G. Tereshchenko,2 Rulan S. Parekh,1 University of Toronto, Toronto, ON, Canada; 2Johns Hopkins University, Baltimore, MD; 3Oregon Health and Science University, Portland, OR; 4University of California, San Francisco and San Francisco VA Medical Center, San Francisco, CA.

**Background:** Waist-to-hip ratio (WHR) is a predictor of cardiovascular disease (CVD) and mortality in the general population. Few studies, however, have examined the association of WHR and risk of CVD mortality, particularly sudden cardiac death (SCD), among end-stage renal disease (ESRD) patients undergoing hemodialysis.

**Methods:** This study included 379 incident hemodialysis patients enrolled in the Predictors of Arterial and Cardiovascular Risk in ESRD (PACE) Study. WHR was calculated as the ratio of waist-to-hip circumference. CV death was defined as deaths arising from arrhythmias, ischemic CVD, and ischemic cerebrovascular disease, as well as SCD. Cox proportional hazards regression was used to estimate the association of baseline WHR with risk of CVD death, SCD, and non-SCD death.

**Results:** At baseline, the mean age was 54.9 years, 41% were female, 73% were African American, 57% had diabetes, the mean comorbidity index was 5.2, the mean body mass index (BMI) was 29.3 kg/m², the mean WHR was 0.95, and 85% were above the World Health Organization WHR threshold for metabolic complications. WHR and BMI were weakly correlated (r = 0.21). During a median follow-up time of 2.5 years, there were 35 CVD deaths, 15 SCD, and 48 deaths from non-CVD causes. An increase in WHR was associated with higher hazard of CVD mortality and SCD, but not non-CVD mortality. In adjusted models, WHR was strongly associated with SCD. There was no evidence of interaction between WHR and race or BMI in any of the models. [Table]

**Conclusions:** WHR is associated with SCD and CVD death in incident hemodialysis patients. The easily measured WHR may be a useful metric to risk stratify ESRD patients for CVD mortality.

**Funding:** NIDDK Support

**FR-PO836**

**A Scoring System to Guide Systemic Oral Anticoagulation Among Incident Dialysis Patients with a Preexisting Diagnosis of Atrial Fibrillation/Flutter**

Robert C. Albrighi,1 John J. Dillon,2 Dena E. Cohen,3 Steven M. Brunelli,1 DaVita Clinical Research, Minneapolis, MN, 4Mayo Clinic, Rochester, MN.

**Background:** Among the general population, patients with atrial fibrillation/flutter (Afib) and a CHA2DS2-VASc score s2 have high stroke risk and may receive systemic oral anticoagulation (SOA). Utility of CHA2DS2-VASc in patients initiating hemodialysis (HD) with pre-existing Afib is unclear.

**Hypothesis:** We considered adult Medicare enrollees who initiated HD at a large US dialysis organization in 2010–2011 with pre-existing Afib, determined from claims. Exposures were risk scores and SOA, based on a prescription fill during the first 3 months of HD. Outcome (stroke/transient ischemic attack [TIA]) was considered from HD start. Exposures were risk scores and SOA, based on a prescription fill during the first 3 months of HD. Outcome (stroke/transient ischemic attack [TIA]) was considered from HD start. Exposures were risk scores and SOA, based on a prescription fill during the first 3 months of HD. Outcome (stroke/transient ischemic attack [TIA]) was considered from HD start.

**Methods:** We considered adult Medicare enrollees who initiated HD at a large US dialysis organization in 2010–2011 with pre-existing Afib, determined from claims. Exposures were risk scores and SOA, based on a prescription fill during the first 3 months of HD. Outcome (stroke/transient ischemic attack [TIA]) was considered from HD start. Exposures were risk scores and SOA, based on a prescription fill during the first 3 months of HD. Outcome (stroke/transient ischemic attack [TIA]) was considered from HD start. Exposures were risk scores and SOA, based on a prescription fill during the first 3 months of HD. Outcome (stroke/transient ischemic attack [TIA]) was considered from HD start.

**Results:** Among 2742 patients initiating HD with Afib, no association was observed between SOA and risk of stroke/TIA across CHA2DS2-VASc categories. Female sex, Hispanic race, use of a central venous catheter, congestive heart failure, and diabetes defined an HD-specific risk score. In the top quartile of this score, SOA (vs. no SOA) was associated, at near statistical significance, with a lower point estimate for risk of stroke/TIA.

**Conclusions:** We developed a risk score that, unlike CHA2DS2-VASc, may identify incident HD patients with Afib who will benefit from SOA. Further work is needed to refine and validate this HD-specific score.

**Funding:** Commercial Support - DaVita, Inc
FR-PO837
Dialysis Modality and Incident Atrial Fibrillation in Older Patients with ESRD Initiating Dialysis Jingbo Niu, Maulin Shah, Jose J. Perez, Medha Airy, Sankar D. Naveenathan, Wolfgang C. Winkelmayer. Baylor College of Medicine, Houston, TX.

Background: The incidence of atrial fibrillation (AF) in older patients with ESRD initiating hemodialysis (HD) is high, at 14.8 per 100 person-years, and AF is associated with increased morbidity and mortality. It has been postulated that peritoneal dialysis (PD) may confer lower AF risk owing to lesser fluctuations of fluid and electrolyte status. We tested whether the incidence of AF differed between patients using PD versus HD for the initiation of dialysis in a national U.S. cohort.

Methods: Patients 67+ years who initiated dialysis for ESRD in the continental US were eligible if they had been continuously enrolled in Medicare A&B during the 2 years pre- and 90 days post-ESRD. Those with any diagnosis of AF prior to initiation of dialysis (~index date) were excluded. Patients were further required to have exclusively used a single modality for these first 90 days (or until they died or received a transplant during that period). Patients were then followed for AF incidence, which was ascertained from 1 inpatient or 2 outpatient diagnoses (ICD-9 code: 427.3x). Follow-up was terminated 3 years after index date or at loss of Medicare A&B coverage. Death and kidney transplantation were handled as either censoring or competing events in separate analyses. Multivariable Cox proportional hazards regression models were used to estimate the cause-specific and sub-distribution hazard ratios (HR [95% confidence interval]) for PD vs HD.

Results: We identified 251,092 patients with ESRD initiating dialysis between 1996 and 2011; 93.2% used HD and 6.8% used PD. During 447,253 years of follow up, 69,656 patients were newly diagnosed with AF; 3,324 received a kidney transplant and 102,202 died. The unadjusted AF incidence rates per 100 person-years were 15.7 for HD and 14.5 for PD, respectively. The unadjusted cause-specific HR for AF comparing PD to HD (referent) was 0.93 (0.91-0.96) and the sub-distribution HR was 0.97 (0.95-1.00). Multivariable adjustment yielded a cause-specific HR of 1.03 (1.00-1.06) and a sub-distribution HR of 1.00 (0.97-1.03).

Conclusions: In older individuals with ESRD initiating dialysis in the U.S., patients using PD had very similar adjusted rates of AF compared with otherwise similar patients using HD.

Funding: NIDDK Support

FR-PO838
Oral Anticoagulation Among Patients Initiating Dialysis with Existing Atrial Fibrillation/Flutter: Association with Outcomes and Risk Score Robert C. Albright,1,2 John J. Dillon,3 Dena E. Cohen,4 Steven M. Brunelli1,5 DaVita Clinical Research, Minneapolis, MN; 2Mayo Clinic, Rochester, MN.

Background: In the general population, systemic oral anticoagulation (SOA) may reduce stroke risk among patients with atrial fibrillation/flutter (Afib). Patients who develop Afib after starting hemodialysis (HD) do not typically benefit from SOA. Guidance for use of SOA among patients who initiate HD with pre-existing Afib is scant.

Methods: This study considered adult Medicare A, B, and D beneficiaries who initiated in-center HD at a large US dialysis organization in 2010 or 2011 with a pre-existing diagnosis of Afib, ascertained from claims data. SOA (exposure) was based on a Medicare D claim for a prescription fill during the first 3 months of HD. Outcomes were considered from HD start until death, loss to follow-up, or study end (31 Dec 2012). Comparisons were made using intention-to-treat principles and negative binomial (hospitalization) or Cox proportional hazard (death, stroke, ischemic stroke, and stroke/transient ischemic attack [TIA]) models adjusted for imbalanced characteristics.

Results: Among 2742 patients initiating HD with Afib, 835 had a fill for SOA, and 1907 did not. No independent association was observed between SOA and any outcome considered. No protective association of SOA was observed in patients with high (or low) CHADS,VS – VAsc risk score (interaction > 0.1 for each). No association was observed between SOA use and risk of gastrointestinal bleed.

Conclusions: Among patients who initiate HD with pre-existing Afib, traditionally accepted stroke risk scores cannot adequately guide clinicians with respect to possible benefit of SOA. Alternate methods are needed to guide use of SOA in such patients.

Funding: Commercial Support - DaVita, Inc

FR-PO839
Relationship between History of Stroke before Dialysis Initiation and All-Cause Mortality in Dialysis Patients Masayasu Kojima,1 Daijo Inaguma,2 Hideaki Shimizu,1 Shigehide Koide,3 Kazuo Takahashi,1 Hiroki Hayashi,2 Midori Hasegawa,2 Yukio Yuzawa,2 Nephrology, Daido Hospital, Nagoya, Japan; 2Neurology, Fujita Health University School of Medicine, Toyko, Japan.

Background: Some reports have shown a relationship between stroke and all-cause mortality in pre-dialysis or maintenance dialysis patients. However, there are few previous studies describing the prognosis of dialysis patients whose baseline was set at the time dialysis was initiated. Therefore, we examined whether all-cause mortality differed between dialysis patients with and without a history of stroke before dialysis initiation.

Methods: The subjects were patients in the 17 centers participating in the Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis (AICOPP) from October 2011 to September 2013. We determined by a survey conducted at the end of March 2015. Thus, we enrolled 1,520 subjects into the study. We classified patients into 2 groups according to the history of stroke (i.e., a stroke group and a non-stroke group). Propensity scores (PS) represented the probability of being assigned to a group with or without a history of stroke. All-cause mortality was compared in PS-matched patients by using the log-rank test for Kaplan-Meier curves. Factors contributing to all-cause mortality were examined using stepwise multivariable Cox proportional hazards analysis.

Results: There were 236 patients in each group after PS-matching. The median of follow up period was 1,318 days (interquartile range: 1,109-1,509 days). During observation, all-cause death occurred in 84 patients (35.6%) in the stroke group and 28 (11.9%) patients in the non-stroke group. Cardiovascular related death occurred in 32 patients (13.6%) in the stroke group and 10 (4.2%) patients in the non-stroke group. The all-cause mortality was significantly higher in the stroke group compared to the non-stroke group after PS-matching (Logrank test: p < 0.001). The all-cause mortality was significantly higher in the stroke group compared to the non-stroke group (hazard ratio = 5.00, 95% confidence interval = 2.81-9.00) in multivariate analysis adjusted for age, gender, comorbidity of diabetes, history of coronary artery disease, body mass index, blood pressure, hemoglobin, eGFR, use of loop diuretics, CRP, and bicarbonate.

Conclusions: History of stroke before dialysis initiation was associated with a higher all-cause mortality.

FR-PO840
Hemoglobin Concentrations and the Risk of Hemorrhagic and Ischemic Stroke in Patients Undergoing Hemodialysis: The Q-Cohort Study Bysuk Lee Yotsuzuka,1 Shigeru Tanaka,1 Masatoshi Taniguchi,2 Hideki Hiraikata,2 Kazuhiko Tsuneya,3 Takanari Kitazono,3 Fukuoka Dental College, Fukuoka, Japan; 2Fukuoka Renal Clinic, Fukuoka City, Japan; 3Kushu University, Graduate School of Medical Sciences, Fukuoka City, Japan.

Background: Several lines of evidence have suggested an association between low hemoglobin concentrations and hemorrhagic stroke, and an association between high hemoglobin concentrations and ischemic stroke. However, the contribution of hemoglobin concentrations to the separate incidence of hemorrhagic or ischemic stroke in patients undergoing hemodialysis remains unclear.

Methods: A total of 3,436 participants undergoing maintenance hemodialysis were followed up for 4 years. The primary outcome was incidence of first development of hemorrhagic or ischemic stroke. Hemoglobin concentrations were divided into quartiles based on baseline data (hemoglobin [g/dL]: Q1, ≤9.7; Q2, 9.8-10.5; Q3, 10.6-11.1; Q4, ≥11.2). The associations between hemoglobin concentrations with each types of stroke were examined using Kaplan-Meier method and Cox proportional hazards model.

Results: During the follow-up period, 77 (2.2%) patients experienced hemorrhagic stroke and 141 (4.1%) experienced ischemic stroke. The 4-year incidence rate of hemorrhagic stroke was significantly higher with lower hemoglobin concentrations. Compared with the quartile of the highest hemoglobin concentrations (Q4), the multivariable-adjusted hazard ratios for hemorrhagic stroke were 1.18 (95% confidence interval, 0.56-2.51), 1.65 (0.85-3.30), and 2.16 (1.14-4.64) in patients with Q3, Q2, and
FR-P0841
Identifying Patients at Risk for Intradialytic Hypotension
Lucia Neri, Milena Chemeris, Carlo Barbieri, Flavio Mari, Stefano Stuard. Fresenius Medical Care, Bad Homburg, Germany.

Background: Despite Intradialytic Hypotension is a prominent clinical problem for patients on dialysis, there currently is no valid risk prediction tool.

Methods: All FME patients registered in Spain (2013 - 2015) have been enrolled in a historical cohort. We extracted medical data from de-identified electronic clinical charts (EuClid database). We partitioned the initial dataset in a training (90%) and validation (10%) sample. We implemented a two-part protocol to evaluate correlates of Intradialytic Hypotension (IDH) and derived a risk score. Stage 1 identified patients at high risk of experiencing at least 1 IDH. Stage 2 predicted IDH rate in patients identified in stage 1 as the IDH cluster. AIC minimization was used for model selection.

Results: Among 7582 patients (Validation set: 758), 4364 had at least one IDH during follow up time (mean=1.58 ± 1.03 years). On average there were 5.1±9.5 events per patient during the follow up (incidence: 0.023±0.036 IDH per person-year). Factors associated with increased IDH risk: ESPRIT stage, previous IDH, variability of intradialytic body weight drop, intradialytic blood pressure drop, ultrafiltration volume, predialysis blood pressure, serum potassium, extracellular water volume, calcium, ferritin, body fat, female sex, use of diuretics, diabetes, CRP, history of stroke, dialysate bicarbonate and sodium, dementia, over-hydration. Factors associated with reduced IDH risk: intradialytic blood pressure variability, dry body weight, low intracellular water volume, intradialytic heart rate variability, urea distribution volume, hematocrit, serum potassium. The risk score had excellent calibration and accurately discriminated across different risk classes (fig1).

Conclusion: We identified potentially modifiable risk factors for IDH. Additionally, our prediction algorithm provides a reliable tool for risk stratification.

FR-P0842
Effects of Blood Pressure Variability on Mortality in Chronic Hemodialysis Patients: OCTOPUS Study Takayuki Adachi, Kentaro Kohagura, Hisatomi Arima, Kunitoshi Iseki. Fukuoka University, Fukuoka, Japan; Tomihiro Central Hospital, Tomigusuku city, Japan; University of the Ryukyus, Nishihara-cho, Japan.

Background: We examined the relationship between blood pressure variability and survival among chronic HD patients.

Methods: We reviewed the results of the multi-center prospective, open trial of the Olmseran Clinical Trial in Okinawa Patients Under Okinawa Dialysis Study (OCTOPUS). In a multicenter, prospective, randomized, open label, blinded-endpoint trial, 469 patients with chronic HD and elevated BP (140–199/90–99 mmHg) were assigned to receive the angiotensin receptor blocker (ARB) olmesartan (at a dose of 10–40 mg daily; n = 235) or another treatment that does not include angiotensin receptor blockers and angiotensin-converting enzyme (ACE) inhibitors (n = 234). For this study, we examined 435 patients after excluding those who died within 1 year after randomization (N=28) and lack of blood pressure data for more than 2 times (N=6). We adopted the coefficient of variation (CV), which was obtained using 6 pre-HD blood pressure within the first year after registration, as a marker of blood pressure variability. Cox proportional hazard analysis was used to examine the relationship between blood pressure variability and mortality after the 1-year visit with adjustment for age, sex, smoking, DM, HD vintage, and use of angiotensin receptor blocker.

Results: During the mean follow-up of 2.5 years after the 1-year visit, we observed 58 deaths. We used five quintile groups of CV pre-HD systolic blood pressure (Q1 to Q5). The mortality rate was 9.2% (255/2780), 12.2% (Q2) 9.1% (Q3), 16.5% (Q4), and 19.5% (Q5), respectively. The adjusted hazard ratio (95% confidence interval) was 1.83 (0.73-4.63) in Q1, 1.83 (0.73-4.63) in Q2, 1.84 (0.77-4.40) in Q4, and 2.42 (1.04-5.62) in Q5 when the Q3 was taken as reference.

Conclusions: Mortality rate was higher among patients with higher pre-HD variability of blood pressure.

FR-P0843
Association of Intradialytic Hypotension and Vascular Calcification in Hemodialysis Patients Aijn Cho, Jung-woo Noh, Dong Ho Shin. College of Medicine, Hallym University, Seoul, Republic of Korea; Hallym University, Seoul, Republic of Korea; Hallym university Kangnam Sacred Heart Hospital, Seoul, Republic of Korea.

Background: Intradialytic hypotension (IDH) is a common complication during hemodialysis (HD). IDH not only causes discomfort, but also increases patient mortality and cardiovascular events (CVEs). Vascular calcification is associated with structural and functional abnormality of the heart and blood vessels. It induces a reduction in vascular compliance and diastolic LV dysfunction. Therefore, IDH may be associated with vascular calcification in HD patients. We investigated the relationship between IDH and vascular calcification in HD patients, and their impacts on CVEs.

Methods: We enrolled 191 maintenance HD patients who underwent plain abdomen radiography for abdominal aortic calcification score (AACS). A nadir systolic blood pressure (BP) < 90 mm Hg or the requirement of bolus fluid administration was required to quantify the hypotension diagnosis. IDH was defined as > 2 hypotension episodes during 10 HD treatments.

Results: Among the 191 patients, IDH occurred in 32. AACS was higher in the IDH group compared with the no-IDH group (8.4 ± 6.0 vs. 4.9 ± 5.2, respectively; P = 0.001). High AACS was an independent risk factor after adjustment for age, diabetes mellitus, ultrafiltration, diastolic BP, and calcium level (odds ratio (OR) = 1.08, 95% CI = 1.060-1.16; P = 0.04). Patients with both IDH and AACS > 4 had the highest cumulative CVE rate (27.9%, P=0.008) compared with 11.2%, 12.5%, and 6% for those with AACS > 4 only, with IDH only, and neither, respectively. In multivariate analysis, the presence of both IDH and AACS > 4 was a significant predictor of CVE (hazard ratio (HR) = 2.84, 95% CI = 1.04–7.74, P = 0.04).

Conclusions: IDH is associated with abdominal aortic calcification and is an independent risk factor for IDH. Both IDH and high AACS were significant predictors of CVE.
FR-PO845

Comparison between 44-Hours Ambulatory Blood Pressure Monitoring (ABPM) and 24-Hours Non-Dialysis Day ABPM in Indian Dialysis Subjects Rajesh B. Kumar, Rachana H. Jasani, SHRIRANG BICHD, Viswanath Billia, Paras Dedhia. Apex Kidney Foundation, Mumbai, India.

Background: ABPM is considered as a gold standard method to assess hypertension in dialysis population. However, 44 hours ABPM is cumbersome and usually encourages reluctance from patients. 24 hours ABPM is more practical and convenient for patients.

Methods: ABPM was performed for 44 hours in between 2 dialysis sessions. ABPM recorded every 20 min during the day (7 am to 11 pm) and every 30 min during the night (11 pm to 7 am) in non-fistula arm. Hourly means were averaged to obtain interdialytic systolic and diastolic blood pressure readings. 24 hours ABPM data was recorded every hour from a non-fistula arm from 6am to 6am. ABPM data with less than 70% readings were excluded from the study. 24 hours mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) were compared with 44 hours measurement using paired t-test.

Results: 35 patients were included in the analysis. Mean age was 54.5 ± 12.7 years and 66% were males and 34% were females. Mean dialysis vintage was 2.7 ± 2.8 years. 49% were diabetic, 97% were hypertensive and 23% had IHD. Mean 44 hour DBP was 151.9 ± 15.8/83.2±13.4 mmHg and mean 24 hour DBP was 151.5 ± 15.9/82.6±13.7 mmHg. There was no statistical difference between 44 hour and 24 hour mean SBP (p value: 0.45) and mean DBP (p value: 0.77).

Conclusions: Mean SBP and DBP of 44-hours ambulatory blood pressure monitoring and 24-hours non-dialysis ABPM were comparable in study subjects. We conclude that 24 hours ABPM on non-dialysis day is an alternate feasible option in assessing IBP in dialysis patients.

FR-PO846

Use of Beta-Blockers Associated with Lower Orthostatic Response in Dialysis Patients Gustavo Laham.1,2 Internal Medicine, Nephrology section, CEMIC, Ciudad de Buenos Aires, Argentina; 2FME CEMIC Saavedra, Ciudad de Buenos Aires, Argentina.

Background: Beta Blockers (BB) are widely used in dialysis patients (pts). However, the evidence supporting their utility in improving cardiovascular (CV) outcomes in this population is conflicting.

Methods: Within a CV evaluation program for pts with ESRD in our Hospital. We evaluated 102 pts attended the interdialysis day. BP and hemodynamics was determined with impedance cardiography in supine position and after the third minute of standing. Following variables: SBP, DBP, heart rate (HR), stroke volume (SV), systemic vascular resistance index (SVRI) and thoracic fluid content (TFC). At the same time, the variability of the frequency was obtained during 3 minutes at rest and in standing position. Patients were classified into 2 groups according to the presence of Hypotension (HYPOT) or not (EST). Orthostatic hypotension was defined as a drop of 20mmHg or more of SBP and/or 10mmHg or more of DBP when standing. Hemodynamic variables were analyzed : 1-baseline conditions and 2-differences (delta standing-lying) between the two groups (t-test and Mann-Whitney U test). Independent predictors of orthostatic hypotension were determined adjusting for age, sex, BP, anthropometric variables, time on dialysis and medication through a logistic regression.

Results: We included 81 patients: age: 59.8 ± 14 years, female 55.5%; SBP: 137.7a 27.2 mmHg, DBP: 83.5 ± 19.7 mmHg. Twenty nine pts (35.8%) had orthostatic hypotension. No significant differences were found in age, sex, BMI, time on dialysis, DM and CV events between both groups. 86.21% of the pts in the HYPOT group received BB compared to 28.8% of the pts in the EST group with a significant difference (p < 0.001). At rest position there were no hemodynamic or autonomic differences between both groups, but in Standing position, HYPOT group, showed delta of SVRI (p < 0.037) lower, as well as lower delta DBP, delta Median Blood Pressure and delta SBP (p < 0.0001) compared to the EST group. There were no significant differences in the delta TFC as well as between autonomic variables. In logistic regression the use of BB was an independent variable for orthostatic hypotension.

Conclusions: In this group of dialysis pts the use of BB was a determining factor to attenuate or mitigate the compensatory increase of the vascular resistance against the bipedestation. Therefore BB could collaborate with the development of hypotension when standing independently of the autonomic response.

FR-PO847

Association of Betaine with Blood Pressure in Dialysis Patients LuLu Wang,1 Mengming Zhao,1 Wenyin Liu,1 Lemin Zheng,2 Junwei Yang.1 2nd Affiliated Hospital of Nanjing Medical University, Nanjing, China; 1Center for Kidney Disease, Second Affiliated Hospital of Nanjing Medical University, Nanjing, China; 3Peking University, Beijing, China; 2Second Affiliated Hospital, Nanjing Medical University, Nanjing, China.

Background: Patients with chronic kidney disease have an increased risk of cardiovascular morbidity and mortality. Hypertension has been considered as one of the most important contributors to the increased risk. Betaine is a zwitterionic quaternary ammonium compound and distributed widely in rich dietary sources. Previous studies suggest a possible link between alteration of circulating betaine and hypertension. However, there is a paucity of data regarding patients on maintenance hemodialysis. We aimed to explore the association of betaine with blood pressure in this disease population.

Methods: Within a CV evaluation program for pts with ESRD in our Hospital. We evaluated 102 pts attended the interdialysis day. BP and hemodynamics was determined with impedance cardiography in supine position and after the third minute of standing. Following variables: SBP, DBP, heart rate (HR), stroke volume (SV), systemic vascular resistance index (SVRI) and thoracic fluid content (TFC). At the same time, the variability of the frequency was obtained during 3 minutes at rest and in standing position. Patients were classified into 2 groups according to the presence of Hypotension (HYPOT) or not (EST). Orthostatic hypotension was defined as a drop of 20mmHg or more of SBP and/or 10mmHg or more of DBP when standing. Hemodynamic variables were analyzed : 1-baseline conditions and 2-differences (delta standing-lying) between the two groups (t-test and Mann-Whitney U test). Independent predictors of orthostatic hypotension were determined adjusting for age, sex, BP, anthropometric variables, time on dialysis and medication through a logistic regression.

Results: We included 81 patients: age: 59.8 ± 14 years, female 55.5%; SBP: 137.7a 27.2 mmHg, DBP: 83.5 ± 19.7 mmHg. Twenty nine pts (35.8%) had orthostatic hypotension. No significant differences were found in age, sex, BMI, time on dialysis, DM and CV events between both groups. 86.21% of the pts in the HYPOT group received BB compared to 28.8% of the pts in the EST group with a significant difference (p < 0.001). At rest position there were no hemodynamic or autonomic differences between both groups, but in Standing position, HYPOT group, showed delta of SVRI (p < 0.037) lower, as well as lower delta DBP, delta Median Blood Pressure and delta SBP (p < 0.0001) compared to the EST group. There were no significant differences in the delta TFC as well as between autonomic variables. In logistic regression the use of BB was an independent variable for orthostatic hypotension.

Conclusions: In this group of dialysis pts the use of BB was a determining factor to attenuate or mitigate the compensatory increase of the vascular resistance against the bipedestation. Therefore BB could collaborate with the development of hypotension when standing independently of the autonomic response.

FR-PO848

Fluid Status (FS) as Predictor of Long Term Survival in Hemodialysis (HD) Patients Adrian M. Guinsburg, Marcelo D. Ferder, Cristina Marelli. Fresenius Medical Care, Moron, Argentina.

Background: Extracorporeal fluid overload (FO) has been typically described as predictor of all-cause mortality in HD patients. A recent publication [Dekker et al, KI (2017), 91, 1214-1223] also demonstrated a beneficial effect of pre and postdialysis fluid depletion on survival. In this study we aim to analyze the relationship between FS and survival in a large cohort of patients from Fresenius Medical Care LatinAmerica (FMCLA)

Methods: Patients on HD at FMCLA between 09/2008 and 12/2016 were included. Body composition after 90 days of dialysis was assessed by multifrequency bioimpedance spectroscopy (BCS™, Fresenius Medical Care). Pre and postdialysis fluid status (FS) groups were defined according to overhydration (OH) as follow: fluid depletion (FD, < -1.1lt); normovolemia (NV, -1.1 to 1.1 lt); moderate FO (MFO, 1.1 to 2.5 lts); severe FO (SFO, 2.5 to 5 lts) and extreme FO (EFO, > 5 lts); A Cox regression model was constructed to analyze independent relationship between FS and survival accounting for age, gender, previous history of cardiovascular disease (yes vs no) and previous history of cardiovascular disease (yes vs no). Multiple linear regression analysis revealed significant associations of betaine with both systolic blood pressure (β= -3.66; P=0.003) and diastolic blood pressure (β= -0.94; P=0.02).

Conclusions: In conclusion, we demonstrated, for the first time, significant association between betaine and blood pressure level in a group of hemodialysis patients. Our data suggests that alteration of circulating betaine possibly contributes to blood pressure regulation in these patients.

Funding: Government Support - Non-U.S.

FR-PO849

Assessment of Pulmonary Congestion by thoracic Fluid Content Predicts Mortality in Hemodialysis Patients Jining Wu, Hong Ye, Junwei Yang. Second Affiliated Hospital, Nanjing Medical University, Nanjing, China.

Background: Pulmonary congestion is prevalent and usually asymptomatic in patients with end-stage renal disease (ESRD). Thoracic fluid content (TFC) measured by thoracic electrical bioimpedance (TEB) is suggested to serve as a non-invasive measure of pulmonary congestion. We explored the clinical and echocardiographic correlates of thoracic fluid content as well as its prognostic value in hemodialysis patients.

Methods: In this prospective observational study, we enrolled 114 patients from a single hemodialysis unit. We used different methods of evaluation: thoracic bioimpedance (pre- and postdialysis) and echocardiography (pre-dialysis). Our aim was to test the prognostic value of TFC in this population. Mortality was analysed after a median of 560.5-day follow-up. The primary outcome was all-cause death.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Results: TEB examination was successfully completed in 114 patients. Patients were divided into two categories based on the TFC measured before dialysis. TFC was strongly associated with left atrial diameter (LAD) (<0.454, P = 0.001), left ventricular posterior wall thickness (LVPW) (r = 0.473, P = 0.001) and ejection fraction (EF) (r = 0.527, P = 0.001). After a median follow-up of 320 days, compared with those patients having lower TFC, patients with higher TFC had 4.9-fold risk of death.

Conclusions: TEB is a technique that could detect pulmonary congestion at a pre-clinical stage in hemodialysis patients, and TFC emerged as a predictor for the mortality in this population.

Funding: Government Support - Non-U.S.

FR-PO850

Changes in Blood Pressure Following a Fluid Management Quality Improvement Project (QIP) during In-Center Hemodialysis (HD) Patients with Non-Contrast Cardiac Magnetic Resonance Imaging (CMR)

Matthew P. Graham-Brown,1 Ludmila Anderson,2 Lisa A. Facelli,2 Patrice B. Taylor,2 Cheryl A. Pierson-Brown,3 Robert J. Kossmann,3 Linda H. Fiocchi,31 Fresenius Medical Care North America, Waltham, MA; 2Renal Research Institute, New Haven, CT.

Background: Fluid and sodium retention are leading causes of hypertension (HT) among HD patients. A QIP with a goal to improve fluid management among patients on thrice weekly HD was conducted. This analysis aimed to determine whether QIP initiation was associated with BP changes among HT patients.

Methods: The QIP utilized CRI-Line® Monitors (CLM III) that non-invasively assess in-aortic relative blood volume (RBV) and provide real-time data to allow for ongoing fluid monitoring and management. De-identified data from electronic medical records of active patients at QIP initiation were analyzed. Average values for parameters at baseline (BL; 1 mo. prior to QIP initiation) and during first 3 mos. of the QIP were assessed. Changes in RBV, ultrafiltration volume (UFV), treatment (TX) time, and BP were analyzed. Stratified analyses by BL hypertension (HT) status (HT defined as pre-HD SBP > 140 or pre-HD DBP > 90 mmHg) were conducted. T-test and a×c-0.05 were used to compare the BL and the 3rd month of the QIP.

Results: In total, 54 out of 83 (65%) patients had HT at BL. Although UFV and TX time did not change between BL and mo.3 of the QIP, the majority of measured parameters of BP (Table) improved. On average, pre-HD SBP decreased from 163.3 ± 15.7 (p = 0.01) and pre-HD DBP decreased from 88.0 ± 15.1 (p = 0.05). Among normotensive patients (n=29), all BP parameters remained unchanged. The % of patients with SBP > 140 or pre-HD DBP > 90 mmHg was 9.6% at baseline, decreased to 8.8% at mo.3 of the QIP.

Conclusions: QIP initiation was associated with a decrease in BP parameters among HT patients. Neither TX nor UFV changed over 4 mos. of observation.

Funding: Commercial Support - Fresenius Medical Care North America

FR-PO851

Defining the Extent of Replacement Myocardial Fibrosis in Hemodialysis Patients with Non-Contrast Cardiac Magnetic Resonance Imaging

Matthew P. Graham-Brown,1 David S. March,1 James Burton,1 1University of Leicester, Leicester, United Kingdom; 2John Wallis Renal Unit, University Hospitals Leicester, Leicester, United Kingdom; 3National Centre for Sport and Exercise Medicine, Loughborough University, Loughborough, United Kingdom. Group/Team: CYCLE-HD.

Background: Extent of myocardial fibrosis predicts patient mortality in advanced renal disease. Gadolinium enhanced cardiac MRI (CMR) defines myocardial fibrosis but real-time functional imaging is not possible in patients with advanced renal disease due to the risk of nephrogenic systemic fibrosis. In this study we describe and assess a non-contrast native T1 CMR signal thresholding technique (T11SD) that may be used for the detection and quantification of myocardial scar burden in hemodialysis patients.

Methods: The T11SD technique defines the mean native T1 and standard deviation (SD) in regions of discretely increased signal on native T1 parametric maps. The mean ± SD of the region of interest are then applied as a threshold to the entire myocardium to give a threshold for replacement fibrosis. We assessed the agreement between T11SD and late gadolinium enhanced CMR (LGE-CMR) defined myocardial scarred (using full width half maximum analysis) in patients with aortic stenosis (AS) (n=25). We then compared T11SD between patients with AS (n=25) and patients on HD (n=25) and assessed inter and intra-observer variability of T11SD in HD patients (n=10).

Results: Myocardial scar assessed by LGE-CMR correlated with T11SD in AS patients (r=0.913) with moderate agreement (ICC=0.55). Bland-Altman showed T11SD was associated with BP changes among HT patients.

Conclusions: Nearly all ped CD pts with HTN at initiation had LVH by LVMI. LVMI was defined using known age and gender norms.

Results: 58 pts (32 male, 55%; 32 chronic HD, 55%), mean age 13.9 years (range 5-19.7 years). Median LVMI from initiation decreased significantly on follow up ECHO (initiation 56.7 ±2.7 g/m² vs. 43.7 ± 15.9 g/m², P = 0.003). LVMI was not associated with persistent HTN and/or increased meds) was significantly associated with persistent HTN on follow up in the group who had LVH at initiation of dialysis (table).

Conclusions: Nearly all ped CD pts with HTN at initiation had LVH by LVMI. LVMI improvement was associated with persistent hypertension in ped CD pts.

Funding: Clinical Revenue Support
Results: Table 1 lists hemodynamic data in C, in pts. with lower sdSV (<6.9 ml, n=72) and in those with higher sdSV (>6.9 ml, n=47) (see Table 1 below). Clinical data were similar in both HD groups with the exception of more prevalent peripheral vascular disease and use of antihypertensive drugs in pts. with higher sdSV. Kaplan-Meier analysis of 5y survival showed a significantly increased mortality in HD pts. with higher as compared with those with lower sdSV (p=0.01).

Conclusions: Our data show that a special group of HD pts are those with high CO, SV and sdSV and decreased TPR. Increased sdSV in HD pts. was associated with decreased survival, as previously reported in pts with high output cardiac failure and preserved renal function. The cause of this syndrome may include inadequate vascular compliance or excessive vasodilatation or the type of vascular access and deserve further investigation.

Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (C)</th>
<th>Lower sdSV (n=72)</th>
<th>Higher sdSV (n=47)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO (L/min)</td>
<td>5.1 (5.1)</td>
<td>5.1 (5.2)</td>
<td>5.7 (2.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>sdSV (L/m2)</td>
<td>0.19 (0.16)</td>
<td>0.19 (0.17)</td>
<td>0.17 (0.03)</td>
<td>0.001</td>
</tr>
<tr>
<td>TRC (mmHg)</td>
<td>121 (15.5)</td>
<td>100 (15.5)</td>
<td>100 (15.5)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data given as median (interquartile range).
lowest DASH score quartile (0-18), the adjusted hazard ratios for cardiovascular mortality in the second (18-20), third (20-23) and fourth (>23) quartile were 0.95 (0.72-1.24), 1.28 (1.00-1.64) and 1.14 (0.85-1.52), respectively; the adjusted hazard ratios for all-cause mortality were 0.98 (0.83-1.16), 1.04 (0.89-1.23) and 0.95 (0.78-1.14), respectively.

**Conclusions:** Mediterranean or DASH dietary patterns were not associated with cardiovascular and all-cause mortality for patients on hemodialysis.

**FR-PO858**

Long-Term Trends in the Co-Morbid Disease Burden of Incident Hemodialysis Patients Rita L. McGill, Jennifer L. Bragg-Gresham, Kevin He, Eduardo K. Lacson, Dana Miskulin, Rajiv Saran.

**Tufts University School of Medicine, Boston, MA; 2University of Michigan, Ann Arbor, MI; 3University of Chicago, Chicago, IL.**

**Background:** Since April 1995, dialysis facilities and kidney transplant centers in the United States have been required to report to the US Renal Data System (USRDS) the characteristics of all new kidney failure patients to the US Renal Data System (USRDS). We examined the prevalence of several relevant comorbid diagnoses of all new hemodialysis (HD) patients reported to USRDS from 1996–2015.

**Methods:** All first-time HD patients initiating treatment between January 1996 and December 2015 were included, and analyzed by year of HD initiation. Diabetes and cardiovascular diagnoses were condensed into single variables, to align data obtained from the 1995 and 2005 versions of the Medical Evidence form. Five year prevalence trends in the proportions of each co-morbid condition were evaluated with logistic regression, treating year of HD initiation as a continuous variable and adjusting for age, sex, and race. Five year prevalence trends were expressed as odds ratios (OR) and 95% confidence intervals (CI), with OR > 1 representing increasing prevalence.

**Results:** Among 1,864,386 incident HD patients were assessed. Mean age increased gradually over time from 60.9 to 63.8 years. Time trends revealed linear increases in the prevalence of hypertension (OR=1.34, 95% CI=1.34-1.35) and diabetes (OR=1.16, 95% CI=1.16-1.17). From 2006 onwards there was decreased prevalence of peripheral vascular disease (OR=0.91, 95% CI=0.91-0.91) and cardiovascular disease (OR=0.92, 95% CI=0.91-0.93). Prevalences of stroke, cancer, and lung disease showed no clinically significant changes.

**Conclusions:** The HD population in the United States is becoming older, with more hypertension and diabetes, but the prevalences of cardiovascular and peripheral vascular disease have decreased over the past ten years.

**Funding:** NIDDK Support

**FR-PO859**

Impact of the Obesity Epidemic on Dialysis Patients Rita L. McGill, Varun Gupta, Klemens B. Meyer.

**Creighton University, Northbrook, IL; 2Tufts Medical Center, Boston, MA; 3University of Chicago, Chicago, IL.**

**Background:** Obesity promotes chronic kidney disease directly via glomerular hyperfiltration, indirectly via increased diabetes and cardiovascular disease, and may reduce the likelihood of dying prior to kidney failure. We examined the impact of the US obesity epidemic on body mass index (BMI) of incident dialysis patients.

**Methods:** Cohorts of all incident adult USRDS patients between 2005 and 2015 with values recorded for BMI were examined, with stratification for hemodialysis and peritoneal dialysis (PD). BMI in kg/m² was categorized as <25, 25-29.9, 30-34.9, 35-39.9, and ≥40. Age, race, sex, and end-stage renal disease (ESRD) network were also recorded. Multivariable linear regression was used to estimate the change in BMI over time separately for HD and PD patients.

**Results:** Among 1,007,774 incident HD patients and 78,745 incident PD patients, the proportions of patients with BMI≥25 decreased, the proportions of patients with BMI ≥29.9 were stable, and the proportions of all groups with BMI≥30 increased between 2005 and 2015. After adjustment for age, sex, ESRD network, and race, BMI at dialysis initiation increased 0.147 kg/m² per year in HD patients and 0.126 kg/m² per PD patient (P<0.0001 for both).

**Conclusions:** Obesity and morbid obesity have been slowly increasing in the US dialysis population. Depending upon transplantation center criteria, 10-20% of patients enter dialysis with a BMI too high to be considered for kidney transplantation. Despite the paradoxical effects on survival, increasing obesity threatens the health of the dialysis patients, who face increased co-morbid disease burdens, reduced opportunities for optimal vascular access, and lower likelihoods that PD clearance will be adequate.

**Funding:** NIDDK Support

**FR-PO860**


**1Indiana University-University of Indianapolis, Indianapolis, IN; 2Massachusetts General Hospital, Boston, MA.**

**Background:** Frailty detection in incident patients on hemodialysis enables prevention strategies for disability, falls, hospitalizations and death. Traditional operational definitions of frailty developed with community-dwelling older adults includes self-report of “involuntary weight loss of >4.5 kg in the past year”. Weight loss in ESKD is difficult to ascertain given volumetric flux during dialysis. We hypothesize that omitting weight criteria from the operational definition of frailty will reclassify incident dialysis patients to capture comorbidities, physical function and disability.

**Methods:** This is a cross-sectional analysis of subjects in the Indiana cohort in LUCID, a longitudinal study of incident dialysis patients. The 5 frailty criteria are weight loss, exhaustion, low physical activity, slowness and weakness, with a sum score of ≥3 termed “frail”. Our “Lighter” (weight free) definition excludes weight loss and categorizes a sum > 2 as “new-frail”. SF36 scores, physical function (gait speed and grip strength), demographics as well as co-morbidities were compared between those “frail” and “new-frail”. We also determined the % of subjects of identified as “disabled” in the frail and new-frail groups, using published FNDR criteria (which are all self-report).

**Results:** Mean (SD) age of the 146 subjects was 54 (13) years; 54% male, 71% black, 53% had DM, and median (IQR) dialysis vintage was 90 (65) days. New-frail criteria (4 elements) increased the number of participants identified as frail using the traditional 5 element definition from 43 to 90. The new frail compared to the traditional definition increased the odds of being identified as frail 1 in diabetics, (OR 1.56 to 2.31) and 2) for those with inability to walk several blocks (OR 3.032 to 7.792) (both p<0.001). (OR 1.381 to 3.047, p<0.003). The new definition also identified more subjects who are frail, but not yet disabled (n=37% vs traditional criteria 16.5%, p<0.001).

**Conclusions:** Use of weight loss in traditional frailty definitions is complicated by its fluctuations during dialysis. The omission of weight and thus changing to a 4 element index demonstrated higher ORs for disease and function. This tool may be better at identifying frailty risk in women and those frail but not yet disabled. Longitudinal outcomes associated with this definition are currently being studied.

**Funding:** NIDDK Support

**Distribution of BMI in Patients on HD and PD over Time**
regression model, higher age, female sex, poor grip strength and the inability to walk several blocks were associated with lower average gait speed (adjusted R²: 0.08, P<0.01).

Conclusions: Lower skeletal muscle strength is associated with impaired mobility in patients new to dialysis. Older females with diabetes remain at greatest risk for mobility impairment. Poor gait speed is associated with decreased ability to perform ADLs in an incident dialysis population.

Funding: NIDDK Support

FR-PO862

Does Hemodialysis Impact Motor Performance beyond Diabetes and Peripheral Neuropathy? Objective Assessment of Gait and Balance Using Wearable Technology in a Hemodialysis Clinic

Noreen Siddiqi,1 Zhongtuo Du,2 Xin Li,3 Kezhao Wang,3 Xiaodong Cai,3 Rong Wang,3 Xiaoguang Huang,2 Jing Li,1 Yi Sun,2 Zhisheng Li3

Background: Poor motor performance is a serious problem for older adults undergoing hemodialysis (HD) treatment. HD process often leaves these patients too fatigued to engage in any physical activity or daily exercise; further deteriorating their gait and balance. In particular, little is known about how HD impacts gait and balance mainly due to difficulty of bringing these highly vulnerable population to a gait lab. In this study, we used wearable sensors to objectively examine the impact of HD on gait and balance.

Methods: 33 eligible subjects (age=66±6 years, body mass index=31±7 kg/m², male=58%) in 3 age-matched groups were recruited: 11 undergoing HD treatment, 11 with diabetes peripheral neuropathy (DPN) not requiring HD and 11 healthy controls (HC). Gait and balance performances were assessed using wearable sensors. Single task walking (ST), dual task walking (DT), and dual task condition (DTC), sensor creating main data mainly due to difficulty of bringing these highly vulnerable population to a gait lab. In this study, we used wearable sensors to objectively examine the impact of HD on gait and balance. Main outcome measures were: (a) walking time, (b) stride length, (c) stride velocity, (d) Cadence, (e) hip sway, (f) ankle sway and (g) ankle sway. The highest effect size to discriminate between HD and DPN as well as between DPN and HC, was ST stride velocity (d=4.825, P<0.001 and d=3.761, P<0.001). The HD group had the worst balance performance of all groups. Between-group differences of ankle sway and hip sway under both EO and EC conditions, reached statistical significance. The largest effect size to discriminate between the HD and DPN groups as well as between the HD and HC, was ST stride velocity (d=4.825, P<0.001 and d=3.761, P<0.001). The HD group had the worst balance performance of all groups. Between-group differences of ankle sway and hip sway under both EO and EC conditions, reached statistical significance.

Results: The HD group had the worst gait performance compared to other groups, which reached statistical significant level after adjusting for demographic information. The highest effect size to discriminate between HD and DPN as well as between DPN and HC, was ST stride velocity (d=4.825, P<0.001 and d=3.761, P<0.001). The HD group had the worst balance performance of all groups. Between-group differences of ankle sway and hip sway under both EO and EC conditions, reached statistical significance. The largest effect size to discriminate between the HD and DPN groups as well as between the HD and HC, occurred at EO hip sway (d=1.692, P<0.001) and EC hip sway (d=1.868, P<0.001).

Conclusions: To our knowledge this is the first study that utilize wearable technology to objectively characterize gait and balance in HD patients during clinical visit. Results demonstrate HD patients have significantly poorer gait and balance, even when compared to DPN patients. Poor balance and gait reduce the ability of HD patients to be active, which in turn may impact the outcomes and associated risk including poorer lower extremities perfusion, foot problems, falls and early frailty.

Funding: Government Support - Non-U.S.

FR-PO863

Low Serum Uric Acid-Mortality Association in Incident Hemodialysis Patients

Shigemoto N.,1 Kenoshio M.,1 Sonsoo M.,1 Maruii A.,1 Kyoka O.,1 Kenichiro Shigemoto,2 Koji Usui,3 Kacoumi Yamashita,4 Michiko Aritfox,4 Takao Masaki.3

Background: The association between serum uric acid (SUA) and mortality is contradictory in studies of hemodialysis (HD) patients. We hypothesized that nutritional status modifies the SUA-mortality association in the HD population.

Methods: We identified 462 patients who had HD treatment over 12 years (2004–2016) and had SUA measurements at HD initiation. Patients were followed-up until death. Kaplan-Meier survival analysis was assessed in each baseline SUA quartile (Q). Univariate Cox regression analyses of 1-year death were performed using data from 10,715 patients with SUA measurements within 6 months prior to the start of dialysis treatment (prelude). Using Poisson regression, we calculated incidence rate ratios (IRR) for hospitalizations during the first year after initiation according to prelude SUA strata, hierarchically adjusting for case-mix and laboratory covariates.

Results: Patients were 67 ± 11 years old, 2% female, 34% African-American and 69% diabetic. The 6-month prelude SUA was 8.1 ± 2.2 mg/dL. The median [IQR] number of hospital admissions during the first year on dialysis was 1 [0–3] with an incidence rate of 2 per 100 patient-years. A U-shaped association was observed between SUA and 1-year post-ESRD hospitalizations. In the fully adjusted model, compared with the reference group (7–8 mg/dL), the IRR were higher among the low and high (IRR [95%CI]: 1.06 [1.00, 1.11] and 1.06 [1.09, 1.14], respectively), but not intermediate (8–9 mg/dL).

Conclusions: High and low prelude SUA levels were associated with a higher rate of hospitalization following the first year of dialysis initiation. Further investigation is needed to develop the mechanism beyond pre-ESRD SUA levels and post-ESRD hospitalizations in this population.

Funding: NIDDK Support

FR-PO865

Depression Is Associated with Mortality Independent of Previous Screenings

John X.,1 Kirsten L. Johansen.2

Background: Depression affects up to 40% of dialysis patients and is associated with higher risk of mortality, but it is not known whether changes in depressive symptoms mitigate the risk. We used a longitudinal cohort to analyze the association between depressive symptoms and changes in symptoms with mortality.

Methods: We examined the association between depression screening at (baseline and 12 months) and mortality using Cox models among 762 prevalent dialysis patients enrolled from 6/2009 to 8/2011 in the ACTIVE/ADIPOSE prospective cohort. The CES-D Scale was used as a screening tool for depression. Death was ascertained through linkage with the USRDS as of 3/31/2014. Among 687 patients with paired baseline and 12m data, differences in mortality risk were assessed in 4 groups defined according to depression screening at baseline and 12 m (neg to neg; neg to pos; pos to pos; pos to neg). Models were adjusted for age, sex, race, frailty, comorbidities, and inflammatory markers.

Results: The cumulative 1-year survival rate of patients belonging to the lowest UA Q1 (<6.2 mg/dl) was 81.1%, and was significantly lower (P<0.05) than patients in Q2 (92.7%, 6.2–7.2 mg/dl), Q3 (94.8%, 7.3–8.3 mg/dl), and Q4 (90.6%, <8.4 mg/dl). The cumulative 3 and 5 year survival rates of UA Q1 group were significantly (P<0.05) lower than those of the UA Q4 group (81.4% vs. 93.4%, and 80.7% vs. 89.6%, respectively). One-year all-cause mortality was found to be significantly associated with sex [hazard ratio (HR): 3.9, 95% CI (3.5–4.3), P<0.01], age (HR: 1.02, 95% CI 1.01–1.03, P<0.01), serum uric acid (HR: 1.04, 95% CI 1.03–1.05, P<0.01), and smoking (HR: 1.01, 95% CI 1.00–1.01, P=0.01). HR was 1.05 (95% CI 1.02–1.08, P=0.01) for UA Q1. The HR of patients with SUA=5.0 mg/dl was 8.4 (P<0.05). In RA, SUA level was significantly associated with age, sex, albumin, creatinine, potassium, phosphate, C-reactive protein, GFRN and nPCR (P<0.05). In multiple RA, SUA level was only associated with serum phosphate (β 0.20, P=0.01), creatinine (β 0.14, P=0.05), and GFRN (β 1.18, P=0.01).

Conclusions: Low SUA level but not high SUA level is associated with 1, 3, and 5-year mortality in incident HD patients, and a link between low SUA concentration and malnutrition status was present in this population.
Conclusions: Positive depression screening was associated with higher mortality risk at any time point regardless of changes over the preceding 12 months. Results suggest that effective treatment of depression has the potential to improve outcomes.

Funding: Veterans Affairs Support

FR-PO866
Adverse Outcomes of Subsequent Depression in ESKD Patients Undergoing Peritoneal Dialysis: A Longitudinal Prospective Study
sasutpon nochartwong,1,4 Chidchanok Ruengorn,1,4 Kiatkrirangsri Koryatkoson,1,2 Chayutthaphong Chaisai,1,4 Khomsan Noppakun,1 Ratanapon Aviphan,1 Wiliawan Chompornkut,1,3 Sirisak Nanta,1,3,4 1 Maesai District Hospital, Chiang Rai, Thailand; 2 Chiang Mai University, Chiang Mai, Thailand; 3 Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand; 4 Pharmacoeconomics and Statistics Research Center (PESC), Chiang Mai University, Chiang Mai, Thailand; 5 Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; 6 Faculty of Medicine, Chiang Mai University, Chiang Rai, Thailand. Group/Team: Thai Renal Outcomes Investigators.

Background: Existing epidemiological studies demonstrated that depression subsequently predicts adverse outcomes in various populations. Nevertheless, evidence were inconclusive and limited with regard to dialysis patients, particularly in patients on peritoneal dialysis (PD).

Methods: We conducted a prospective single cohort study from the Kidney Center, general hospital, Chiang Mai, Thailand from May 2012 to December 2014, involving adults treated with long-term PD. Participants were followed up until December 2016. Depression was defined by the Beck Depression Inventory (BDI) score ≥14 at baseline. Adverse outcomes of interest included all-cause mortality, cardiovascular (CV) mortality, CV hospitalization, and health-related quality of life (HRQOL). Multivariable Cox regression analyses were used to estimate mortality and hospitalization risk. HRQOL scores using the Kidney Disease Quality of Life (KDQOL-S36) instrument were also compared by linear regression. Baseline sociodemographics and known risk factors were adjusted in the models.

Results: Our cohort consisted of 409 PD patients with mean age of 59.3 ± 12.4 years and 44.0% were female. Depression presented in 28.6% at recruitment. After a median follow-up of 1.73 years (835.2 person-year), 139 (34%) participants had died, of which 59 (36%) were attributable to CV death.

Conclusions: Depression is common in PD patients and is strongly associated with increased risk of death, CV hospitalization, and worse HRQOL scores. Further investigation is warranted to establish whether recognition and treatment of depression can improve patient outcomes.

Funding: Government Support - Non-U.S.

FR-PO867
Temporal Variations in Hemoglobin before and after Transition to ESRD among Veterans: A Transition of Care in CKD Study
Melissa Soohoo,2 Christine Park,1 Connie Rhee,1 Csaba P. Kovessy,1 Kamyr Kalantar-Zadeh,1 Elani Stejra,3 1UCLA, Los Angeles, CA; 2UC Irvine, Orange, CA; 3University of Tennessee Health Science Center, Memphis, TN.

Background: Hemoglobin (Hgb) levels decrease as renal function deteriorates and higher Hgb variability is associated with poorer outcomes in patients transitioning to end-stage renal disease (ESRD). However, the relationship of pre- and post-transition Hgb trajectories as well as its association with post-ESRD outcomes is unclear.

Methods: We used a mixed-effects regression model to evaluate the trajectories of Hgb over the 1-year pre- and post-ESRD initiation periods in 31,472 US veterans who transitioned to ESRD in 2007-2014. Trajectories were stratified by baseline 6-month pre-ESRD (prelude) Hgb concentrations. With hierarchically adjusted Cox models, we examined the association of 1-year prelude Hgb slope with early post-ESRD mortality.

Results: The mean±SD age of the cohort was 68±11 years, with a median[IQR] 1-year prelude Hgb slope of -1.6[-2.6, -0.7] g/dL/year. In the prelude period, all Hgb groups showed a gradual decreasing trend and patients with a lower baseline Hgb (<10 g/dL) had the steepest drop before transition. Hgb levels were then corrected towards a normal range with reduced variation across groups in the post-ESRD period. Those with the steepest Hgb decline in the 1-year prelude (+3 g/dL/year) had the highest risk of early post-ESRD mortality (HR[95%CI]: 1.16[1.07, 1.26] ref: slope <2 to <4 g/dL/year) after demographics adjustment, yet the relationship was attenuated after further laboratory and medication adjustments (HR[95%CI]: 1.03[0.95, 1.12]).

Conclusions: Hemoglobin levels rapidly decrease before dialysis initiation and then quickly normalize after initiation and steep pre-ESRD Hgb decline is associated with higher early post-ESRD mortality risk. Further studies are needed to examine the impact of anemia management during the pre- and post-ESRD period on post-transition dialysis outcomes.

Funding: NIDDK Support
FR-PO869

Screening for Peripheral Vascular Disease in Hemodialysis Patients by Measurement of Skin Perfusion Pressure


Background: Peripheral vascular disease (PVD) is common in hemodialysis patients, but the optimal noninvasive screening test is unclear. Ankle Brachial Index (ABI) is the most commonly used test, but its accuracy in ESRD patients is limited by medial calcific sclerosis. Skin perfusion pressure (SPP) in the feet may be a more accurate measure of the severity of PAD, but its use in hemodialysis patients has not been evaluated. An SPP less than 50 mm Hg indicates significant PVD. We analyzed the association of SPP with clinical characteristics of these patients.

Methods: We studied 78 chronic hemodialysis patients. After administration of a brief screening questionnaire and physical examination of the lower extremities, SPP was measured in both lower extremities immediately before a dialysis session. We analyzed the association of SPP (the lower value between the 2 extremities) and individual clinical characteristics.

Results: Among the 78 study patients, 51% had diabetes, and 10% had a history of a lower extremity amputation. Seven patients (9%) had an SPP < 50 mm Hg. Among patients with a history of lower extremity amputation, the SPP in the remaining lower extremity was significantly lower than that measured in patients without prior amputation (p=0.01). There was no significant association of SPP with patient age, gender, diabetes, smoking history, history of stroke, claudication or LDL cholesterol (Table).

Conclusions: Of all the clinical risk factors evaluated, only a history of lower extremity amputation was significantly associated with a lower SPP. We are currently following these patients prospectively to determine the predictive value of SPP for future lower extremity ischemia.

Skin perfusion pressure measurement in hemodialysis patients (N=78)

<table>
<thead>
<tr>
<th>Variable</th>
<th>SPP ≤ 50 mm Hg</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>76 (6)</td>
<td>0.44</td>
</tr>
<tr>
<td>Male</td>
<td>82 (2)</td>
<td>0.71</td>
</tr>
<tr>
<td>Diabetes</td>
<td>82 (3)</td>
<td>0.53</td>
</tr>
<tr>
<td>History of amputation (any)</td>
<td>59 (2)</td>
<td>0.61</td>
</tr>
<tr>
<td>Ever smoked (any)</td>
<td>84 (4)</td>
<td>0.43</td>
</tr>
<tr>
<td>Hc- CVA</td>
<td>83 (1)</td>
<td>0.30</td>
</tr>
<tr>
<td>Conduction delay (ms)</td>
<td>76 (4)</td>
<td>0.60</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>87 (3)</td>
<td>0.09</td>
</tr>
<tr>
<td>LDL &gt; 100 (mg/dl)</td>
<td>90 (5)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

FR-PO870

Understanding Early Mortality after Dialysis Initiation: The Role of Severity of Illness, AKI, and ESRD Certification

Diane Stieflick, Kevin He, Maggie Yin, Jennifer L. Bragg-Gresham, Yahahn B. Shahbani, Michael Heung, Rajiv Saran. Kidney Epidemiology and Cost Center, University of Michigan, Ann Arbor, MI; University of Michigan, Ann Arbor, MI.

Background: Analysis of CMS-certified ESRD patient mortality has consistently shown an increase in the first weeks after dialysis initiation, peaking at 6-8 weeks and then declining. The factors underlying this mortality pattern are unclear. To explore this, we examined mortality rates from the first dialysis session, which often occurs prior to ESRD certification for many patients, for those patients on Medicare prior to ESRD.

Methods: This retrospective cohort study used the Medicare 5% sample of patients with a dialysis claim, merged with the USRDS ESRD database. Patients had no dialysis in 2005 and their first claim in 2006-2014 was selected. Patients with an ESRD first service date before the first dialysis claim were excluded. Poisson regression was used to calculate weekly mortality rates, standardized to the sample mean age, sex, and race. differences in patient characteristics or quality of care and care coordination, or both. Differences in outcomes across these settings may reflect the association between dialysis setting and hospitalization and hospital days (respectively) within 2-years after dialysis initiation ( censoring at renal transplant or death), adjusting for patient demographic and clinical characteristics.

Conclusions: Of the 27,301 cohort members, 67% received dialysis outside the VA under Medicare, 11% received dialysis outside the VA through VA-PC, 4% were treated in VA facilities, and 18% were treated in two or more of these settings (Table 1). Most Veterans were hospitalized (83%) and spent an average of 22.7 days in the hospital (median=14, IQR=8) during follow-up. Only Veterans receiving dialysis in two or more settings had higher rates of hospitalization versus those receiving dialysis under Medicare (OR=1.3; 95% CI=1.1, 1.5). There were no differences between groups in length of stay (p=0.26).

Conclusions: Veterans who received dialysis in more than one setting were at increased risk for hospitalization during the first two years after dialysis initiation. Funding: Veterans Affairs Support

FR-PO871

Comparative Effectiveness of Dialysis for Veterans in VA and Non-VA Settings

Virginia Wang, Cynthia Coffman, Karen M. Stechuchak, Paul L. Hebert, Ann M. O’Hare, David Edelman, Hollis J. Weidenbacher, Matthew L. Maciejewski, Durham VAMC, Durham, NC; Duke Univ, Durham, NC; VA Puget Sound Health Care System, Seattle, WA.

Background: Veterans with ESRD have different options for obtaining dialysis including: Medicare-funded community dialysis; VA in-house; and VA-purchased community dialysis (VA-PC). Differences in outcomes across these settings may reflect differences in patient characteristics or quality of care and care coordination, or both. This study compares hospitalization rates and days of care between Veterans receiving outpatient dialysis in VA, VA-PC, and Medicare settings.

Methods: We used VA and Medicare administrative data to construct a national cohort of VA-enrolled Veterans who initiated maintenance dialysis in 2008-2011. Cohort members were classified based on dialysis setting during the 2-year period immediately following dialysis initiation: 1) VA dialysis (VA); 2) VA-PC in non-VA dialysis units; 3) Medicare-financed dialysis in non-VA units (Medicare); or 4) “Mixed”. We used logistic and negative binomial regression models to examine the associations between dialysis setting and hospitalization and hospital days (respectively) within 2-years after dialysis initiation ( censoring at renal transplant or death), adjusting for patient demographic and clinical characteristics.

Results: Of the 27,301 cohort members, 67% received dialysis outside the VA under Medicare, 11% received dialysis outside the VA through VA-PC, 4% were treated in VA facilities, and 18% were treated in two or more of these settings (Table 1). Most Veterans were hospitalized (83%) and spent an average of 22.7 days in the hospital (median=14, IQR=8) during follow-up. Only Veterans receiving dialysis in two or more settings had higher rates of hospitalization versus those receiving dialysis under Medicare (OR=1.3; 95% CI=1.1, 1.5). There were no differences between groups in length of stay (p=0.26).

Conclusions: Veterans who received dialysis in more than one setting were at increased risk for hospitalization during the first two years after dialysis initiation. Funding: Veterans Affairs Support
Institute for Adult Diseases, Asahi Life Foundation, Tokyo, Japan; 2Okinaka Higashiyamato Nangai Clinic, Tokyo, Japan; 4Higashikurume Ekimae Clinic, Shigeko Hemodialysis with Gastrointestinal Complications in Patients with ESRD on Dialysis Patients' Health Outcomes. Impact of Social Capital and Other Environmental Factors on Social Determinants on Patient’s Outcomes.

Results: A total of 49,195 patients were included in the study. From the analysis, it was estimated that both household income (beta=-0.001, p=0.1052) and education (beta=-0.00001, p=0.8255) had only a small, non-significant impact on patients' hospitalizations rates. However, patients who married (β=0.05, p=0.0001), living in a rural setting (β=-0.062, p=0.0017) and, to a lesser extent, in areas with more social capital (β=-0.020, p=0.1588), have a favorable impact on hospital admissions.

Conclusions: Rural settings and the existence of social networks may encourage neighbors' awareness, which may reduce hospital admissions. Our analysis suggests that, in addition to the health status and access of care, dialysis patients' clinical outcomes may be affected by their environmental and social surroundings. Deeper analyses are warranted to better understand the effects of social determinants on patients' outcomes.

Methods: We included all patients who initiated dialysis treatment in the Fresenius Kidney Care clinics from Jan-2013 to Dec-2016. Patient’s data was collected during the first 120 days on dialysis and included laboratory values and demographic data. Household income, educational level and rurality data was extracted from the United States Census Bureau at the zip code level. Data of county level measure of social capital was obtained from Rupasingha, et al., 2006. We calculated the impact of these variables on patients' hospital admissions for the reminder of the first year on dialysis using Poisson model with log of exposure days as offset variable.

Results: A total of 3,134 patients from 72 dialysis facilities were enrolled in this study. Among them, 277 (21%) were diagnosed with DRA. EQ-5D scores were significantly lower in patients with DRA compared to those without DRA (median (interquartile range): 0.649 (0.533–0.768) vs. 0.768 (0.693–1.000); P=0.001). Among the all patients, 931 (71%) could be followed for two years and were divided into three groups according to baseline and follow-up DRA status: patients with DRA at baseline (G1, n=190), those who had not had DRA at baseline, but developed DRA during the follow-up period (G2, n=44), and those without DRA both at baseline and after two years (G3, n=697). Although G3 had shorter dialysis vintage (15 years) compared to G1 (27 years) and G2 (23 years), age, sex, and previous history of cardiovascular diseases were comparable among three groups. Decline in QOL was observed in significantly greater proportion in G1 (45% (95% CI: 0.05 and 0.20)) and G2 (66% (95% CI: 0.10 and 0.50)) respectively. The EQ-5D scores were significantly lower in G2 than G3.

Methods: DRA was associated with lower QOL in hemodialysis patients with long-term dialysis therapy.

Results: A total of 3,134 patients from 72 dialysis facilities were enrolled in this study. Among them, 277 (21%) were diagnosed with DRA. EQ-5D scores were significantly lower in patients with DRA compared to those without DRA (median (interquartile range): 0.649 (0.533–0.768) vs. 0.768 (0.693–1.000); P=0.001). Among the all patients, 931 (71%) could be followed for two years and were divided into three groups according to baseline and follow-up DRA status: patients with DRA at baseline (G1, n=190), those who had not had DRA at baseline, but developed DRA during the follow-up period (G2, n=44), and those without DRA both at baseline and after two years (G3, n=697). Although G3 had shorter dialysis vintage (15 years) compared to G1 (27 years) and G2 (23 years), age, sex, and previous history of cardiovascular diseases were comparable among three groups. Decline in QOL was observed in significantly greater proportion in G1 (45% (95% CI: 0.05 and 0.20)) and G2 (66% (95% CI: 0.10 and 0.50)) respectively. The EQ-5D scores were significantly lower in G2 than G3.

Methods: DRA was associated with lower QOL in hemodialysis patients with long-term dialysis therapy.

Results: A total of 3,134 patients from 72 dialysis facilities were enrolled in this study. Among them, 277 (21%) were diagnosed with DRA. EQ-5D scores were significantly lower in patients with DRA compared to those without DRA (median (interquartile range): 0.649 (0.533–0.768) vs. 0.768 (0.693–1.000); P=0.001). Among the all patients, 931 (71%) could be followed for two years and were divided into three groups according to baseline and follow-up DRA status: patients with DRA at baseline (G1, n=190), those who had not had DRA at baseline, but developed DRA during the follow-up period (G2, n=44), and those without DRA both at baseline and after two years (G3, n=697). Although G3 had shorter dialysis vintage (15 years) compared to G1 (27 years) and G2 (23 years), age, sex, and previous history of cardiovascular diseases were comparable among three groups. Decline in QOL was observed in significantly greater proportion in G1 (45% (95% CI: 0.05 and 0.20)) and G2 (66% (95% CI: 0.10 and 0.50)) respectively. The EQ-5D scores were significantly lower in G2 than G3.
FR-PO876

The Moisturizer Improves Pruritus of Dialysis Patients by Increasing Water Content in the Stratum Corneum Yukie Yoshida,1 Kazumasa Hashimoto,2 Hidemasa Saeki,3 Seiki Fujimoto,1 Shuichi Tsuruoka,1 1Department of Nephrology, Nippon Medical School, Tokyo, Japan; 2Kidney Clinic, Nippon Medical School, Tokyo, Japan; 3Department of Dermatology, Nippon Medical School, Tokyo, Japan; Maruko Co., Ltd., Osaka, Japan.

Background: In dialysis patients, skin disorder (dryness, itching, etc.) is frequently observed and treated with moisturizers without sufficient evidence. We therefore evaluated the usefulness of a moisturizer in the treatment of dry skin in dialysis patients in an exploratory manner.

Methods: This study was an open-label, randomized, before-after, parallel group comparison study conducted after approval by the Institutional Review Board of Nippon Medical School. The study was funded by Maruho Co., Ltd. (Osaka, Japan), and registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry as UMIN000037016. Included were 12 maintenance hemodialysis outpatients in stable condition in our hospital, randomized to receive treatment with a lotion containing maruhosan (Maruko) for 2 weeks followed by 2-week washout (Group A: 6 subjects) or another 2-week treatment (Group B: 6 subjects). The primary efficacy measure was water content in the stratum corneum in the hydrometry (flank). Secondary measures included visual analogue scale (VAS) itching score. Safety was evaluated based on adverse events. Efficacy data were collected on Day 1 and after 1, 2, 3, and 4 weeks of treatment, on which the water content was measured using a Corneometer (Courage-Khazaka) at 1 to 2 hours after the start of dialysis. Subjects additionally assessed their itching at the application site on a 100-mm VAS before dialysis.

Results: The moisture in the stratum corneum significantly increased at Weeks 1 and 2, then significantly decreased in Group A, in which study treatment was discontinued, but was almost maintained in Group B, in which treatment was continued. Itching VAS score significantly decreased at Weeks 1 and 2, indicating reduction of itching, then increased in Group A but not in Group B, indicating that itching returned to the baseline condition. The score decreased in Group B, indicating further reduction of itching. At Week 4, the score was significantly different between Groups A and B. As for safety, mild upper respiratory tract infection was reported in 1 subject during treatment, but was not related to study treatment.

Conclusions: Continuing a moisturizer with a preparation containing moisturizing and astringent ingredient may be effective and safe to reduce dry skin and maintain good skin condition in dialysis patients.

Funding: Commercial Support - Maruho Co., Ltd. (Osaka, Japan).

FR-PO877

The Present Status of Fatigue in Maintenance Hemodialysis Patients and Its Influencing Factors Bing Zhang1, Junwei Yang1.1Second Affiliated Hospital, Nanjing Medical University, Nanjing, China; The second affiliated hospital of nanjing medical university, Nanjing, China.

Background: Fatigue is a common and complex phenomenon in maintenance hemodialysis patients that significantly decreases the health-related quality of life, especially after hemodialysis treatment, frequently require time to recover. The aim of this study was to analyze the fatigue status of hemodialysis patients in our dialysis center, explore the influencing factors of fatigue in these patients and propose effective intervention measures.

Methods: This study is an observational study. From June 2016 to February 2017, 120 maintenance hemodialysis patients were enrolled in the research in our center. The patients completed the questionnaires, including the Fatigue Assessment Scale(FAS) and the time of recovery from a dialysis session. The serum concentration of hemoglobin, albumin, electrolyte and the levels of PH, bicarbonate, lactic acid were examined to statistics and analysis.

Results: 120 questionnaires were distributed and 111 were taken back, and 109 (90.8%) were effective among the questionnaires. The incidence of fatigue in maintenance hemodialysis patients was high, 63 of 109 (57.8%) patients enrolled in the study assessed of fatigue, 9.2% of patients had a severe fatigue. The time of recovery from hemodialysis (TIRD) is different from 30 minutes to 24 hours. 66.1% of patients’ recovery time was shorter than 2 hours, 29.3% was 2 hours and 6.6% of patients took longer time to recover after a dialysis session. Most of them required more rest or sleep immediately after dialysis. The result of analysis is that the fatigue of patients was correlated with comorbidities (OR=0.202), the levels of lactic acid (OR=5.933) and the bicarbonate (OR=0.643) after dialysis. The rate of ultrafiltration, the levels of serum sodium and the levels of lactic acid varies are different to the TIRD, the raised of lactic acid (OR=4.21) is associated of longer recovery time.

Conclusions: The incidence of fatigue patients in our dialysis center is more than a half, a few number of patients had a heavy fatigue, required more rest or sleep immediately after dialysis. The levels of lactic acid was the significant influencing factor of the fatigue in hemodialysis patients,TIRD was correlated with the raised of lactic acid during the dialysis process.

Funding: Government Support - Non-U.S.

FR-PO878

The Cataract Surgery Related Complications in Patients with ESRD Chia-Chun Wu1. Chi Mei Medical Center, Tainan, Taiwan.

Background: Higher surgery risk in end stage renal disease (ESRD) patients is well known, but most reports focus on major surgeries. Cataract is the most common cause of visual loss worldwide. Although cataract surgery is a minor surgery, surgery related complications still happen. Herein, we want to know if ESRD patients have higher risk of cataract surgery related complications.

Methods: The National Health Insurance Research Database in Taiwan was used to identify patients who received cataract surgery. Patients with regular hemodialysis(HD) or peritoneal dialysis longer than 3 months were selected as study group. Control group is patients without chronic kidney disease and matched on age, gender and surgery year. Other exclusion criteria is any eye surgery within 3 years prior cataract surgery. The main outcome measures are cataract surgery-related complications within 3 months after surgery. Conditional logistic regression was used to test the risk of complications.

Results: Patients with ESRD have higher percentage of hypertension, diabetes mellitus and more likely to have a cataract surgery in medical centers. Patients with ESRD have a 6.81 times higher risk to have vitreous hemorrhage within 3 months after cataract surgery. The odds ratios of vitreous hemorrhage are 4.20, 4.86, 9.8 in the 1st, 2nd and 3rd nth individually.

Conclusions: Patients with ESRD have a higher risk of vitreous hemorrhage after cataract surgery. Heparin is frequently used during HD to prevent clot formation in blood circuit, this analysis result might afford a reference to adjust the heparin dose in HD patients after receiving cataract surgery.

The multiple complications after cataract surgery within 3 months in ESRD patients and Control group

ESRD –End stage renal disease; OR– Odds ratio.

Adjusted factors :Hypertension, Diabetes mellitus, Myopia, Hospital level, use Anti-platelet drugs or anti-coagulant

FR-PO879

Sex-Based Immunological Disparity in ESRD Patients Fang-Ing Yu,1,2 Ying-Ling Chiu.1,3 1Graduate Institute of Medicine, College of Medicine, National Taiwan University Hospital, Taipei, Taiwan; 2Internal Medicine Department, National Taiwan University Hospital, Tainan Branch, Tainan, Taiwan; 3Internal Medicine Department, Far Eastern Memorial Hospital, Banciao, New Taipei City, Taiwan.

Background: Sex differences in the immune response and in infectious disease susceptibility have been well described, although the mechanisms underlying these differences remain incompletely understood. Patients with end-stage renal disease may face higher risk of infection. The activity and distribution of T cell and monocyte subsets between the sexes is still unknown.

Methods: The immunity in ESRD study (iESRD) recruited 412 hemodialysis patients from both northern and southern Taiwan. Peripheral blood were sampled before hemodialysis session and processed immediately for mononuclear cell isolation. Using multicolor flow cytometry, lymphocytes were separated into subpopulations including naive T cells, central memory TCM, effector memory TEM, and staining. Using multicolor flow cytometry, lymphocytes were separated into subpopulations including naive T cells, central memory TCM, effector memory TEM, and staining. Using multicolor flow cytometry, lymphocytes were separated into subpopulations including naive T cells, central memory TCM, effector memory TEM, and staining.

Results: Among CD4+CD8+ T cell subsets, male patients showed decreased percentage of naïve CD4+/CD8+ T cell and increased percentage of effector memory CD4+CD8+ TEM. Among monocytes subset, female patients showed increased percentage of classical monocytes and decreased percentage of nonclassical monocytes CD14+/CD16− monocytes. The M1 percentage of ESRD was lower than general population ~80%. Low M1 and high M3 indicating more inflammatory response in the this group. Besides, female patients have more numbers of naïve CD4+CD8+ T cell and central memory CD8 TCM but less numbers of nonclassical monocytes M3.

Conclusions: Males and females differ in innate and adaptive immune responses. These sex-based immunological disparities contribute to variations in the incidence of autoimmune diseases and malignancies, susceptibility to infection. Our study showed the immune age of female was younger than male in ESRD. Male have more ‘Non-classical’ subpopulations which are associated with inflammatory character. Sex associated immune response should be further investigated in the pathogenesis of infection and aging in ESRD.

FR-PO880

A Comparison between Hemodialysis and Peritoneal Dialysis on the Risk of Hip Fractures in Diabetics with Chronic Renal Disease Ammar Oureshi,1 Fernando R. Aguilar,1 Nesreen Benhamed,2 Georgetown University Hospital, Washington, DC; 1Internal Medicine, Marshall University, Huntington, WV; 1Internal Medicine, MUSOM, Barbourville, WV.

Background: It is well established that bone fragility and fractures are common complications of patients on dialysis, notably if they are diabetics. It remains uncertain if the risk of fractures changes depending on the dialysis modality either hemodialysis (HD) or peritoneal dialysis (PD). We aim in this study to set the risk of bone fractures between those two modalities in patients with DM2.

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

Underline represents presenting author.
Methods: Data was extracted from the 2005 to 2012 Nationwide Inpatient Sample (NIS). Using propensity score matching, ESRD-DM patients on PD were matched with patients on HD at a 1:1 ratio. Analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results: Among 586,238 patients with incident ESRD, 568,469 (96.97%) and 17,769 (3.03%) were initiated on HD and PD, respectively, during the hospitalization. After matching both groups, we found no difference in the rate of ulnar (0.1 vs 0.1; p=0.78) and hip fractures (0.3 vs 0.31; p=0.0001) while spine (0.21 vs 0.15; p=0.01) occur significantly more in the HD group.

Conclusions: Diabetic patients with ESRD on HD have higher risk for spine and humeral fractures. Further studies are needed to evaluate the different bone pathogenesis of both dialysis modalities to explain our findings.

FR-PO881

Association of Pre-ESRD Serum Bicarbonate with Post-ESRD Mortality among Incident Dialysis Patients: A Transition of Care in CKD Study Yoshitsugu Ohji,1 Christina J. Catabay, Melissa Soohoo,1 Christina Park,2 Elani Streja,3 Csaba P. Kovsevsy,3 Kamyar Kalantar-Zadeh,1 1UC Irvine, Orange, CA, 2University of Tennessee Health Science Center, Memphis, TN.

Background: Serum bicarbonate (S-CO2) levels decline as CKD progresses and rise after dialysis initiation. While the current clinical guidelines suggest maintaining S-CO2 > 22 mEq/L among pre-ESRD patients with CKD, there are scarce data on the impact of pre-ESRD S-CO2 levels on post-ESRD mortality.

Methods: Among 32,655 US veterans who transitioned to dialysis between October 2007 and March 2014, we calculated 6-month averaged levels and annual decline rate of S-CO2 during the last pre-ESRD period, and then estimated their risk for all-cause mortality with Cox regression adjusting for demographics, comorbidities, BMI, and eGFR.

Results: Mean baseline concentrations and rates of decline of S-CO2 were 23.4±2 mEq/L and 0.1±0.5 mEq/L/year, respectively. Higher S-CO2 > 20 mEq/L showed higher adjusted mortality risk while there was no clear trend in the lower range. Compared to S-CO2 of 22 mEq/L, adjusted HRs (95%CI) were 0.96 (0.94–0.97), 1.09 (1.07–1.12), and 1.22 (1.18–1.27) at 20, 24, and 26 mEq/L, respectively. Consistent associations were observed irrespective of sodium bicarbonate use. There was a U-shaped association between the rate of decline in S-CO2 and mortality with the lowest risk being approximately -2.0 mEq/L/year. Both faster decline and rise in S-CO2 were more strongly associated with mortality among sodium bicarbonate users vs. non-users.

Conclusions: Pre-ESRD S-CO2 levels above 20 mEq/L exhibited an incrementally higher risk of post-ESRD death. Further studies are needed to elucidate whether high S-CO2 is a surrogate of low protein intake, comorbid states, or other mechanisms.

Funding: NIDDK Support

FR-PO882

Phosphate Binder Use and Cost Trends in US Dialysis Patients Wendy L. St. Peter,1 Lori Wazny,1 Eric D. Weinhard,1,2 Manitoba Renal Program, Winnipeg, MB, Canada; 1NxStage Medical, Inc., Victoria, MN; 1University of Minnesota, Minneapolis, MN.

Background: Phosphate binder costs for US dialysis patients having Medicare Part D was almost $31 billion in 2014. Our objectives were to examine current trends in use and cost data for phosphate binders and to determine gross Medicare Part D costs per equivalent phosphate binding dose.

Methods: Using data from United States Renal Data System, we report trends in phosphate binder use and costs for Medicare-covered dialysis patients with Medicare Part D prescription drug coverage from 2006-2013. We identified all medication fills for phosphate binders (calcium acetate, lanthanum carbonate, sevelamer hydrochloride) and all Part D-covered drugs. For each year, we calculated percent of patients using phosphate binders (overall and by binder), weighted by cumulative follow-up time per patient, cumulative gross costs, gross costs per patient-year and gross costs per user-year. For each phosphate binder, we estimated gross costs per calcium carbonate-equivalent gram by applying relative phosphate binding capacities equal to 1.00 for calcium acetate, 2.00 for lanthanum, and 0.75 for sevelamer products.

Results: Number of dialysis patients with Medicare Part D coverage filling phosphate binder prescriptions steadily increased from 174,974 in 2006 to 263,404 in 2013 (50% cumulative increase), while percentages filling phosphate binder prescriptions remained stable at around 75% while gross costs per user-year for phosphate binders increased from $1433 to $3716 (159% cumulative increase, or 15% year-over-year increase). Gross costs per user-year for all other Part D-covered prescription medications in dialysis patients cumulatively increased by 44% (5.4% year-over-year growth). Between 2006 and 2013, gross costs per user-year for calcium acetate, sevelamer carbonate, and lanthanum carbonate increased by 153%, 284%, and 307%, respectively. Adjusted for relative phosphate binding capacity, gross costs of calcium acetate, lanthanum carbonate, and sevelamer carbonate were $0.79, $4.67, and $4.85, respectively, per one calcium carbonate-equivalent gram in 2013.

Conclusions: Growth in cost of phosphate binders outpaced growth in costs of other Medicare Part D medications in dialysis patients. To achieve an equal degree of phosphorus control in an average patient, Medicare expended roughly 6 times as much on sevelamer carbonate and lanthanum carbonate as on calcium acetate in 2013.

FR-PO883

Differential Effects of Hemodialysis and Transplantation on Cognitive Function in ESRD Mark D. Findlay,1 Patrick B. Mark,1,2 Jesse Dawson,1,2 1University of Glasgow, Glasgow, United Kingdom; 1Queen Elizabeth University Hospital, Glasgow, United Kingdom.

Background: Cognitive impairment (CI) is common in people receiving hemodialysis (HD). We examined for changes in cognitive functioning during the HD setting and the effect of continued HD or renal transplantation on cognitive function at 12 months.

Methods: Prospective observational study in adult patients on chronic HD. A neurocognitive battery was performed during a routine dialysis session and on a non-dialysis day. Cognitive tests included the Montreal Cognitive Assessment and additional tests of language, memory, processing speed and executive function. Mean flow velocity (MFV) was measured in the middle cerebral artery before, during and after dialysis using transcranial Doppler ultrasound. We compared cognitive function and MFV on and after dialysis and assessed the relationship between any changes using Spearman's rank correlation. Cognitive function was reassessed in a similar fashion 12 months later.

Results: 97 participants were enrolled (median age 59y [IQR 51, 67], 40% female, median duration of end stage renal disease 1.76 years [IQR 0.6, 4.0]). 88 participants attended both intradialytic and non-dialysis day assessments. CI was present in 44(50%). Those with CI were more likely to have hypertension (95.5 v 81.8%, p<0.05). MFV declined during dialysis (mean; 49.8 to 43.2cm/s, p<0.001) correlating with UF volume, r=0.49 p<0.001. Participants scored lower on tests of processing speed and executive function during dialysis when compared to their non-dialysis day scores, p<0.001. Decline in MFV was associated with language and executive function correlated with the dialysis-related fall in MFV, r=-0.27 p=0.02 and r=-0.44 p<0.001 respectively. At 12 months, 59 remained on dialysis; 15 transplanted, 5 withdrew and 5 died. Improvements in language and attention tests were observed in those continuing HD, whereas those who received a transplant demonstrated improvements in executive function and processing speed, p<0.05.

Conclusions: Overt CI is common and cognitive function demonstrably worse during dialysis. Cerebral blood flow is reduced during HD, relating to UF volume and a measurable decline in cognitive function. The transient decline in executive function during dialysis does not appear to be a progressive effect at 12 months, however its significant improvement following transplant highlights an aspect of cognitive function vulnerable to continued HD.

Funding: Government Support - Non-U.S.

FR-PO884

Implications of Variation in Cognitive Performance on Dialysis: A Pilot Study of an Electronic Cognitive Battery Meera N. Harhay,1 Lucy Robinson,2 Hasan Arif,3 Kartik M. Ranganna,2 Maria T. Schulteis,1 1Drexel University, Philadelphia, PA; 2Medicine, Drexel University College of Medicine, Philadelphia, PA.

Background: Cognitive impairment (CI) is common among dialysis patients, and some patients may exhibit a transient deficit during dialysis. However, neurocognitive testing has limited feasibility for use in clinical settings, and no studies have examined whether a decline in cognition during dialysis predicts health outcomes. We examined the association of variation in performance on the electronic Cogstate Brief Battery, consisting of four card-based cognitive tasks called Detection (processing speed), Identification (attention), One Card Learning (visual memory) and One Back (working memory), on the risk of subsequent hospitalization in a cohort of hemodialysis patients.

Methods: We enrolled 28 participants from a single dialysis unit in Philadelphia, PA, with 10 participants completing the Cogstate battery twice, once prior to dialysis and again during the last hour of dialysis therapy. For both sessions, participants were defined as “low” scorers on individual tasks if they scored below the cohort median score. We estimated age-adjusted Poisson regression models for the association of pre-dialysis and intradialytic cognitive performance and the number of hospitalizations participants experienced during six months of follow-up.

Results: The average age of the cohort was 58 years (SD 13), 97% were black, 60% were female. Mean dialysis duration was 6 years (range 2-20). After 6 months of follow-up, the cohort had at least 1 hospitalization, and 18% of participants (n=5) had >1 hospitalization. In age adjusted Poisson regression models, compared to participants who scored higher than the median both times for the Identification task, those who scored 1) higher pre-dialysis and lower during dialysis and 2) those that scored lower before dialysis and had a 9-fold and a 4-fold increase in the expected number of hospitalizations in six months, respectively (p=0.03 for both). Reasons for hospitalization in low scorers included syncope and mechanical fall.

Conclusions: In this pilot study, we found that consistently low performance on a self-administered electronic cognitive task, or poorer performance during dialysis, signaled hospitalization risk among prevalent hemodialysis patients. Given limitations
due to low sample size, future studies should confirm and expand on these findings in larger cohorts.  
Fund: NIDDK Support, Commercial Support - Frenova Renal Research, Private Foundation Support

FR-PO885

Fall Injury Prediction Using Quadriceps Thickness by Ultrasound Measurement of Patients with ESRD on Hemodialysis: A Prospective Study

Yoshitaka Tanaka,1,2 Kentaro Tanaka,1,2 Akifumi Kushiyama,1 Atsumi Kuki,1 Ken Sakai,1 Shigeo Hara,1 Yui Izumi,1 Takashi Ozawa.2 1Division of Diabetes and Metabolism, The Institute for Adult Diseases, Asahi Life Foundation, Tokyo, Japan; 2Higashiyamaotono Nangai Clinic, Tokyo, Japan

Background: Patients with end stage renal disease (ESRD) have an increased risk of fall injury. Recently, quadriceps muscle thickness (QT) by ultrasound (US) measurement has been reported as valid assessment of muscle wasting and physical function and easily applicable at the bedside. The aim of this study is to investigate if QT by US can prospectively predict fall injury in patients with ESRD on hemodialysis.

Methods: Within 752 patients with ESRD on hemodialysis at our 4 dialysis Clinics in April 2015, 182 patients provided written informed consent. The QT by US is indicated as the sum of both legs. The relative reliability of QT by US measurement was confirmed using intraclass correlation coefficient (ICCC): QT ICC(1,2)=0.99 and left QT ICC(1,2)=0.98. Patients with discharge or initiation of oral steroid administration, or drop out before the first measurement were excluded. 179 patients (men127, women52) were studied. A fall was defined as an event in which a person was inadvertently located on the ground or other low position. Fall injury was defined as any injury with a fall, based on patient’s self-report including bone fracture, crack, bleeding, bruise, and abrasion.

Results: Over median 12-month follow-up period, 42 patients (23.4%) developed the fall injury in 179 patients. When subjects were stratified by QT level into sex-specific tertiles, the patients in the lowest tertile (men<3.66cm, women<3.52cm) indicated a significantly higher risk of fall injury than the middle and highest tertiles by using Kaplan Meier estimate (logrank test, p<0.05). In a univariate analysis using Cox regression model, 1cm decrease of the QT by US indicated significant risk increase (hazard ratio 1.85, 95% CI 1.33-2.70, p=0.0002). In multivariate analysis, the hazard ratios between the QT by US remained significant after adjusting various confounding factors such as sex, age, dialysis vintage, BMI, diabetes mellitus, nutritional state, grip strength (1.64, 1.04-2.63, p<0.05).

Conclusions: QT by US is an independent and useful predictor of fall injury in patients with ESRD on hemodialysis.

FR-PO886

Evaluating the Real-World Safety and Effectiveness of Sucroferric Oxysudroxide in Dialysis Patients: An Interim Analysis of the VERIFIE Study

Marc Ketteler,1 John Boletis,2 Angel Luis M. de Francisco,3 Denis Fouque,1 Philip A. Kalra,4 Markus Ketteler,4 Piet Giorgiorgio,7,8 Manuela Stauss-Grabo,9 Viatcheslav Rakov,10 Sebastian Walpen,10 Linda H. Figiocelli,1 Jacques B. Rotteurnp,4 Christoph Wanner,4 Jorge B. Cannata-Andia,2 Fresenius Medical Care - North America, Waltham, MA; 2Hospital Universitario Central de Asturias, Oviedo, Spain; 3Fresenius Medical Care Deutschland GmbH, Bad Nauheim, Germany; 4Groupe Hospitalier Pitié-Salpêtrière, Paris, France; 5Marques de Valdecilla University Hospital, Santander, Spain; 6Coburg Clinic and KFH-Dialysis Center, Coburg, Germany; 7Salford Royal Hospital NHS Trust, Salford, United Kingdom; 8University Hospital of Würzburg, Würzburg, Germany; 9VU University Medical Centre, 2013 VN Overveen, Netherlands; 10Fresenius Medical Care Deutschland GmbH, Bad Nauheim, Germany; 11University Claud de Bernard, Pierre Bonite, France; 12Laiko University Hospital, Athens, Greece; 13Maggiore Hospital, Milan, Italy.

Background: Sucroferric oxysudroxide (SFOH) is a non-calcium-, iron-based phosphate binder. The VERIFIE study aims to investigate the real-life safety and effectiveness of SFOH in prevalent dialysis patients with hyperphosphatemia.

Methods: This was a non-interventional, prospective, multicenter, European cohort study (cohorts 1 and 2: 13 centres, 27 dialysis units; cohort 3: 3 cohorts of 1000 patients). The non-interventional design allows the observation of patients in a broad range of settings following routine clinical practice. SFOH initiation was based on the physician’s decision and was not influenced by study inclusion.

Results: An interim analysis presents data from 244 patients (mean age: 63.8 [standard deviation: 14.7] years; 64.0% male) included in the safety analysis set, of whom 1000 patients). The non-interventional design allows the observation of patients in a broad range of settings following routine clinical practice. SFOH initiation was based on the physician’s decision and was not influenced by study inclusion.

Conclusions: These interim real-world data show that SFOH is well tolerated, and no new safety risks were identified. In addition, SFOH was effective at reducing serum phosphorus in real-world practice.

Fund: Veterans Affairs Support

FR-PO887

Mineral Bone Disorder Management in Hemodialysis Patients: Comparing PTH Control Practices in Japan with Europe and North America: The Dialysis Outcomes and Practice Patterns Study (DOPPS)

Suguru Yamamoto,1 Angelo Karaboyas,2 Hirokata Komaba,3 Masahito Taniguchi,4 Takanobu Nomura,4 Brian Bieber,2 Patricia De Sequera,6 Anders Christenson,7 Ronald L. Pisoni,8 Bruce M. Robinson,9 Masafumi Fukagawa.3 1Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; 2Arbor Research Collaborative for Health, Ann Arbor, MI; 3Division of Nephrology, Endocrinology and Metabolism, Tokai University School of Medicine, Isehara, Japan; 4Fukuoka Renal Clinic; Fukuoka, Japan; 5Medical Affairs Department, Kyowa Hakko Kirin Co Ltd, Tokyo, Japan; 6Department of Nephrology, Skåne University Hospital, Malmö, Sweden.

Background: High circulating level of parathyroid hormone (PTH) is associated with elevated mortality. While the Japanese Society for Dialysis Therapy suggests a low/narrow PTH target, other international guidelines suggest much higher PTH targets. This discrepancy may help explain better survival in Japanese hemodialysis patients, and we analyzed PTH control practices in Japan compared with other regions.

Methods: We analyzed data from hemodialysis patients with 3 measurements of PTH during the first 9 months in DOPPS phase 4 and 5 (2009-2015). PTH control was defined by slope of log (PTH), parameterized as % change per month, and PTH mean was defined by the geometric mean of all measurements over the 9 month run-in period. Distribution of PTH slopes and means were assessed by regions [Europe/Australia/New Zealand-Eur-ANZ, Japan and North America] and dialysis vintage (<90 days, 90 days-1 year and >1 year). Mortality rates were compared across PTH slope and mean using Cox regression models.

Results: Our sample included 6035 patients in Eur-ANZ, 2644 in Japan and 18485 in North America. Mean PTH was much lower in Japan than in other regions across dialysis vintage categories. In patients with dialysis vintage <90 days, PTH level was more likely to decline >5% per month in Japan (49% of patients) vs. Eur-ANZ (34%) and North America32%). In patients with dialysis vintage ≥1 year, Japanese patients were most likely to maintain steady PTH (APTH within +/-5% per month: 47% in Japan vs 41% in Eur-ANZ and 41% in North America), with patients in Eur-ANZ and North America more likely to experience increase in PTH. During 13.5 (IQR, 5.9-22.9) months follow-up, prevalent patients with the highest mean PTH (>600 pg/mL) had the highest mortality rate [HR=1.22 (95% CI 1.02-1.47) vs. PTH 200-400 pg/mL]. PTH slope was not clearly associated with all-cause mortality.

Conclusions: PTH control was measured by keeping a stable PTH level over 9 months, is better in Japan vs. other regions. No additional survival benefit for PTH control was observed, further study is needed to understand the reasons of keeping low PTH levels and its impact on survival advantage in Japan.

Fund: Commercial Support - Kyowa Hakko Kirin, Aigen, Baxter Healthcare, Astrazeneca, Hexal AG, Janssen, Keryx, Relypsa, Roche, and Vifor Fresenius Medical Care Renal Pharma
FR-PO888
Associations between Dialysate Magnesium, Serum Magnesium, and Mortality: A Retrospective Cohort Study of the Monitoring Dialysis Outcomes (MONDO) Initiative Xiaoiling Ye,1 Adrian M. Guinsburg,2 Cristina Marelli,1 Bernard J. Canaud,1 Stefano Stuard,1 Xiaoqi Xu,1 Jeroen Kooman,5 Frank van der Sunde,1 Albert J. Power,1 Len A. Usvyat,4 Yuedong Wang,6 John T. Danser,4 Peter Kotanko,3 Jochen G. Raimann,7 1FMC Deutschland GmbH, Bad Homburg, Germany; 2Fresenius Medical Care, Moron, Argentina; 3Fresenius Medical Care Argentina, buenos Aires, Argentina; 4Fresenius Medical Care Asia Pacific, Hong Kong, China; 5Fresenius Medical Care North America, Melrose, MA; 6Maastricht University Medical Centre, Maastricht, Netherlands; 7Renal Research Institute, New York, NY; 8Richard Bright Renal Unit, Bristol, United Kingdom; 9University of California - Santa Barbara, Santa Barbara, CA; 10University of Illinois College of Medicine, Burr Ridge, IL. Group/Team: MONDO initiative.

Background: Serum magnesium (Smg) associated with mortality and particularly its deficiency substantially increases the risk of adverse outcomes. We studied the relationship between dialysate magnesium (Dmg) and Smg and the effects Dmg on all-cause mortality in a large global cohort.

Methods: All the patients started in-center hemodialysis (HD) between 2000 and 2012 were included. Following the first available Dmg data point we established a 3 months baseline. All the value were average during baseline. Follow-up defined as 1 year after that. A multivariable regression model was applied to study the association of 1.0 versus 0.75 mmol/L Dmg on Smg. Then we used 1:1 propensity score matching (age, gender, catheter, and vintage) to create two cohorts with Dmg of 1.0 and 1.5 mmol/L, respectively. We compared survival times between these 2 cohorts using KM analysis, log rank-test and Cox regression analysis adjusted for age, gender, and catheter.

Results: We studied 15,211 pts (57.4 yrs, 58% males, 41% DM, 24% catheter; Dmg 0.75: 1,055 (7%); 1.0: 12,608 (82%) and 1.5: 222 (1%)). In multivariate regression accounting for age, nPCR, NLR and albumin, a Dmg increase by 0.25 mmol/L (from 0.75 to 1.0 mmol/L) was associated with a Smg increase by 0.09 (95% CI 0.03 to 0.14) mmol/L. Propensity score-matching created 2 well balanced cohorts with Dmg of 1.5 and 1.0. Uni- and multivariate survival analysis did not show significant differences between the two Dmg groups [Figure 1; adjusted HR of Dmg 1.5: 1.1 (95% CI 0.6 to 2.0)].

Conclusions: Our results indicate a direct association between Dmg and Smg. This finding is of importance, since higher Smg are associated with better outcomes in observational studies. Prospective studies are warranted to further delineate the complex interaction between Dmg, Smg, and patient outcomes.

FR-PO890
Ultrafiltration Profiling: Association with Clinical Outcomes among Incident Dialysis Patients Scott Sibbel, Adam G. Walker, Steven M. Brunelli.
DaVita Clinical Research, Minneapolis, MN.

Background: Ultrafiltration (UF) profiling is the practice of varying the UF rate during dialysis in order to mitigate the consequences of decreased effective circulating volume. In practice, UF profiling may be used on a standing basis, a PRN basis, or not at all. We conducted parallel matched analyses comparing standing UF profiling to PRN UF profiling and to no profiling.

Methods: We considered all incident hemodialysis patients at a large dialysis organization (Jan 2010-Jun 2015). We identified all patients who received a first-ever order for standing UF profiling. We considered eligible controls of two types: PRN profile patients, who initiated a first-ever order for UF profiling on a PRN basis in the same vintage month; and patients who had not used UF profiling through the same vintage month. Each standing UF profile patient was matched (separately) to an eligible control of each type based on race and Charlson comorbidity index score using intention-to-treat methods. Rates of death, all-cause hospitalizations, missed dialysis treatments, and episodes of intradialytic hypotension (IDH) were assessed over the subsequent 12 months on an intention-to-treat basis.

Results: No UF profiling (vs standing UF profiling) was associated with lower rates of IDH and hospitalization, but indistinguishable rates of death and missed treatments. PRN UF profiling (vs standing UF profiling) was associated with lower rates of IDH, but higher rates of hospitalization and missed treatments; no difference in death rate was observed.

Conclusions: We did not detect a benefit of standing vs no UF profiling, nor evidence to suggest that PRN UF profiling is superior to standing UF profiling. These data call into question the rationale underlying commonplace use of UF profiling in clinical practice.

Funding: Commercial Support - DaVita, Inc

FR-PO889
Effect of Bioelectrical Impedance Analysis-Guided Comparing with Standard Clinical-Guided Dry Weight Assessment on Sleep Quality in Chronic Hemodialysis Patients Sethanant Sethakaran, Pariya Phanachet, Chagiya Kitiyakara, Sirimon Reutrakul, Arkom Nongmuich. Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

Background: Sleep disturbances are common among chronic hemodialysis patients, leading to poor quality of life, increased morbidity and mortality. Hypervolemia has been linked to poor sleep quality in these patients, but optimizing fluid status might improve sleep quality in such patients. This study aims to compare subjective and objectively measured sleep parameters, using Pittsburgh Sleep Quality Index (PSQI) questionnaire and actigraphy recordings, between bioelectrical impedance analysis (BIA)-guided and standard clinical-guided dry weight assessment during 6 months period.

Methods: We randomly assigned 19 chronic hemodialysis patients with subclinical hypervolemia; defined as clinically euvoemlic status despite the ratio of extracellular water to total body water more than 0.4 on BIA, who were poor sleeper (PSQI≥5) to either BIA-guided (BIA group) or standard clinical-guided dry weight group (clinical group). The outcomes were changes in PSQI score, and sleep parameters by actigraphy at 1, 3 and 6 months.

Results: Mean age was 63.53 ± 11.12 years and 42.11% were male. The baseline characteristic and sleep quality were comparable. At 3 and 6 months, subjective sleep quality in the BIA group significantly improved as reflected by a greater decline in PSQI score compared to the clinical group [3 months: mean difference -1.8 (-2.98 to -0.63), p<0.003; 6 months: mean difference -3.11 (-4.31 to -1.92), p<0.003].

Conclusions: Better optimization of fluid status using BIA significantly improves subjective sleep quality in chronic hemodialysis patients. This should be further explored in larger clinical trial.

Funding: Private Foundation Support

Figure 1. Change in PSQI score during study period.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
**FR-PO891**

Effects of Hemodialysis, Isolated Ultrafiltration, and Isolated Diffusion on Oxygen Extraction Ratio (OER) Silverio Rotondi,1 Lida Tagliatelle,4 Luciano Carbone,6 Maria Luisa Muci,1 Marzia Passaluci,2 Sandro Mazzafferro.3 Polyclinico Umberto I Roma, Italy; Polyclinico Umberto I, Rome, Rome, Italy; Sapienza University of Rome, Rome, Italy; sapienza university of rome, Rome, Italy; 3Nephrology and Dialysis Unit, ICGOT Hospital, Polo Pontino, Sapienza University of Rome, Latina, Italy; 4ICOT, Latina, Italy.

**Background:** Hemodialysis sessions cause tissue hypoxia which is not routinely measured. OER (r.v. 25-30%), obtained as the ratio between SaO2 and Central Venous Oxygen Saturation (ScvO2), is employed in ICU to quantify tissue hypoxic stress. We aimed to evaluate if the OER is a. Increases during dialysis session; b. is different after long (HD), short (HD) or short (HD) dialysis intervals; c. is differentially affected by isolated ultrafiltration (iUF) or isolated diffusion (iD).

**Methods:** We enrolled 20 clinically stable patients on HD since >6 months, with Central Venous Catheter. We measured SaO2 (by capillary oxymeter) and ScvO2 (by blood gas analysis) to calculate the OER basally, 15', 30', 60', 120' and end of HD session. In 10 of them, OER was re-measured during the first hour of the first and second HD session performed by applying, alternatively, iUF or iD. During each HD, UF rate was kept at+10 ml/kg/h and symptoms were recorded.

**Results:** In the HD session, OER increased within 30' (post hoc test p<0.05) and then progressively up to the end of HD, by 38%. Mean basal OER of HD (34.4±7), HD (33.8±7), HD (36.2±6), were not different (Tab. 1). In the two HD sessions, OER changes overlapped with those in HD. During the first hour of the HD session, we observed a significant increment of OER, at variance with the significant increase recorded during the HD session, with iD (Tab. 1). All HD sessions were asymptomatic with no change in blood pressure (systolic or diastolic) or heart rate. During sessions, no significant change was evident for capillary SaO2 (98±1%), while ScvO2 progressively decreased.

**Conclusions:** a. OER increases significantly during HD sessions; b. HD intervals do not modify the adaptive process to hypoxia; c. iD affects this adaptive response possibly more than iUF; OER might be a marker of HD stress, potentially useful in fragile patients.

**FR-PO892**

Extended Weekly Hemodialysis Hours Selectively Improves Kidney Disease-Specific Quality of Life: A Secondary Analysis of the ACTIVE Dialysis Trial Brandon Smyth,2 Oliver van den Broek-Best,6 Li Zuo,1 Nicholas A. Gray,7 Christopher T. Chan,1 Janak R. de Zoysa,6 Kirsten Howard,8 Kris Rogers,1 Meg J. Jardine,3 Vlad Perkovic,7 The George Institute for Global Health, UNSW, Sydney, NSW, Australia; 2Penn University People's Hospital, Beijing, China; 3Sunshine Coast University Hospital, Birtinya, NSW, Australia; 4Toronto General Hospital, Toronto, ON, Canada; 5Waienata District Health Board, AUCKLAND, New Zealand.

**Background:** End-stage kidney disease is associated with high symptom burden and poor quality of life (QOL). The ACTIVE Dialysis Trial randomized 200 hemodialysis (HD) patients to standard (median 12) or extended (median 24) weekly HD hours for 12 months. Extended hours HD did not affect EQ-5D utility-based QOL, but had a small but significant effect on general health-related QOL measured by the SF-36. We aimed to determine the impact of extended hours HD on kidney disease-specific QOL.

**Methods:** QOL assessments were administered by blinded interviewers at 3-monthly intervals during the trial. The Kidney Disease Component Summary (KDCS) is a disease-specific summary measure ranging from 0-100 including disease-specific dimensions such as disease impact, dialysis delivery and symptoms. The average intervention effect of KDCS was determined using mixed linear regression adjusted for time and baseline score. Pre-specified subgroups were defined by residence in China or other, dialysis in an urban or rural setting in China or other, dialysis in an institution or at home and dialysing for more or less than 6 months.

**Results:** Mean baseline KDCS scores were similar in participants randomised to standard and extended weekly dialysis hours (66.6 [95% CI 61.4-68.9] and 66.0 [95% CI 63.2-68.7] respectively). Extended weekly HD hours improved mean KDCS by 3.94 points (95% CI 1.44-5.51, p=0.0001). Subgroup analysis demonstrated the improvement in KDCS was individually significant in those from China, dialysing in an institution or of dialysis vintage >6 months (4.54 [95% CI 2.04-7.05], 4.05 [95% CI 1.83-6.27] and 4.20 [95% CI 1.90-6.48] respectively, all p<0.001).

**Conclusions:** Extended hours HD is associated with improvement in kidney disease-specific QOL, despite having no effect on overall EQ-5D measured QOL. The impact in defined patient populations warrants further investigation. NCT00649298

**Funding:** Commercial Support - Baxter International Inc., Government Support - Non-U.S.

**FR-PO893**

Evaluation of Sex Difference in Fluid and Nutritional Statuses at the Initiation of Hemodialysis Using a New Bio-Impeadence Spectroscopy Device Tatsunori Toide,2,3 Shin Fukunaga,1 Reiko Toide,2 Shigehiro Uezono,2 Hiteto Nakagawa,2 Yuji Sato,3 Shouchi Fujimoto,3 Noheoka Prefectural Hospital, Noheoka, Japan, 4Chiyoda Hospital, Hyogo, Japan; 5University of Miyazaki, Miyazaki, Japan.

**Background:** Recently, the sex differences in health outcomes among patients undergoing maintenance dialysis were reported (JASN, 2017). The maintenance of an appropriate body fluid volume and nutritional status in hemodialysis patients is important for improving their prognoses. We herein cross-sectionally evaluated sex difference in over-hydration (OH) and the nutritional status (lean tissue index; LTI and skeletal muscle index; SMI) at the initiation of hemodialysis (HD) using a bio-impeadence spectroscopy device (Body Composition Monitor, BCM).

**Methods:** 119 patients at the initiation of hemodialysis (female vs. male, 49 vs. 70; mean age, 69.7 ± 11.2 years; mean BMI, 23.9 ± 4.5 kg/m², 59 diabetic patients) were enrolled between February 2015 and December 2016 at Noheoka Prefectural Hospital and Chiyoda Hospital. Measurements were performed before HD in the early phase after the initiation of HD by BCM and relationships between clinical data were also assessed. Furthermore, the nutritional statuses of HD patients in the present study were compared with our previous findings obtained in healthy Japanese volunteers (Biomed Mater Eng, 2015).

**Results:** Patients with diabetes or pleural effusion showed significantly higher OH levels compared to those without diabetes or pleural effusion. Serum NT-proBNP values and BMI were positively correlated with OH levels, respectively. OH level was not different between male and female. LTI and SMI were negatively correlated with age in males, respectively, but not in females. LTI and SMI were not correlated with the levels of serum albumin or C-reactive protein. These indexes were not different between patients with or without diabetes. In males, LTI and SMI were lower in HD patients than in healthy volunteers, but not in females.

**Conclusions:** Present study suggests that BCM is a useful tool for evaluating the body fluid and nutritional status in patients at the initiation of HD. Furthermore, malnutrition is a concern in males at the initiation of HD. Follow-up observations using BCM may be useful for managing HD patients.

**FR-PO894**

HEMO Study Results Suggest that “Clinically Negligible” Residual Kidney Function (RFK) is a Significant Contributor to Uremic Solute Clearance Stephanie M. Toth-Manikowski,1 Tammy L. Sirich,4 Thomas H. Hostetter,1 Seungyoung Hwang,3 Josef Coresh,1 Neil R. Powe,3 Tariq Shafi,2 Case Western Reserve University, Cleveland, OH; 2Johns Hopkins University School of Medicine, Baltimore, MD; 3Priscilla Chan and Mark Zuckerberg San Francisco General Hospital & University of California SF, San Francisco, CA; 4Stanford University, Palo Alto, CA; 5Welch Center for Prevention, Epidemiology & Clinical Research, Baltimore, MD.

**Background:** RFK is thought to exert its beneficial effects through improved clearance of uremic toxins but the level of native kidney function where this clearance becomes negligible is not known. The HEMO study excluded patients with RFK >1.5 mL/min, as a level below was regarded as “clinically negligible.” We aimed to assess whether the levels of non-urea solutes associated with clinical outcomes differed among patients with this “clinically negligible” RFK compared to those with no RFK.

**Methods:** We measured 8 non-urea solutes in plasma from 1,280 patients of the HEMO Study 3-6 months post-randomization. We calculated the relative difference in solute levels among patients with and without RFK and compared it to the relative difference achieved by high vs standard hemodialysis (HD) dose (mean Kt/Vurea 1.7 vs 1.3, respectively).

**Results:** At baseline, 34% of patients had “clinically negligible” RFK (mean 0.7±0.4 mL/min); 66% had no RFK. Those with RFK were older, had more recent onset of dialysis, and had lower UF requirements than those without RFK. Patients with RFK had significantly lower non-urea solute levels than patients without RFK. The differences were comparable or more pronounced than in those randomized to high HD dose (Table).

**Conclusions:** Even at a very low level, RFK is not “negligible” as it continues to provide clearance of solutes associated with clinical outcomes.

**Funding:** NIDDK Support
Effect of RKF on Uremic Solutes in 1,280 HEMO Participants

Patients with RKF had 54% lower odds of an ED encounter compared to Medicare Primary, Medicare secondary patients/Medicare HMO had 54% lower odds of an ED encounter compared to Medicare Primary.

Conclusions: Patient ED encounters within 30 days after a hospital discharge occur frequently for chronic dialysis patients. Patient characteristics of SDS/SES (DE status, younger age, female sex) are associated with a higher risk of ED use following a hospital discharge. These ED visits represent an opportunity for greater coordination to reduce potentially preventable acute care.

Funding: Other U.S. Government Support

FR-PO985

Post-Hospitalization Dialysis Facility Processes of Care and Pulmonary Edema-Related Hospital Readmissions among Hemodialysis Patients

Background: Both dialysis facilities and hospitals are accountable for 30-day readmissions among U.S. hemodialysis (HD) patients. Steps taken at the dialysis facility post-hospitalization may prevent pulmonary edema-related (PER) readmissions.

We examined the association of post-hospitalization HD processes of care with PER readmissions.

Methods: Using electronic health record (EHR) data from 23 Southeastern dialysis facilities, starting in 2010 and linked with national registry data for complete follow-up through 2014, we identified 4,545 in-center HD patients who had ≥1 hospitalizations (first=index), survived ≥30 days, and had ≥3 contiguous dialysis sessions following the index discharge. Readmissions were defined as admissions that occurred within 30 days of the index discharge; PER readmissions were further defined by the presence of discharge codes for pulmonary edema, fluid overload, and/or congestive heart failure (CHF). Indicators of processes of care were defined by EHR data as present vs. absent in the first 3 sessions post-index discharge.

Results: Overall, 19.9% of patients were readmitted, and 8.3% had PER readmissions (3.7% of all readmissions). Compared to patients who did not, patients who had PER readmissions were slightly older (63.9 vs. 61.6 years; P=0.09), less likely to be black (54.6% vs. 63.4%; P=0.09) and more likely to have history of CHF (76.0% vs. 39.7%; P<0.001) or index admissions also related to pulmonary edema (72.7% vs. 35.1%; P<0.001). New dialysis orders, particularly with target weight changes, were more common among those with PER readmissions. Higher epoetin dose was less common in readmitted patients; drawing of labs was not different by readmission status (Table).

Conclusions: Patients who had PER readmissions were more, not less, likely to have target weight changes in dialysis orders and medication reductions within 3 sessions of index admission discharge. In general, these results suggest that usual post-hospitalization care at the dialysis facility may not prevent PER or all-cause readmissions.

Funding: Other U.S. Government Support

FR-PO986

Factors Associated with Higher Risk of Emergency Department Use within 30 days of Hospital Discharge

Methods: Data on ED visits (outpatient or observation stays) for dialysis patients in 2014 were obtained from Medicare Outpatient Claims. Adjustment was made for patient and area level clinical and SDS/SES characteristics. A two stage multivariate logistic regression model determined odds of an outpatient ED encounter within 30 days of an index hospital discharge adjusted for these SDS/SES and clinical factors.

Results: 14.5% of the 423,165 index discharges among 201,674 unique patients in 2014 were followed by an outpatient ED visit within 30 days. Females, younger age, longer ESRD vintage and black race were associated with higher odds of an ED encounter within 30 days. Dually-eligible (DE) patients (Medicare and Medicaid) had 13% higher odds compared to Medicare Primary; Medicare secondary patients/Medicare HMO had 54% lower odds of an ED encounter compared to Medicare Primary.

Conclusions: Outpatient ED encounters within 30 days after a hospital discharge occur frequently for chronic dialysis patients. Patient characteristics of SDS/SES (DE status, younger age, female sex) are associated with a higher risk of ED use following a hospital discharge. These ED visits represent an opportunity for greater coordination to reduce potentially preventable acute care.

Funding: Other U.S. Government Support

FR-PO989

In-Patient Hospitalization of Dialysis Patients in Canada: Opportunities to Decrease the Burden on Patients

Background: All-cause hospitalization rates for dialysis patients is high, with 1.7 hospitalizations per patient-year reported in the United States. In Canada, the Canadian Organ Replacement Register program at the Canadian Institute for Health Information examined hospitalization in Canada for both all-cause, and infections related to dialysis treatment.

Methods: A cohort of 38,369 incident dialysis patients between 2005 and 2014 were included in the study. Crude rates for hospitalization (all cause and infection) and in-hospital mortality were calculated. A frailty model was used to calculate hazard ratios for covariates including age, sex, race, income, comorbidity, primary diagnosis, year of dialysis start, care type, modality and pre-dialysis hospitalization.

Results: The all-cause hospitalization rate for dialysis patients was 1.1 hospitalizations per patient-year. Pediatric patients (HR = 2.73; p<0.001) and Indigenous patients (HR = 1.20; p<0.001) had higher risk than peers for hospitalization, and patients on home hemodialysis and peritoneal dialysis (HR = 0.84; p<0.001) had a lower risk of being hospitalized than in-centre patients. Similar results were observed for hospitalization for infections related to dialysis. All-cause hospitalizations were more frequent at dialysis initiation and decreased over time for both patients receiving peritoneal or hemodialysis.

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

Underline represents presenting author.
Conclusions: Targeted national interventions such as promoting greater arteriovenous fistula use to reduce catheter infections, earlier vitamin D analogues and the most common phosphate binding utilized was calcium carbonate. Median time of follow up was 48 months (Interquartile range 22-64) Univariate analysis showed that CAD (hazard ratio [HR] 1.89; 95%CI 1.54-2.32), DM (HR 1.32; 95%CI 1.09-1.60), and PAD (HR 2.05; 95%CI 1.22-3.44) were associated with increased mortality. In multivariate analysis only CAD was associated with an increased risk of death (HR 2.00; 95%CI 1.61-2.46). Hemodiafiltration, as compared with low flux dialysis, was associated with a decreased mortality (HR 0.34; 95%CI 0.149-0.89). There was no difference in the risk of death between low-flux and high-flux hemodialysis (HR 1.19; 95%CI 0.92-1.55). Median survival time was not yet reached but it was longer in the hemodiafiltration group. (p<0.0001)

Conclusions: This study suggests that HDF, as compared with low-flux dialysis, may reduce the risk of mortality. The magnitude of the effect size is possibly overestimated by the observational nature of study.

FR-PO901
Opioid Overdose Hospitalizations with Patients with ESRD – Nationwide Trends and Outcomes
Swati Sakhuja,1 Ankit Sakhuja,1 Kianoush Banai-Kashani,1 Mayo Clinic, Rochester, MN; University of Alabama at Birmingham, Birmingham, AL.

Background: Opioid overdose is responsible for more deaths than firearms or motor vehicle crashes in the United States. Recent studies have shown opioid use to be widely prevalent in end stage renal disease (ESRD) patients, however, epidemiology and outcomes of opioid overdose in this population are unclear.

Methods: Using data from National/Nativio Inpatient Sample database from year 2000-2013, we identified patients 20 years or older with opioid overdose admissions and those with ESRD using ICD-9-CM codes. Using data from US Census and USRDS render, we assessed the trend of incidence of opioid overdoses in ESRD and general population. We also examined the associated mortality and if ESRD is an independent predictor of mortality in these patients in a model adjusted for age, sex, race, primary payer, Charlson’s score, hospital bed size, volume, region, location & teaching status, use of mechanical ventilation, classification of poisoning as suicidal, homicidal, accidental or unknown and year of admission.

Results: Of total 558,737 opioid overdose admissions, 7496 (1.3%) had ESRD. The incidence of opioid overdose (per 100,000 population) increased from 92 to 183 in ESRD and 19 to 31 in general population (Fig 1). Patients with ESRD were more often in 45-79 yr age-group, blacks and Hispanics and with higher co-morbidities. Inpatient mortality was higher in patients with ESRD (4.0% vs 2.5%; p<0.001). In addition, having ESRD was an independent predictor for mortality in these patients (OR 1.42; 95% CI 1.02-1.98).

Conclusions: The incidence of opioid overdose is higher in ESRD patients and is rising at a rapid pace. ESRD patients with overdose have higher mortality and ESRD is an independent predictor for mortality in patients with opioid overdose.

Fig 1: Trends of incidence of opioid overdose in ESRD and general population.

FR-PO902
Novel Prediction Score for Early Death upon Transition to Dialysis: A Veterans Affairs (VA) and Kaiser Permanente Southern California (KPSC) Big Data Approach
Yoshitsugu Oh1,2 Danh V. Nguyen,3 Hui Zhou,4 Elani Streja,1 Melissa Soohoo,1 Lishi Zhang,5 Yanjun Chen,6 Miklos Z. Molnar,7 John J. Sim,1 Steven J. Jacobsen,8 Connie Rhee,8 Csaba P. Kovesda,9 Kamyar Kalantar-Zadeh,1 Kirk Toy,1 Debra Messer,2 Lori Lasko,2 William Schaeffer,2 Peter L. Tolson,2 Daniel G. Clarenza,2 David K. G. Hailpern,2 Grant Cornish,2 Charles H. McCulloch,2 William L. Black,2 Brian Couper,2 Cell Effects,2 Malcolm Lee,2 Michael Eastwood,2 John J. Geraldes,2 Carlos Gonzalez,2 Paul Giraud,2 Margaret Graf,2 David Green,2 Karl Green,2 Jeanna Harrell,2 Sheryl Hooper,2 Robert J. Hotchkiss,2 Hironori Ishizaki,2 Alwin Kheswa,2 Kevin White,2 David C. Kopp,2 Christine Kuehn,2 Jana Kim,2 John M. Lawler,2 Michael Lee,2 Paul Marshall,2 Elyse Mathis,2 Kari Mattson,2 Robert McLaughlin,2 Christopher Nassetta,2 Hans Poeschel,2 Aaron Paladino,2 Kenneth Pan,2 William O. Pelletier,2 Marjorie Phelan,2 Sarah Pinson,2 Alphonse Prenzler,2 Steven Ruppert,2 T. Smith,2 Gail Smith,2 Andrew Stavros,2 Timothy Stansel,2 Ellen Steiner,2 Michael T. Stewart,2 Karen Talamantez,2 Ruadhaí Ó Tongail,2 Adam Uhl,2 Michael (Mike) Walls,2 George Wang,2 Benjamin Watts,2 Bill White,2 Andrew W. Whitley,2 Reiner Wolters,2 Randy Xie,2 Amy Yang,2 Linda Zyla,2 Andrea Zyorin,2 John F. McDonald,2 Fredric N. Lewis1,2

Background: Mortality is exceptionally high during the first year among incident dialysis patients, aimed to establish a risk prediction tool for early mortality based on pre-ESRD conditions.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Methods: Among 35,853 US veterans who transitioned to dialysis over 6.5 years (10/2007-03/2014), we developed new risk scores based on demographics, primary ESRD causes, comorbid conditions, and pre-ESRD laboratory data. We stratified patients by low and high eGFR (i.e., <15 and ≥15 mL/min/1.73m², respectively), and then applied a Cox model with AIC-based backward variable selection to 14-month survival data. The final model was validated among 4,284 KPSC patients over 8.75 years (01/2007-09/2015).

Results: Observed 1-year mortality was 27% in the VA cohort, and was not significantly different from predicted mortality. C-index values in the VA cohort were 0.71 and 0.67 among patients with low vs. high eGFR, respectively. The external validation using the KPSC cohort showed C-index values of 0.77 and 0.74 among men vs. women with low eGFR, respectively, and 0.71 and 0.67 among men vs. women with high eGFR, respectively.

Conclusions: New risk scores for early mortality have been developed and externally validated among a cohort of racially, ethnically, and gender diverse ESRD patients transitioning to dialysis. It would help with the identification of a high risk population and provide information that may contribute to dialysis initiation planning.

Funding: NIDDK Support

FR-PO0903

First-Year Mortality among Patients Initiating Hemodialysis with a Functional Arteriovenous Fistula Compared with Peritoneal Dialysis
Purna Mukhopadhyay,1 Kenneth J. Woodside,2 Keith McCullough,1 Kaitlyn Ratkowia,1 Douglas E. Schaubel,1 Ronald L. Pisoni,1 Vahakan B. Shahinian,2 Rajiv Saran.2 1Arbor Research Collaborative for Health, Ann Arbor, MI; 2University of Michigan, Ann Arbor, MI

Background: Comparison of initial outcomes between in-center HD and PD are subject to bias, as typically PD patients (pts) are younger, healthier, & may have received longer pre-ESRD care. Restricting comparisons to better prepared pts who initiate HD with a functional arteriovenous fistula at start of renal replacement (HDAVF) may minimize this bias.

Methods: Five annual cohorts (USRDS 2010-2014, CMS Form 2728) of incident HDAVF pts (N=81,850) & PD pts (N=77,850) were followed up to 1 year for the outcome of death. Death & time at risk for cohorts were determined in each of 12 consecutive 30-day segments, censoring for transplantation, switch to PD (or HD), recovery of renal function, loss to follow-up, or end of study. Death rates are expressed per 100 patient years (PY). Unadjusted and adjusted hazard ratios for death averaged over 2010-2014 were calculated for four 90-day risk periods.

Results: HD pts were on average older (64 vs 57 years), male (63.4% vs 56.8%), had received pre-ESRD care (89% vs 85.8%), & had greater comorbid burden at start of ESRD. The average unadjusted mortality rate for the HD cohort was higher, with 9.9 PY deaths in the first 30 days vs 5.6 PY deaths for PD. The hazard ratio of HD vs. PD in the unadjusted model was 1.6 (p <0.001) in the 0-90 day period, declining to 1.2 (p <0.001) post-180 days. In the adjusted model, the HR for first 30 days was 1.05 (p=0.34), & decreased to 0.88-8.82 (p <0.01) in the post-90 day period (Figure).

Conclusions: After accounting for pt characteristics, those who start renal replacement therapy on HDAVF appear to have a survival advantage over those that initiate with PD, particularly after 90 days. These findings could guide providers in advising the patients on modality & vascular access choice at dialysis start, have policy implications, & provide impetus for future research.

Funding: NIDDK Support

FR-PO0904

Options Education before Initiation of Dialysis Is Associated to Improved Hospitalization and Mortality Rates
Martina Reviriego-Mendoza, Yue Jiao, John W. Larkin, Rob Lynch, Len A. Usvyat, Jeffrey L. Hymes, Franklin W. Maddux. Fresenius Medical Care North America, Waltham, MA.

Background: KDOQI guidelines recommend that chronic kidney disease patients receive options education to learn optimal ways to prepare for dialysis. Little is known about the impacts of options education on patient outcomes after the progression to end stage renal disease (ESRD). We investigated if options education is associated with improved hospitalization and mortality outcomes in incident dialysis patients.

Methods: We studied data from incident Fresenius Kidney Care (FKC) patients who initiated dialysis between 2009 and 2016. Patients were grouped by enrollment in FKC options education prior to initiating dialysis or not, as well as whether patients started dialysis as an outpatient or inpatient. In these groups, we calculated and compared the mean annual hospital admission and mortality rate during the first 120 days of dialysis.

Results: We analyzed data from a total of 300,818 patients; of these, 68,721 patients received options education prior to initiating dialysis. Throughout 2009-2016, patients who received options education generally exhibited lower rates of hospital admissions and mortality during the first 120 days of dialysis, as compared to those who did not receive education. Similar findings were observed, yet less pronounced, for admission and mortality rates in patients starting dialysis as an outpatient versus outpatient. Specifically, in 2016, outpatient patients without education had 1.74 admissions per patient year (ppy) and 0.19 deaths per 100 patient years (p100py). When compared to those with education, we observed a 23.6% decrease in admissions (1.33 admissions ppy) and a 52.6% decrease in death rate (0.09 deaths p100py). Inpatients without education had 2.1 admissions ppy and 0.27 deaths p100py, while patients with options education were observed to have a 7.14% decrease in admissions (1.95 admissions ppy) and a 37% decrease in death rate (0.17 deaths p100py).

Conclusions: The analysis herein indicates that receiving options education before progression to ESRD is associated with lower rates of hospital admissions and mortality in the incident dialysis period. More analyses are needed to confirm these observations.

Funding: Commercial Support - Fresenius Medical Care North America

FR-PO0905

Race, Ethnicity, and End-of-Life Care in US Dialysis Patients, 2000 to 2011
Robert N. Foley,2 Paul E. Drawz,2 Donal J. Sexton,1 Scott Reule.1 1The Irish Longitudinal Study on Ageing (TILDA), Trinity College Dublin., Dublin, Ireland; 2University of Minnesota, Minneapolis, MN.

Background: End-of-life care is an increasingly prominent consideration, especially in situations where death appears imminent and quality of life is poor. As little is known regarding potential racial and ethnic disparities, we performed a national study to determine whether end-of-life care in US dialysis patients was subject to racial or ethnic disparity.

Methods: Retrospective United States Renal Data System files were used to examine the primary outcome, a composite of withdrawal of dialysis and death in a non-hospital or hospice setting (2000 to 2011, N=910,559). The following racial-ethnic groups were examined: (non-Hispanic) white, African American, Native American, Asian; Hispanic. Logistic regression was used to calculate odds ratios for end-of-life care outcomes per race-ethnicity.

Results: The primary outcome was less likely in patients from any minority group (10.1%) than in the non-Hispanic white population (21.5%, P-Value < 0.001). Corresponding values for dialysis withdrawal, hospice and non-hospital death were 16.3% Vs. 30.8%, 8.8% Vs. 15.7% and 33.1% Vs. 45.0%, respectively (P-Value < 0.001 for each comparison). After extensive covariate adjustment, the primary outcome was less likely in the combined minority group than in the white population (adjusted odds ratio [AOR] 1.03, 95% confidence interval [CI] 1.03-1.05, P-Value < 0.001); within individual minority groups, AOR values arrayed as follows (Vs. white, P-Value < 0.001 for each):

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

637
Results: Currently, 30% of our prevalent advanced CKD patients were able to both identify a decision maker for health care and provide verbal or written documentation in our EMR. Among our prevalent ESRD patients on dialysis, more than 30% of these patients have been invited to a Next Steps facilitated discussion and 16% of patients completed the discussion. Finally, 20% of highest risk ESRD patients have completed the Advanced Steps.

Conclusions: As an integrated health care system, KPNC is well suited to provide ongoing ACP and serious illness conversations for Nephrology patients. Future research is needed to identify effect of our LCP model at end of life including concordance with patient’s identified wishes.

FR-PO907
Advanced Care Planning (ACP) among CKD and ESRD Patients: Kaiser Permanente Northern California (KPNC) Experience

Background: Patients with advanced CKD and ESRD face difficult choices around extending life and managing quality of life with treatment burdens. ACP related to dialysis therapy are rarely addressed. Nephrologists identify multiple barriers including lack of time, communication skills, and supportive tools. KPNC is an integrated health care delivery system providing care to more than 35,000 advanced CKD and 4,000 ESRD patients. KPNC Nephrology operationalized a structured ACP program called Life Care Planning (LCP) based on Respecting Choices® that follows the trajectory of CKD to ESRD.

Methods: The KPNC LCP Nephrology program is an organized process to discuss future health care decisions and to create a written plan based on patient values and current health status. The program is operationalized with a three step staged approach using standardized communication including scripted conversations delivered by trained facilitators. First Steps is targeted to CKD 3 and 4 patients. Next Steps is targeted to prevalent ESRD patients on dialysis focusing on critical functions and trade-offs with dialysis therapy. Advanced Steps is targeted to ESRD patients with a predicted survival of less than 12 months based on clinical indicators. Registries in our EMR are used to identify at risk nephrology patients and identify the appropriate LCP step.

Results: Thirty three patients were referred to KPCC, with a no show rate of 18%. Fifteen patients met inclusion criteria, ten patients and three caregivers were consented. Cognitive impairment or psychiatric diagnosis led to patient exclusion. Hospitalization, fatigue, or pain led to attrition after consent and the potential bias towards a healthier population being interviewed. Some patients were confused by palliative care or became emotionally distressed during interview. Patients could stop interviews and supportive conversations took place, however, maintaining a focus on the research question rather than immediately addressing clinical needs was complex. Logistically the consent process was difficult given patients had to stay past their already 60 minute long appointment. Patient physical and cognitive vulnerability, the emotional nature of palliative care topics, and provider-researcher conflict were observed challenges.

Conclusions: We uncovered barriers to palliative care research that are unique to patients living with advanced kidney disease. Future kidney palliative care research will need to consider the patient’s emotional and physical state as well as the provider-researcher challenge when crafting study design to encourage patient participation and ongoing study of this essential field. Funding: ASN Small Grants Program for Scholarly Work in Geriatric Nephrology and Renal Palliative Care

Figure 1: Survival of patients with predicted 1-Y survival in the lowest quartile (blue line) and higher quartiles (red line)

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO909
Single Questions for the Diagnoses of Restless Legs Syndrome, Anxiety, and Depression in Hemodialysis (SQUIRREL) David T. Collister, 1,2 Jennifer C. Rodrigues, 1,2 Andrea E. Mazzetti, 2 Kelsi Salisbury, 2 Laura M. Morosini, 1 K. S. Brimble, 1,2 Michael Walsh, 1,2 1 McMaster University, Hamilton, ON, Canada; 2 St. Joseph’s Healthcare Hamilton, Hamilton, ON, Canada.

Background: Symptoms in patients with kidney disease, such as restless leg syndrome (RLS), depression and anxiety, are common, reduce quality of life and are potentially treatable. Simple, accurate screening tools are needed. We examined the operating characteristics of the single questions for RLS, depression and anxiety from the revised Edmonton Symptom Assessment System (ESAS-r) in hemodialysis patients.

Methods: We conducted a cohort study of adults receiving chronic hemodialysis in Hamilton, Canada. Diagnoses of RLS, anxiety and depression were made using the 2012 IRLS SG criteria and the Hospital Anxiety and Depression Scale. Participants were asked to the degree to which they experienced restless legs, anxiety and depression using the ESAS-r; 11-point scales anchored at 0 (no symptoms) and 10 (worst possible symptoms). ESAS-r single questions were compared to their reference standards using cutoffs greater than 0 indicating the presence of symptoms using logistic regression from which receiver operating characteristics (ROC) curves were generated.

Results: We recruited 50 participants with a mean age of 64 (12.4) years, of whom 52% were male and 92% were on 3x weekly hemodialysis. Using the reference standards, 14 (28%) had a diagnosis of RLS, 27 (54%) had depression and 28 (56%) had anxiety, 27 (54%), 36 (72%) and 25 (50%) expressed symptoms of RLS, anxiety and depression. Areas under the ROC curves were 0.65, 0.81, 0.82 for RLS, anxiety and depression respectively (Figure 1). A screening tool, an IRLS cutoff of 19 had the highest area under the ROC curve at 0.76 with a sensitivity of 71% and specificity of 81%.

Conclusions: The ESAS-r single question for RLS has poor discrimination for the diagnosis of RLS in a hemodialysis population although the ESAS-r single questions for anxiety, depression and the IRLS demonstrate reasonable discrimination.

Funding: Government Support - Non-U.S.

FR-PO911
Improving Advanced Care Planning in Maintenance HD Patients with ESRD Bashir El-Khouri, Chandandeep Takkar. University of Texas Health Science Center San Antonio, San Antonio, TX.

Background: More than 80,000 Americans die every year while receiving maintenance dialysis therapy for ESRD. The adjusted mortality rate of maintenance dialysis patients is nearly twice that of adults with cancer and more than twice that of adults with CHF or stroke. Rates of hospitalization and ICU admission during last month of life are also higher in ESRD patients. Although studies have shown that dialysis patients with a treatment-limiting advance directive were less likely to be hospitalized, receive intensive procedures, and die in the hospital, advanced care planning (ACP) or completion of Advance Directives (ADPs) or Medical Power of Attorney (MPOA) is lacking in the ESRD population compared to other chronic illnesses.

Methods: We conducted a pilot quality improvement project aimed at improving ACP in the maintenance HD community. Our goal was to increase the percentage of MWF second shift hemodialysis patients at University Dialysis Northwest (one of four dialysis units affiliated with us) with AD/MPOAs on file by 25% between November 2016 and February 2017. An inter-disciplinary team was convened. We surveyed our patients to obtain baseline information on current rates of AD/MPOA completion, knowledge of ACP, desire to participate in ACP, and identify barriers to collaboration. We collaborated with the Department of Palliative Medicine and implemented a series of interventions aimed towards facilitating the completion of ADs/MPOAs in our patients.

Results: We were able to increase the percentage of completed ADs/MPOAs to 28% from a baseline of 4.2% during our timeline. We are currently implementing measures including dedicated training in ACP for dialysis staff at all our outpatient dialysis facilities, incorporating ACP into interdisciplinary team meetings, establishing on-site notaries, and providing patient education in order to sustain results and expand the program to all UHS outpatient HD units.

Conclusions: Advance care planning is a vital aspect of patient-centered care at the end of life. Unfortunately it is lacking in the maintenance dialysis patient population due to a variety of cultural, provider and institutional barriers. We demonstrated that a comprehensive multidisciplinary approach to advance care planning improves AD/MPOA completion rates in our patient population.

FR-PO912
CKD Measures and Physical Function in Older Adults: The Atherosclerosis Risk in Communities (ARIC) Study Yugoh Shibagaki, 1,2 Priya Palta, 3 B G. Windham, 2 Josec Coresh, 3 Kunihiro Matsushita, 4 Division of Nephrology and Hypertension, St Marianna University Hospital, Kawasaki, Japan; 2UMMC, Jackson, MS; 3University of North Carolina at Chapel Hill, Chapel Hill, NC; 4Welch Center for Prevention, Epidemiology & Clinical Research, Baltimore, MD; 5Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.

Background: Reduced estimated glomerular filtration rate (eGFR) has been shown to be related to impaired physical function. However, data on the other chronic kidney disease (CKD) measure, albumin-creatinine ratio (ACR), in this context are sparse. Furthermore, whether cognitive function modifies these associations is unknown.

Methods: Among 4,608 community-dwelling older adults at ARIC visit 5 (2011-2013), we studied cross-sectional associations of eGFR with cystatin C (cysC) and urine albumin-creatinine ratio (ACR) with physical function based on the Short Physical Performance Battery (SPPB). Cognitive function was classified as no cognitive impairment, mild cognitive impairment (MCI), or dementia according to a diagnostic review of neuropsychiatric, neurologic, and brain imaging assessments.

Results: Mean age of participants was 75.7 (SD 5.1) years, and median SPPB was 10 (IQR 8-11), with 13.8% (n=636) having impaired physical function (defined as SPPB score <6). Adjusted for potential confounders, the odds ratio of having impaired physical function was 1.98 (95%CI 1.21-3.24) in eGFR <45 ml/min/1.73m2, 1.42 (0.88-2.30) in eGFR 45-59 ml/min/1.73m2, 0.98 (0.61-1.57) in GFR 60-89, compared to GFR ≥90 (Table). Similarly, the odds ratio was 1.92 (95%CI 1.20-3.05) in ACR ≥300 mg/g and 1.71 (1.38-2.14) in ACR 30-299, compared to ACR <30. When stratified by cognitive function (n=3,449 with normal and 1,159 with MCI/dementia), of the associations of eGFR and ACR with impaired physical function were stronger in normal cognition than in MCI/dementia (Table).

Conclusions: Both high albuminuria and low eGFR were independently associated with impaired physical function, with more evident results when cognition was preserved.
FR-PO913
Kidney Function Is Not Associated with an Accelerated Decline in Objective Tests of Physical Performance in Older Adults

Background: It is well known that malnutrition is implicated with increased morbidity and mortality in end-stage renal disease (ESRD) patients. Therefore, exploring risk factors for malnutrition has clinical relevance in these patients. In the present study, we aimed to investigate the significant association between fluid overload, inflammation, and malnutrition in ESRD patients on hemodialysis (HD).

Methods: A cross-sectional study was undertaken in 76 prevalent HD patients in South Korea. Geriatric nutritional risk index (GNRI) was calculated to determine nutritional status. Ratio of extracellular water (ECW) to total body water (TBW) was measured to determine fluid overload using multi-frequency bioimpedance (Inbody S20, Biospace, Seoul, Korea). Independent association between variables and GNRI were tested by linear regression analyses.

Results: The mean age was 59.1 ± 13.4 years, and 44 patients (57.9%) were male. Mean GNRI value was 97.2 ± 6.6 (median 97.8, interquartile range 94.4 to 101.8). The mean ratio of ECW to TBW (ECW/TBW) was 0.38 ± 0.02. In univariate analysis, age (per 1 year, β=0.13, 95% confidence interval [CI]=0.24 to 0.02), ECW/TBW (per 0.01, β=1.89, 95% CI=2.58 to -1.19), and C-reactive protein concentrations (per 1 mg/l, β=1.98, 95% CI=1.79 to -2.28) were negatively associated with GNRI, while serum potassium (per 1 mg/dl, β=2.46, 95% CI=0.36 to 4.55) and calcium-phosphorus products (per 1 mg/dl², β=0.18, 95% CI=0.06 to 0.29) were positively associated with GNRI. Moreover, men and patients with previous cardiovascular disease history had lower GNRI values. Multivariate analysis demonstrated that higher values of ECW/TBW (per 0.01, β=1.33, 95% CI=2.06 to -0.59) and C-reactive protein (per 1 mg/l, β=2.88, 95% CI=5.07 to -0.68) were independently associated with lower GNRI values after adjustment of confounding variables.

Conclusions: Extracellular volume expansion and inflammation showed an independent association with lower GNRI values in HD patients. This result suggest that avoiding fluid overload and inflammation could be helpful to mitigate malnutrition in these patients.
FR-PO917
Effect of Lower BMI on Mortality Risk in Older Patients Starting Dialysis Is Time-Dependent
Harmke A. Polinder-Bos,1 Ron T. Gansevoort,2 Merel Van diepen,1 Friedo W. Dekker,3 Ellen K. Hoogeveen,1 Casper F. Franssen,2 Carlo A. Gaillard.2 1Leiden University Medical Center, Leiden, Netherlands; 2University Medical Center Groningen, Groningen, Netherlands; 3University Hospital, Busan, Republic of Korea.

Background: Lower body mass index (BMI) has been associated with worse survival in older individuals in the general population and in chronic disease populations. Remarkably, in older dialysis patients no association of BMI with mortality was found. Therefore, we performed an in-depth analysis on this association in the NECOSAD cohort.

Methods: 908 patients aged ≥65 years were followed from start of dialysis until death or kidney transplantation, and were divided into tertiles by baseline BMI (BMI <23 (lower), 23-26 (reference), ≥26 (higher) kg/m²). Because the hazards changed significantly during follow-up, the effect of BMI was modeled for the short-term (<1 year after dialysis initiation) and longer-term (>1 year after dialysis initiation) using time-dependent Cox-regression models. Furthermore, differences between lower BMI patients who survived versus died during the first day of dialysis therapy were evaluated.

Results: During a median follow-up period of 3.8 years, 567 deaths occurred. Cumulative survival proportions at end of follow-up were 30%, 28% and 31% for the lower, middle and higher BMI groups, respectively. Lower BMI was associated with a higher short-term mortality risk (HR 1.57 [1.10-2.23] P=0.01), and a lower longer-term mortality risk (HR 0.77 [0.60-0.99] P=0.04), adjusted for age, sex, race, and smoking. Patients with a lower BMI who died during the first year of dialysis therapy had significantly more comorbidity, less physical mobility and ability to perform usual activities, and had lower albumin levels compared with those who survived the first year.

Conclusions: In older patients who start dialysis therapy lower BMI is associated with increased 1-year mortality. Remarkably, when surviving the first year of dialysis, patients with lower baseline BMI had a similar or even lower mortality risk compared with patients who had a normal or higher baseline BMI. Especially those older patients with BMI that have limited comorbidity and mildly or non-impaired physical function may benefit from having started dialysis.

FR-PO919
A Frailty Screening Tool for Use in CKD by Medical and Nursing Staff
Andrew Nixon,1,2 Theodoros M. Bampouras,1 Alastair R. Petrie,3 Atinuke J. Afolabi,1 Neil Pendleton,1 Sandip Mitra,1 Ajay P. Dhayagude.2 1Lancashire Teaching Hospitals NHS Foundation Trust, Preston, United Kingdom; 2University of Manchester, Manchester, United Kingdom; 3Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom.

Background: Frailty is associated with adverse clinical outcomes in chronic kidney disease (CKD) including an increased risk of hospitalisation and mortality. Nephrologists need a well-validated frailty screening tool.

Methods: Fifty-eight dialysis-dependent CKD and pre-dialysis stage 4 and 5 CKD patients were recruited. Patients were assessed by a doctor and nurses using the Clinical Frailty Scale (CFS). Frailty was also assessed using two operationalised frailty definitions: the frailty phenotype (FP) and the frailty index (FI). CFS scores were compared with FP and FI scores and ROC curves were calculated.

Results: Median age was 70 years old (IQR: 58.75-77.00) with 28 male patients. Half were receiving haemodialysis. Mean Charlson Comorbidity Index was 3.12 (SD: 1.29). Using the CFS, 29% were identified as frail by a doctor and 31% by nurses. Using the FP, frailty prevalence was 24%. Mean FI was 0.32 (SD: 0.13). Doctor and nurse CFS scores correlated well with each other (r=0.81, 95% CI: 0.70-0.89). Doctor CFS scores correlated well with FP (r=0.80, 95% CI: 0.70-0.87) and FI (r=0.85, 95% CI: 0.75-0.92) scores. Nurse CFS scores correlated moderately well with FP (r=0.66, 95% CI: 0.51-0.77) and FI (r=0.67, 95% CI: 0.52-0.79) scores. The ROC AUC was 0.90 (95% CI: 0.82-0.98) for the doctor CFS and 0.81 (95% CI: 0.70-0.93) for the nurse CFS (figure 1). A CFS score ≥2 gave a sensitivity of 1.00 and 1.00 with a specificity of 0.41 and 0.43 for identifying frailty (as defined by the FP) by a doctor and nurse, respectively.

Conclusions: The CFS is a useful frailty screening tool in those with CKD and can be effectively used by medical and nursing staff. Further study is needed to evaluate its ability to risk stratify patients prior to the commencement of renal replacement therapy.

Figure 1. Using the CFS to Identify Frailty.
Results: Median age was 70 years old (IQR: 58.75-77.00) with 28 male patients. Half were receiving haemodialysis. Mean Charlson Comorbidity Index was 3.12 (SD: 1.29). The PRISMA 7 identified 48% as frail. Using the FP, frailty prevalence was 24%. Mean FI was 0.32 (SD: 0.13). The PRISMA 7 scores correlated moderately well with FP (r=0.66, 95% CI 0.52-0.78) and FI (r=0.76, 95% CI 0.66-0.84) scores. Figure 1 demonstrates the ROC curve for the PRISMA 7. The ROC AUC for the PRISMA 7 was 0.87 (95% CI 0.77-0.97) for the PRISMA 7. A PRISMA 7 score ≥3 had a sensitivity of 0.93 and specificity of 0.66 for identifying frailty, as defined by the FP.

Conclusions: The PRISMA 7 questionnaire is an effective patient-directed frailty screening tool with excellent sensitivity for identifying frailty. It can be easily incorporated into routine clinical care. Further research is needed to evaluate its prognostic accuracy.

Figure 1. ROC Curve Assessing the PRISMA 7 Questionnaire’s Ability to Identify Frailty

FR-PO921

Step Length as a Novel Predictor of Physical Function in Patients with CKD

Rima N. Pai,1 Rupinder singh Buttar,2 William Paredes,2 Matthew Custodio,1 Hina Faroq,3 BUSHRA ZAIDI,4 Nabin R. Karhi,3 Aagat Sharma khattivada,5 Stephen Ansah-Addo,1 Ashley Tran,6 Meredith Hawkins,7 Matthew K. Abramowit2z.1 Albert Einstein College of Medicine, New York, NY; 2Albert Einstein College of Medicine, Bronx, NY; 3Ambra Health, Holmdel, NJ; 4Louis A. Weiss Memorial Hospital, Chicago, IL; 5Meditar Harbor Hospital, Baltimore, MD; 6Albert Einstein College of Medicine, Bronx, NY; 7University of Leicester, Leicester, United Kingdom; 8Jacobi medical center, Bronx, NY.

Background: Impaired mobility and disability are common in patients with CKD and contribute to morbidity and mortality. Novel predictors of functional decline could facilitate earlier identification of at-risk patients.

Methods: We measured average step length (SL) in 32 patients with CKD stages 4 and 5 who had physical function assessments performed every 3 months (median, 4 assessments). SL was calculated based on the number of steps needed to complete a 4m walk at usual pace. We also assessed lower extremity performance (Short Physical Performance Battery), muscle strength, endurance capacity (2 minute walk distance), self-reported physical function (SF-36 Physical Component Score (PCS)), and symptom burden (Renal Palliative Care Outcome Scale (POSS)). Age and sex-adjusted linear regression and mixed effects models were used to test the association of SL with baseline characteristics and with physical function parameters over time, respectively.

Results: The mean age was 64±13 years, 44% were women, mean eGFR 20±10 mL/ min/1.73m², mean BMI 32±7 kg/m², 59% had diabetes, and 16% had peripheral vascular disease. Lower PCS and higher POSS associated with shorter SL (4.7cm (1.8-7.7) and 6.3cm (2.7-9.9) per 10 point difference, respectively), as did 2 SPPB domains (2.3cm (1.7-2.9) per 0.1m slower gait speed and 7.3cm (1.1-13.5) shorter SL with impaired balance). Over time, each 10cm shorter SL was associated with 1.4kg (0.2-2.7) weaker hand grip strength and 26.5ft (8.6-44.5) shorter 2-minute walk distance, and with 0.4 point (0.02-0.7) decrease in SPPB during follow-up. Furthermore, SL was shorter in patients experiencing a fall (36±11 vs. 56±8 cm, p=0.008).

Conclusions: In a cohort of patients with advanced CKD, shorter SL associated with poorer subjective and objective measures of physical function and with the likelihood of falling. SL may be a useful predictor of fall risk and functional decline in CKD patients.

FR-PO922

Serious Fall Injury History and Adverse Health Outcomes after Initiating Hemodialysis among Older US Adults

Carolyn A. Merrick,1 Anjali Karki,2 Asha Laura Plantinga,2 Durham VA Medical Center, Decatur, GA; Emory University, Atlanta, GA; Duke University, Durham, NC; 3Atlanta VAMC, Decatur, GA.

Background: Although older adults with pre-dialysis CKD are at increased risk for falls, the prognostic significance of a serious fall injury prior to dialysis initiation has not been well described in the end-stage renal disease population.

Methods: We examined the association between a serious fall injury in the year prior to starting hemodialysis and adverse health outcomes in the year following dialysis initiation using a retrospective cohort study of U.S. Medicare claims data from the 2 years spanning dialysis start, among patients initiating dialysis in 2010-2012. Participants included Medicare beneficiaries aged ≥67 years. Serious fall injuries were defined using diagnostic codes for falls in combination with an injury code for a fracture, joint dislocation, or head injury. Outcomes were defined as time-to-event variables within the first year of dialysis for four outcomes: subsequent serious fall injury, hospital admission, post-acute skilled nursing facility (SNF) utilization, and mortality.

Results: Among this cohort of 81,653 initiating hemodialysis, 2,958 (3.6%) patients had a serious fall injury in the year prior to hemodialysis initiation. Compared to those without serious fall injuries, those with a serious fall injury in the prior year were older (mean age 78.1 vs 76.7), more likely to be female (57.7% vs. 46.8%) and white (73.5% vs. 65.2%), and more likely to need assistance with daily activities (27.2% vs. 17.8%). In the first year of dialysis, 7.6%, 67.6%, 30.7%, and 26.1% had a serious fall injury, hospital admission, SNF claim, or death, respectively (95% confidence intervals for a serious fall injury, hospitalization, SNF claim, or death for those with vs. without a history of serious fall injury in the prior year to hemodialysis initiation were 2.94 (2.71-3.20), 1.20 (1.15-1.26), 1.62 (1.52-1.73), and 1.28 (1.20-1.43), respectively). In the multivariable model, serious fall injury in the year prior to dialysis was associated with an increased risk for adverse health outcomes. For older adults initiating dialysis, a history of a serious fall injury may be novel marker for frailty and provide prognostic information to support decision-making and establish expectations for life after dialysis initiation.

Conclusions: A serious fall injury in the prior year to dialysis was associated with an increased risk for adverse health outcomes. For older adults initiating dialysis, a history of a serious fall injury may be a novel marker for frailty and provide prognostic information to support decision-making and establish expectations for life after dialysis initiation.

Funding: Veterans Affairs Support, Private Foundation Support

FR-PO923

Kidney Function Is Not an Independent Predictor of Falls among Community-Dwelling Older Adults

Robert McDermott,1,2 Daniel Carey,1 Rose Anne M. Kenny,1 Mark A. Little,2 Connall M. O’Seaghda,3 The Irish Longitudinal Study on Ageing, Trinity College Dublin, Dublin, Ireland; 3Trinity Health Kidney Centre, Trinity College Dublin, Dublin, Ireland; 4Department of Nephrology and Transplantation, Beaumont Hospital, Dublin, Ireland.

Background: While several studies have identified a link between chronic kidney disease and markers of frailty in older age, it is largely unknown if this association translates into meaningful outcomes such as a greater risk of falls. We sought to examine the relationship between kidney function and falls in a large representative cohort of older adults.

Methods: Prospective analysis of 5060 participants from the first 3 waves (2009-2015) of The Irish Longitudinal Study on Ageing, a nationally representative sample of community-dwelling adults aged ≥50 years. All participants had estimated glomerular filtration rate (eGFR) calculated from cystatin C at wave 1. Data regarding falls (any fall in the last year or between waves) were captured via a computer-assisted personal interview at each wave. We used mixed effects logistic regression to examine the association between eGFR (eGFR ≥60 [reference], 60-89, <60mL/min/1.73m²) and reporting a fall injury, adjusted for age, sex, frailty (pre-frail/frail versus robust), diabetes, cardiovascular disease, pulse pressure, polypharmacy and chronic health conditions. Each covariate was modelled as a main effect and as a time*covariate interaction. An inverse probability weight was applied to all estimates to account for differential non-response and attrition.

Results: Mean (standard deviation) age of participants was 62.8 (9.1) years, 46% were male and median (interquartile range) eGFR was 80 (67-93) mL/min/1.73m². After adjusting for age and sex, participants with eGFR <60mL/min/1.73m² had a 5.0% (95% confidence interval 1.3 to 8.6%) increased probability of a fall versus the reference group (eGFR ≥90mL/min/1.73m²). This association was attenuated in the extended model (2.6% increased probability [-1.1 to 6.2%]). Results did not vary by age (over or under 65) or sex. The time*eGFR interaction was not statistically significant after adjusting for age and sex (p=0.65). Frailty and the number of chronic conditions were both independent predictors of falls in the multivariable model.

Conclusions: In this large prospective study of older community-based adults, kidney function was not found to be an independent predictor of falls. Our data suggest that, in the general population of older individuals, frailty status and comorbidity burden are more important predictors of falls than kidney function alone.

Funding: Government Support - Non-U.S.
FR-PO924
Improving Physical Function and Social Networks of Older Adults with ESRD: Development and Testing of Seniors Optimizing Community Integration to Advance Better Living with ESRD (SOCIAble) Deirdra C. Crews,1 Alice M. Delaney,1 Janiecee L. Walker,2 Thomas K. Cudjoe,3 Allyson Evelyn-Gustave,1 Jill Roth,4 David L. Roth,4 Sarah Szten,3 1Johns Hopkins School of Medicine, Baltimore, MD; 2Johns Hopkins School of Nursing, Baltimore, MD; 3Johns Hopkins University School of Medicine, Baltimore, MD; 4Johns Hopkins University School of Medicine, Baltimore, MD; 5Johns Hopkins School of Nursing, Baltimore, MD; 6Department of Medicine, Section of Nephrology, Baystate Medical Center, Springfield, MA; 2Department of Psychiatry, Baystate Medical Center, Springfield, MA; 3Department of Medicine, Section of Nephrology, West Virginia University School of Medicine, Morgantown, WV; 7Department of Medicine, Section of Nephrology, Baystate Medical Center, Springfield, MA.

Background: Older adults with ESRD have increased morbidity, life constraining fatigue and decreased physical function. These conditions can inhibit self-care and social engagement while restricting ability to leave home. We developed a home-based program to improve physical and social functioning of low income, older adults on hemodialysis (HD).

Methods: We 1) identified daily functional needs and home environmental barriers to engaging social networks among low income older patients on HD through focus groups (n=7 patients), 2) mapped focus group findings onto as aspects of an established program for low income older adults with physical limitations (which includes home visits with an occupational therapist, nurse and handyman to provide ≤$1300 worth of repairs, modifications and devices) tailoring the newly developed program (SOCIAble) to the needs of HD patients; and 3) piloted the program among 12 adults. We used a randomized wait list design to deliver the services in a staggered fashion that allowed a control comparison.

Results: Focus group themes included those in the Table. We adapted the original program to engage and improve SOCIAble. All participants were African American (50% male), mean age was 68 (SD: 5.9). From baseline to month 6 follow up, participants improved on average from 2.3 in Activities of Daily Living (ADL) difficulties (scale of 8) and improved 2.5 (scale of 8) Instrumental ADL difficulties. Participants’ mean social network scores increased from 18.4 to 23.1 (out of a possible 40). Satisfaction with social support improved less.

Conclusions: Our results show that it is possible to improve physical and social function of low income older adults with ESRD via a home based intervention. As people with ESRD have low quality of life and account for substantial costs to the U.S. healthcare system ($33 Billion), it is important to better understand how to improve life and decrease costs for this population with a full-scale efficacy trial.

Funding: Other NIH Support - National Institute on Aging

Representative Focus Group Quotes

**There**

Desire for Independence

In reference to Nursing Home: “They’re worried, not independent. It’s like, ‘you're at their beck and call all the time.’ Even, you know, you’re not a person, for example, you are stuck.”

Fatigue

“Fatigue is an ever-present issue. I think it’s like an invisible, non-visible disability. Like nobody notices it except you.”

Lack of Social Support

“They kings of like, they dismiss themselves, they try to do it their own way, and you try to do it in different ways. And I will not because you don’t have them there as an option so you will have at it.”

FR-PO925
Association of Kidney Disease Quality of Life (KDQOL-36) Subscale Scores with Mortality and Hospitalization in Older Dialysis Patients Rashaeda K. Hall, Alison Luciano, Carl F. Pieper, Colleen Colon-Emeric. Duke University, Durham, NC.

Background: The Kidney Disease Quality of Life (KDQOL-36) instrument is routinely administered to dialysis patients. Subscale scores may be useful for prognostication but their association with clinical outcomes has not been reported in older adults.

Methods: We conducted a longitudinal study of 3500 adults aged ≥75 years receiving dialysis through a large dialysis organization in 2012 and 2013. We used Cox and Fine and Gray models to evaluate the association of KDQOL-36 subscales (1- Burden of kidney disease, 2- Effects of kidney disease, 3- Symptoms of kidney disease, 4- SF-12 physical component score (PCS), and 5- SF-12 mental component score (MCS)) with risks of death and hospitalization, respectively. All models were adjusted for sociodemographic variables, hemodialysis access type, laboratory values, and Charlson index. We compared models with and without the KDQOL-36 subscales using likelihood ratio (LR) statistics. Results: Among members of this cohort, 32% died with the KDQOL-36 completed. From the date of KDQOL-36 completion, 929 (25.6%) patients died and 2,005 (61.4%) had at least one hospitalization over a median follow-up of 511 and 204 days, respectively. In unadjusted analyses, cohort members with KDQOL-36 scores in the lowest quintile (relative to the highest) had a lower risk of death and hospitalization, respectively. Inclusion of KDQOL-36 subscales improved model fit both for death (LR 41.04; p-value = 0.004) and hospitalization (LR 68.14; p-value < 0.001).

Conclusions: Routinely administered KDQOL-36 subscales may improve risk stratification of older adults receiving dialysis for death and future hospitalizations.

Funding: Other NIH Support - NCATS, NIA, Private Foundation Support

FR-PO926
An Integrated Prognostic Model for Shared Decision-Making with Patients with Stage 4-5 CKD Daniel L. Landry,1 Lewis Cohen,2 Rebecca J. Schmidt,3 Alvin H. Moss,4 Brian H. Nathanson,5 Michael J. Germain,6 1Department of Medicine, Section of Nephrology, Baystate Medical Center, Springfield, MA; 2Department of Psychiatry, Baystate Medical Center, Springfield, MA; 3Department of Medicine, Section of Nephrology, West Virginia University School of Medicine, Morgantown, WV; 4OptiStat, LLC, Longview, WA; 5Department of Medicine, Section of Nephrology, Baystate Medical Center, Springfield, MA.

Background: Patients with advanced chronic kidney disease (CKD) have high mortality and often die before needing dialysis. Studies show that prognostic information is important to patients facing the decision to pursue or forgo dialysis. A model that integrates clinical intuition with objective measures to predict 12-month mortality in patients with advanced CKD could help inform decisions.

Methods: In this prospective, observational study, 749 patients with CKD stage 4 or 5 were followed for 2 years. Demographics and laboratory data were collected while providers assessed functional status by the Karnofsky Performance Scale Index (KPSI) and answered a “surprise” question (SQ), “Would you be surprised if your patient died within the next 6 months?” upon each clinic visit.

Results: Mean (SD) age of the cohort was 69.3 (14.6), 50.9% were male, and 83.6% were Caucasian. Mean (SD) Charlson Comorbidity Index score was 5.9 (2.1) and 136 patients (18.2%) had a KPSI score of 50 (“requires considerable assistance and frequent medical care”) worse. By 12 months, 101 (13.5%) died and 99 (13.2%) initiated dialysis. A logistic regression model was constructed with 5 predictors of mortality. Area under the ROC curve was 0.81 indicating good discrimination.

Conclusions: In this model, advanced age, poor functional status, and the SQ predicted 12-month mortality in advanced CKD patients. The model is being validated and may assist nephrologists in shared decision-making with CKD patients who are choosing between dialysis versus conservative management.

Funding: Private Foundation Support

Logistic Regression Model of 12-Month Mortality (n = 736 patients with complete data)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age per 10-year increase</td>
<td>1.40 (1.24, 1.53)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Karnofsky Performance Scale Index (KPSI)</td>
<td>2.22 (1.24, 3.93)</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>KPSI (70 vs 40)</td>
<td>3.13 (1.37, 7.06)</td>
<td>0.016</td>
<td></td>
</tr>
</tbody>
</table>

FR-PO927
Accelerated Brain Aging in ESRD Patients Yi-Fang Chuang,1 Kai-Hsiang Shu,1 Yu-sen Peng,1 Yen-Ling Chiu,2,3 Nephrology, Far Eastern Memorial Hospital, Bantian, New Taipei City, Taiwan; 2Graduate Institute of Clinical Medicine, National Taiwan University, Taipei, Taiwan; 3Postgraduate Institute of Medicine and Surgery, Capital Medical University, Beijing, China.

Background: End-stage renal disease (ESRD) suffers from higher risk of cognitive impairment and dementia compared to the general population. It is known that brain structure changes appear years before the development of cognitive impairments and dementia. However, the relationship between brain structure changes and cognitive changes in ESRD patients has never been studied.

Methods: Twenty-six patients on maintenance hemodialysis without dementia and fifty-two age-matched non-renal failure control individuals were recruited from the Far Eastern Memorial Hospital (For ESRD patients, average age: 59.9 years and 31% had diabetes). All patients lives an independent life and can attend to the treatment independently. Brain structure was measured by 3T-MRI and analyzed using Freesurfer. A battery of neuropsychological tests were also performed.

Results: Mini Mental State Examination (MMSE) scores were comparable between ESRD patients and control subjects (29.5 vs 28.6). However, ESRD patients showed poorer performance in psychomotor speed and executive function, measured by symbol search, symbol substitution, trail making task and Stroop test after adjusting for age, gender, diabetes and education level (all P < 0.05). Nevertheless, there was no difference in both immediate recall or delayed recall memory tests. In addition, ESRD patients showed decreased volume in total gray matter and numerous brain structures, especially decreased volume of hippocampus (-0.98 mm3), amygdala (-0.34 mm3), and putamen (-1.61 mm3), all P < 0.05.

Conclusions: As the overall ESRD population grow older, how to prevent cognitive decline and dementia is a pressing issue. Our study indicates that ESRD patients exhibit numerous accelerated brain aging represented by decreased brain volume in specific areas pertinent to the development of mild cognitive impairment (MCI) and dementia. Whether these changes are predictive of further cognitive decline requires further study.

Funding: Government Support - Non-U.S.

FR-PO928

Geriatric Nephrology

Poster Friday

Geriatric Nephrology

Octogenarians in the Emergency Room: AKI, Risk Factors, and
Outcomes Mohsen Abu Alfeilat,1 Itzchak N. Slotki,1 Linda Shavit.2 1Share
Zedek Medical Center, Jerusalem, Israel; 2Shaare Zedek Medical Center,
Jerusalem, Israel.
Background: The prevalence of acute kidney injury (AKI) in the elderly is growing
and the prognosis is dismal. The structural and functional changes of the aging kidney,
multiple comorbidities and exposure to medications explain this susceptibility to AKI
in elderly. The aim of this study was to evaluate the incidence, risk factors, clinical
characteristics and outcomes of AKI in octogenarians admitted to the emergency room
(ER) and to compare these parameters with those in a younger group of patients admitted
in the same period.
Methods: This is a prospective, observational, single center study that enrolled adult
patients admitted to the ER of Shaare Zedek Medical Center, Jerusalem, Israel. Patients
were stratified by age (> or < 80 years) and followed up prospectively until discharge.
Incidence of AKI, in hospital mortality and duration of hospital stay were recorded.
Results: Of 319 patients, 128 were octogenarians (mean age 86.7, range 80 to
105) and 191 were younger (mean age 60.6, range 18 to 79). The incidence of AKI
and in hospital mortality was significantly higher in octogenarians (16.4 % vs 12.6 %,
p= 0.039 and 15.6% vs 3.1 %, p= 0.001, respectively). In univariate analyses, sepsis
and low blood pressure were associated with AKI in octogenarians, whereas history of
CVA or CKD, hypoalbuminemia and anemia were associated with AKI in the younger
group. In multivariate analysis, only low systolic blood pressure (SBP) at admission
in octogenarians (p=0.002) and history of CKD and hypoalbuminemia in the younger
patients (p<0.001; p=0.001) were independent risk factors for AKI.
Conclusions: Our results confirm the observation that AKI is common in
octogenarians and is associated with significantly higher mortality. We identified SBP
as the only independent variable associated with AKI. However, the role of therapeutic
strategies aimed to increase SBP and diminish complications in octogenarians remains
to be elucidated.

FR-PO929

Poster Friday

Geriatric Nephrology

Geriatric Nephrology: AKI in Elderly Patients; Differences in Etiology,
Morbidity, and Mortality; Age Is Not a Prognostic Factor Francisco
javier Lavilla, Pedro Errasti, Christian I. Alfaro Sanchez. Clinica Universidad
de Navarra, Pamplona, Spain.
Background: Age is considered an acute kidney injury (AKI) prognostic factor. But
can be more important than biologic age, the” clinical age” that include morbidity, acute
and chronic health status. The objective is evaluate acute kidney injury (AKI) in elderly
and very patient, and the influence of age as a prognostic factor.
Methods: In a cohort with 2714 hospitalizated patients (medium age 62 years, SD
0.3; 66.3 % males) with AKI (KDIGO), we made three groups (group A with age lower
than 65 years, group B between 65 to 85 years and group C with more than 85 years). We
evaluate AKI etiology, treatment and index prognosis (ISI –individual severity index-),
chronic morbidity (cancer, chronic renal and cardiac failure, diabetes), health chronic
status (Karnofsky) and acute morbidity (inflammatory status, lower hemoglobin level).
We use SPSS 20.0.
Results: Exitus (%): (A: 19.5, B: 14.6, C: 14) (p=0.003) Etiology: AKI functional (%)
(A: 33.1, B: 48, C: 64) (p=0.001). ATN (%) (A: 22, B: 18.7, C: 14) (p=0.001). Complex
AKI (%) (functional and ATN) (A: 39.1, B: 27.6, C 20.9) (p=0.001). Renal replacement
therapy (%) (A: 28.4, B: 24.4, C: 14) (p=0.001). Acute disease: Acute inflammatory
disease (%) (A: 46.8, B: 35.6, C 29.1) (p=0.001). Surgical procedure (%) (A: 16.8, B: 25.3,
C: 28.4) (p=0.001). Chronic disease: Diabetes (%) (A: 6.7, B: 12.3, C 16.3) (p=0.001).
Previous chronic kidney disease (%) (A: 34.4, B: 55.1, C: 66.3) (p=0.001). Chronic Heart
disease Previous chronic kidney disease (%) (A: 2.9, B: 4.9, C: 12.8) (p=0.001). Cancer
(%) (A: 62.9, B: 41, C: 14) (p=0.001). Analytical parameters: C reactive protein peak (mg/
dL) (A: 15.1 SD 0.4, B: 15.4 SD 0.42, C: 11.3 SD 1.39) (p=0.038). Lowe Hb level (g/L)
(A: 8.5 SD 0.07, B: 9.2 SD 0.15, C: 9.82 SD 0.3) (p=0.001). Acute anc chronic health
status: ISI (A: 0.2818, B: 0.3272, C: 0.3651) (p=0.001). Karnofsky (A: 69.5 SD 0.4, B:
68.28 SD 0.4, C: 61.3 SD 2.02) (p=0.001)
Conclusions: The AKI in very elderly patients were more functional and less
complex, with lower mortality and acute disease, but more chronic disease. Age is not the
more important prognostic factor in AKI. Is more important others (some acute diseases
–inflammatory-, chronic diseases –cancer-, health chronic and acute status and AKI
etiology–complexity related with previous factors-).

FR-PO930

Poster/Friday

medications and the number of ‘medication groups’ (by therapeutic indication) per person
were recorded at baseline. Hospitalisation, irrespective of cause, was measured as the
number of days per person per 12 month follow up. Comorbidities were dichotomised
to 0-2 and ≥3. Negative Binomial (NB) regression and Modified Poisson regression
were used to assess associations medication had with hospitalisation rate and mortality
respectively, first at univariate level, then after adjusting for confounders including
comorbidities.
Results: Individual medications ranged from 2 to 20 (IQR 8 to 12) while the
medication groups ranged from 2 to 15 (IQR 6 to 10). Most participants (83.5%) took
between 3-8 ‘medication groups’. The most common ‘medication groups’ were metabolic
bone disease related (87%), haemotenics (76%), cholesterol management (66%) and
antithrombotics (65%). There was a significant increase in hospitalisation rates for each
increase in medication group (RR 1.12, 95% CI: 1.02-1.23). Univariate analysis showed
an 8% increase in the risk of mortality with each medication (RR 1.08, 95th CI 1.05-1.11)
and an 11% increase in risk of mortality with each increase in ‘medication group’ (RR
1.11, 95% CI 1.09-1.13). Similarly, multivariate analysis showed an increase in individual
medications increased the risk of death by 8% (RR= 1.08, 95% CI: 1.07-1.09) and each
individual ‘medication group’ by 11% (RR= 1.11, 95% CI: 1.09-1.12)
Conclusions: In this high risk population, who may require polypharmacy,
polypharmacy is also an indicator of increased risk of hospitalisation and mortality in
those with ESKD ≥65 years. 1. Walker et al. BMC Nephrology 2013, 14:175

FR-PO931

Poster Friday

Geriatric Nephrology

Impact of Age and Glomerular Filtration Rate on Cardiovascular Drug
Use in CKD Patients Cédric Villain,7,8 Sophie Liabeuf,6,8 Marie Metzger,8
Christian Combe,5 Denis Fouque,4 Luc Frimat,3 Christian Jacquelinet,1,8
Maurice Laville,4 Ronald L. Pisoni,2 Benedicte Stengel,8 Ziad Massy.7,8
1
Agence de la biomedecine, Saint-Denis La Plaine, France; 2Arbor Research
Collaborative for Health, Ann Arbor, MI; 3CHRU Nancy-Brabois, Vandoeuvre
les Nancy, France; 4CHU Lyon Sud, Pierre Benite, France; 5CHU de
Bordeaux, Bordeaux, France; 6Service de Pharmacologie Clinique, CHU
Amiens, Amiens, France; 7CHU Ambroise Paré, APHP, Boulogne-Billancourt,
France; 8CESP, INSERM U1018, Univ. Paris-Sud, UVSQ, Univ Paris-Saclay,
Villejuif, France.
Background: Evidence for prescribing cardiovascular drugs is low in elderly patients
(pts) with chronic kidney disease (CKD). We analyzed the impact of age and glomerular
filtration rate (GFR) on use of drugs recommended for several cardiovascular diseases
(CVD) among pts with CKD.
Methods: We used baseline data from the CKD REIN cohort including 3033 adult
pts with CKD stage 3-4. We studied use of several CVD-specific drugs according
cardiovascular antecedents: antiplatelet agents, renin-angiotensin-aldosterone system
(RAAS) blockers, beta-blockers, and statins or ezetimibe in coronary heart disease;
antiplatelet agents or oral anticoagulant drugs (vitamin K antagonist or oral direct
anticoagulant) in stroke or transient ischemic attack; oral anticoagulant drugs in atrial
fibrillation with CHADS2-VASc2 score ≥2. Odds-ratios (OR) of drug use according to
age and estimated GFR were adjusted for sex, educational, activities of daily living, and
other CVD specific relevant confounders.
Results: Mean age was 66.8 yr, and mean CKD-EPI GFR 32.9 ml/min/1.73m2.
Prevalence of coronary heart disease was 24.5% (81.3% of these pts were receiving
antiplatelet agents, 75.7% RAAS blockers, 66.1% beta blockers, and 82.9% statins or
ezetimibe), that of stroke or transient ischemic attack was 10.1% (88.3% pts receiving
antiplatelet agents or oral anticoagulant drugs), and that of atrial fibrillation and CHADS2VASc≥2 11.2% (69.0% receiving oral anticoagulant drugs). Results of logistic regression
are shown in Table 1.
Conclusions: Although the management of CVD was appropriate in the majority of
CKD patients, old age and to a lesser extend low eGFR were associated with underuse
of certain recommended drugs. The cross-sectional design of our study, however, does
not enable to show whether these drugs were never used or were discontinued due to
side effect.
Funding: Commercial Support - Amgen, Baxter, GSK, Fresenius Medical Care, Lilly,
MSD, Otsuka supported the CKD REIN cohort.

Poster Friday

Geriatric Nephrology

Polypharmacy
and
Outcomes
in
Older
Dialysis
Patients Sashika Samaranayaka,2 Robert J. Walker,2 Ari Samaranayaka,2
2
11
Sarah Derrett, John B. Schollum. Dunedin Hospital, Dunedin, New Zealand;
2
University of Otago, Dunedin, New Zealand.
Background: The impact of polypharmacy on patients with end stage kidney disease
(ESKD) and associated comorbidities is uncertain since a direct causation cannot be
determined. More medications could be an indicator of more complex patients with a
higher risk of poor health outcomes, regardless of polypharmacy. This study investigated
the association between polypharmacy, comorbidities and patients’ health outcomes as
measured by hospital admissions and mortality in a cohort of ESKD patients ≥65 years
Methods: 225 participants aged ≥ 65 years, either already on dialysis or eligible for
dialysis (eGFR<15 ml/mn/1.73m2) were recruited and followed for 3 years1. Individual

FR-PO932

Poster Friday

Geriatric Nephrology

ANCA Associated Vasculitis and Treatment Associated Morbidity in
the Very Elderly – A Single Centre Experience Turren tarun S. Chaggar,1
Marie B. Condon,2 David Makanjuola.2 1Epsom and St Helier NHS Trust,
London, United Kingdom; 2St. Helier Hospital, Surrey, United Kingdom.
Background: ANCA-associated vasculitis presents in later life and is not uncommon
in the very elderly (>80 years) patients, but published data concerning the safety and

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
644


tolerability is lacking. Concerns about treatment toxicity and tolerability may be a barrier to starting immunosuppressive therapy.

Methods: Retrospective review of our local database identified all patients presenting between 2006 and 2015 with ANCA associated vasculitis, and data from those aged >80 at presentation were analysed for the purposes of this study. Follow-up was until the patient died or the end of 2015. The incidence of treatment related complications; leukopaenia and infections was recorded. Survival data were analysed with respect to age, sex, renal function at diagnosis as well as treatment regime used. Cause of death was reviewed where available.

Results: We identified 32 cases with a mean age of 83.5 yrs (range 80-90), mean follow-up period of 35.5 months (range 0.2 – 106). Of these, 14 were PR3 positive and 18 were MPO positive. Mean admission creatinine was 406 µmol/L and 38% (12/32) required RRT within 72 hours. Induction therapy was combined with steroids and 78% received cyclophosphamide (25/32), 6% azathioprine (2/32), 3% MMF (1/32) and 3% rituximab. Maintenance therapy was with Azathioprine in 55% (16/29), MMF 15% (4/29) and steroid alone 21% (6/29). Leukopaenia was recorded in N = 5. Of these, cyclophosphamide induction therapy was associated with two episodes of leucopenia. Azathioprine therapy was associated with 2 cases. The 5th case was identified following Rituximab therapy. There were 10 documented cases of infection. Three patients died during the induction therapy. Induction of remission was achieved in 24/25 patients with cyclophosphamide and steroid therapy. Renal survival was 79% (23/29) at 3 months and 85% (22/26) at 1 year. Patient survival was 91% (29/32) at 3 months and 90% (26/29) at 1 year. Overall 50% (16/32) patients died during the period up period with a mean time to death of 25.2 months.

Conclusions: The results of the retrospective study show that induction therapy with cyclophosphamide was generally well tolerated with low rates of leucopaenia and infection. The incidence of renal toxicity was comparable in this cohort of patients when compared to elderly patients (aged >80) with CKD 5.

FR-PO933
Progression of CKD4 to CKD5/ESRD versus Death in the Very Elderly and Factors Associated with Survival Hui Xue, Shayna L. Henry, Quoiling Chen, Mark P. Rutkowski, Nichole Mihara, Mi Chang. Kaiser Permanente Southern California, San Diego, CA.

Background: Geriatrics is the fastest growing population with End Stage Renal Disease (ESRD), and there is limited knowledge of transition from CKD4 to CKD5/ESRD vs death in this group. This study aims to shed light on the rate of progression from CKD stage 4 to CKD stage 5 or ESRD and deaths in-association with factors associated with survival in patients with eGFr<20 and >75yrs old.

Methods: From 2003 to 2008, 1,431 adults, mean age 81.4±7yrs (range 75-99), with 15% eGFR ≤ 20 for at least 3 consecutive months RRT, were followed for 5 years with censoring at Dec 31, 2008, 192 subjects were followed for more than 5 years, and those who maintained eGFR≥ 15 were censored at 5yrs. Survival of those who transitioned to CKD5/ESRD were separated into conservative care vs Renal Replacement Therapy (RRT) groups and followed until death or censoring at 5yrs. Multivariable hazard ratios were calculated for survival for the study population.

Results: Among older adults with CKD4, 930 (65%) reached CKD5/ESRD first, while 432 (30.2%) died without renal replacement therapy (RRT) and 30 (2.1%) remained on conservative care and 716 received RRT. In the conservative management group, 140/214 (64.4%) died, vs in the RRT group 467/716 (65.2%) died. Median survival was 46 and 37 months for RRT and non-RRT groups, respectively, and not statistically different (p=0.314). Age was the greatest influence on death, followed by other medical comorbidities except hyperlipidemia. Asian race, statin, phosphate binder, and ACEi/ARB use offered survival advantages.

Conclusions: Among >75yrs old CKD4 patients, the risk of progression CKD5/ESRD is still higher than death up to age 90. Factors associated with improved survival, statin, phosphorous binders, ACEi/ARB, use, hyperlipidemia, and Asian race, warrant closer evaluation in future studies.

Funding: Clinical Revenue Support

FR-PO934
Predicting Long-Term Renal and Patient Survival by Histological Diagnosis in Elderly Patients Undergoing a Renal Biopsy Arunraj Navaratnarajah, Candice A. Roufosse, H. Terence Cook, Michelle Willicombe. Imperial College NHS Healthcare Trust, London, United Kingdom.

Background: Evidence on long-term outcomes following renal biopsies in the elderly are lacking. This study aims to describe renal and patient outcomes in the elderly aged 60-70 year and more than 70 year group were 1.77 and 1.35 times greater than that in the non elderly group. There was no significant difference in the incidence of age III/IV renal toxicity. Subgroup analysis of different platinum drugs confirmed carboplatin had less risk of nephrotoxicity than cisplatin. The risk of renal toxicity in the elderly patients from Asia in 2.63 times higher than that in young patients, which was significantly higher than those of North America and Europe. Although treatment with hydration, the risk in the elderly group was still 2.07 times higher than that in the control group. Presumably, the protective effect of hydration is more pronounced in non elderly patients who have better reserve of renal function. The risk of nephrotoxicities in the 60-70 year and more than 70 year group were 1.77 and 1.35 times greater than that in the non elderly group, respectively. There were no significant differences in the response rate, median survival time and 1-years survival rate between the elderly and the young patients with IIIB or IV grade of non-small cell lung cancer. The 1-year survival rate in the renal toxicity group is 44.8%, which is significantly higher than that in the non renal toxicity group (33.2%) (p=0.035).

Conclusions: Renal biopsies in the elderly not only provide a histological diagnosis but also prognostic information on renal and patient survival. Data from this study may be useful for informed decision making by patients and nephrologists.

FR-PO935
Deletion of the Gene for Adiponectin Accelerates Age-Related Kidney Injury Jun Hui Bai,1 Hong sang Choi,1 Ha yeon Kim,2 Chang Seong Kim,1 Seong Kwon Ma,2 Soo Wan Kim.1 Chonnam National University Hospital, Gwangju, Republic of Korea; 2Chonnam National University Medical School, Dongdu, Republic of Korea; 1Chonnam National University Hospital, Gwangju, Republic of Korea.

Background: Aging causes renal fibrosis, and aging related renal changes are characterized by oxidative stress. However, the role of adiponectin in aging process has not been elucidated. The present study was aimed to investigate the role of adiponectin in renal progression in aging.

Methods: We used male 2 and 12 months old C57BL/6 (wild type, WT) mice and adiponectin knock out (APN−/−) mice. The protein expression of transforming growth factor β (TGF-β), Smad-2/3, Smad-4, α smooth muscle actin (α-SMA), collagen IV, pro-apoptotic Bax and anti-apoptotic protein Bcl-2, phosphorylated AMP-activated protein kinase (p-AMPK) was determined by semiquantitative immunoblotting. For the in vitro experiments, human proximal tubular epithelial (HK2) cells were treated with TGF-β with or without pretreatment of adiponectin.

Results: Among 12 month old APN−/− mice decreased body weight, increased albuminuria and kidney to body weight ratio compared to 12 months WT mice. Fibrosis markers such as α smooth muscle actin and collagen IV were increased. The protein expression of TGFβ, Smad-2/3, Smad-4 and α-SMA was increased, while inhibitory Smad-6 didn’t change. The protein expression of TGF-β1 increased, while Bax expression was decreased which was consistent with decreased AMPK phosphorylation in HK2 cells. Pre-treatment of adiponectin attenuated fibrosis markers, apoptosis marker expression and ROS generation.

Conclusions: Our results suggest that adiponectin plays a role in the pathogenesis of progressive kidney injury associated with aging process.

FR-PO936
Impact of Aining on the Risk of Platinum-Related Renal Toxicity, Clinical Response, and Prognosis: A Systematic Review and Meta Analysis Guoan Cai,1,2 Nephrology, Chinese PLA General Hospital, Beijing, China; 1State Key Laboratory of Kidney Diseases, National Clinical Research Center of Kidney Diseases, Beijing, China.

Background: Renal toxicity limits clinical use of platinum-based therapy in the elderly. In order to clarify the impact of aging on (1) the risk of platinum-related nephrotoxicity; (2) clinical efficacy and prognosis of platinum therapy, the following meta analysis were carried out.

Methods: We searched multiple databases for the studies published before January 2017. The inclusion criteria were case-control, cohort studies published in any language.

Results: 34 studies with a total of 10,637 patients were included. The risk of platinum nephrotoxicity in the elderly group was 1.43 times higher than in the non elderly group (Risk Rate). The risk of grade I/II renal toxicity in the elderly group was 1.64 times higher than that in the non elderly group. There was no significant difference in the incidence of grade III/IV renal toxicity. Subgroup analysis of different platinum drugs confirmed carboplatin had less risk of nephrotoxicity than cisplatin. The risk of renal toxicity in the elderly patients from Asia in 2.63 times higher than that in young patients, which was significantly higher than those of North America and Europe. Although treatment with hydration, the risk in the elderly group was still 2.07 times higher than that in the control group. Presumably, the protective effect of hydration is more pronounced in non elderly patients who have better reserve of renal function. The risk of nephrotoxicities in the 60-70 year and more than 70 year group were 1.77 and 1.35 times greater than that in the non elderly group, respectively. There were no significant differences in the response rate, median survival time and 1-years survival rate between the elderly and the young patients with IIIB or IV grade of non-small cell lung cancer. The 1-year survival rate in the renal toxicity group is 44.8%, which is significantly higher than that in the non renal toxicity group (33.2%) (p=0.035).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
**Conclusions:** Aging increases the risk of platinum nephrotoxicity by 43%, in which mild renal toxicity is dominant. There are no significant effects of aging on clinical efficiency and prognosis of platinum therapy. The 1-year survival rate of renal toxicity group is significantly higher than that without renal toxicity group.

**FR-P0937**

Kidney Size in Relation to Aging, Gender, Function, and CKD Risk Factors

Antonello Panji,1 Doloretta Piras,1 Marco Masala,2 Alessandro Delitala,3 Silvana A. Urru,4 Lenua Balaci,5 Liana Ferelli,6 Francesco Loi,7 Alice Atzeni,8 Walter Racugno,9 Laura Ventura,9 Magdalena Zolezdziwska,9 Mariella Steri,9 Edoardo Fiorillo,9 David Schlessinger,10 Francesco Cucco,5,9 CRSA, Pula, Italy; 2National Institute on Aging, Baltimore, MD; 3University of Cagliari, Cagliari, Italy; 4Padova University, Padova, Italy; 5Nefrologia e Dialisi, Azienda Ospedaliera G. Brotzu, Cagliari, Italy; 6Istituto di Ricerca Genetica e Biomedica (IRGB), CNR, Cagliari, Italy; 7Center ProgeNA, Istituto di Ricerca Genetica e Biomedica (IRGB), CNR, Cagliari, Italy.

**Background:** Renal function is known to decrease progressively with age even in healthy individuals, in a process known as nephropoiesis. However, the relation of aging to renal volume is less clear. In our study we examined the relationship between renal function and kidney size, with a focus on the progressive effect of aging and the effect of several variables (heritability, CKD risk factors) on renal volumes.

**Methods:** Ultrasound kidney size parameters (total kidney volume, parenchymal kidney volume, and kidney length) were systematically determined using cross-sectional data from a general population cohort encompassing an age range 18-100. Among them, we separately analyzed 2,421 “healthy” and 1,539 “comorbid” individuals carrying CKD risk factors. Kidney volumes were adjusted for BSA.

**Results:** Gender and age effects on kidney size parameters were observed. In healthy volunteers, an early increase in kidney size was followed by progressive decrease in males, whereas females showed a different pattern: their kidney size were influenced by both gender, age, and CKD risk factors. Heritability was overall relatively modest, while substantial effects of metabolic comorbidities and modifiable risk factors (e.g., smoking and lipid levels) were seen.

**Funding:** Other NIH Support - NIA

**FR-P0938**

How Do Creatinine Based GFR Equations Perform in Chinese Nonanergians Mengjie Wang,1 Xinyu Dong,1 Minmin Zhang,1 Li Ni,2 Zuyun Liu,1 Xiaofeng Wang,2 Jing Chen.1 Huashan Hospital, Fudan University, Shanghai, China; 2Huashan Hospital affiliated to Fudan University, Shanghai, China; 3State Key Laboratory of Genetic Engineering and Ministry of Education Key Laboratory of Contemporary Anthropology, School of Life Sciences, Fudan University, Shanghai, China; 4State Key Laboratory of Genetic Engineering and Ministry of Education Key Laboratory of Contemporary Anthropology, School of Life Sciences, Fudan University, Shanghai, China.

**Background:** The clinical and prognostic meaning of evaluating Glomerular filtration rate (GFR) may be different in the very old population. This study aimed to elucidate the performance and predictive value of 4 GFR estimation equations in Chinese nonanergians.

**Methods:** We calculated baseline eGFR from serum creatinine using the CKD epidemiology collaboration (CKD-EPI) equation, the Modification of Diet in Renal Disease Study (MDRD) equation, Berlin Initiative Study-1 (BIS1) equation, and modified MDRD equation from Chinese population in 278 nonanergians from the Raguo longevity cohort over the period of 2007 to 2014. We compared the association of GFR estimated from 4 equations with risk of all-cause mortality using fully-adjusted Cox model. Overall interaction term in the model based on clinical eGFR categories was assessed applying net reclassification improvement (NRI).

**Results:** Mean age of participants was 97.2±7.7 years old with 77% of women. Follow-up time was 2.8±1.8 years. Median (IQR) eGFR by CKD-EPI, MDRD, BIS, and modified MDRD equations were 73.9 (62.2-77.6), 87.5 (71.7-104.8), 56.6 (47.9-63.9), and 107.9 (88.4-129.2) ml/min per 1.73m², respectively. Higher eGFR was associated with lower mortality after multivariate adjustment which included frailty (for continuous eGFR HR: 0.997, 95%CI:0.976-0.998; for categorical eGFR: HR: 0.782, 95%CI:0.628-0.945), while GFR estimated from other equations didn’t show any associations with mortality. NRI for death by the CKD-EPI equation compared to MDRD, BIS1 and modified MDRD equations was 0.06, 0.06, and 0.03 (P=0.05 for all, respectively).

**Conclusions:** The CKD-EPI equation showed more appropriate estimation of GFR in long-lived individuals with respect to GFR distribution and risk of long-term mortality as compared to the other equations, suggesting improved clinical usefulness in Chinese nonanergians.

**Funding:** Government Support - Non-U.S.
Conclusions: This study is novel in being both prospective and in excluding patients with chronic renal failure for whom eligibility may limit suitability for dialysis. It indicates that dialysis increases survival in older patients, as the statistically significant difference in survival only appeared when eGFR was ≤10 mL/min/1.73 m². This advantage may be offset by the increase in time spent at hospital. Hence, a future focus on quality of life is needed to establish the true benefits of dialysis in older people.

FR-PO941

Hydrogen Sulfide Ameliorates Aging Associated Kidney Changes in Mice

Hak Joo Lee,1 Denis Feliers,1 Jeffery L. Barnes,1 Sae Byeol Oh,2 Goutam Ghosh-Choudhury,1 Veronica Galvan,3 Rajeev J. Brong,1 James F. Nelson,1 Adami Salomon,1 Christopher ed Kivel,2 Balakuntalam S. Kasinath,1 1University of Texas Health Science Center, San Antonio, TX; 2Louisiana State University Health Science Center, Shreveport, LA; 3Ball State University, Muncie, IN.

Background: Hydrogen sulfide (H2S) ameliorates renal fibrosis and proteinuria in chronic kidney disease. We examined the status of H2S in aging kidney.

Methods: First study: the status of H2S metabolism and signaling pathways related to synthesis of proteins including matrix proteins were studied in renal cortical extracts from C57BL/6 male young (5 months old, n=10) vs old (30 months old, n=10). Second study: We randomized 18-19 month-old male to receive NaHS in drinking water (30 μmol/L) in NaHS group (n=20 mice) vs water alone (Control group, n=14 mice) for 12 weeks.

Results: First study: Compared to young mice, increase in renal cortical tissue and type 1-collagen content in old mice was associated with decreased generation of H2S, increase in tyrosine phosphorylation of insulin receptor (IR) and IR2, decrease in AMPK activity and activation of Akt-mTORC1-mRNA translation signaling axis. Second study: Administration of NaHS to 18-19 month-old mice increased plasma free sulfide levels. Food, water intake and body weights were similar and blood glucose normal in the two groups throughout the study duration. Systolic, diastolic, and mean blood pressures (BP’s) were high at baseline and continued to rise in the Control group; NaHS reduced the BP’s. NaHS abolished the progressive increase in urinary albumin to creatinine ratio seen in control mice and reduced serum cystatin C levels. NaHS inhibited the increase in renal cortical content of laminin and type 1-collagen and ameliorated the increase in glomerular fractional mesangial matrix volume. NaHS inhibited tyrosine phosphorylation of renal cortical IR and IR2, NaHS restored decreased AMPK activity to normal and inhibited the Akt-mTORC1-mRNA translation axis that leads to increase in protein synthesis. Aging mice showed increase in renal cortical monocyte infiltration and content of p21, IL-1β, IL-6, components of Senescence Associated Secretory Phenotype, SASP, which appear to contribute to tissue injury; NaHS inhibited these changes.

Conclusions: Aging-induced kidney changes are associated with H2S deficiency. Administration of H2S ameliorates aging-induced kidney changes; the mechanisms appear to involve reduced hypertension, inhibition of signaling pathways leading to matrix protein synthesis, and SASP.

Funding: Other NIH Support - Nathan Shock Center, Veterans Affairs Support

FR-PO942

Age-Related Changes in Nuclear Reduced Glutathione Levels in Rat Kidney Cortex and Medulla

Mariannu J. Zamauski-Tucker, Bingwei Ye, Ball State University, Muncie, IN.

Background: Aging is associated with changes in the cell related to oxidative stress caused by free radicals produced in aerobic metabolism. Maintenance of reduced glutathione (GSH), the major antioxidant inside cells, provides protection against cell damage caused by free radicals. Although age-related changes in GSH levels in cell organelles, such as the mitochondria, have been reported in previous studies, there is limited information on GSH levels in the cell nucleus and age. The present study was limited information on GSH levels in the cell nucleus and age. The present study was undertaken to investigate the effect of age on changes in nuclear GSH levels in rat kidney cortex and medulla.

Methods: Young (3 months of age) and Old (22 months of age) female Lewis rats were used. The kidneys were harvested from anesthetized rats after being perfused with isotonic saline. Differential centrifugation was used to isolate the nuclear fractions. GSH and oxidized glutathione (GSSG) levels were measured in the fractions using a spectrophotometric assay, and expressed as nmol/g kidney wet weight. Total GSH was determined from the sum of GSH and GSSG expressed in GSH equivalents. The redox ratio (i.e., GSH/GSSG) was also determined. Differences were evaluated using a Student’s t-test.

Results: There was a significant decrease in GSH, GSSG and TOTAL GSH levels with age in the nucleus of rat kidney cortex. There was not a significant decrease in the aforementioned variables with age in the nucleus from rat kidney medulla. The redox ratio was not changed with age in either the kidney cortex or medulla.

Conclusions: The findings indicate that nuclear free thiol in rat kidney cortex do undergo a significant decrease in the antioxidant glutathione with age. This indicates the nucleus from rat kidney cortex is experiencing increased oxidative stress and thus, damage with age.

FR-PO943

Outcomes of Peritoneal Dialysis Associated Peritonitis in the Elderly Population: A Single Centre Experience

Huy Ung,1 Huy Linh,1 Su Ch. Pang,1 Min Hian Sim,2 Jun Jie Benjamin Seng,3 Sin Yan Wu,1 Marjorie W. Foo.1,5 1Department of Renal Medicine, Singapore General Hospital, Singapore; 2Department of Pharmacy, Singapore General Hospital, Singapore, Singapore.

Background: The clinical outcomes of peritonitis in the elderly peritoneal dialysis (PD) patients have not been well studied before. The study aimed to determine the outcomes of peritonitis in elderly patients.

Methods: This was a single centre retrospective cohort study, including all peritonitis episodes between 2011 and 2014. The primary outcome was medical cure (defined as peritonitis episode cured by antibiotics without complicated by catheter removal, haemodialysis (HD) transfer, relapsed/recurrent peritonitis and/or death) in elderly peritoneal dialysis patients >65 years old. The secondary outcome was the mortality of peritonitis. These outcomes were compared between elderly and younger patients using multivariable logistic regression.

Results: Total 377 episodes of peritonitis occurred in 247 patients during the study period. Of these, 169 episodes occurred in 105 elderly patients. Of 105 elderly, 51% were male, 79% were Chinese, 65% had diabetes mellitus, 95% had hypertension and 54% had cardiovascular disease. Diabetes nephropathy (52%) was the commonest cause of renal failure. The causative organisms were Gram-positive (32%), Gram-negative (29%), culture negative (22%), polymicrobial (12%), fungal (4%) and mycobacterial (1%) organisms. Elderly patients were less likely to present with fever (17% versus 30%) and cloudy effluent (85% versus 92%) than younger patients. Total 112 episodes (66%) of peritonitis occurred in elderly patients achieved medical cure. The remaining 57 episodes were not cured because of one or more of the following complications: catheter removal (n=29), haemodialysis transfer (n=20), relapsed/recurrent peritonitis (n=19), and/or death (n=11). There was no significant difference in the odds of medical cure (Odds ratio (OR) 0.93, 95% confidence interval (CI) 0.56 - 1.54; p=0.78) between the elderly and the younger patients after adjusting for cardiovascular disease, primary renal disease and causative organisms. Similar results were observed for complications of peritonitis (catheter removal, transfer HD, relapse/recur) except that the odds of peritonitis-related death was significantly higher in the elderly patients (adjusted OR 2.59, 95% CI 1.07-6.29; p=0.04).

Conclusions: Elderly PD patients achieved comparable medical cure but had higher peritonitis-related mortality than younger patients.

FR-PO944

Peritoneal Dialysis-Related Peritonitis in the Era of the Elderly Population: A Retrospective, Multicenter Study in Thailand

Kiatkrongkrai Koyraktoson,1 2 surapon nochaiwong,4 6 Chidchanok Ruengorn,1 3 5 Chayuthphong Chaisai,1 4 5 Kajohnsak Noppakun,6 Ratanaporn -, Awiwan,2 3 Wilaivan -, Chongrusit,2 4 Sirisak Nanta,1 3 1Maesai District Hospital, Chiang Rai, Thailand; Chiang Rai, Thailand; 2Chiangrai University, Chiangrai, Thailand; 3Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand; 4Pharmacoepidemiology and Statistics Research Center (PESC), Chiang Mai University, Chiang Mai, Thailand; 5Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; 6Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand.

Background: Peritonitis, a major complication of peritoneal dialysis (PD), contributes to treatment failure, hospitalization, and mortality, particularly in elderly PD cases. Regardless of technical problems, social difficulties, and burden of comorbidities, it remains unclear whether elderly patients have a significantly amplified risk of peritonitis than younger patients. Thus, we aimed to evaluate the impact of advanced age on the risk of PD-related peritonitis.

Methods: We conducted a retrospective cohort study using the PD registry database of an incident PD patients with aged ≥ 18 years. PD initiation, subjects were categorized into <55, 55-65, and >65 years of age groups. Clinical characteristics regarding age groups were compared among participants from three large PD centers in Thailand during January 2006 and December 2016, and followed through April 2017. Time-to-first PD-related peritonitis and longitudinal rates were analyzed by multivariable Cox’s proportional hazards model and Poisson regression, respectively.

Results: Among 1,023 PD patients included, 401 (39.2%), 312 (30.5%), and 310 (30.3%) patients aged <55, 55-65, and >65 years, respectively. After a total follow-up of 19,463.4 person-months, 519 (50.7%) were recognized as having PD-related peritonitis. There was no significant difference in spectra of causative microorganisms among patient age groups.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: The risk of first episode peritonitis is not increased in elderly PD patients; however, compared with younger patients, the higher peritonitis rate is observed in elderly PD patients. Large prospective trials are needed to validate these findings.

Funding: Government Support - Non-U.S.

Hazard Ratios for First Episode PD-Related Peritonitis and Incidence Rate Ratio for Longitudinal PD-Related Peritonitis Rates by Patients’ Age Group (n=1,023)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Hazard Ratio (95% CI) Reference</th>
<th>P Value</th>
<th>Adjusted HR (95% CI) Reference</th>
<th>P Value</th>
<th>Create HR (95% CI) Reference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 65 years</td>
<td>1.16 (0.99 – 1.34)</td>
<td>0.07</td>
<td>1.15 (1.02 – 1.30)</td>
<td>0.06</td>
<td>1.13 (0.99 – 1.28)</td>
<td>0.09</td>
</tr>
<tr>
<td>&gt; 65 years</td>
<td>1.42 (1.14 – 1.75)</td>
<td>0.0001</td>
<td>1.37 (1.08 – 1.73)</td>
<td>0.03</td>
<td>1.34 (1.22 – 1.70)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; IRR, incidence rate ratio; PD, peritoneal dialysis.

FR-PO945

Safety Profile of Outpatient Percutaneous Native Renal Biopsy: A Large Monocentric Single Operator Cohort

Dario Roccatello,1 Savino Sciascia,1 Roberta Fenoglio,1 None, TORINO, Italy;1 OSPedale San Giovanni Bosco, Torino, Italy;1 Center of Research of Immunopathology and Rare Diseases (CMID), Division of Clinical Immunology, Giovanni Bosco Hospital and University of Turin, Turin, Torino, Italy.

Background: In the study we aim to evaluate the safety of performing percutaneous renal biopsies as an outpatient procedure compared to the traditional inpatient policy. Additionally, the rate and risk factors of complications after a procedure were investigated.

Methods: We ambispectively studied native kidney biopsies performed in our Institution between January 2000 and November 2015. Since January 2012, we began performing renal biopsies as outpatient procedures. Two groups of patients were considered: group I, in whom kidney biopsy was performed and followed by at least 1-day hospital admission; and group II, in whom renal biopsy was performed in the outpatient department and followed by 6 hours’ observation period and then by regular outpatient visits.

Results: All biopsies were performed by a single nephrologist with the use of real-time ultrasound and automated biopsy needle (18 gauge), following a structured protocol. Results: 462 biopsies were reviewed, 210 (45.5%) of patients were female and the mean age was 54.7 ± 17.9 years. One-hundred and twenty-nine (27.9%) of these biopsies were performed in outpatient. A total of 36 (7.8%) of patients developed a complication, and of those 9 (1.9%) suffered for a major complication (arteriovenous fistula (6 cases, 1.2%), ischaemic stroke (2, 0.4%), thromboembolic pulmonary embolism (1, 0.2%) and 27 (5.8%) for minor [macroscopic haematuria (12 cases, 2.6%), haematomas on sonography not requiring intervention (15 cases, 3.2%)]. When comparing the complication rate between group I and II, no statically difference were observed (overall 24 (7.2%) complications in group 1 and 12 (3,9%) in group II; 5 (1,5%) and 4 (3,1%) major, 19 (5,5%) and 8 (6.2%) minor complications, respectively in group I and II). When analysing together both groups, after multivariate analysis, serum creatinine >3 mg/dl (OR 2.03 95%CI 1.18-6.81) and known severe hypertension (OR 2.01 95%CI 1.14-3.49) were found to be independent risk factors for minor and major complications, respectively. Conversely, we found no association of risk with the number of biopsy passes, needle pass (8.9 vs 6, p = 0.05) with lower rate of inadequate tissue (6.9% vs 18.6%, p < 0.05) in the IRP group. There were no differences in post-biopsy complications such as hematoma, needle mark, infection/sepsis, or patient death were observed between the groups.

Conclusions: Outpatient biopsy could be a valuable, safe, and perhaps cost-effective method of obtaining diagnostic renal tissue in the majority of patients.

FR-PO946

Should Kidney Biopsies Be Done via CT-Guidance? Comparison of Percutaneous Native Kidney Biopsy Complications and Glomerular Yield between Interventional Radiologists and Nephrologists

Briana G. Amante,1 Alkesh Manish,1 2UNIVERSITY OF COLORADO, HOUSTON, TX; 3University of Denver Colorado, Aurora, CO.

Background: Percutaneous native kidney biopsy (PNKB) is performed as an outpatient procedure by interventional radiologists (IR) & nephrologists. However, data on tissue yield & complication rates comparing IR performed PNKB vs. nephrologist performed (NP) PNKB are lacking. Also, there is no published study that directly compares outcomes of PNKBs performed via computed tomography (CT) vs. ultrasound (US) guidance.

Methods: 131 PNKBs performed at the University of Colorado Health System from 1/2014-12/2016 were included. Biopsies were performed by nephrologists using real-time US guidance or IR using CT guidance.

Results: 72 biopsies were done by nephrologists & 59 by IR. The NP group had a significantly longer duration of patient observation post-biopsy (20.7 vs 5.0 hrs, p < 0.05), used a larger biopsy needle (16G in 93% vs 18G in 100% of patients, p < 0.05), had lower number of needle passes (2.8 vs 3.5, p < 0.05), & had higher glomerular yield; needle pass (8.9 vs 6, p = 0.05) with lower rate of inadequate tissue (6.9% vs 18.6%, p < 0.05) in the IRP group. No differences in post-biopsy complications such as hematoma, hematuria, need for transfusion or intervention, analgesic use, emergency room visits, infection/sepsis, or patient death were observed between the groups.

Conclusions: Out-patient PNKB done via CT guidance had similar complication rates vs. real-time US guidance, and required a significantly shorter period of patient observation post-biopsy. Tissue yield was significantly better with real-time US guidance than with CT guidance, likely due to use of a larger-gauge needle. CT guided biopsy by IR offers similar complication rates for significantly less observation time vs US by Nephrologist.

Funding: Government Support - Non-U.S.
Results: We screened 344 charts to include 100 patients. Admission diagnoses were sepsis (26%), atrial fibrillation (31%), surgical (18%) and renal (15%). 36% of patients required ICU, CCU, or cardiac surgery ICU (CSICU) care at one point. Possible AKI etiologies cited: pre-renal (51%), ATN (68%), AIN (16%), and post-renal (6%). Contrast-induced nephropathy was suggested in 27%. Volume overload was the most common indication for initiating RRT, hyperkalemia was cited as an indication in 32%. Relative hypotension from anti-hypertensives was cited as an AKI contributor in 7%. With regards to nephrotoxins post-AKI, NSAIDs were continued in 3%, ACEI/ARB in 16%, and spironolactone in 13%. Of the 32 patients dialyzed with hyperkalemia, only 43.7% were placed on a low K+ diet, and 7% received a form of additional K+ after AKI and with a serum K+≤5.

Conclusions: Our study includes many seriously ill patients with AKI where RRT is likely unavoidable. However, we have identified potentially harmful events. These include nephrotoxic medications, iodinated contrast dye, potassium supplementation, and hypertension management. Upon completion, we plan to use our data to create solutions that will hopefully reduce the risk of iatrogenic harm for hospitalized AKI patients.

FR-PO949

Patient Attendance Alert to Specialty System (PAASS): An Automatic Alert as a Novel Approach to Identify Patients with Advanced Kidney Disease for Early Specialty Input on Admission Bhavna Pandya, Samantha Dolan. University of Liverpool, UK, LIVERPOOL, United Kingdom. Group/Team: Aintree Nephrology Dept; Aintree Business Intelligence System.

Background: Patients with pre-existing advanced renal disease admitted in emergency to hospital are managed by the admitting team. Renal specialists are involved at a late stage depending upon the mode of communication and rely on admitting team for notification. Delays in specialist input contribute to increased morbidity, length of stay, untoward incidences and even mortality. To avoid this delay, we designed an automatic, secure Patient Attendance Alert to Specialty System (PAASS) which alerts the renal team via e-mail and SMS message to notify the attendance of these patients to the appropriate specialist.

Methods: We carried out a retrospective analysis of patients admitted within several weeks between July-August 2016 with advanced renal disease. Comparison was made between PAASS alerted and manually referred patients. Length of stay, 30 day/6 month/12-month readmission rate and patient mortality rate were measured to compare with data prior to the implementation of PAASS alert. Trust’s business intelligence system was used for alert details.

Results: The PAASS alert had acceptable sensitivity (95.2%) and specificity (100%). There was no difference in 6-month mortality and readmission rate between groups; however alerted patients had a significantly reduced ‘length of stay’ in hospital (p=0.0002, 95% CI -12.9,-7.6, SE 0.95), compared to those patients who were referred manually.

Conclusions: Our findings indicate that early notification of patient attendance to hospital using the PAASS alert contributed to reducing length of stay significantly.

FR-PO950


Background: Few quantitative assessments have been undertaken to assess the disaster preparedness of kidney transplant patients, a population at risk due to their dependence on immunosuppression. This is a survey-based assessment of the disaster preparedness of a cohort of 200 patients recruited from the UCSF Kidney Transplant clinic.

Methods: We recruited 200 kidney transplant recipients from the waiting room of the transplant clinic. They answered short pencil and paper questionnaires assessing their level of preparedness as well as what barriers they faced in becoming adequately prepared. Preparedness was scored based on the response to 7 different items and an index created. Medical and demographic data was extracted from the clinical chart. We analyzed the data using univariate analyses of different participant characteristics against three categories of preparedness – low (scores between 0-2), medium (scores of 3-4) and high (scores of 5-7). We created average scores of preparedness for various counties in California and geocoded them on maps created with Google Fusion Tables.

Results: Only 30 percent of patients were highly prepared for disasters. Participants were most prepared in stockpiling medications (78.5%) and least prepared in having a medical ID bracelet that identifies them as transplant patients (13%). A significant minority of patients (at least 40% of patients or more) were unprepared with lists of medications, important phone numbers and disaster kits. There were no major associations between preparedness and different participant characteristics such as age, race, gender, number of years since transplant or various clinical variables including type of immunosuppression or other comorbid conditions. Thirty-one of the 34 counties sampled were from California, of which Monterey County was the most prepared with an average preparedness score of 4.4 (out of 7).

Conclusions: Patients of all demographic and clinical backgrounds should be educated on the importance of disaster preparation. Since most deficiencies in preparedness are in general items, there should be a concerted effort on the part of city and medical services to address specialized populations in general preparedness planning.

Funding: NIDDK Support, Private Foundation Support

FR-PO951

Development and Usability Testing of a Patient Safety Educational Program in CKD Claire J. Diamantidi, Jena J. St. Clair, Joseph Lunyera, Janell R. Wayte, Nikita Shari, Jeffrey C. Fink. 1Duke University School of Medicine, Durham, NC; 2Duke University—-, Durham, NC; 3University of Maryland, Baltimore, MD.

Background: Chronic kidney disease (CKD) threatens patient safety, yet few interventions educate patients about kidney-specific safety hazards. We sought to develop and usability test an educational program designed to promote patient awareness of relevant safety topics in CKD.

Methods: We included 4 patient safety objectives in a tablet-based educational program: 1) avoidance of non-steroidal anti-inflammatory drugs (NSAIDs); 2) hypoglycemia awareness (only for individuals with diabetes); 3) temporary cessation of certain medications while acutely volume deplete (i.e. “sick day protocol”); and 4) contrast dye risk awareness. Content was developed for each objective using plain language principles. Teaching strategies optimized human-computer interaction and content retention; audio, animation, and clinical vignettes reinforced themes. For example, using a vignette of a CKD patient with pain and pictures of common NSAIDs, participants are asked, “which of the following pain medicines are safe for Mr. Smith to take for his belly pain?” Assessment methods consisted of pre- and post- knowledge surveys, with provision of correct responses and explanations. Usability testing was performed among patients with CKD, and program tasks completion were rated as 1) no error, 2) non-critical error (self-corrected), or 3) critical error (not completed).

Results: All usability participants owned a mobile device and used it daily. Of 318 total tasks there were 3 non-critical errors (1%) and 6 critical errors (2%). One participant accounted for 7 of all total errors. All participants rated use of the tablet as ‘very easy,’ activity length as ‘just right’ (vs too long/short), the use of clinical vignettes as helpful, and would recommend this activity to others; the majority felt the program was ‘very’ or ‘somewhat easy’ to use (80%) and use of the audio was helpful (60%). All rated the activity between 8 (60%) and 10 (20%) on a scale of 1 to 10 (best). All usability testing recommendations were incorporated into the final version of the educational program.

Conclusions: A tablet-based patient safety educational program is acceptable and usable among individuals with CKD. Future studies will explore its impact on health outcomes in this high-risk population.

Funding: NIDDK Support

FR-PO952


Background: Commencing haemodialysis (HD) is a time of physical and psychological distress, with a high incidence of hospitalization. Despite good pre-dialysis care many patients experience a suboptimal start to HD. Mortality is at its highest within
the first 90 days of commencing dialysis. Aim: To develop, test and evaluate the impact of a novel, personalised nurse led pathway for patients commencing HD on a range of patient centred process and outcome measures. 

Methods: Sequential PDSA cycles were used to develop a personalised nurse led pathway for the first 6 sessions of HD (see fig). Patient distress was recorded at week 2, 4 and 8 using the validated Patient Distress Thermometer (Renal). Baseline control data were retrospectively collected for patients commencing HD from July 2015-June 2016. Our prospective pilot recruits patients from July 2016-June 2017, and we report 90 day follow-up data.

Results: There were 78 patients in the historic control cohort (mean age 58.4y, 62% male, 45% diabetic). 90 day follow up data are available for 37 patients who started HD using the new pathway (mean age 56.2y, 51% male, 27% diabetic). All outcome measures have improved (see table). Patient distress score has dropped from 4.3 (week 2) to 2.4 (week 8). Patient and staff feedback has been strongly positive. 

Conclusions: These data suggest improvements in patient experience and outcomes using this novel intervention.

Funding: Private Foundation Support

Innovations in Patient Outcome Measures

<table>
<thead>
<tr>
<th>Historic control group</th>
<th>New patient pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>% patient on initial 4 week or of HD</td>
<td>72%</td>
</tr>
<tr>
<td>% of patient with access at HD</td>
<td>48%</td>
</tr>
<tr>
<td>% with haemofilter plan at HD</td>
<td>8.3%</td>
</tr>
<tr>
<td>Days in hospital (first HD)</td>
<td>17.2 days</td>
</tr>
<tr>
<td>Un saturated HD mortality</td>
<td>5.1%</td>
</tr>
</tbody>
</table>

Components of nurse led pathway

FR-PO953

Prevalence of Depression in Patients with ESRD on Hemodialysis and Peritoneal Dialysis in the West Area of Puerto Rico Sheryll D. Mitchell.

Background: Depression symptoms and depression are major public health problems and the most frequent psychological problems reported among ESRD patients being treated by hemodialysis. We assessed the prevalence of depressive symptoms among hemodialysis and peritoneal dialysis patients at West area of Puerto Rico. Despite these findings, depression may remain under recognized and undertreated, particularly among ESRD patients. A systematic assessment of depression in hemodialysis patients would supply information about patient feelings of well being. Existing data suggest that screening for depression may help identify patients at higher risk for death and hospitalization.

Methods: This cross-sectional study was represented with a sample of 146 hemodialysis patients selected from 3 dialysis centers of West Area at Puerto Rico. We provided written informed consent before filling questionnaires to patients. The Beck Depression Inventory (BDI-II) is considered to be the standard instrument for assessing symptoms of depression and screening for clinical depression. We used this scale of 21 short answer question for assess degree of depression in studied patients.

Results: The prevalence of depression in peritoneal dialysis patients is 36% in our study when we compare the depression between HD and PD patients we noted that there is more prevalence of depression in Hemodialysis patients with a 53% than in the peritoneal group. There is significant effect between these groups (DF=1, Value = 2.9849 and P-Value= 0.0084) with a significance level at 10%. For age ranges no significant effect was observed in depressive symptomatology (DF=1, P-value= 0.8453, Value=0.0381). In relation to the variable weather time in PD treatment and prevalence of depression there is not found significant differences (DF=2, P-value=0.8474, Value=0.3511). More results to come further.

Conclusions: Based on our investigation the prevalence of depression is present in ESRD on PD and HD patients at West area of Puerto Rico. This supports the recommendations of early implementation psychological measures and medical treatment and in an effort to influence the prognosis associated with the progression related morbidity/ mortality and decrease hospitalization in ESRD on HD patients and improve quality of life!

FR-PO955

Meta-Analysis and Commentary: Preemptive Correction of Arteriovenous Access Stenosis Joohen G. Raimann,1,2 Lei D. Waldron,1 Elsie Kob,3 Gregg Miller,4 Murat Sor,1 Richard J. Gray,1 Peter Kotanko,1,2 CUNY School of Public Health, New York, NY; 3Research Division, Renal Research Institute, New York, NY; 4Presenius Vascular Care, Woodland Park, NJ; 5Icahn School of Medicine at Mount Sinai, New York, NY.

Background: A recent meta-analysis (Ravani et al., Am J Kidney Dis 2016) studied the effect of pre-emptive correction of arterio-venous (AV) vascular access versus deferred care, based on data from 10 trials. It reported a non-significant protective effect of pre-emptive correction on access loss and a significant protective effect on thrombosis rates conferred by pre-emptive correction. We revisit this analysis, including data extraction and effects of heterogeneous study populations.

Methods: We repeated data extraction from referenced publications, and corrected event counts where applicable. As a next step we repeated the meta-analyses for studies that recruited patients with AV fistulae (AVF) and grafts (AVG), using a random effects model with VA access loss as the outcome.

Results: Our conclusions differ from the original findings: After amendment of the extracted event counts we find a significant overall positive effect of pre-emptive correction on AV access loss in the overall study population [RR 0.80 (95% CI 0.64 to 0.99), RD -0.07 (95% CI -0.12 to -0.02); Figure 1]. Whereas the data do not conclusively show a benefit of pre-emptive correction for AVG (RR = 0.87, 95% CI 0.69 – 1.11), they show a strong protective effect for AVF (RR = 0.5, 95% CI: 0.29 to 0.86).

Conclusions: These findings corroborate clinical arguments such as superior long-term patency of AVF and the nature of AVG failure that often involve infectious causes. The available data indicate mild or no benefit of pre-emptive correction for AVG, but support tight monitoring of AV dialysis accesses and preemptive intervention and correction upon the detection of access stenosis for AVF. Figure 1: Meta-analysis of AV access loss, overall and by access type.

FR-PO956

Calculating Maximum Allowable Contrast Dose to Minimize Contrast Induced Nephropathy Following Coronary Angiography: Comparison of Validated Methods with Implications for Practice Habib Mawad,1 Kelly M. Zett,2 Anurag Singh,2 Simon Robinson,3,1 Sean C. Hardiman,1,3 Adeera Levin,1,5 Cardiac Services BC, Vancouver, BC, Canada; Department of Cardiology, Univ of British Columbia, Vancouver, BC, Canada; St. Paul’s Hospital and University of British Columbia, Vancouver, BC, Canada; 4BC Renal Agency, Vancouver, BC, Canada.

Background: The contrast volume used during angiographic procedures represents an important modifiable risk factor for contrast-induced nephropathy (CIN). As a result, efforts have been made to limit contrast exposure by determining maximum allowable contrast dose (MACD), using specific equations. Two published methods exist, but they use different components to derive the MACD: Method A uses weight and creatinine, and Method B uses the estimated GFR (eGFR) multiplied by a specific ratio. Our study compared and contrasted the 2 methods with respect to concordance, and implications for incorporating into clinical practice. The goal was to find a simple equation to implement which would be safe (i.e. give the lowest MACD).

Methods: We calculated the MACD for a wide range of serum creatinine levels, weights and demographic variables (i.e. age, sex and race), using the 2 methods. Method A: MACD (mL) = (5* Body Weight (kg) * 88.42) / Serum Creatinine (umol/L); and Method B: MACD (mL) = Ratio* eGFR (mL/min per 1.73m²). A ratio of 3 was used if

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

Underline represents presenting author.

650
The impact of implementation of these methods on MACD used, subsequent incidence of alternative method which suggests lower contrast doses in those at highest risk of CIN.

The implementation of these methods may lead to different and higher contrast exposure for some patients. We recommend an alternative method which suggests lower contrast doses in those at highest risk of CIN.

Consolidation: Discrepancies in available contrast doses based on published formula
can lead to different and higher contrast exposure for some patients. We propose an alternative method which suggests lower contrast doses in those at highest risk of CIN.

Results: The results show a marked discordance in calculation of MACD depending on the equation used (see Figures). In the majority of cases method B gives a more conservative estimate of MACD. The difference is most marked for those who are heavier, older and are female, particularly non-black females.

Consensus: Discrepancies in allowable contrast doses based on published formulae may lead to different and higher contrast exposure for some patients. We propose an alternative method which suggests lower contrast doses in those at highest risk of CIN.

The impact of implementation of these methods on MACD used, subsequent incidence of CIN and dialysis as well as cardiovascular outcomes remains to be studied.

FR-PO957

Provider versus Pharmacy Led Initiation of ACEI or ARB

Kelly Mazureck, Margaret E. Fleet, Bessie A. Young. University of Washington, Seattle, WA.

Background: Guideline attainment in diabetes and early diabetic nephropathy is difficult. Primary care provider (PCP) directed recommendations can either be from a specialist or from a pharmacist. Studies looking at the efficacy of either approach have been mixed. The purpose of this study was to determine whether a provider (Nephrologist) versus pharmacy led intervention, consisting of initiation of an ACEI or an ARB (Ac/Ar), was more effective.

Methods: Data were collected from the Diabetes Registry at the Veterans Affairs (VA) Puget Sound Health Care System. Search criteria were: diabetes mellitus, hypertension or blood pressure >140/90 mmHg, albuminuria >30 mg/g, and not being on an Ac/Ar. Exclusion criteria were taking an Ac/Ar, previously enrolled in pharmacy clinic, anaphylaxis or angioedema to an Ac/Ar, ESRD or no longer being a VA patient. Patients were followed over 7 months. Nephrology recommendations and guidelines were given to PCPs for starting an Ac/Ar. PCPs had the option to place an electronic nephrology consult to manage the intervention. On the other hand, the pharmacy team identified patients and placed referrals to a pharmacy clinic. The primary pharmacist made decisions on drug initiation, monitoring, titration and laboratory tests based on the same recommendations.

The primary outcome was the rate of Ac/Ar initiation.

Results: A total of 34 patients were found in the provider group and 19 patients in the pharmacy group. There was a trend towards increased efficacy in the pharmacy led team (58%) over the provider led team (41%). However, there was no statistical difference (p = 0.56). A post study survey showed that majority of participants favored that pharmacists identify, start and manage recommendations.

Methods: A pharmacy led intervention was more effective than a provider led intervention in implementing current standards of care for diabetic patients. On the pharmacy arm, patients were more likely to have follow-up appointments if they were by telephone rather than in person. Telephone intervention is less burdensome and may lead to more successful interventions and continuity of care. PCPs are often overwhelmed with their patient panel and correct medication management can go overlooked. Pharmacists are just as effective, are more accessible health care practitioners and are well positioned to implement appropriate medication use.

FR-PO958

Renal Safety of Cisplatin-Based Chemotherapy in Urothelial Carcinoma Patients with a Solitary Kidney

Masahiro Kondo,1 Yuji Hotta,2 Ryosuke Ando,2 Takahiro Yasui,1 Kazunori Kimura.1 1Pharmacy, Nagoya City University Hospital, Nagoya, Japan; 2Hospital Pharmacy, Graduate School of Pharmaceutical Sciences, Nagoya City University, Nagoya, Japan.

Background: There is little information on renal safety to cisplatin-based chemotherapies in patients with a solitary kidney after nephroureterectomy. We evaluated the nephrotoxicity and hematologic toxicities of gemcitabine plus cisplatin (GC) in urothelial carcinoma patients with a solitary kidney.

Methods: We retrospectively reviewed patients treated between August 2007 and December 2016. Eligible patients received GC as first-line chemotherapy, including as neo-adjuvant and adjuvant treatment. Patients with one kidney comprised the solitary kidney (SK) group, those with both kidneys comprised the BK group. Incidences of renal insufficiency and hematologic toxicities were examined and compared between the two groups.

Results: There were 18 and 43 patients in the SK and BK groups, respectively. Mean serum creatinine (SCr) levels at baseline were significantly higher in the SK group than in the BK group (P<0.001). There were no significant differences in median numbers of administered cycles and doses of GC between the groups. No significant differences were observed between the groups in the incidence of acute kidney injury (SK: 11.1%, BK: 7.0%, P=0.627). SCr levels in both groups did not significantly increase during treatment (Fig.1); mean differences in SCr levels between baseline and each post-chemotherapy cycle were similar between the groups. The incidence of hematologic toxicity (grade 3/4) was not significantly different between the groups. Multivariate analysis revealed no statistically significant association between having a solitary kidney and severe hematologic toxicities.

Conclusions: Renal safety and treatment tolerability to GC chemotherapy is not inferior in patients with a solitary kidney.

FR-PO959

Awareness and Knowledge among Internal Medicine House-Staff for Dose Adjustment of Diabetes Medications in SK and BK Matthew S. Styler1, Joshua Fogel2, Sofia Rubinstein1. 1Nephrology and Hypertension, Nassau University Medical Center, East Meadow, NY; 2Brooklyn College, Brooklyn, NY.

Background: Drug dosing errors result in adverse patient outcomes and are more common in patients with diabetes mellitus (DM) and chronic kidney disease (CKD). As internists treat the majority of patients with DM and CKD, we study if Internal Medicine house-staff (IMHS) have awareness and knowledge about the correct dosage of commonly used diabetes medications in those with CKD.

Methods: We surveyed 353 IMHS to evaluate incorrect awareness of whether a medication needs dose adjustment in patients with CKD (IR) and incorrect knowledge at what level of glomerular filtration rate a medication needs to be adjusted (IR-GFR) for Glipizide (GLI), Pioglitazone (PIO), and Sitagliptin (SIT).

Results: There were high percentages for lack of awareness and knowledge, with the highest for PIO at 72.8% (Figure). Multivariate logistic regression analyses showed that PGY1 had higher odds than PGY3 for GLI and SIT for both IR and IR-GFR and PGY2 had higher odds than PGY3 for PIO for both IR and IR-GFR. More Nephrology training and exposure in medical school or residency was each associated with lower odds for both IR and IR-GFR.

Conclusions: There is poor awareness and knowledge among IMHS for dose adjustment of diabetes medications in patients with DM and CKD. IMHS should receive more nephrology exposure and formal didactic educational training during medical school and residency to better manage complex treatment regimens and prevent medication dosing errors in those with DM and CKD.

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

Underline represents presenting author.
Prevention of Medication Reconciliation Errors: Results of a QI Study

Manisha Singh,1 Temekis D. Hampton,4 Sherida R. O’neal-wright,3 Shree G. Sharma,1 Michelle W. Krause.2 1Arkana Laboratories, Little Rock, AR; 2University of Arkansas for Medical Sciences, Little Rock, AR; 3DCI, Little Rock, AR; 4UAMS, Little Rock, AR; 5Nephrology/Internal medicine, University of Arkansas for Medical Sciences, Little Rock, AR.

Background: Medication errors are one of the leading preventable causes of adverse patient outcomes. Accurate reconciliation can greatly decrease this risk. Dialysis patients have increased risk with polypharmacy of up to 5-10 medications/patient. We attempt to enable the patient himself to carry the information for their own care in a quality-improvement project using medication wallets.

Methods: Wallet design: Wallet contains contact information, care-buddy details, dialysis unit information, Physician and APN contacts, immunization record, current dialysis prescription with medications, known medical history and allergy information. The wallet has space to keep a driver’s license, credit cards and cash. Method: Project consisted of 3 phases: Phase 1: Identify patients for participation.12/15 home dialysis patients consented for study. Phase 2: Review and compare medications in patient’s record from available admission/discharge lists. Phase 3: Introduce intervention (Dialysis Wallet) and monitor its effectiveness through a questionnaire-based survey at each clinic visit.

Results: 67% of the patients had a medical visit since previous clinic visit. 17% of patients were hospitalized. Their dialysis prescription was unchanged during that hospitalization.100% of patients feel that their dialysis prescription were continued as prescribed.33% of patients felt that, after discharge from medical visit, their medication lists were not updated. They felt that the contribution positively to their care. They reported that other providers appreciated this input at all physician and APN visits. Their immunization records helped expedite care. After the use of this wallet, participants report they would probably continue use of wallet/hard copy. 67% of patient brought the wallet to clinic visits.

Conclusions: Our results indicate that the medication wallet may be a very effective way to minimize medication errors during transitions and an effective way to enable better patient care. The limitations are failure to update the wallet by some treating teams and patients forgetting to bring the wallet during some treatment visits. We hope that over time, this will get corrected as the importance of this step will be more apparent to providers as well as the patients.

Medication Dosing in Dialysis Dependent ESKD Patients: A Retrospective Single Center Review

Daryl U. Nnani,1 Timothy V. Nguyen,2 Archna Jariwala,1 Vijay Lapsia.1 1Icahn School of Medicine at Mount Sinai, New York, NY; 2Long Island University - AMS College of Pharmacy and Health Sciences, Little Ferry, NJ; 3Mount Sinai Hospital, New York, NY.

Background: Patients with hemodialysis (HD) dependent end stage kidney disease (ESKD) are more prone adverse events and poor outcomes due to inappropriate medication dosing. A significant number of medications are converted into active metabolites and failure to adjust doses may result in toxicity. Medication errors account for a majority of adverse events within the inpatient setting. The purpose of this study was to assess the appropriateness of medication dosing in hospitalized HD dependent ESKD patients.

Methods: This was an IRB-approved, single-center, retrospective medication chart review of adult HD-dependent patients diagnosed with ESKD admitted between 1/2016 and 8/2016. Patients were excluded if they were on peritoneal dialysis, admitted for kidney transplantation, or had missing pertinent information. The appropriateness of medication dosing was assessed by evaluating inpatient medication orders on day one of admission and was compared to drug manufacturer and tertiary reference renal dose adjustment recommendations.

Results: A total of 509 patients were included in this study and 6,964 medication orders were reviewed. A mean of 13.7±8.3 medications per patient. A total of 221 inappropriate medication orders were identified and 32.4% (165 of 509) of patients included in this study had an inappropriate medication order on admission. A total of 20 medication classes were ordered inappropriately on day one of admission. The most frequently inappropriately ordered medication classes were anticonvulsants 26.1% (58 of 221), opioids 25.6% (57 of 221), antibiotics 16.2% (36 of 221), histamine-2 receptor antagonists 8.1% (18 of 221) and HMG-CoA reductase inhibitors 6.3% (14 of 221). Morphine sulfate accounted for 83% (47 of 57) of inappropriate opioid medication orders. Gabapentin accounted for 91% (78 of 85) and levetiracetam accounted for 28% (16 of 58) of inappropriate anticonvulsants medication orders in this study.

Conclusions: Anticonvulsants and opioids accounted for greater than 50% of inappropriate medications orders. Mandatory pharmacist medication reconciliation in this patient population and implementation of a best practice alert integrated into the computerized physician order system may result in a reduction of inappropriate medication orders in this patient population.

Hydralazine-Associated Death and CKD

Mayurkumar P. Patel,1 Rany Al haj,1 Harry J. Dounis,1 Seyedehsara Seyedi,2 Ali Nayer,1 Arif Asif.1 1Jersey Shore University Medical Center, Neptune, NJ; 2Miami Renal Institute, North Miami Beach, FL.

Background: Despite the widespread availability of effective anti-hypertensive agents (calcium channel blockers, ACE-Inhibitors/ARBs, diuretics, aldosterone receptor, and beta-blockers), hydralazine continues to be used as one of the first line agents in the management of hypertension.1 It is known to cause cardiac mortality and morbidity as well drug-induced anti-neutrophil cytoplasmatic antibody (ANCA) associated vasculitis (DIV).

Methods: Herein we describe three male and one female patients (age: 53, 83, 87, 89 years) treated with hydralazine therapy, who presented with acute kidney injury, proteinuria, and hematuria. All demonstrated positive anti-histone antibodies. The two patients with DIV demonstrated pauci-immune, necrotizing crescentic glomerulonephritis on renal biopsy. The other two were found to have features consistent with drug-induced lupus (DIL) and immune complex deposition in the sub-endothelial, subepithelial, and mesangial areas. All patients with DIV were initiated on hemodialysis. One of them recovered successfully, whereas the other patient’s condition deteriorated and hospice care was initiated. Of the two patients with DIL neither one required dialysis. One patient developed severe sepsis with subsequent withdrawal of care, while the other one was discharged with hemochromatosis at baseline.

Results:

Conclusions: Our report calls for heightened awareness and prompt diagnosis of DIL and associated with the therapy to minimize morbidity and mortality associated with this agent. Given an extremely unfavorable side effect profile and multiple alternatives available on the market, hydralazine should generally be avoided. In situations where its use is necessary either due to other agents’ unavailability, intolerance, or inefficacy, we find that it is imperative for a clinician to monitor closely the patients on a long-term/high dose hydralazine regimen.

Tramadol Induced Severe Hypoglycemia in a Non Diabetic ESRD Patient

Ameen Taleb,1 Michael E. O’Brien,2 Brianna D. Jewell,2 Yuvaraj Thangaraj,1 1Mercy Medical Center-North Iowa, Mason City, IA; 2Mercy North Iowa, Mason City, IA; 3None, Mason City, IA; 4University of Iowa, West Union, IA.

Background: Tramadol is a generally well-tolerated medicine in ESRD patients on hemodialysis. We present a case of severe hypoglycemia in an ESRD patient within days of initiating tramadol for pain at appropriate dose and timing interval.

Methods: A 54 y/o man with a history of ESRD on hemodialysis, hypertension and chronic back pain presented with hypoglycemia on the day of dialysis after receiving tramadol treatment. He reported taking 100 mg of tramadol after dialysis. He was noted to have severe symptomatic hypoglycemia with a blood sugar of 33 mg/dl. The patient required multiple ampules of IV dextrose 25% and subsequently received 50% dextrose infusion in the critical care unit for persistent hypoglycemia. Lab findings including drug screen and acid base status were unremarkable aside from hypoglycemia. Insulin levels, -c-peptide level and IGF1 level were within normal limits. Screen for metilidines and agonists of dopamine receptors were negative. CT abdomen and pelvis with contrast showed small hydromedulysis within the pancreas. The CT findings were not radiographically consistent with insulinoma and represented small cysts that appeared to be unchanged from the previous CT. Patient’s clinical condition and hypoglycemia significantly improved within 48 to 72 hours after discontinuation of tramadol and receiving dialysis treatment. The patient did not have any further episodes of hypoglycemia in post hospitalization follow up.

Results: Tramadol’s hypoglycemia effect appears to be due to a synergistic effect between tramadol opioid receptor stimulation and decreased serotonin and epinephrine reuptake in nerve endings, which subsequently promotes higher levels of intracerebral serotonin and epinephrine. Tramadol depends on a cytochrome P450 enzyme, the expression of which is highly variable for activation into its active metabolites. Those metabolites are then reuptake in nerve endings, which subsequently promotes higher levels of intracerebral serotonin and epinephrine.

Conclusions: This case illustrates the importance of early recognition and appropriate management of tramadol induced life threatening hypoglycemia in ESRD patients including the need for heightened vigilance and slow up titration of dose to prevent severe hypoglycemia.

Influence of Communication of Hypertension Outcomes

Kirsten Sallone,2 Jeffrey J. Silberzweig,1 Stephanie Tsai,2 Clara Oromendi,2 Vesh Srivatana,3 Gordon Hicks-Smith,2 1Department of Nephrology/Internal medicine, New York Medical College, New York, NY; 2Department of Nephrology/Internal medicine, Weill Cornell Medical College, New York, NY; 3Department of Nephrology/Internal medicine, New York, NY.

Background: Despite the growing body of literature documenting the prognostic importance of hypertension, it is commonly treated as a peripheral issue during hospital admissions. We seek to quantify the degree to which hyponatremia is reported to outpatient providers and to evaluate factors associated with communication and interactions between communication and standard outcome measures.
Methods: With IRB approval, we designed a retrospective cohort study of patients undergoing dialysis at the Weill Cornell Campus of the New York Presbyterian Hospital in January 2014 with corrected serum sodium <130 mEq/L who survived the hospitalization. Discharge summaries were manually reviewed for mention of hyponatremia; charts were reviewed for pertinent information. Patients who did and did not have hyponatremia mentioned in the discharge summary were compared. 3 h-chlorite (or Fisher's Exact and Kruskal-Wallis tests for categorical and continuous variables, respectively. Statistical significance was determined at the 0.05 alpha level.

Results: Of 101 patients, hyponatremia was mentioned in discharge summaries in 37%, with a mean hyponatremia level removed by GAC <130 mEq/L (mean ± SD: 135.7 ± 18.2), and there was a non-significant trend towards Caucasian race (57% vs. 38% p < 0.05), other demographic features did not differ. Nadir sodium (125.3 vs. 127.3 mEq/L; p = 0.001), and discharge sodium (132.2 vs. 134.7 mEq/L; p = 0.10) were lower for the hyponatremia group. Mean duration of hospitalization was shorter (12 vs. 21 days; p = 0.008). Communication of hyponatremia was not associated with one-year mortality, readmissions or readmissions with hyponatremia. Differences in subsequent outpatient providers’ assessment of sodium levels were not significant (60% vs. 49%; n = 50 vs. 66.5%). Only 2 patients had hyponatremia labeled as a problem in the encounter note; in just one of these was it also mentioned in the discharge summary.

Conclusions: Despite its diagnostic significance, our results suggest that hyponatremia is infrequently communicated to outpatient providers. Higher rates of communication can be achieved with education on hyponatremia and another hospital stay. A lack of specific outpatient provider response to hyponatremia may explain the lack of association between communication of hyponatremia and outcome measures.

Funding: Clinical Revenue Support

FR-PO967

Changes in Creatinine and Potassium after Initiating Renin Aldosterone Inhibitor and Diuretic Therapy in CKD: A Cohort Study from Outpatient Providers

Background: Clinical trials of renin aldosterone system inhibitors (RASi) have demonstrated major cardiovascular and renal benefits to patients with chronic kidney disease (CKD), but these benefits must be weighed against the risks of a decline in glomerular filtration rate (eGFR) and hyperkalemia. Since random controlled trials do not include the breadth of patients in real world clinical settings, we assessed changes in creatinine (Cr), estimated glomerular filtration rate (eGFR) and potassium in a large cohort of CKD patients prescribed a new RASI or diuretic.

Methods: Retrospective cohort study of adults with pre-diagnosis CKD stage 3-5 who received a new outpatient RASI or diuretic prescription during 2009-2011. Lab data was collected electronically and analyzed for changes in Cr, eGFR, and potassium.

Results: A total of 8,272 individuals (mean age 72 yrs ± 13.5, 44% male, 86% white) with CKD (90% stage 3, 7% stage 4, 2% stage 5) were included; 52% received a RASI and 48% received a diuretic. In the 2 weeks before the scheduled GAC replacement date. Although CIO₂ is detected using the standard testing for total chlorine, chlorine is not. The effects of chronic low level exposure to chlorine are unknown, but potentially could lead to erythropoietin stimulating agent resistance and/or increased red blood cell destruction. Dialysis providers should be aware of this hazard, and recognize that more intensive monitoring and more frequent replacement of GAC may be required when CIO₂ is present in municipal or hospital water.

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

Underlines represent presenting author.
FR-PO969
Metagenomic Analysis of Microbial Nanovesicle in Blood of Maintenance Hemodialysis Patients
Un Sil Jeon,1,2 Jinho Yang,1 Seung Hee Yang,1 Yoon-Keun Kim,1,3 Nephrology, Sheikh Khalifa Specialty Hospital, Ras Al Khaimah, United Arab Emirates; 1,2 Medicine, Seoul National University Hospital, Seoul, Republic of Korea; 1 MD Healthcare Inc., Seoul, Republic of Korea; 1 Kidney Research Institute, Seoul National University, Seoul, Republic of Korea.

Background: Gut dysbiosis in uremic patients is known to contribute to progression and complications of chronic kidney disease (CKD). Extracellular vesicles (EVs) excreted from bacteria contain not only bacterial DNA and RNA, but also endotoxins and other virulent proteins. EVs can enter systemic circulation through intestinal mucosal membrane freely and be key communication messengers in host-microbe communication in human diseases.

Methods: We performed metagenomic analysis of bacteria-derived EVs in blood of 20 maintenance hemodialysis (HD) patients (10 diabetic and 10 non-diabetic) and 20 healthy controls. EVs in human serum were isolated using the differential centrifugation method described previously (Prokopenko 2007:7:3143–3153). DNA was extracted from 1 μg of serum EVs, and 16S ribosomal RNA (16S rRNA) gene sequencing was performed using high-throughput 454 pyrosequencing after amplification of the V1–V3 region of the 16S rDNA. Taxonomy assignment was carried out by using UCLUST and QIME against the 16sRNA sequence database in GreenGenes.

Results: The value of alpha-diversity was lower in HD patients than in healthy controls, which means HD patients had a lower diversity of microbiome than healthy controls. The value of beta-diversity was significantly different between HD patients and controls. At the level of Phylum, HD patients had a significant higher level of Acidobacteria EVs than controls, but a lower level of Proteobacteria EVs. At the level of genus, we found remarkable trends which revealed different levels between HD patients and controls (29 elevated and 18 decreased EVs in HD patients). Streptococcus, Koribacteraceae, Ecteinascidia, and Burkholderia spp. EVs were higher in HD patients than in controls, and Enterobacteriaceae EVs, Acinetobacter, Pseudomonas, Akkermansia, Proteus and Lactobacillus spp. EVs were lower in HD patients. However, there were no differences between diabetic and non-diabetic HD patients.

Conclusions: In conclusion, we observed significant differences in the composition and amounts of bacteria-derived EVs in blood between HD patients and healthy controls using metagenomic analysis. Metagenomic analysis of bacteria-derived EVs could be a useful tool to investigate microbial dysbiosis and biomarkers in CKD patients.

FR-PO970
Comparing Raman Spectroscopy-Derived Metabolomic Signatures of Urine from Patients with CKD to Those with Normal Kidney Function
James L. Pirke,1,2 John L. Robertson,1,3 Mitchell Warren,2 Ryan S. Senger1,3 (Virginia Tech, Blacksburg, VA; 1Wake Forest School of Medicine, Winston Salem, NC).

Background: The field of metabolomics is being used increasingly in clinical research to improve aspects of clinical care ranging from early diagnosis to monitoring treatment progress and prognosis. It would be useful to have an affordable metabolomic test for urine that could identify patients with chronic kidney disease in the absence of albuminuria. Raman spectroscopy is an analytic tool used chiefly in solid state chemistry that has shown increasing application in analyzing molecular compositions of biological samples. We performed a pilot study to assess the ability of Raman spectroscopy analysis of urine samples to differentiate between patients with CKD and those with normal kidney function.

Methods: Free-catch urine samples were collected from 93 patients with CKD (on peritoneal dialysis) and from 25 generally healthy volunteers with normal kidney function. Raman spectra were analyzed using an Agilent PeakSeeker Pro spectrometer with 785 nm laser excitation at 5 mW. A 1 s integration time was used, spectra were collected between 200-2000 cm⁻¹, and each sample was scanned 10 times. Spectra were analyzed by a multivariate statistical pipeline involving (i) principal component analysis and (ii) discriminate analysis of principal components following baseline correction and vector normalization of raw spectra.

Results: The individual raw spectra show that only the urea band at 1003 cm⁻¹ is distinguishable. The multivariate statistical pipeline was used to determine whether differing molecular signatures existed elsewhere for urine from patients with CKD and those with normal kidney function. Results are shown in a canonical plot, where every data point represents an entire Raman spectrum. Distinct clusters of data points are observed between the urine of CKD patients (receiving PD) and those with normal kidney function, indicating recognizably different Raman signals and molecular compositions for each group.

Conclusions: Raman spectroscopy provides a rapid, cost-effective way to assess differences in the molecular composition of urine between patients with CKD and those with normal kidney function. Future research will focus on quantifying these differences and developing a clinical test for CKD. Potential clinical applications for this technology would include community screening for CKD using rapid urine testing.

FR-PO971
The Differential Expression of Circular RNAs in Exosomes from Serum and Urine in Patients with IMN
Hualin Ma,1,2 Xin-zhou Zhang,1,2, I. Department of Nephrology, Shenzhen People's Hospital, Shenzhen, China; 2Key Renal Laboratory of Shenzhen, Shenzhen, China.

Background: To further explore the pathogenesis of idiopathic membranous nephropathy (IMN), the technique of gene-sequencing was used to analyze the differentially expressed circRNAs in exosomes from both the serum and urine of patients with IMN, which may lay the foundation for the research of circRNAs as a new class of exosome-based idiopathic membranous nephropathy diagnosis biomarkers.

Methods: Ten patients with idiopathic membranous nephropathy (IMN group) and ten normal controls (NC group) were recruited as experimental subjects in our study. The exosomes were extracted from the collected serum and urine by the ExoQuick Exosome Precipitation Solution and ultracentrifugation. Then, the pure circRNAs were extracted from the exosomes with a series of enzymatic reactions. Afterwards, the significantly differentially expressed circRNAs were chosen by the method of gene-sequencing to analyze the function of corresponding target genes.

Results: Compared with normal controls, the circRNAs were reduced in the exosomes from serum of patients with IMN, which mostly originated from intron gene regions. Meanwhile, a total of 89 circRNAs were significantly differentially expressed, which were also mostly derived from intron gene regions, including 54 up-regulated and 40 down-regulated genes. However, the species were increased in the exosomes from the urine of patients with IMN compared to normal controls, and they mainly originated from exon gene regions. Simultaneously, a total of 60 circRNAs were significantly differentially expressed, which primarily belonged to intron regions, including 32 up-regulated and 27 down-regulated regions.

Conclusions: The significant differential and specific expression of circRNAs in the exosomes from the serum and urine of patients with IMN were observed. For example, MUC3A, which originated from chr7:100550800:100551062, could be considered a potential diagnostic biomarker of IMN. Furthermore, these figures suggested that different circRNAs differentially expressed circRNAs can be used as a reference or supplement in the research of the pathogenesis of IMN.
Opaque plastic sheets (10 cm * 0.5 cm) Absorbable sheets (1 cm * 0.5 cm) immersed in picric alkaline solution for an hour then glued to test strip. 200 ul of creatinine solutions have been applied on test strips Using Matlab to measure creatinine color intensity from a mobile image of test strip

Results: A standard curve is established from results by using Matlab software image 1. A mobile app will be used to detect creatinine level from color intensity of test strip when apply a blood drop. We observed when applying higher creatinine concentration, test strip color become darker image 2

Conclusions: By using the chemical property of picric acid when react with creatinine, a relation is established as a standard curve between creatinine concentration and color intensity. Using the mobile phone cameras, anyone at home can measure creatinine level by taking an image of test strip.

Funding: Other U.S. Government Support, Private Foundation Support

Relation between color intensity and creatinine concentration

<table>
<thead>
<tr>
<th>Creatinine Concentration</th>
<th>Image 1</th>
<th>Image 2</th>
<th>Image 3</th>
<th>Image 4</th>
<th>Image 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red Intensity</td>
<td>254</td>
<td>201</td>
<td>204</td>
<td>200</td>
<td>199</td>
</tr>
<tr>
<td>Blue Intensity</td>
<td>198</td>
<td>197</td>
<td>198</td>
<td>203</td>
<td>214</td>
</tr>
<tr>
<td>Color Intensity</td>
<td>123</td>
<td>115</td>
<td>25</td>
<td>35</td>
<td>40</td>
</tr>
</tbody>
</table>


FR-PO975

Parallel Cross-Flow Filtration Microfluidic Device for Renal Micro-Environment Emulation Zach Ogled, Nephrology, First Affiliated Hospital of Dalian Medical University, Dalian, China.

Background: Whole human blood, a non-Newtonian fluid, can effectively be filtered on a microfluidic device. Past microfluidic design approaches utilized dead-end filtration concepts that lead to clogging since the cells are trapped in the direction of flow. This limitation also precludes the filtration of plasma, an important component to investigate renal inflammation. There is a need for a novel design that can mimic capillary action and fenestrations gaps akin to the renal micro-environment. The primary aim of this study was to design, fabricate, and test a novel microfluidic device for separating whole human blood (plasma, white blood cells, and red blood cells).

Methods: Development of the microfluidic device utilizes photolithography and micro-molding techniques that involve the following basic components: silicon wafer (111), chrome masks, glass, and polydimethylsiloxane (PDMS). Design assumptions called for human blood as the testing fluid. The design utilized a five-row filtration system in the first modular section with varying gap sizes (between pillar edges) from 6.5 microns to 2.5 microns. The second modular design included three channels with the main channel flanked by weir micro filtration barriers of consistent gap slits of 3.5 microns.

Results: The combined (pillar and weir) cross-flow design was shown to rapidly separate different categories of blood cells simultaneously based on size-exclusion principles despite spacing anomalies. The pillar filtration segment appears to show gradient changes, especially in the last two filtration tunnels. The other weir filtration segment does not show as drastic a color gradient change.

Conclusions: This microfluidic chip, based on a multi-level parallel cross-flow design, offers enhanced features over prior microfluidic approaches. It effectively addressed dead-end filtration limitations with no visible clogging obstacles. It demonstrates a successful integration of modular micro-feature units (pillar and weir).

FR-PO976

Bioengineering an Organotypic Normal and Diseased Kidney Tubule Array Balaji karthick Subramanian,1,2 Oguzhan Kaya,1 Jing Zhou,1 Medicine - Nephrology, Brigham and Womens Hospital /Harvard Medical School, Boston, MA; 1Medicine - Nephrology, Beth Israel Deaconess Medical Center, Boston, MA.

Background: Maintenance of homogenous kidney tubular structures is critical to retain kidney shape and function, and in accordance aberrations in their structures are manifested in disease conditions. Lack of in vitro kidney tubule models that are homogeneous in tissue geometry structures and also emulating aberrations in disease conditions have limited the understanding of their pathology and the therapeutics development.

Methods: Homogenous tubular tissue geometry micropaniters were imprinted in different extracellular matrix combinations as an array using a combination of photolithography and soft lithography techniques. Tubular kidney epithelial cells were then cultured in the3D micro-molded extracellular matrix array and were evaluated for...
the morphogenic outcomes. Cystic kidney disease emulation was achieved by treatments with cAMP-elevating agents, while for acute kidney injury emulation cisplatin drug treatment was used.

**Results:** Both mouse and human epithelial cells formed homogeneous tubular structures as defined by the tissue geometry yielding kidney tubular arrays. The tubule features in the array were validated based on the characteristic distribution of actin (F-actin), cilia (acetylated tubulin), tight junction (ZO-1), and Na^+K^+/ATPase pump. Further, the disease emulations of cystic kidney disease and acute kidney injury were confirmed for tubule to cyst transformation and kidney injury molecule (Kim-1) expression respectively.

**Conclusions:** The tubule array yielded organotypic homogeneous tubules with in vivo-scale dimensions, which can be utilized for assessing nephrotoxicity of drugs and the mechanistic studies of various tubular kidney disease, making it an alternative to animal studies.

FR-PO977

**Development of Functional Vasculature in Decellularized Whole Porcine Kidneys with Human Endothelial Cells**

Morgan D. Cabral,1,2 Dominique Setcaptum,3 Senthuran Ross,3 Morgan D. Black.3

**Background:** End stage renal disease (ESRD) represents a major epidemiologic burden in the US and worldwide. Patients with ESRD have two options: kidney transplantation or hemodialysis. Due to the organ donor shortage, only a few patients receive transplants. The alternative, hemodialysis, has a 5-year mortality rate of 35% compared to only 3% for transplantation. With ~500,000 hemodialysis patients in the US, a new therapy is needed. The ultimate solution would be a bioengineered kidney to solve the chronic shortage. A critical first step is the demonstration of a functional vasculature to continuously perfuse blood. We demonstrate that a functional vasculature can be achieved by repopulating decellularized kidneys with human primary cells.

**Methods:** Whole porcine kidneys were perfusion decellularized without compromising the native microarchitecture of both the vascular and tubular compartments. Human umbilical vein endothelial cells (HUVEC) and primary human epithelial cells (HPE) were seeded into the vascular and tubular compartments respectively. Whole organ culture was performed under continuous perfusion and key metabolic parameters were monitored daily to assess cell proliferation and viability. Functional vasculature assessment was performed with blood loops using whole porcine blood to model in vivo performance.

**Results:** Cellular engraftment and viability were measured by metabolic parameters including glucose consumption over 3 to 4 weeks (n=12) to achieve the desired level. These data were further corroborated by histological analysis of formalin fixed sections demonstrating the presence of a single layer of engrafted cells on vascular and tubular compartments. Furthermore, cells positive for the endothelial cell marker CD31 were confined to the vascular compartment and cells positive for the epithelial cell marker e-cadherin were confined to the tubular compartment. Vascular functionality was characterized by blood loops and demonstrated long-term continuous perfusion of whole blood compared to physiological pressures compared to non-recellularized kidneys that demonstrated the lack of flow after a few minutes.

**Conclusions:** These results demonstrate the ability to generate a functional vasculature in recellularized kidney grafts, a critical first step in the engineering of a fully bioengineered kidney.

_Funding:_ Commercial Support - Miromatrix Medical Inc.

---

FR-PO978

**The Role of Endothelial Nitric Oxide Synthase Expression in Arteriovenous Fistula Remodeling and Hemodynamic Adaptation**

Timmy C. Lee,1 Daniel Pike,2 Tatyana Isayeva Waldrop,1 Lingling Guo,1 Maheshika S. Somarathna,1 Yan-Ting Shiu.2

**Background:** Endothelial nitric oxide synthase (NOS3), via its role in producing nitric oxide (NO), plays an important role in arteriovenous fistula (AVF) maturation following AVF creation. NOS3 dysfunction may play an important role in AVF development.

**Methods:** Carotid (side)jugular (end) AVFs were created in NOS3/-/- (knockout), NOS3+/+ (wildtype), and NOS3 overexpression (OE) mice on C57/BL6 background. Serial AVF lumen and hemodynamic changes were characterized using non-contrast MRI-imaging and computing fluid dynamic imaging (Fig. 1). Mice were sacrificed at 21 days for histologic and biochemical studies.

**Results:** At day 21, NOS3 OE AVFs have large venous lumen at and near the anastomosis, smooth velocity streamlines, low vorticity, as well as relatively uniform and low wall shear stress (WSS), suggesting desired vascular remodeling and restoration of WSS. In contrast, both NOS3/-/- and NOS3+/+ AVFs have small lumen, disturbed velocity streamlines, high vorticity, and high venous WSS. AVF vein MMP9 protein expression was reduced at 21 days in NOS3 OE mice compared to NOS3+/+ and NOS3/-/- mice (p<0.05). AVF vein average intima/media thickness was significantly lower in NOS3 OE mice compared to NOS3+/- and NOS3-/- mice (p<0.0001) at 21 days. cGMP levels were significantly higher in NOS3 OE AVFs vs NOS3-/- and NOS3+/- AVFs (p<0.05)

**Conclusions:** Increased NOS3 expression improves AVF hemodynamics and remodeling and reduces neointimal hyperplasia development. Future interventions that target increasing NOS3 expression and NO delivery may be beneficial to improving AVF development.

_Funding:_ Clinical Revenue Support

---

FR-PO979

**Renal Protection during Cardiopulmonary Bypass (CPB) with a Leukocyte Modulatory Device (L-MOD)**

H. David Humes,1 A. Westover,2 D. Buffington,3 K. Johnson.3

**Background:** Leukocyte activation during cardiopulmonary bypass (CPB) contributes to a systemic inflammatory response that can cause organ injury and dysfunction, including the kidney. The therapeutic value of incorporating an extracorporeal leukocyte modulatory device (L-MOD) during and after CPB was investigated. Assessment of the mediated organ injury in a pre-clinical animal model was the primary outcome criteria.

**Methods:** Twenty-two pigs underwent a simulated cardiothoracic surgical procedure with 180 minutes of CPB and 5 hours post-operative observation. Pigs received CPB with no intervention (Group 1, n=9), 3 hours of L-MOD therapy by incorporation of L-MOD into the CPB circuit (Group 2, n=6) or 8 hours of L-MOD therapy using a femoral veno-venous extracorporeal circuit during and after CPB (Group 3, n=7). Leukocyte counts and activation were serially measured. Hemodynamics, pulmonary parameters and urine output were monitored as indices of organ function. Serum troponin-I and urine neutrophil gelatinase-associated lipocalin (NGAL) served as biomarkers of organ injury for heart and kidney, respectively.

**Results:** Leukocyte activation at the end of CPB was significantly increased in Groups 1 and 2 but not Group 3. Leukocyte counts, namely neutrophils, significantly increased post-operatively in Groups 1 and 2 but not in Group 3. Systemic vascular resistance was not as reduced post CPB for the L-MOD treated pigs and at 5 hours post CPB, organ injury markers, troponin-I and NGAL, were lowest in Group 3.

**Conclusions:** 8 hours of L-MOD therapy limited leukocyte activation and the inflammatory response to CPB which resulted in less organ injury and dysfunction, including the kidney. Continuation of L-MOD therapy into the post-operative period was required for therapeutic impact.

_Funding:_ Other NH Institute - HL127830
FR-PO980

A Comparison of Electronic Health Record (EHR) Phenotype Definitions for CKD

C. Blake Cameron, John W. Stanifer, Rachel Richerson. Duke University, Durham, NC.

Background: Multiple methods for identifying patients with CKD using EHR-based phenotypes have been proposed. Few studies have systematically compared or prospectively validated these phenotype definitions.

Methods: In a rural, community-based healthcare system, we applied five distinct CKD phenotype definitions (A-E) to the EHR. Phenotype A defined CKD as ≥2 eGFR values <60mL/min/1.73m² separated by 90-730 days. Phenotype B was the same but also included individuals with albuminuria ≥30mg/g. Phenotypes C and D defined CKD by a single eGFR result <60 or <45 mL/min/1.73m² respectively. Phenotype E defined CKD as having ≥2 ambulatory encounters associated with an eligible ICD-9-CM or ICD-10-CM diagnosis code. We evaluated inter-rater agreement between each phenotype pair by calculating Cramer’s percent positive agreement and Cohen’s Kappa statistic.

Results: We identified 59,848 unique adults with at least one ambulatory encounter occurring over a two-year period, of whom 6,620 (11%) were classified as having CKD by any one of the phenotypes. Only 666 (1%) were classified as having CKD by all five phenotypes. Phenotype C classified the most patients as having CKD (n=5,596; 9%), followed by phenotype B (n=3,837; 6%); phenotype A (n=3,268; 5%); phenotype D (n=2,552; 4%); and phenotype E (n=1,615; 3%). Phenotypes A and B showed the greatest agreement (Kappa=0.915), followed by phenotypes A and C (Kappa=0.718) and phenotypes B and C (Kappa=0.693). Phenotype E showed low agreement with any of the phenotypes.

Conclusions: In a rural, community-based healthcare system, several commonly used phenotype definitions showed poor agreement in classifying CKD. Additional studies using external reference standards that include prospective laboratory assessment of kidney function and albuminuria are required in order to validate performance characteristics of these phenotypes. Once validated, one or more CKD phenotypes could be promoted as a standard to define similar populations for clinical research and population health management.

Funding: Private Foundation Support

Positive overlap, percent positive agreement (PPA) and Kappa statistic for phenotype pairs

<table>
<thead>
<tr>
<th>Phenotype A</th>
<th>Phenotype B</th>
<th>Phenotype C</th>
<th>Phenotype D</th>
<th>Phenotype E</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPA 92.2%</td>
<td>Kappa 0.913</td>
<td>Kappa 0.718</td>
<td>Kappa 0.693</td>
<td>Kappa 0.693</td>
</tr>
<tr>
<td>PPA 95.8%</td>
<td>Kappa 0.718</td>
<td>Kappa 0.693</td>
<td>Kappa 0.693</td>
<td>Kappa 0.693</td>
</tr>
<tr>
<td>PPA 93.5%</td>
<td>Kappa 0.718</td>
<td>Kappa 0.693</td>
<td>Kappa 0.693</td>
<td>Kappa 0.693</td>
</tr>
<tr>
<td>PPA 92.1%</td>
<td>Kappa 0.718</td>
<td>Kappa 0.693</td>
<td>Kappa 0.693</td>
<td>Kappa 0.693</td>
</tr>
<tr>
<td>PPA 97.0%</td>
<td>Kappa 0.718</td>
<td>Kappa 0.693</td>
<td>Kappa 0.693</td>
<td>Kappa 0.693</td>
</tr>
</tbody>
</table>

FR-PO981

VA MobileKidney App – A Mobile Educational and Clinical Engagement Tool for Veterans with CKD and Their Providers

R. Brooks Robey, Sr, Susan T. Crowley, 1, DeVasmita Choudhury, 2, 1White River Junction VA Medical Center, White River Junction, VT; 2Geisel School of Medicine at DHMC. Hanover, NH; 3VA Connecticut Health Care System, West Haven, Salem, VA; 6Virginia Tech Carilion School of Medicine, Roanoke, VA.

Background: Using mobile devices and securely share these data with their providers for asynchronous review, information resources housed in the cloud-based virtual VA Kidney Clinic (http://ckd.vacloud.us/) promises to enhance patient buy-in and engagement in self-monitoring activities, as well as improve patient-provider communication, documentation, and care coordination.

Methods: The VA Kidney Clinic is scheduled for field testing and launch by Kidney Week 2017. It will provide accessible education resources to Veterans with CKD and their providers, as well as a mobile digital platform for sharing detailed self-gathered interval health information for joint review at regularly scheduled clinic visits. Free text journaling capabilities also allowed flexibility to tailor application use to specific clinical needs. This novel digital tool for interval healthcare data acquisition, delivery, and review also provides a structured replacement for traditional hardcopy health diaries and

promises to enhance patient buy-in and engagement in self-monitoring activities, as well as improve patient-provider communication, documentation, and care coordination.

FR-PO982

Engineering Design of Robust Ultrafiltration Profiles in Hemodialysis

Rambham M. Abolture, 1, Christopher V. Hollo, 1 Joseph Horowitz, 2 Yossi Chait. 3 Department of Electrical and Computer Engineering, University of Massachusetts Amherst, Amherst, MA; UMass, Florence, MA; 1University of Virginia, Charlottesville, VA.

Background: Fluid removal during hemodialysis (HD) by ultrafiltration can lead to intradialytic hypotension, which is associated with an increase in morbidity and mortality. We design a robust, individualized ultrafiltration rate (UFR) profile to achieve a target volume removal under constraints on maximal UFR and maximal hematocrit (HCT) levels.

Methods: We used nonlinear model comprising intravascular and interstitial pools, microvascular refilling/filtration, and lymphatic flow. Model parameters, red blood cells volume (Vrbc), plasma protein mass (mP), and filtration coefficient (Kf), were estimated using 30 minutes of UFR and HCT clinical data and validated using remaining data. Anticipated parameter changes during HD and estimation errors were accounted for by allowing parameter uncertainty ranges of ±2.5%. The profile was designed using an optimization algorithm to remove 2.8 L in 4 hrs, with UFR not exceeding 10 mL/hr/kg, and HCT not exceeding 110% of initial HCT, and to guarantee performance over the entire range of parameter uncertainty.

Results: Model parameters (Vrbc = 22.4 L, Kf < 0.006 L/min/mmHg, and mP = 179.58 gr) of a 75 kg patient were estimated based on the initial 30 minutes of the HD session (Figure, top right) and validated over an additional 170 minutes of the session (Figure, bottom left). Simulation of the designed UFR profile (Figure, top right) over the range of model parameter uncertainty confirmed that all specifications were achieved (worst case HCT shown in Figure, bottom right); the worst case of HCT is simulated for a particular set of parameters within the parameter uncertainty range of the model.

Conclusions: The divergence of the validated response later in the HD period demonstrates that the underlying patient’s response can deviate from model prediction due to, for example, autonomous adaptation not captured in the model. This motivated the use of robust design of UFR profiles. Our UFR profile is designed to satisfy HCT and UFR constraints, and to guarantee that performance criteria are met over the entire model parameter uncertainty range.

Funding: NIDDK Support
FR-PO984

Engineering-Based Individualized Anemia Management in Hemodialysis Patients

Background: Management of erythropoietin stimulating agents and parenteral iron in hemodialysis (HD) patients is performed according to protocols derived from population response data. This pilot study examined whether individualized dosing can reduce hematocrit (Hb) variability and increase the proportion of Hb levels within range compared with standard protocol results, while transferrin saturation (TSAT) and Ferritin levels would remain similar, and that the use of medications could be reduced.

Methods: We enrolled 25 maintenance HD patients treated using a bi-weekly titration and dosing protocol. We switched into a computerized, individualized protocol based on feedback principles and a mathematical model [1]; The ESA protocol has been validated in prior studies while the IV Iron protocol was newly derived. In the individualized protocol dosing schedule was switched to weekly. Target and range Hb were 11.5 and (11,12) g/dl, respectively. Results are reported from the first 9 months of the year-long, crossover study with 3-month washout period; Hb variability measure was the standard deviation (sd). Baseline refers to the 6-month period prior to the study, and Study refers to the most recent 6-month. For normal data we used the t-test to compare means and Pitman’s test for sds; medians of nonnormal data were compared by the signed rank test; and McNemar’s test was used for binary data and statistical significance is defined as P-value < 0.05.

Results: (Table)

Conclusions: The individualized anemia protocol has improved %Hb in range and reduced Hb variability compared with standard protocol, while Aranesp and Venoferr doses were reduced. However, TSAT and Ferritin levels decreased suggesting that our Iron IV algorithm may require modification. 1. Chait Y, Horowitz J, Nichols B, Shrestha R, Pilley CR, Germain MJ. Control-relevant erythropoietis modeling end-stage renal disease. IEEE Trans Biomed Eng. 2014

Funding: NIDDK Support

FR-PO985

Sodium MRI Identifies Differences of Sodium Concentration with Age, Gender, and Race in Muscle and Skin of Healthy Subjects from the US

Background: Sodium (Na+) balance is important in managing hemodialysis patients; however, its assessment is difficult and incomplete. Experimental studies show that Na+ is a significant volume water accumulators and who may vary until levels measured in the serum. Our study implemented quantitative 23Na MRI imaging of the calf muscle and skin of healthy subjects compared with ex vivo reference standards. Contributions from age, gender and race were examined.

Methods: A total of 30 subjects were enrolled for the study [(15M/15F), 46.4±14.8 yrs. (10 White/20 African-American)]. Studies were performed on a 3.0 Tesla Siemens MRI using a 23Na coil (Helmut Stark;Germany)[Fig 1]. Scan-rescan reproducibility was assessed the same day and 1 week later for a total of 4 time points/subject. Regions of interest were defined in the skin and following muscles: lateral gastrocnemius (LGM), medial gastrocnemius (MGM), soleus, tibialis anterior and peroneus. A mixed effects model was used based on repeated measures to determine the marginal multivariate effects of age, gender and race versus sodium MRI concentrations. A Bland-Altman plot assesses scan-rescan variability with the smallest real difference (SRD) calculated as 2.77*SEM.

Results: The Bland-Altman plots indicated high agreement between runs in all regions. The SRD was 9.7% and 4.1% within the same day and 10.9% and 12.2% comparing runs a week apart. Sodium increased in all muscles and skin with age. An association in muscle sodium was seen in the LGM (p=0.03), anterior (p=0.04) and peroneus (p=0.03) muscles with gender. No significant association was seen between sodium levels and race.

Conclusions: Tissue Na+ content was confirmed to increase with age in both muscle and skin of healthy controls. Differences in muscle sodium levels were also found with gender but not race. Reproducibility of 23Na MRI in the muscle and skin resulted in an SRD that shows promise to assess serial changes in patients with renal insufficiency.

Funding: Private Foundation Support

FR-PO986

Computational Volume-Analysis of Compensatory Hypertrophy of the Kidney after Contralateral Nephrectomy

Background: Kidney volume usually increases after contralateral nephrectomy according to the preoperative disease-affected kidney function. We preliminarily assessed post-nephrectomy-parenchymal volume divided into two regions (cortex and medulla) to examine compensatory hypertrophy by each using computational volume analyzer on new computational imaging technologies.

Methods: The arterial-phased enhanced imaging data (DICOM formatted) of 11 patients (age ranged between 51 and 86) were obtained from the institutional database. Nephrectomy was underwent in all patients in which 7 renal cell carcinoma, 3 pelvic and ureteral cancer and 1 pyonephrosis were included. Pre- and postoperative (after completion of compensatory hypertrophy) parenchymal volumes were calculated using Synapse Vincent, Fujifilm and compared regional increasing ratio in each area (total parenchyma, cortex and medulla).

Results: Mean preoperative total kidney volume was 181.95 (31.38) ml, 112.53 (25.57) ml and 67.40 (16.85) ml and mean postoperative one were 200.81 (41.65) ml, 126.66 (34.94) ml and 74.15 (16.81) ml, respectively. Cortex volume increases significantly comparing to the preoperative status (p=0.04); however, medulla volume and cortex-medulla volume ratio did not change significantly. Body mass index, gender and preoperative estimated glomerular filtration ratio (eGFR) did not affect the cortex hypertrophy. When comparing the cortex increasing ratio to the change in eGFR, cortex hypertrophy indicated fewer decline in eGFR (fig: p=0.2, R=0.41).

Conclusions: Within the small preliminary experience, computational volume-analysis indicated kidney volume increase after nephrectomy in the cortex region superiority to the medulla. Cortex hypertrophy might correlate with better preservation of renal function in eGFR.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
FR-PO987

Contrast Enhanced Ultrasound (CEUS): A Novel Marker of Kidney Disease
Mona Shaban,1 Emily H. Chang,2 Anush Sridharan,4 Paul Dayton,1
1 UNC Chapel Hill and NC State University Raleigh, Chapel Hill, NC; 2 UNC Kidney Center, Chapel Hill, NC; 3 Nephrology, University of North Carolina at Chapel Hill, Chapel Hill, NC; 4 University of North Carolina, Chapel Hill, NC.

Background: The number of patients with chronic kidney disease (CKD) is on the rise and non-invasive methods of detecting early stages of kidney insufficiency are limited. Rise in creatinine often lags behind loss of kidney function and current ultrasound technology to evaluate severity of CKD hinges on kidney size and echogenicity, which is a subjective marker. Contrast enhanced ultrasound (CEUS) provides qualitative and quantitative measurements of perfusion, which may lead to earlier diagnosis of CKD and provide a better marker of kidney disease progression.

Methods: Patients with various stages of CKD were subjected to CEUS of the kidney. Contrast agent (Definity) was infused at a constant rate based on BMI. High mechanical index flash perfusion imaging was captured. Baseline serum creatinine and urinalysis was collected. Time-intensity curves (TICs) were generated for regions of interest (ROIs) from the kidney parenchyma, as well as maximum intensity projections and perfusion maps. TICs are used to generate a wash-in rate, area under the curve, and time-to-peak intensity.

Results: A total of 30 patients with CKD and 3 healthy controls participated in this study. We have found that the enhancement of kidney parenchyma was markedly reduced in patients with lower glomerular filtration rate (GFR) (image 1A). Additionally, we have demonstrated a linear inverse correlation between reperfusion rate and stage of CKD (image 1B). These values will be compared to multiple metrics including GFR and proteinuria in hopes of establishing a novel technique that detects degree of CKD, particularly early stages.

Conclusions: CEUS is a novel, non-invasive imaging modality measuring kidney perfusion, which may be an earlier marker of kidney injury. The generation of wash-in rate, area under the curve, and time-to-peak intensity values will lead to quantitative measurements of kidney function. We are currently working to determine the diagnostic accuracy of these metrics.

T2 Relaxation Times of Different Tissues as Measured by MRI

FR-PO989

Portable Magnetic Resonance Sensor to Detect Volume Changes
Lina A. Colucci,4 Kristin M. Corapi,2 Xavier F. Parada,2 Herbert Y. Lin,3 Michael J. Cima,1 MIT, Cambridge, MA; 3 Massachusetts General Hospital, Boston, MA; 4 Massachusetts General Hospital/Harvard Medical School, Boston, MA; 1 Massachusetts Institute of Technology, Cambridge, MA.

Background: Magnetic resonance technology provides information about the quantity, volume, and motion of water. In this study, we used portable, non-invasive MR sensors to monitor water movement in healthy controls and hemodialysis (HD) patients.

Methods: Adult, male HD patients and controls were enrolled. A custom, single-sided MR sensor developed by the Cima Lab at MIT was used to collect data from the upper calf of HD patients before and after dialysis. Controls had data collected before and after 4 hours of bedrest. The MR sensor collected T2 relaxation time measurements of a cubic centimeter voxel that included subcutaneous tissue and muscle. The T2 relaxation time measurements were analyzed with an inverse Laplace transformation to generate a relaxogram. The individual relaxograms were averaged together in each group.

Results: Demographics are shown in table 1. Free fluids are associated with long T2 relaxation times whereas bound hydrogen in connective tissues are associated with short T2 relaxation times. We observe that controls have nearly identical relaxograms at 0 and 4 hours of bedrest and that the relaxogram of the HD patients becomes comparable to controls (Figure 1a-d).

Conclusions: Portable MR sensors may quantify fluid overload in HD patients non-invasively. Further study is necessary to understand the sensitivity of these sensors to fluid shifts during HD and develop an absolute scale that relates relaxation time measurements to fluid overload.

Funding: Private Foundation Support

FR-PO988

Effect of Hemodialysis on T2 Relaxation Times in Body Tissues
Kristin M. Corapi,2 Lina A. Colucci,4 Xavier F. Parada,2 Herbert Y. Lin,3 Michael J. Cima,1 MIT, Cambridge, MA; 3 Massachusetts General Hospital, Boston, MA; 1 Massachusetts General Hospital/Harvard Medical School, Boston, MA; 4 Massachusetts Institute of Technology, Cambridge, MA.

Background: Quantitative magnetic resonance (qMRI) can inform about the water content of different tissues. In this study we performed qMRI of the calf, pre and post-HD, to detect fluid changes in muscle and subcutaneous (SC) tissues.

Methods: Adult, male HD patients and healthy controls were enrolled. HD patients underwent qMRI before and after HD while controls underwent qMRI before and after 4 hours of bedrest. MRI scans were done on a 1.5T Siemens MRI Scanner using a knee coil. Quantitative T2 relaxation maps of the upper calf were generated using a spin echo sequences with 32 echoes, TR 3,300ms, TE 8ms, and 4 slices of 5mm thickness. Regions of interest (ROIs) were manually drawn. Histograms of the T2 relaxation values in those ROIs were generated from the pre and post scans.

Results: Demographics are shown in table 1. HD patients have longer T2 relaxation times in both the muscle and SC tissue (figure 1a and 1b). We also observed a statistically significant (p=0.01) change in the T2 relaxation time for muscle, but not SC tissue (p=0.45), after treatment with hemodialysis (figure 1c and 1d).

Conclusions: Our results suggest that there is a larger change in relaxation time in muscle than in SC tissue during hemodialysis. This suggests more water movement from the muscle compartment than the SC tissue. Devices to better understand the kinetics of fluid shifts during HD may help alter prescriptions and mitigate symptoms.

Funding: Private Foundation Support

Demographics of participants

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>HD patients (n=4)</th>
<th>Healthy Controls (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>50.6 (9.9)</td>
<td>55.3 (5.9)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.4 (1.1)</td>
<td>25.0 (5.3)</td>
</tr>
<tr>
<td>Fluid status (mL)</td>
<td>2725 (504)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
using HIF-1α imaging tracer in the kidney compared to an impairment model. Furthermore, comparison with existing hypoxic imaging tracer, FR-PO990, was in good agreement, it was confirmed that FMISO, was also conducted. It is reported that hypoxia is important as a final common pathway in current in vitro diagnosis. We have investigated the basic properties of a new intratumoral hypoxic imaging agent 1-(2,2-Dihydroxymethyl-3-Fluoropropyl) Azomycin (18F) DiFA, the uptake in the kidney cortex was presented hypoxia of the renal cortex portion (Figure.1). These analysis results were shown in the following table. Since the localization of 18FDiFA, the uptake in the kidney cortex exhibited a size of approximately 400 nm and a negative surface charge. In vivo fluorescence imaging of mice determined the extent of renal localization via varying administration routes and doses. We used intravitral and ex vivo fluorescence confocal microscopy to determine tissue-level distribution of MNPs. Finally, we performed toxicity experiments in mice via histology, blood counts, and renal biochemical panels to ascertain the safety of the particles up to one month in mice. We synthesized MNPs from a biocompatible polymer (PLGA-PEG) to encapsulate a fluorescent dye for biodistribution and toxicology studies. Particles exhibited a size of approximately 400 nm and a negative surface charge. In vivo fluorescence imaging of mice determined the extent of renal localization via varying administration routes and doses. We used intravitral and ex vivo fluorescence confocal microscopy to determine tissue-level distribution of MNPs. Finally, we performed toxicity experiments in mice via histology, blood counts, and renal biochemical panels to ascertain the safety of the particles up to one month in mice. Results: We found that via intravenous administration, MNPs selectively localize to the kidneys up to 25-fold more than any other organ, uniquely selective among drug carrier systems. Within the kidneys, the localization was primarily to the proximal tubular epithelial cells, which is also novel to this system. Further, we found that these particles degrade and release their payload over weeks while they cause no renal or systemic toxicity.

Conclusions: Together, these results portend the pre-clinical development of therapeutic nanoparticles that are highly selective, safe, and provide long-term drug release with a single intravenous dose to treat renal diseases such as AKI and CKD.

FR-PO991 Mesoscale Nanoparticles Selectively and Safely Target Renal Proximal Tubules Ryan M. Williams,1 Janki Shah,1 Xi Chen,1,2 Edgar A. Jaines,1,2 Daniel A. Heller,1,2 1Memorial Sloan Kettering Cancer Center, New York, NY; 2Well Cornell Medical College, New York, NY.

Background: Acute kidney injury accounts for 1% of hospital admissions in the US and over 20 million US adults (~11%) have chronic kidney disease. To address this problem, we developed mesoscale nanoparticles (MNPs) to selectively deliver therapies to the renal proximal tubules.

Methods: We synthesized MNPs from a biocompatible polymer (PLGA-PEG) to encapsulate a fluorescent dye for biodistribution and toxicology studies. Particles exhibited a size of approximately 400 nm and a negative surface charge. In vivo fluorescence imaging of mice determined the extent of renal localization via varying administration routes and doses. We used intravitral and ex vivo fluorescence confocal microscopy to determine tissue-level distribution of MNPs. Finally, we performed toxicity experiments in mice via histology, blood counts, and renal biochemical panels to ascertain the safety of the particles up to one month in mice.

Results: We found that via intravenous administration, MNPs selectively localize to the kidneys up to 25-fold more than any other organ, uniquely selective among drug carrier systems. Within the kidneys, the localization was primarily to the proximal tubular epithelial cells, which is also novel to this system. Further, we found that these particles degrade and release their payload over weeks while they cause no renal or systemic toxicity.

Conclusions: Together, these results portend the pre-clinical development of therapeutic nanoparticles that are highly selective, safe, and provide long-term drug release with a single intravenous dose to treat renal diseases such as AKI and CKD.

FR-PO992 3-D Kidney-on-Chip Platform for Quantitative Screening of Podocyte Structural Integrity Smiti Bhattacharya,1,2 Amit Ron,1 Rhodora C. Calizo,2 Robert Wiener,1 John C. He,1 Ravil Yenigar,1 James C. Hone,2 Evren U. Azeloglu,3 1Columbia University, New York, NY; 2Columbia University, New York, NY; 3Icahn School of Medicine at Mount Sinai, New York, NY; 4Mount Sinai School of Medicine, New York, NY; 5Department of Pharmacological Sciences, Ichan School Of Medicine at Mount Sinai, New York, NY.

Background: Podocytes have an intricate in vivo morphology that is critical for their physiological function. Under disease conditions or upon isolation and culture, podocytes dedifferentiate and lose their specialized morphology, which prevents the use of primary or immortalized podocyte lines as translatable in vitro models of chronic kidney disease. In order to systematically study podocyte mechanobiology and drug response, we developed an in vitro culture system that utilizes microfabricated 3-D biopos to mechanically induce formation of fine peripheral processes in podocytes.

Methods: We microfabricated 3-D biopos using photolithography. We developed biopos of varying size formats from standard 96-well plates to 25-mm coverslips. Immortalized human podocytes were plated on 3-D biopos and differentiated for five days at 37 degrees Centigrade. Transcriptomic expression of differentiation markers was quantified using RT-PCR. Spatial localization and protein expression were quantified using immunochemistry. Spatial biomechanics were quantified using atomic force microscope elastography.

Results: Podocytes in 3-D biopos displayed significant upregulation of a wide range of genes associated with the differentiated phenotype. The peripheral processes were selectively enriched for slit diaphragm components nephrin, podocin and nep11 as well as crosstalken actin bundles. Micropatterned podocytes exhibited heterogeneous biomechanical properties with significantly increased elastic modulus in peripheral processes. This spatial phenotype was lost when cells were treated with known nephrotoxic drugs or inhibitors of cytoskeletal integrity. When we looked at phenotypic signatures of protein localization, focal adhesion maturation and cytoskeletal integrity,
podocytes in bioships showed reduced cell-to-cell variability and high reproducibility compared to mouse unoccupied and glass surfaces.

Conclusions: We developed a 3-D-disk kidney-on-chip system that provides a quantitative, high-throughput in vitro platform for studying podocyte morphology, biomechanics and drug response with high reproducibility.

Funding: NIDDK Support, Private Foundation Support

FR-PO993

Biomimetic Microenvironment Promotes In Vivo-Like Phenotype of Conditionally Immortalized Podocytes Matthew Ishahuk, Ellery Jones, Alessia Fornoni, Ashutosh Agarwal. University of Miami, Miami, FL.

Background: Microenvironmental cues are integral in providing signals that modulate podocyte development and function. However, standard culture conditions fail to recapitulate the chemical, physical, and architectural cues presented by the glomerular basement membrane (GBM). We report the effect of an engineered GBM-mimic hydrogel on conditionally immortalized human podocyte cultures.

Methods: A hydrogel was developed through the enzymatic crosslinking of denatured collagen to serve as a GBM-mimic. 3D grooves were microfabricated into the surface of the biomimetic hydrogel. Mechanical properties of the GBM-mimic hydrogel were characterized using a rheometer fitted with a metal parallel plate in oscillation mode. Conditionally immortalized human podocytes were cultured on various substrates in permissive conditions. Once cells reached ~90% confluence, they were moved to non-permissive conditions and cultured for 14 days to allow for differentiation. Phenotypic features were assessed by fluorescent imaging and scanning electron microscopy (SEM).

Results: A GBM-mimic hydrogel that recapitulates the protein composition, mechanical properties, and 3D surface topography of the GBM was successfully fabricated. The stiffness of the hydrogel (E=5.4±0.6 kPa) was much closer to the physiological stiffness of the glomerulus than that of other cell culture substrates (Fig 1A). SEM revealed the formation of processes branching from the main cell body of podocytes grown on the GBM-mimic hydrogels (Fig 1B).

Conclusions: These results demonstrate that microenvironmental cues induce in vivo-like podocyte morphology. Current studies are focused on incorporating additional GBM components (e.g. laminin) and dynamic physiological phenomenon (e.g. fluid flow, pressure differential, and protein gradient). Ultimately, an integrated platform that maintains and measures long term glomerular filtration will be developed to serve as a powerful addition to the toolkit for studying kidney disease and developing therapeutics.

Funding: NIDDK Support, Private Foundation Support

FR-PO994

Multiscale Mechanical Properties of Glycated Kidney Extracellular Matrix Nicholas J. Ferrell,1 Sarah Dillender,1 Rishabh Agarwal,1,2 Minhal H. Abidi,1 Gwyneth D. Walker.1 Vanderbilt University Medical Center, Nashville, TN; 2University of Illinois at Chicago, Lisle, IL.

Background: Non-enzymatic glycation of the extracellular matrix (ECM) contributes to diabetic nephropathy. A subset of advanced glycation end-products (AGEs) crosslink GBM components (e.g. laminin) and dynamic physiological phenomenon (e.g. fluid flow, pressure differential, and protein gradient). Ultimately, an integrated platform that maintains and measures long term glomerular filtration will be developed to serve as a powerful addition to the toolkit for studying kidney disease and developing therapeutics.

Methods: Cortical and glomerular ECM were isolated from porcine kidney cortex by gross dissection and differential sieving, respectively. Mouse tubules were isolated from wild type mouse kidneys by microdissection. ECM was decellularized and evaluated by histology and immunostaining to evaluate the effects of decellularization on ECM structure. ECM was glycated by incubation in glucose or ribose (0-500 mM) for 30 days. Following glycation, ECM was subjected to either compressive or tensile mechanical testing using custom microscale measurement techniques (for tubules and glomeruli) or commercial testing techniques (for cortical matrix).

Results: Histological examination and immunostaining for ECM proteins (collagen IV and laminin) showed that structural proteins were retained in the ECM and the matrix retained its three dimensional structure following decellularization. Biomechanical testing showed that glycation increased ECM elastic modulus (stiffness) following exposure to both glucose and ribose at concentrations >5 mM. This effect was more pronounced for ribose given its higher reactivity relative to glucose. The origin of the ECM (cortical, glomerular, or tubular) and the method of applied stress (tension or compression) had a significant effect on the measured stiffness. This variability is likely due structural differences between the matrix components and anisotropy in the tensile versus compressive mechanical properties.

Conclusions: These data suggest a potential role for ECM stiffening in progression of diabetic kidney disease. Care should be taken in interpretation of the measured elastic modulus depending on the origin of the matrix and the method of characterizing the ECM stiffness.

Funding: NIDDK Support

FR-PO995

Genomic Analysis of Primary Human Kidney Podocytes Reveals Numerous Differences from Widely Used Podocyte Cell Lines Karen B. Sieber1, Shreeram Akillesh,2,1 GlaxoSmithKline, King of Prussia, PA; 2University of Washington, Seattle, WA.

Background: Kidney disease is a major and increasing burden on society, affecting ~10% of adults worldwide and causing increased risk of all-cause mortality. The glomerular podocyte is an important cell type with limited proliferative/regenerative potential that is the target of many proteinuric kidney diseases. Despite extensive cell biological characterization, very few studies have focused on characterizing the podocyte-specific epigenetic architecture and transcriptome. Such studies promise to shed light on the mechanisms of genome regulation in this important cell type and to calibrate and improve commonly used and emerging (e.g. iPSC-derived) podocyte cell culture systems.

Methods: We generated high resolution chromatin accessibility (DNase-seq) and gene expression (RNA-seq) data for primary cultures of human podocytes (n=4), and compared them to similar datasets generated from a widely used conditionally immortalized human podocyte cell line cultured under growth-permissive and differentiation-inducing conditions.

Results: Initial transcriptomic analyses revealed that nearly 2000 genes are differentially expressed between the primary podocytes and a widely-used podocyte cell line. Of these genes, more than 100 transcription factors are differentially expressed; notably, primary podocytes retain strong expression of the lineage-defining transcription factor WT1, in contrast to the podocyte cell line which has weak expression of this gene. Many of the other differentially expressed transcription factors have not been specifically studied in podocytes. To understand their functional consequence, we are analyzing recently generated chromatin accessibility data to elucidate the transcription factor regulatory networks that drive the unique podocyte phenotype.

Conclusions: Compared to primary podocytes, these findings indicate widespread genome regulatory differences in the conditionally immortalized podocyte cell lines and suggest caution in their use. Ongoing studies are focusing on the impact of these differentially expressed transcription factors on the unique chromatin accessibility landscape of primary podocytes.

Funding: NIDDK Support

FR-PO996

Targeting Renal Fibrosis Using Self-Assembled Nanoparticles Joan Li, Justin Cooper-White,1 The University of Queensland, Brisbane, QLD, Australia; 2Biomedical Manufacturing, Manufacturing Flagship, CSIRO, Melbourne, VIC, Australia.

Background: MicroRNAs (miRNAs) are emerging as potential therapeutics for Chronic Kidney Disease (CKD) to reduce fibrosis, and myofibroblast proliferation. However, the lack of targeted delivery of miRNAs with sustained expression or sufficient on-target effects are major challenges in translating miRNA therapy to treat CKD. We have developed a novel self-assembled nanoparticle (SAnP) delivery system that, when functionalised with a specific cell-targeting ligand, is recognised by both interstitial fibroblasts and injured epithelial cells within the kidney, enabling cell-specific delivery of miRNA via receptor-mediated uptake.

Methods: In vitro epithelial-to-mesenchymal transition (EMT) model was induced in cultured MDCK cells with TGF-β (10 ng/mL) and treated with or without miR-29 (1 nM) for 72 hours. Renal fibrosis model was created using F344-Nr/o Rats bred 6-8 weeks, subjected to Unilateral Ureteral Obstruction (UUO). The miR-29 mimic (0.1 mg/kg), either packaged into the SAnP system targeting receptor “X” or as “naked” microRNA, was directly delivered into the renal parenchyma of the UUO model, at the time of the obstruction. Mice were euthanized 7 days after UUO. Kidneys were collected and processed for histology analysis.

Results: To test the specificity of our SAnP delivery system, we packaged Cy3-labelled miR-29 into the SAnP and infected cells expressing receptor “X”: MDCK cells. Uptake of Cy-3 was only detected in cells transfected with SAnP-Cy3-miR (97% vs 0% for Cy-3) with miR-29, subjected to Unilateral Ureteral Obstruction (UUO). The miR-29 mimic (0.1 mg/kg), either packaged into the SAnP system targeting receptor “X” or as “naked” microRNA, was directly delivered into the renal parenchyma of the UUO model, at the time of the obstruction. Mice were euthanized 7 days after UUO. Kidneys were collected and processed for histology analysis.

Conclusions: Our preliminary data demonstrate that whilst miR-29 alone can inhibit the EMT model in vitro, “naked” miR-29 had no effect in vivo. Our SAnP system however could affect cell-specific targeted delivery of miR-29, significantly reducing tubular dilatation, interstitial infiltration and collagen deposition in the UUO model.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Effects of Nitric Oxide Releasing Bionanomatrix Gel on Reducing Neointimal Hyperplasia and Inflammation

Background: Vascular access is the lifeline for hemodialysis patients. An arteriovenous fistula (AVF) is the preferred type of vascular access. However, neointimal hyperplasia (NIH) formation and poor vascular remodeling. The aims of this study are to evaluate oxide (NO) therapy administered at the time of AVF creation can inhibit venous NIH formation and mitigate local inflammation following AVF creation.

Results: A total of 8 patients were identified who suffered severe symptoms of ANS dysfunction including signs of orthostatic intolerance and syncope in all, and significant gastrointestinal symptoms in 7 that began concurrently with adrenarcheal failure. Symptoms of ANS dysfunction occurred 1 - 3 weeks post-transplant. Symptoms present post-transplant included lower blood pressure, hypoalbuminemia, anemia requiring transfusion in 5 of 8 patients. Paraneoplastic autoimmune panel was drawn in 4 patients and abnormal in 3. Complications of autonomic failure in these patients resulted in prolonged and recurrent hospitalizations.

Conclusion: Autonomic testing confirmed the presence of significant autonomic neuropathy in those tested, and autonomicides associated with autoimmune autonomic neuropathy were present in 3 of 4 patients tested, suggesting a potential autoimmune cause. Ultimately, the autonomic failure resolved in all patients with established long-term follow-up.

Methods: All experiments were performed using male rats, ten groups of animals were assessed [N=5-6]: 1) Syngeneically (Lewis Brown Norway F1 to Lewis Brown Norway F1) and allogeneically (Lewis Brown Norway F1 to Lewis Brown Norway F1) transplanted rats without immunosuppression, as well as allogeneically transplanted rats receiving either standard or modified prednisolone at two different concentrations (4mg/kg/12h or 16mg/kg/12h). Immunosuppressive treatment was either preventive (continuous treatment until the end of the experiment 4 days post surgery; six groups) or therapeutic (started 4 days after surgery and maintained for 3 days until day 7 post surgery; 4 groups, no low dose treatment). Treatment efficiency was evaluated by FDG-PET positron emission tomography in the preventive experimental setting 4 days post surgery, as well as on day 4 (baseline), day 5 and day 7 post surgery in the therapeutic setting. Moreover, histological analyses were performed and blood glucose levels were measured to assess systemic effects.

Conclusion: High dosage treatment with normal prednisolone significantly increased renal FDG-PET accumulation and histological signs of rejection both in the preventive and the
therapeutic setting, low dose treatment had no effect. In comparison, animals treated
with modified prednisolone did not result in elevated blood glucose levels, contrary to normal prednisolone.

Conclusions: Immunosuppressive treatment with the modified, kidney specific prednisolone proved to be as least as effective as normal prednisolone and may even outperform the latter. In the case of renal transplantations, organ-specific immunosuppression is possible.

FR-PO1002

In Proximal Tubular Cells, Cyclosporine Triggers Actin Reorganization and MRTF-SRF Inhibition through Changes in Collin Oligomerization and Activity Bastien Bruat,1 Pierre Marquet,1 Marie Essig.1 CHU Limoges, Limoges, France; INSEER UM UBS, Limoges University, Limoges, France.

Background: Calcineurin Inhibitors, Cyclosporine A (CsA) and Tacrolimus, are the keystones of immunosuppressive regimens in solid organ transplantation. However, they induce a nephrotoxicity whose mechanisms remain widely elusive. We have previously shown that CsA affect actin organization in proximal tubular cells. Here, we explored the intracellular pathways leading to this actin reorganization and its downstream consequences.

Methods: Porcine proximal tubular LLC PK-1 cells were exposed for 24 hours to CsA (5umM), and S3R (10umM) a specific inhibitor of calcineurin phosphorylation. LLC PK-1 proteome was analyzed with iTRAQ shotgun proteomics by nano-LC-TOF tandem mass spectrometry. The actin cytoskeleton was analyzed by TRITC-phalloidin labeling and F-actin. Collin oligomerization state was investigated by Western blot in non-reducing conditions after formaldehyde cross-linking Na/K-ATPase activity was quantified by colorimetric assay of inorganic phosphate. Serum response factor (SRF) activity was assessed by luciferase gene reporter assay.

Results: CsA induced a decrease in perinmembranous branched F-actin meshwork, and a significant decrease in Factin fluorescence positive area, (-3.3%, p < 0.0001). iTRAQ analysis showed that CsA induced a decrease in F-Actin/G-Actin ratio and a decrease in G-actin/actin ratio resulting from a global actin overexpression. Furthermore, CsA increased a 20% shift from tetramer to dimer’s forms of collin. These modifications of F-actin/G-actin ratio and collin oligomerization were associated with an inhibition of SRF activity (~56% of control activity). CsA induced a 21% inhibition of the Na+/KATPase activity. A decrease in Na/KATPase activity has been previously demonstrated to activate collin. The collin inhibitor S3-R, which has no significant impact on F-Actin/G-Actin ratio or SRF blocked CsA effects on actin organization and SRF activity.

Conclusions: Our results suggest that CsA deeply affects the actin cytoskeleton of proximal tubular cells through the decrease in the tetrameric, polymerized form of collin. This effect favored the depolymerization activity of collin leading to a decrease in branched actin microfilament. This reorganization of actin cytoskeleton leads to G-Actin increase and SRF inhibition, which may trigger tubular atrophy, one of the typical lesions of CsA toxicity.

FR-PO1003

Ginseng Extract Reduces Tacrolimus-Induced Oxidative Stress by Modulating Autophagy in Pancreatic Beta Cell Sun Woo Lim,1 Yoo-Jin Shin,2 Kang Luo,3 Chul Woo Yang.1,3 Seoul St. Mary’s Hospital, Seoul, Republic of Korea; 2The Catholic University of Korea, Seoul, Korea, Seoul, Republic of Korea.

Background: Growing evidence suggests that regulation of autophagy may be an effective approach to protect beta cells against various extra-intraacellular stimuli. We previously demonstrated that long-term treatment of calcineurin inhibitor causes excessive autophagosome burden and impaired autophagy clearance in pancreatic beta cells. This study investigated the effect of Korean red ginseng extract on autophagy modulation focused on oxidative stress.

Methods: The rat islets in cell line INS-1 was treated with Tac (0.4 mg/kg) and KRGE (100 mg/ml) with or without 3-methyladenine (3-MA, 10 mM) or bafilomycine A1 (BA, 2mM) for 6h. Mice were treated with Tac (1.5 mg/kg, subcutaneously) and KRGE (0.4 g/kg, oral gavage) for 4 weeks. The effect of KRGE on Tac-induced diabetes was evaluated by assessing intraperitoneal glucose tolerance test, plasma insulin level, beta cell mass, and atherosclerotic plaque formation. The effect of KRGE on Tac-induced diabetes was evaluated by measuring either microtubule-associated protein 1 light chain 3 beta expression, the number of autophagic vacuoles, and lysosome function of oxygen consumption and mitochondrial membrane potential.

Results: In mice with Tac-induced diabetes mellitus, KRGE improved islet dysfunction, and decreased oxidative stress and autophagic vacuoles. In vitro study, KRGE decreased autophagosome formation and improved lysosomal degradation, accompanied by improved beta cell viability and insulin secretion. Addition 3-methyladenine (3-MA), an inhibitor of autophagosome, to KRGE further improved cell viability and insulin secretion, and bafilomycine A (BA), an inhibitor of lysosomal function, reduced those effects of KRGE. At subcellular level, Tac caused mitochondrial dysfunction (impaired mitochondrial oxygen consumption, ATP production, and increased reactive oxygen species production). But, KRGE improved these parameters. The effect of KRGE on the mitochondrial function enhanced by 3-MA but decreased by BA, suggesting causal relationship between KRGE effect and autophagy modulation in Tac-induced mitochondrial dysfunction.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
active caspase-3 and decreased antiapoptotic Bcl-2 expression by TAC was reversed with cilastatin treatment. Cilastatin has anti-oxidative and anti-apoptotic properties and this may be responsible for protection of TAC-induced nophrotoxicity.

FR-PO1006

Effect of Conversion to Belatacept on Tacrolimus-Induced Diabetes Mellitus in Rats Long Jin. The First Affiliated Hospital of Dalian Medical University, Dalian, China.

Background: Belatacept is a promising immunosuppressant for replacing calcineurin inhibitors (CNIs). However, its effect on CNIs-induced diabetes mellitus (DM) is not adequately studied. Therefore, we tested the effect of conversion to belatacept on tacrolimus-induced DM.

Methods: Two separate experiments performed. The first experiment was conducted to determine diabetogenicity of belatacept. We administered five doses of belatacept via tail vein injection at the weekly basis for four weeks. The second experiment was conversion study. After inducing tacrolimus-induced DM with three weeks treatment with tacrolimus (TAC), TAC was converted to belatacept for three additional weeks. The effect of belatacept on TAC-induced pancreatic islet dysfunction was evaluated. The influence of oxidative stress was evaluated by measuring markers of oxidative stress (8-OHdG and antioxidant enzyme marker of MsSOD) in pancreas tissues. The effect of conversion to belatacept on macrophage infiltration and apoptosis was detected by ED-1 and caspase-3. We also measured cell viability AO/PI staining in isolated rat islets. Finally, the direct effect of belatacept on TAC-induced ROS production and cell viability in vitro were investigated.

Results: The first experiment showed that treatment with belatacept showed similar blood glucose level compared with VH group. However, there was no difference between the other groups and time course. From the first study, we found that 1 and 2 mg/kg of belatacept have a clinically relevant therapeutic level. As expected, conversion from TAC to belatacept significantly improved TAC-induced pancreatic β-cells dysfunction compared with the TAC and TAC withdrawal groups. TAC treatment increased the level of 8-OHdG and reduced the level of MnSOD, and conversion could recover this effect. Conversion to belatacept significantly decreased the level of ED-1 and caspase-3 compared with that in the TAC and TAC withdrawal groups. AO/PI staining showed that conversion to belatacept effectively decreased TAC-induced islet cell death. In vitro study revealed that belatacept treatment significantly decreased ROS production and cell viability compared with that reported with TAC alone.

Conclusions: Our study indicated that conversion from TAC to belatacept is effective in improving TAC-induced DM, and belatacept has a protective effect against TAC-induced pancreatic islet injury.

FR-PO1007

Insulin Resistance Promoting the Progression of Chronic Renal Allograft Dysfunction via the ERK1/2-GSK3β-NF-κB Signaling Pathway Qin Zhou, 1 Zhihong Zhao, 1 Hequn Zou, 2 The Third Affiliated Hospital of Southern Medical University, Guangzhou, China; 2 The Third Affiliated Hospital of Southern Medical University, Guangzhou, China.

Background: Several studies had reported that insulin resistance (IR) was an important noninmunological risk factors for chronic renal allograft dysfunction (CRAD). However, the pathogenesis of IR-mediated CRAD is still unclear. The aim of this study is to investigate the role of the insulin resistance on ERK1/2-GSK3β-NF-κB signaling pathway in renal transplantation rats with insulin resistance.

Methods: The rats in CRAD group received classical orthotopic F344-Lewis kidney transplantation and then fed with normal diet. The rats in CRAD+IR group administrated with belatacept (1 mg/kg/week, tail vein injection) based on above CRAD+IR model. The controls were transplanted rats and then fed with normal diet. The rats in CRAD+IR group administrated with belatacept (1 mg/kg/week, tail vein injection) based on above CRAD+IR model. The controls were transplanted rats and then fed with normal diet. The rats in CRAD+IR group administrated with belatacept (1 mg/kg/week, tail vein injection) based on above CRAD+IR model. The controls were transplanted rats and then fed with normal diet.

Conclusions: everolimus showed similar effect of belatacept on the tacrolimus concentration in improving TAC-induced DM, and belatacept has a protective effect against TAC-induced pancreatic islet injury.

FR-PO1008

Everolimus Has Effect on the Tacrolimus Concentration within the Renal Proximal Tubular Cells in Dose Dependent Manners Haewon Lee, 1 Yang Wook Kim, 1 Bongsoo Park, 1 Sihyung Park, 1 Yoo jin Lee, 1 Seok ju Park, 2 Sang Youb Han. 2 Haemundae Paik Hospital, inje university, Pusan, Republic of Korea; 2 Inje University, Busan, Republic of Korea.

Background: It was reported that everolimus in combination with varying levels of Tacrolimus is efficacious and associated with good kidney function. We aimed to investigate the effect of everolimus on the tacrolimus intracellular concentration in the kidney cells when it is used concommitantly.

Methods: HK-2 Cells immortalized Human Renal Proximal Tubule Cells were treated with tacrolimus at the dose of 5 ng/ml, 10 ng/ml and 15 ng/ml. After 30 minutes, we treated with everolimus at the dose of 3 ng/ml, 9 ng/ml and 15 ng/ml, additionally, in the absence or presence of tacrolimus for 1 hour. We measured the intracellular tacrolimus concentrations using LC/MSMS.

Results: Tacrolimus intracellular accumulation was significantly decreased by everolimus in a concentration dependent manner. At the concomitant treatment with 5 ng/ml of tacrolimus and everolimus (3 ng/ml, 9 ng/ml, 15 ng/ml), the intracellular tacrolimus concentrations was significantly decreased compared with absence of everolimus. The intracellular tacrolimus was decreased by everolimus showing 0.348±0.034 ng/ml/1x10 6cells, 0.279±0.034 ng/ml/1x10 6cells, 0.232±0.025 ng/ml/1x10 6cells vs 0.643±0.087 ng/ml/1x10 6cells (P=0.01), respectively. At the concomitant treatment with 10 ng/ml of tacrolimus and everolimus (3 ng/ml, 9 ng/ml, 15 ng/ml), the intracellular tacrolimus concentrations was significantly decreased compared with absence of everolimus. The intracellular tacrolimus was decreased by everolimus showing 0.103±0.013 ng/ml/1x10 6cells, 0.096±0.013 ng/ml/1x10 6cells, 0.0579±0.021 ng/ml/1x10 6cells, vs 0.822±0.059 ng/ml/1x10 6cells (P=0.038), respectively. The effect of everolimus on intracellular tacrolimus concentration decreased as the dose of tacrolimus increased. At the concomitant treatment with 15 ng/ml of tacrolimus and everolimus (3 ng/ml, 9 ng/ml, 15 ng/ml), the intracellular tacrolimus concentrations was significantly decreased compared with absence of everolimus. The intracellular tacrolimus was decreased by everolimus showing 0.654±0.043 ng/ml/1x10 6cells, 0.635±0.096 ng/ml/1x10 6cells, 0.579±0.251 ng/ml/1x10 6cells, vs 8.022±0.069 ng/ml/1x10 6cells (P=0.043), respectively.

Conclusions: We suggest that everolimus has effect on the tacrolimus concentration within the kidney proximal tubular cells in dose dependent manners.
A Role for IgE-Mediated Immune Response in the Pathogenesis of Chronic Antibody-Mediated Rejection (CAMR)  

FR-PO1010  
Lewis) with intermittent cyclosporine A administration (CyA 5mg/KG) on every parameters, including urinary protein excretion and serum creatinine concentration were assessed. Flow cytometry was used to assess changes in leukocyte (CD11b/c, CD3, CD4, CD8) and complement-dependent cytotoxicity (CDC) assay. DSA IgG subclasses were also assessed. The graft distribution of leukocyte and B cell subsets was assessed by immunohistochemistry. Results: We observed a significant increase in tubular and glomerular deposition of IgE in CAMR patients (1876±197 pixels/area) and SLE (1678±178 pixels/area) compared with IFTA (379a±7 pixels/area) and CTRL (3535±93 pixels/area) (p<0.001). Interestingly, the staining for triptase, a marker of mast cells, and CD203c; a specific marker of basophil activation, revealed a significant infiltration of both cell types IgE in CAMR grafts (tripartes/cells/IEdL: CAMR 15±5 vs. LES 3±0.4 and CTRL 2±0.4, p=0.02). We also observed that the absolute number of circulating basophils was significantly increased in Graft: (48±3±ai) compared to CTRL (20±1±ai) and IFTA (15±5±ai, p<0.02). MxA serum levels were significantly higher in CAMR compared to CTRL (23±2±2±6 vs 4±2±3±7 ng/ml, p<0.002) and directly associated with the extent of IgE deposits (r=0.347, p<0.01).  

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO1014

Adenosine Pathway Implication in M2 Macrophage Phenotype Switch in Deceased Renal Donors
Montserrat M. Diaz Encarnacion,1,2 Elena Guillaumondez,1 L. Guiardo,1 Jose Ballarin.1 Fundación Puigvert, Barcelona, Spain; 2Fundación Puigvert, Barcelona, Spain; Fundación Puigvert, Barcelona, Spain; None, Barcelona, Spain; Medicine, Autonoma de Barcelona University, Barcelona, Spain.

Background: A recent publication from our group shows that kidney transplantation there is an activation and infiltration of immune cells in grafts from deceased donors. Adenosine levels increase during inflammation and hypoxia, principally through the hydrolysis of ATP, which is released after cell damage/death. This adenosine increment could initiate a macrophage phenotype shift from an ATP-driven pro-inflammatory environment to an anti-inflammatory and even pro-fibrotic macrophage phenotype.

Methods: The aim of this study is to address the implication of purine membrane elements in inflammation and fibrosis driven by macrophages in renal grafts. Purinergic markers from pre-implantational renal allograft biopsies from living (LD) and deceased (DD) donors were quantified by qPCR and western-blot.

Results: Kidney samples from DD showed activation of both macrophage M1 inflammatory and M2 anti-inflammatory pathways evidenced by an increased expression of M1 and M2 markers. This result point to an early inflammatory response followed by activation of mechanisms for inflammation resolution. We found that expression of CNT2, a high-affinity Na+ dependent adenosine transporter, is decreased. This is consistent with the need to increase extracellular adenosine concentration by inhibiting its uptake, since the extracellular conversion to adenosine is also limited by the ecto-5'-nucleotidase CD73 activation of A2AR-the extracellular conversion to adenosine is also limited by the ecto-5'-nucleotidase CD73.

Conclusions: Persistent inflammation in DD and M2 macrophage activation by extracellular adenosine even before implantation would contribute to the induction of pro-fibrotic processes in grafts from DD.

FR-PO1015

Role of Ubiquitin Proteasome System during Renal Cold Storage and Transplantation

Background: We previously reported that renal cold storage (CS) leads to increased mitochondrial injury and renal damage following transplantation (Tx). However, CS induced molecular pathways responsible for worsening mitochondrial function, and renal damage following Tx are poorly understood. Alteration of Ubiquitin Proteasome System (UPS) has been reported in numerous diseases. The goal of this study was to evaluate if UPS was altered, and if this contributes to mitochondrial and renal damage after CS vs Tx.

Methods: Rat kidneys exposed to CS (18h) followed by Tx (CS/Tx) were used. Sham, autotransplant (ATx, a Tx without CS), and CS alone kidneys were used as control. The proteasomal function in the renal extracts was measured using fluorogenic peptide substrate and spectrophotometer. Mitochondrial function was assessed via high resolution respirometry.

Results: Proteasomal function (chymotrypsin-like) was compromised after CS/Tx, but not in sham, ATx, or CS alone kidneys. A selective reduction of I5 (catalytic) subunit of the proteasome was observed only after CS/Tx. None of the groups showed change in expression of the predicted molecular weight of Rp66 subunits of the proteasome. However, only CS/Tx kidneys showed an intense Rp66 reactive bands of high and low molecular weights. Co-immunoprecipitation of renal extracts with Rp66 antibody showed an association of Rp66 subunit with heat shock proteins, which was significantly altered after CS/Tx. Similarly, compromised mitochondrial function was evident after CS, which was exacerbated after CS/Tx. Proteasome inhibition of NRK cells with Bortezomib showed reduced activity for mitochondrial complexes I, II and III. Similarly, antimycin A, a mitochondrial complex III inhibitor, treatment of NRK cells showed compromised proteasomal function.

Conclusions: These data suggest, for the first time, that renal CS/Tx leads to altered expression/function of the UPS as well as its compromised association with heat shock proteins. Similarly, in vivo data suggest that the mitochondrial dysfunction precedes proteasome inactivation during CS/Tx. In vitro studies confirmed that a functional interaction exists between renal mitochondria and the UPS. New studies designed to preserve the UPS/mitochondrial function may have promising therapeutic implications for better outcomes after renal transplantation.

Funding: Other NIH Support - American Heart Association

FR-PO1016

Caspase Inhibition during Cold Storage Improves Graft Function and Histology of Transplanted Kidneys
Swati Jain, Trevor L. Nydaim, Robert J. Pfleuter, Alkesh Jani.1 UC Denver, Aurora, CO; 1University of Colorado Denver, Aurora, CO.

Background: Prolonged cold ischemia is a risk factor for delayed graft function (DGF) of kidney transplants, and is associated with caspase-3-mediated apoptotic tubular cell death. We hypothesized that treatment of a donor organ with the caspase inhibitor, QVD-OPh, prior to kidney transplantation would be associated with significantly reduced renal tubular epithelial cell (RTEC) apoptosis, histology, and improved renal function post-transplant in a mouse kidney transplant model of DGF.

Methods: For in vitro studies, mouse RTECs were incubated with either DMSO or QVD-OPh during cold storage in saline followed by rewarmin in RPMI media. For in vivo studies, donor kidneys from C57BL/6 mice were perfused with either cold saline, DMSO (vehicle), or QVD-OPh, recovered, stored in the same solution at 4°C for 60 minutes, and transplanted into syngeneic C57BL/6 recipients. RTEC apoptosis, histological changes and ccr were quantitated.

Results: Tubular cells treated with the caspase inhibitor QVD-OPh had significantly reduced capase-3 protein expression, capase-3 activity, and apoptotic cell death vs saline or DMSO (vehicle) in a dose dependent manner. Treatment of donor kidneys with QVD-OPh significantly reduced ccr, and resulted in significantly less tubular cell apoptosis, brush border injury, tubular injury, cast formation, and tubule lumen dilatation vs saline and saline treated kidneys (Table 1).

Conclusions: Treatment of RTECs and donor kidneys with Q-VD-OPh significantly reduces apoptosis, histological injury and improves renal function in a mouse model of kidney transplantation. Caspase inhibition may be a useful strategy to prevent DGF and increase the donor pool.

Funding: Veterans Affairs Support

<table>
<thead>
<tr>
<th>Caspase-3 protein</th>
<th>***</th>
<th>***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=4)</td>
<td>1.00 (1.00)</td>
<td>1.00 (1.00)</td>
</tr>
<tr>
<td>QVD-OPh (n=6)</td>
<td>0.97 (0.86)*</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Caspase-3 activity</th>
<th>0.199 ± 0.035</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=4)</td>
<td>0.199 ± 0.035</td>
</tr>
<tr>
<td>QVD-OPh (n=6)</td>
<td>0.079 (0.060)*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Apoptotic cell death</th>
<th>21.9 ± 5.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=4)</td>
<td>21.9 ± 5.7</td>
</tr>
<tr>
<td>QVD-OPh (n=6)</td>
<td>5.5 ± 0.9*</td>
</tr>
</tbody>
</table>

*p<0.05 vs. Saline & DMSO

FR-PO1017

Intensive Home Hemodialysis Survival Is Comparable to Deceased Donor Kidney Transplant
Angie G. Nishio-Lucar,1 Genevieve R. Lyons,2 Subhashis Bose,3 Robert S. Lockridge,1,5* University of Virginia HS, Charlottesville, VA; 4Lynchburg Nephrology Physicians, Lynchburg, VA.

Background: Kidney transplant (KT) is the treatment of choice for end-stage renal disease (ESRD) but, unfortunately, kidney donors are scarce. A prior Canadian study suggested intensive home hemodialysis (IHHHD) had similar survival to deceased donor (DD) KT. Herein; we compare the survival of a large cohort of IHHHD patients with kidney transplant recipients (KTR) in the same U.S. region.

Methods: We included all consecutive adult patients who received a first KT or started IHHHD in the same Virginia region between October 1997 and June 2014. We obtained data on KTR from the Scientific Registry of Transplant Recipients and data on IHHHD patients from Lynchburg Nephrology Physicians practice in Lynchburg, Virginia. We excluded recipients of en-bloc kidneys, multi-organ transplants and subsequent KT. Those receiving other home dialysis therapies, in-center hemodialysis (HD) or home HD getting < 20hrs/week or <4 sessions/week were also excluded. Kaplan-Meier method was used to estimate the overall survival (OS) among different modalities: IHHHD versus living donor (LD) and DD KT. Adjusted hazard ratios (HR) were estimated using multivariate Cox proportional hazards regression.

Results: We identified 3097 KTR and 116 IHHHD patients. Both cohorts had similar proportion of females (40.5% KTR vs 41.4% IHHHD), African Americans (48.9% vs 50.0%) and diabetics (36.5% vs 37.1%). Compared to KTR, IHHHD patients were more likely to be obese and have history of malignancy. LD KT had the highest survival feature (1). At 5 years, the survival probability in IHHHD patients was 79% (CI 0.69-0.90) compared to 84% (CI 0.82-0.86) in DD KT, however the HRs did not significantly differ (HR 1.05, CI 0.68-1.62, p=0.837) after adjusting for ESRD cause, sex, age, and peripheral vascular disease.

Conclusions: In this study, survival of IHHHD patients was not statistically different from DD KTR suggesting IHHHD could be a reasonable alternative to DD KT.
FR-PO1018

The Effect of Donor-Recipient Size Mismatch on Graft Survival Is Modified by Kidney Transplant Recipient and Donor Age

Catherine Delmaç-Frenette,1 Xun Zhang,2 Ruth Sapir-Pichhadze,3 Bethany J. Foster,2 Heloise Cardinal,3 ‘McGill University, Montreal, QC, Canada; 2McGill University Health Center, Montreal, QC, Canada; 3McGill University Health Centre, Montreal, QC, Canada; 4None, Westmount, QC, Canada; 5Centre de Recherche du CHUM, Montreal, QC, Canada

Background: Advanced donor age, recipient age and donor-recipient size mismatch are all independent risk factors for poorer kidney graft survival, but how these variables interact is unknown.

Methods: We performed a retrospective cohort study using the Scientific Registry of Transplant Recipient (SRTR). All first deceased donor kidney transplantations performed between Jan 1st 2000 and Jan 1st 2015 in recipients aged ≥40 years were included. We used a multivariable Cox proportional hazards models to assess the association between donor-recipient body surface area (BSA) ratio (a:0.9 vs. >0.9) and overall graft survival, defined as death with function, return to dialysis or retransplantation. We considered interactions between BSA ratio and each of recipient age (≥54 vs. >54 years; the median age) and donor age (≥60 vs. >60 years), as well as a 3-way interaction term of BSA ratio by recipient age and donor age.

Results: From a total of 118,101 patients, 39,330 (33.3%) experienced graft loss over a median follow-up of 4.8 years. The 3-way donor-recipient BSA ratio by donor age by recipient age interaction was statistically significant (p=0.02). Among recipients ≥54 years, a donor-recipient BSA ratio ≤ 0.9 was associated with a higher risk of graft failure when donors were younger than 60 (hazard ratio (HR): 1.11, 95% confidence interval (CI) 1.07-1.14); when the donor was older than 60, donor-recipient BSA ratio ≤ 0.9 was not associated with graft failure (HR: 0.92, 95% CI 0.81-1.04). In recipients >54 years, donor-recipient BSA ratio ≤ 0.9 was significantly associated with graft failure regardless of donor age (HR: 1.07, 95% CI 1.03-1.10 for donors ≥60 and HR: 1.09, 95% CI 1.02-1.16) for donors >60.

Conclusions: We find donor-recipient size mismatch to have a small but significant impact on graft survival in all but younger recipients of older deceased donors. We hypothesize that in the latter group, the adverse impact of donor age supersedes the effect of donor-recipient size mismatch, and a size mismatch should not be considered as adversely affect graft survival in this patient population.

FR-PO1019

Contralateral Deceased Donor Kidney Procurement Biopsy Predicts Allograft Outcomes

Syed A. Husain,1 Dustin Carpenter,1 Raphael Rosen,2 Dominic Santorioti,3 Mariana C. Chiles,2 Leigh-Anne Dale,2 Lloyd E. Ratner,2 Sumit Mohan,1 Columbia University, New York City, NY, 1Columbia University Medical Center, New York, NY; 2New York Presbyterian - Columbia, New York, NY; 3New York Presbyterian Columbia, New York, NY

Background: Deceased donor kidney (DDK) procurement biopsies are often used to assess organ quality but have limited ability to predict outcomes, likely due to sampling error. We studied whether combining bilateral kidney biopsy results improves the prediction of allograft survival.

Methods: We identified all DDKs transplanted at our center from 2005-2009 that had procurement biopsies performed. Biopsy results from these kidneys and their contralateral partners (if available) were obtained from donor charts. Histology was classified as optimal if glomerulosclerosis (GS)≤10%, interstitial fibrosis/tubular atrophy (IFTA)≤10%, and vascular disease was none/mild. We compared death-censored graft failure for kidneys based on histologic category.

Results: 256 donors had a procurement biopsy on both kidneys, among whom 80.1% had concordant bilateral histologic categorization (99 both optimal, 106 both suboptimal) (κ=0.6, p<0.001). Agreement was higher for IFTA and vascular disease (both 75.8%) than GS (58.6%). When bilateral kidney biopsy results were combined, death-censored graft failure was highest for suboptimal kidneys with suboptimal partners, lower if only one kidney in the pair had optimal histology, and lowest for optimal kidneys with optimal partners (Figure). Kidneys (16.8%) had contralateral biopsies that were discarded. Discarded contralateral kidneys were more likely to have GS<5% (58.1% vs 38.0%, p=0.02), as were their transplanted partners (60.5% vs 41.3%, p=0.02). IFTA and vascular disease were not associated with discard. Partner discard did not predict transplanted kidney outcomes beyond biopsy results.

Conclusions: Adding contralateral kidney biopsy findings to DDK procurement biopsy appears to improve predictive power. When available, contralateral kidney biopsy findings should be provided to clinicians as part of the organ offer.

FR-PO1020

Outcomes of HLA-Incompatible Living Donor Kidney Transplantation Compared to Deceased Donor Kidney Transplantation or Dialysis and HLA-Compatible Living Donor Kidney Transplantation

Tat veon Koo,1 Jung-hwa Ryu,1 Ji-Jing Yan,1 Kyoungok Min,1 Jaeseok Yang.2 Seoul National University Hospital, Seoul, Republic of Korea

Background: HLA-incompatible (HLAi) living donor (LD) kidney transplantation (KT) is one of efforts to increase opportunity for sensitized end-stage renal disease patients due to organ shortage. Recently there are controversies for outcomes of HLAi KT. US data showed better outcomes of HLAI LDKT compared to HLA-compatible(HLAc) deceased donor(D) KT or dialysis, whereas UK data demonstrated that waiting for DDKT or HLAc LDKT has good outcomes comparable to HLAI LDKT. Therefore, we tried to compare outcomes of HLAI LDKT with those of DDKT or dialysis, and HLAc LDKT in Korea

Methods: Forty-eight patients underwent HLAI LDKT after desensitization between 2006 and 2017. Indications of desensitization were positive complement-dependent cytotoxicity cross-match, positive flow-cytometric cross-match, high panel-reactive antibody tests, and positive donor-specific antibodies. We compared outcomes among HLAI LDKT patients, wait-listed patients who had continued to undergo dialysis(n=2047), patients who underwent either dialysis or DDKT (dialysis-or-transplantation group; n=2610), DDKT patients(n=563) and HLAc LDKT patients(n=654).

Results: In the HLAI LDKT group, patient survival rates were 97.8% at 1 year, 97.8% at 5 years and 97.8% at 8 years, as compared with rates of 98.4%, 96.4%, and 94.8% respectively in dialysis-group, rates of 98.3%, 97.2%, and 95.2% respectively in dialysis-or-transplantation group, rates of 99.7%, 99.4% and 98.6% respectively in DDKT group. There was no significant difference in graft survival rates after 6 months between HLAI LDKT and any other group. Patient and graft survival rate of HLAI LDKT were better than dialysis or DDKT. In safety aspects, incidence of either antibody-mediated rejection or infectious complication did not differ among the groups.

Conclusions: In conclusion, outcomes of HLAI LDKT were comparable with those of dialysis or DDKT, dialysis alone, and HLAc LDKT. Therefore, we should consider many factors such as outcomes of dialysis, mean waiting time for HLAc DDKT, donor exchange program and experience of desensitization before decision of HLAI LDKT in sensitized candidates.

FR-PO1021

Predicting Expanded Criteria Donor Transplant Outcomes

Ruth Sapir-Pichhadze,1 Jean Tchervenkov,2 Carly Rabin,3 Dana Baran,4 Justin Morein,2 Paramita Saha chaudhuri. 1McGill University, Montreal, QC, Canada; 2McGill University Health Center, Montreal, AB, Canada; 3Royal College of Surgeons in Ireland (RCSI), Montreal, QC, Canada; 4Royal Victoria Hospital, Montreal, QC, Canada

Background: Decisions on expanded criteria donor (ECD) organ utilization or discard rely primarily on selected clinical and histological features of ECD grafts. We
sought to identify which of the donor, recipient, and transplant characteristics are most predictive of long-term ECD transplant outcomes.

Methods: We conducted a retrospective cohort study in first time ECD kidney transplant recipients (KTR) transplanted between January 1, 2008 and December 31, 2014 at a Canadian Centre. The value of baseline donor (kidney donor risk index (KLDRI), eGFR, and DGF) and frozen sections of procurement biopsies, recipient (age, cause of ESRD) and transplant (HLA mismatch, pulsatile perfusion, cold ischemia time, induction therapy, maintenance immunosuppression, and delayed graft function (DGF)) characteristics in predicting all-cause graft failure, defined as return to dialysis, re-transplantation, and death with function, was determined using univariate Cox proportional hazards models. Given the small sample size, variables that were statistically significant at level $\leq 0.1$ in the univariate analysis were considered for inclusion in multivariable models. In addition to baseline characteristics, a multivariable model including time-varying post-transplant eGFR measured at 3-months intervals was also fit. For the multivariable Cox proportional hazards models, p-value $<0.05$ was considered statistically significant.

Results: A total of 163 first-time ECD KTR with a median post-transplant follow-up of 3 years were included. Of the baseline donor, recipient and transplant characteristics, recipient age, cause of ESRD, and DGF were statistically significantly associated with all-cause graft loss in univariate analyses (p-value of likelihood ratio test 0.04, 0.07, and 0.01, respectively). In the time-fixed and time-varying multivariable Cox proportional hazards models, only recipient age (hazard ratio (HR) 1.04 [95% confidence interval (CI): 1.00, 1.08]; p-value=0.06) and time-varying eGFR (HR 0.96 [95%CI: 0.94, 0.98]; p-value=0.01), respectively, were independently associated with all-cause graft loss. C-indices were 0.62 and 0.696 (SE=0.05), respectively.

Conclusions: In our study, recipient age and post-transplant eGFR were most predictive of ECD transplant outcomes. Caution should be exercised when considering organ discard based on ECD donor characteristics alone.

FR-PO1022
Inter-Correlations between Psychosocial Pre-Transplant Determinant of Post-Transplant Kidney Allograft Function

Suan P. Shih,
Beijing,
Brenner, C. Schreiber,
Flor E. Espinosa,
Ann Kathleen N. Gamilla-Crudo,
Rohan Patankar,
Omar A. Aliter,
Wayne G. Fischer,
Muhammad A. Mujtaba,
University of Texas Medical Branch, Galveston, TX.

Background: Psychosocial factors are common in patients with advanced and end stage kidney disease and they may be associated with post kidney transplant outcomes. When these patients are referred for transplant evaluation psychosocial and nutrition history is an important component of evaluation however there is lack of data on post-transplant implication of these factors. The aim of this study was to determine the correlations between pretransplant, nonclinical and psychosocial factors to post-transplant clinical outcomes.

Methods: We selected the following pre-transplant factors: gender, food stamp, marital relationship, insurance, education, Karnofsky score, history of depression, exercise, albumin level history of substance abuse, distance from transplant center. The posttransplant clinical outcomes selected were quality of kidney allograft at 6 months expressed as serum creatinine. The study involved retrospective analysis of 136 kidney transplant patients. There were 56 female patients and 75 male patients. We had 72 Hispanics (53%), 33 African Americans (24%), 22 Whites (16%), 9 Asians (7%). Patients age ranged from 25 years to 77 years. We used nominal logistic regression analysis and multinominal logistic regression analysis to identify the significant relationship between one dependent nominal variable and one or more continuous-level independent variables. A p-value of $\leq 0.05$ was considered significant.

Results: Factors associated with significantly better serum creatinine at 6 months included: Female gender (p=0.014), active pre listing clinic follow up (0.0001), compliance with dialysis (0.06), and serum albumin $\geq 3.5$ gm/dl (0.007). Patient primary insurer, family support, marital status, exercise, food stamp status, history of depression, history of substance abuse, education level, race, distance from transplant center, and retransplant status was not found to be associated with 6 months serum creatinine.

Conclusions: Pre-transplant psychosocial factors are associated with the post transplant kidney allograft function. This also shows the pretransplant psychosocial history is an integral but often ignored part of evaluation and should be stressed upon. More prospective trials are required to confirm our findings.

FR-PO1023
The Reproducibility and Prognostic Capability of Procurement Frozen Section Renal Allograft Biopsies

Columbia University, New York, NY; Columbia University New York City, NY; Columbia University Medical Center, New York, NY; New York Presbyterian - Columbia, New York, NY.

Background: Biopsies taken at the time of deceased donor kidney procurement are frequently used to assess organ quality and are cited as a leading reason for discard. However, the reproducibility and prognostic capability of these biopsies are controversial.

Methods: We compiled a retrospective, single institution, continuous cohort of all deceased donor recipients transplanted between January 2012 and March 2016 were followed up to four years were included in this study. Pre-implantation histopathological biopsies were re-evaluated per the Banff 97 classification and chronic allograft damage index (CADI) and graft function was monitored. Glomerular filtration rate (GFR) as at the last visit was categorized into a staging variable (Stage) after which multinominal logistic regression was used to determine the association between stage and the cofactors. Ordinary linear regression was also used to assess the association between GFR at last visit and the cofactors. Logistic and linear regressions were used to assess the association between Banff and CADI scores and the donor OPO.

Results: Inter-observer correlation between the two pathologists for total Banff score (ICC = 97%) and CADI score (ICC = 92%) were excellent. The presence of glomerulosclerosis (GS, -10.15) and tubular atrophy (TA, -10.39) in CADI score were found to be associated with final GFR. In addition to GS, glomerular mesangial matrix (GM) in CADI was also associated with stages of GFR. Only presence of glomerular mesangial matrix (CM) parameter in Banff score was found to be associated with stage and graft function. In separate multivariable analyses after adjusting for other significant variables, CM present and CM present were associated with chronic kidney disease stage.

Conclusions: A multiparametric approach may be developed by incorporating pre-implantation biopsy information along with important clinical variables to predict outcome.

FR-PO1024
The Deceased Donor Implantation Biopsy and Histopathological Characteristics for Predicting Graft Outcomes in Kidney Transplant Recipients

Columbia University, New York, NY.

Background: Histology in deceased donor kidneys is critical for advising transplant centers of organ quality. Although the presence of glomerulosclerosis (GS), interstitial fibrosis/tubular atrophy (IF/TA), and chronic allograft damage index (CADI) has been identified as poor predictors of graft survival, discrepancy in the correlations between pretransplant, nonclinical and psychosocial factors to post-transplant clinical outcomes. The aim of this study was to determine the correlations between pretransplant, nonclinical and psychosocial factors to post-transplant clinical outcomes.

Methods: We conducted a retrospective cohort study in first time ECD kidney transplant recipients (KTR) transplanted between January 1, 2008 and December 31, 2014 at a Canadian Centre. The value of baseline donor (kidney donor risk index (KLDRI), eGFR, and DGF) and frozen sections of procurement biopsies, recipient (age, cause of ESRD) and transplant (HLA mismatch, pulsatile perfusion, cold ischemia time, induction therapy, maintenance immunosuppression, and delayed graft function (DGF)) characteristics in predicting all-cause graft failure, defined as return to dialysis, re-transplantation, and death with function, was determined using univariate Cox proportional hazards models. Given the small sample size, variables that were statistically significant at level $\leq 0.1$ in the univariate analysis were considered for inclusion in multivariable models. In addition to baseline characteristics, a multivariable model including time-varying post-transplant eGFR measured at 3-months intervals was also fit. For the multivariable Cox proportional hazards models, p-value $<0.05$ was considered statistically significant.

Results: A total of 163 first-time ECD KTR with a median post-transplant follow-up of 3 years were included. Of the baseline donor, recipient and transplant characteristics, recipient age, cause of ESRD, and DGF were statistically significantly associated with all-cause graft loss in univariate analyses (p-value of likelihood ratio test 0.04, 0.07, and 0.01, respectively). In the time-fixed and time-varying multivariable Cox proportional hazards models, only recipient age (hazard ratio (HR) 1.04 [95% confidence interval (CI): 1.00, 1.08]; p-value=0.06) and time-varying eGFR (HR 0.96 [95%CI: 0.94, 0.98]; p-value=0.01), respectively, were independently associated with all-cause graft loss. C-indices were 0.62 and 0.696 (SE=0.05), respectively.

Conclusions: In our study, recipient age and post-transplant eGFR were most predictive of ECD transplant outcomes. Caution should be exercised when considering organ discard based on ECD donor characteristics alone.
Is There a Role for Implantation Biopsies in the Era of Kidney Donor Profile Index (KDPI)?

Background: Implantation biopsies (IBx) are commonly performed after deceased donor transplantation (DD). However, its role in the management of these grafts and the impact on outcomes are not fully described. We evaluated the role of IBx on OS and long-term graft function and their relationship with KDPI.

Methods: We analyzed all the DD performed at our center between 2007 and 2013. Grafts not eligible for IBx (e-bloc pediatric) were excluded. Multivariable analysis was used to adjust for confounding variables.

Results: Out of 885 DD performed, 477 had a IBx and 411 had not. The two groups were not different in terms of gender, age, race (donors and recipients), e-transplant, diabetes, PRA, or HLA mismatches, proportions of ECD, DCD, deaths from CVA, local procurement, pulsatile perfusion, terminal creatinine, and distribution of KDPI. There was a lower proportion of DCD in the IBx group (15 vs 21%, p<0.02) and lower mean cold ischemic time - CIT (23 vs 25h, p<0.006). The IBx group had a significantly better one year graft survival (96 vs 91%, p<0.001). By multivariable analysis IBx was associated with 60% (CI 21.9 – 72.1%, p<0.002) decreased risk of graft loss within the first year when adjusted by DCD, KDPI, and cold ischemia time. Long term graft survival was worse across strata of KDPI (p<0.006). However, there were no difference in graft survival between the IBx and no IBx groups (p=0.16), even within the strata of KDPI: <35% (p=0.7), 35 – 85% (p=1), and >85% (p=0.7). The composite chronicity score: (glomerulosclerosis-GS plus interstitial fibrosis-IF) was different across strata of KDPI (14, 44, and 66%, p<0.001). However, there were no differences in graft survival by the percentage of GS (p=0.4), IF (p=0.4), or GS-IF (p=0.08) on IBx. There was a lower incidence of delayed graft function on the IBx group (19 vs 31%, p=0.001) that persisted even after adjustment for CIT and DCD. There were differences in e-GFR at 1, 3, and 5 years across strata of KDPI. However, no differences in e-GFR were found between the IBx and no IBx groups at the same time points.

Conclusions: Implantation biopsy is independently associated with better one year graft survival. However, KDPI becomes the most important factor associated with long term graft survival. The specific management modifications based on the results of IBx should be the focus of future investigation.

Clinical Revenue Support

Histologic Findings on Time-Zero Allograft Biopsies Correlate with Kidney Donor Profile Index (KDPI) and 30-Day Serum Creatinine

Background: KDPI is used as a numerical measure of deceased donor kidney quality relative to other recovered kidneys. It uses 10 donor factors but does not consider histologic findings. Correlation of KDPI to histologic findings is lacking. In this study, we examined the correlation between KDPI and chronic changes seen in time zero biopsies. We also assess whether such histologic findings add to the predictive ability of KDPI for 30-day serum creatinine and delayed graft function.

Methods: All deceased donor kidney transplants at our institution from 07/01/2016 to 12/31/2017 that had a time-zero biopsy were included. The biopsies were graded according to Banff 2015 guidelines. Distribution of KDPI was compared by Banff scores for chronicity (ci) and acute changes (ab, ch, and ac) and chronic vascular disease (ah and cv). Linear regression was used to assess: 1) correlation between Banff scores and donor KDPI and 2) the ability of KDPI and Banff scores (either individually or together) to predict 30-day serum creatinine. Logistic regression was used to assess the ability of KDPI and/or Banff scores to predict delayed graft function.

Results: 134 recipients had a time-zero biopsy performed. There was a correlation between the following Banff scores and KDPI: ci, ch, ah, and ac (Table 1), ah score of greater or equal to 2 most closely correlated with KDPI. 30-day serum creatinine was predicted by KDPI, as well as ci, ch, and ac scores. Using KDPI with ci + cc scores resulted in the best prediction of 30-day serum creatinine, with a correlation coefficient of 0.27. There was no correlation between Banff scores and the occurrence of delayed graft function. A KDPI score of 20–85% predicted delayed graft function at an OR of 8.18 (95% CI 1.80–37.2, p-value 0.007). The incidence of delayed graft function (DGF) was significantly higher in the AKI group than in the non-AKI group (P<0.011), but not in the ECD group and the high KDPI group. The estimated glomerular filtration rate (eGFR) of the AKI group was significantly lower at 1 week, 2 weeks and 1 month after transplantation compared to the non-AKI group. After 3 months of KT, there was no significant difference in eGFR between the AKI group and non-AKI group, the ECD group and standard criteria donor group, and the high KDPI group and low KDPI group. Patient survival rate showed no significant difference between AKI, ECD, or high KDPI. Allograft survival rate showed no significant difference in the AKI, ECD, and high KDPI groups compared with the control groups. However, allograft survival rate was significantly lower only in the group with acute rejection (AR) than in the group without AR (P<0.001). In a multivariate analysis, AR was an independent risk factor for graft failure (hazard ratio 85.75, 95% confidence interval, 7.02-1047.77, P< 0.0001), but AKI, ECD, or high KDPI were not.

Conclusions: AKI of DD kidney showed significant association with increased incidence of DGF. However, KT using AKI, ECD, or high KDPI donor kidney performed similarly to the control group in terms of graft function, graft survival, and patient survival. More detailed criteria for selecting a proper DD will be needed.

Impact of the Kidney Allocation System (KAS) in Highly Sensitized Patients

Background: Highly sensitized (HS) patients, defined as a PRA of 99-100% are awarded additional priority points in the new KAS instituted December 2014. We evaluated the impact of these changes at our institution in 1 and 2 year post transplantation of HS candidates who received a transplant on or after 12/4/2014 were prospectively monitored. Treatment included induction with anti-thymocyte globulin & IV corticosteroids, maintenance with tacrolimus, mycophenolate & prednisone. Designated care providers followed the HS recipients with more intensive frequency, donor specific anti HLA antibody (DSA) & viral monitoring, implantation & 6 month surveillance biopsies. Outcomes of interest were rate of transplantation, patient & allograft survival and function, acute cellular or antibody mediated rejection (ABMR), and were compared in a matched control population in a 1:2 fashion for age, race, and time of transplant.

Results: There were 15 HS patients transplanted between 12/4/2014 to 10/5/2015. The rate of transplantation for a successful outcome that benefits a very specific subset of patients. More detailed criteria for selecting a proper DD will be needed.
FR-PO1029
Recipient Age Is Significantly Associated with Immunological and Infective Complications Post Kidney Transplantation Rachel Hung,¹ Sumoyee Basu,¹ Gabrielle Goldet,¹ Raymond Fernando,¹ Sacha A. De Serres,² Paul Bass,² Mark Harber,¹ Alan D. Salama,¹ Ciara N. Magee,¹ ¹None, Boston, MA; ²Royal Free Hospital, London, United Kingdom; ³Royal Free Hospital, London, United Kingdom; ⁴UCL centre for Nephrology; London, United Kingdom; ⁵University Health Center (CHU) of Quebec, Laval University, Quebec, QC, Canada.

Background: In recent years, there has been a marked increase in the number of older patients (≥65) undergoing kidney transplantation. While there is increasing evidence that the ageing immune system is characterised by immunosenescence, many centres do not have age-specific protocols for immunosuppression. In this study, we sought to examine the effect of recipient age on the development of complications of over- and under-immunosuppression post-transplantation.

Methods: We investigated the outcomes of 90 patients aged ≥65 who underwent kidney transplantation in our centre between April 2009-March 2018, 42 of whom were aged ≥70; these patients were compared to 57 controls aged 18–64, who were matched for number of HLA mismatches. Recorded variables included % cRF pre-transplant across the groups;18-34, 17.75%; 35-49, 29.65%; 50-64, 36.29%; 65-69, 17.1%; and ≥70, 8.4%; p=0.008. The rate of rejection was markedly increased in the control group compared to those aged ≥65 years (19.3% vs. 11.1%), although this did not reach statistical significance. Conversely, rates of CMV viraemia were significantly elevated in recipients ≥65 when compared to recipients <65 (75.6% vs 50.9%, p=0.03). Rates of de novo Class I DSA were also significantly higher in the younger age groups (18.8%, 0% & 23.8% in patients aged 18-34, 35-49 & 50-64, compared to 4.2% & 7.1% in recipients aged 65-69 & >70, respectively; p=0.025), while the development of de novo Class II DSA followed a similar trend (6.3%, 20% & 14.3% in patients aged 18-34, 35-49 & 50-64, versus 2.1% & 4.8% in recipients aged 65-69 & >70, respectively; p=0.077).

Conclusions: These data indicate that older recipient age is associated with reduced rates of rejection and de novo DSA but significantly increased infectious complications post-transplantation. Given the significant morbidity consequent to over-immunosuppression, consideration should be given to the development of age-specific protocols for immunosuppression.

FR-PO1030

Background: The impact of donor factors on kidney allograft outcomes and infectious complications has been suggested in many previous studies. However, analysis of left or right donor kidney pairs are rarely performed, although individual recipients risk factors may be analyzed in a paired difference test and significantly reduce donor cofounders.

Methods: Here, we studied all transplanted left/right deceased donor kidney pairs at our center between 2003 and 2015. A total of 174 paired kidney transplantations were performed from 87 donors. To account for identical donor characteristics among left/right donor kidney pairs a paired difference testing was performed.

Results: Patient survival, allograft survival and allograft function were not correlated among left/right donor kidney pairs (p>0.05). In a paired analysis recipient age, gender, BMI, preformed diabetes, cold ischemia time, HLA-match did not impact nonfunction, acute cellular rejection, BK viremia, EBV viremia, sepsis, and cancer were more likely detected in both kidney pairs than one pair only (p=0.05). Malignancy was associated with delayed allograft function among kidney pairs (p=0.021). Primary nonfunction, acute cellular rejection, BK viremia, EBV viremia, sepsis, and cancer were more likely detected in one pair only (p=0.001). A higher number of HLA-mismatches was associated with BK viremia among kidney pairs (p=0.006). Re-transplantation in one pair was associated with a higher incidence of acute cellular rejection.

Conclusions: Despite an increased incidence of delayed allograft function in left/right kidney pairs, our results suggest low impact of donor factors on patient and allograft outcomes. In contrast, our data suggest a strong impact of individual recipient characteristics as common infectious complications as CMV or BKV don’t appear solely attributable to donor origin, but to impaired immunity of the recipient.
FR-PO1032
Long-Term Outcomes of Kidney Transplantation Using Non Conventional Donors

Background: With the donor-recipient gap widening the pressure to utilize more non-conventional deceased donors (NCD) has increased. However, analysis of long term outcomes of such transplants is lacking. We described our experience with NCD over the past decade.

Methods: We included all deceased donor transplants performed at our center between 2005 and 2013 using donors with cardiac death, dual grafts, extended criteria, and with acute kidney injury: the NCD group. We compared their graft survival (Kaplan-Meier and Cox-regression) and renal function (MDRD eGFR) with our standard criteria donor (SCD) cohort.

Results: Of all 996 adult deceased donors transplants 459 were NCD and 537 were SCD. The groups were not different in terms of gender, race, dialysis or HCV exposure, type of insurance, and BMI at transplant. The NCD group was older and had more diabetics. PRA was lower and less re-transplants. More often their kidneys came from older donors, were non-local, had a longer cold ischemic time, placed on pulsatile perfusion, and donor death by CVA (p<.001, all comparisons). Death censored graft survival was not different between groups (fig 1). After adjusting for all significant variables only age of recipients (p=.02) and donors with CVA (p=.002) were significant factors for graft failure. Renal function was lower on the NCD group at all time points. However, the eGFR was stable (and above 50 ml/min) within the groups for up to 7 years (table 1).

Conclusions: The use of NCD kidneys resulted in similar long term outcomes in terms of graft survival and function, as compared to SCD. The nephrology community and their patients should be aware of the benefits of accepting these grafts.

Funding: Clinical Revenue Support

FR-PO1034
Referral Rates for Renal Transplant in Dialysis Clinic, Inc. Antonio Harford,1 S. Painc,2 R. Schrader,2 Ambreen Gul,2 Philip Zager,1
1UNM, Albuquerque, NM; 2DCI, Albuquerque, NM.

Background: Kidney transplantation (TXP) is the treatment of choice for medically appropriate End-Stage Renal Disease (ESRD) patients. Dialysis facilities play pivotal roles in (1) referring ESRD patients for the initial TXP evaluation; (2) assisting in the evaluation process; and (3) listing. Renal transplantation rates reflect significant racial disparity. Among ESRD patients incident in the US in 2011, overall the percent waitlisted or transplanted (WL/TXP) within 3 years was 13.7% but varied greatly by race, highest among Asians (32.7%) & lowest among Native Americans/Alaskan Native (11.1%). Dialysis Clinic, Inc. (DCI), a large not-for-profit provider, founded by a transplant nephrologist, is developing an innovative education program to enhance referral, WL/TXP & reduce health disparities.

Methods: The present study was conducted to obtain baseline data that will facilitate future annual assessments of the impact of this program. We studied 2,677 dialysis patients under age 70 who began dialysis in 2015, in 230 facilities operated by DCI. We used DCI’s MIS to calculate referral, WL/TXP & refusal rates, stratified by race, sex & diabetes status at the first year of dialysis.

Results: Overall, the referral rate was 62.6%; 19.0% were WL/TXP, 43.6% were referred but not yet WL/TXP, 43.6% were referred but not yet WL/TXP & referrals, stratified by race, diabetes status, & sex are shown. There were no significant differences in referral or refusal rates across racial groups. Referral & refusal rates, respectively, did not differ significantly by race, sex or diabetes status. However, the point estimates for WL/TXP were lower in Blacks & Native Americans vs. Whites & in diabetics vs. non-diabetics.

Conclusions: Excellence in patient & staff education is essential to maximize transplant referral, WL/TXP, and minimize TXP related disparities. To accomplish these objectives innovative educational programs need to be developed & implemented for both dialysis facility staff & patients across the full-range of providers.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO1035
Discrepancy in the Documented Causes of Death among Kidney Transplant Recipients between USRDS and UNOS Databases
Jingbo Ni1, Sankar D. Navaneethan,1 Sreedhar A. Mandayam,2 Jenny S. Pan,1 Kevin F. Erickson,1 Wolfgang C. Winkelmaier,1 Venkat Ramanathan,1 Baylor College of Medicine, Houston, TX; None, Bellevue, TX.

Background: Accurate reporting of cause of death is critical towards identifying specific interventions to improve survival. For U.S. kidney transplant recipients (KTR) cause of death is reported in the United Network for Organ Sharing (UNOS) and United States Renal Data System (USRDS) registries. Herein, we compared the causes of death reported in these two national databases.

Methods: We identified all adult first-time KTRs (1996-2012) with functioning graft who died and specifically ascertained their reported causes of death from the USRDS and UNOS databases. Deaths were classified into: cardiovascular, infectious, cancer, malignancy, d) others and e) unknown.

Results: Of 196,748 KTRs, for whom USRDS reported causes of death for 40,742 and UNOS reported causes of death for 40,424 patients, we included 30,721 patients with cause of death information available in both databases. As shown in Table 1, cause of death was coded as unknown for 28% in UNOS and for 57% in USRDS among KTRs. Among 12424 (40%) KRTs with exact cause of death documented in both databases, the agreement on kidney cause of death (KCD) was 76%.

Conclusions: In both national registries, the exact cause of death is unknown for a sizable proportion of patients who die with a functioning graft. There is considerable discrepancy between the two national registries for causes of death that are reported. Documenting the correct diagnosis is pivotal to design future clinical studies to extend survival of KTR.

Table 1. Course of death among kidney transplant recipients from two national databases

<table>
<thead>
<tr>
<th>Cause of death (USRDS data)</th>
<th>N (%)</th>
<th>Cardiac related</th>
<th>Infection</th>
<th>Multigraft</th>
<th>Others</th>
<th>Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>5555 (3.3)</td>
<td>960 (38)</td>
<td>279 (11)</td>
<td>345 (13)</td>
<td>755 (29)</td>
<td>173 (6)</td>
<td>6462 (25)</td>
</tr>
<tr>
<td>Infections</td>
<td>1100 (6.4)</td>
<td>156 (6)</td>
<td>78 (3)</td>
<td>15 (1)</td>
<td>308 (12)</td>
<td>60 (3)</td>
<td>1672 (6.1)</td>
</tr>
<tr>
<td>Multigraft</td>
<td>720 (41)</td>
<td>70 (3)</td>
<td>217 (8)</td>
<td>171 (6)</td>
<td>236 (9)</td>
<td>100 (4)</td>
<td>1242 (40)</td>
</tr>
<tr>
<td>Others</td>
<td>1112 (6.3)</td>
<td>202 (8)</td>
<td>190 (7)</td>
<td>267 (10)</td>
<td>275 (10)</td>
<td>714 (27)</td>
<td>1711 (6.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>293 (1.7)</td>
<td>128 (5)</td>
<td>58 (2)</td>
<td>52 (2)</td>
<td>49 (2)</td>
<td>17 (1)</td>
<td>475 (1.8)</td>
</tr>
<tr>
<td>Total</td>
<td>7045 (42.9)</td>
<td>1307 (6)</td>
<td>321 (1)</td>
<td>398 (1)</td>
<td>980 (4)</td>
<td>197 (1)</td>
<td>8782 (24)</td>
</tr>
</tbody>
</table>

FR-PO1036

Background: African American (AA) ethnicity increases the risk for developing chronic kidney disease (CKD). There is limited data on graft outcomes based on donor ethnicity. Donor ethnicity is a variable in the kidney donor profile index (KDPI) designed to aid in organ allocation and in predicting long-term transplant outcomes. We aimed to evaluate long-term kidney transplant outcomes based on donor ethnicity under different KDPI groups.

Methods: Using the OPTN/UNOS database, adult deceased donor kidney (DDK) transplant recipients from 2000 to 2015 who received induction therapy and were discharged on calcineurin inhibitor/mycophenolate mofetil-based maintenance were included. Patients were further divided into four KDPI categories (0-20%, 21-50%, 51-85% and >85%). Long term graft and patient outcomes were compared for recipients of AA vs. non-AA donor kidneys under each KDPI group in a multivariate Cox model.

Results: There were 59,648 participants in the study cohort with a median follow-up of 47.2 months. Adjusted graft and patient outcomes among recipients of AA vs. non-AA donor kidneys by KDPI groups are shown in Table 1 and Figure 1. Overall and death-censored graft failure risks were higher for recipients of AA donors kidneys among higher KDPI (51-85% and >85%) groups but similar among lower KDPI (0-20% and 21-50%) groups. Patient survivals were similar.

Conclusions: Our study showed inferior graft outcomes among recipients of AA donor kidneys in higher KDPI groups despite ethnicity being a variable in deriving KDPI. One could speculate that higher prevalence of risk factors for CKD progression such as APOI and sickle cell trait gene mutations among other factors in AA population as well.

Table 1

<table>
<thead>
<tr>
<th>KDPI (0-20%)</th>
<th>AA vs. non-AA</th>
<th>AA vs. non-AA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aa vs. non-Aa</td>
<td>120 (2.8)</td>
<td>100 (2.5)</td>
<td>0.15</td>
</tr>
<tr>
<td>AA vs. non-Aa</td>
<td>120 (2.8)</td>
<td>100 (2.5)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

FR-PO1037
Living Kidney Donor Evaluation Time and Pre-emptive Kidney Transplantation Steven Haboush, Amit X. Garg.1 Western University, London, ON, Canada;2 London Health Sciences Centre, London, ON, Canada.

Background: A pre-emptive kidney transplant avoids the risks of initiating dialysis and may result in better outcomes than other treatment options available to patients with kidney failure.

Methods: Using healthcare databases in Ontario, Canada, we retrospectively studied 478 living donor kidney transplants from 2004-2014 where the recipients were not receiving dialysis when their donors’ evaluation was underway (for at least three months). We assessed how often dialysis was initiated before transplantation, and explored factors associated with a higher likelihood of dialysis initiation prior to transplant. Results are presented as median (25%, 75% percentile).

Results: A total of 167/478 (35%) of patients with kidney failure initiated dialysis 9.7 (5.4, 18.7) months after their donor candidate began their evaluation, and received dialysis for 8.8 (3.6, 16.9) months before transplantation. The total cost of initiating and receiving dialysis was CAD $8.1 million and 44/167 (26%) patients initiated their dialysis urgently in hospital. The median total donor evaluation time (time from evaluation start to donation) was 10.6 (6.4, 21.6) months for pre-emptive transplants and 22.4 (13.1, 38.7) months for donors whose recipients started dialysis prior to transplant. Characteristics associated with a higher likelihood of the recipient initiating dialysis prior to transplantation included donor female sex, non-white donors, lower donor and recipient neighbourhood income quintile, and a longer time until the transplant program received the recipient referral. Results varied across transplant centres.

Conclusions: One-third of living donor kidney transplant recipients start dialysis prior to transplantation with significant costs to the healthcare system.

Funding: Government Support - Non-U.S.

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

Underline represents presenting author.
Cr within a KDPI group results in better long-term outcomes since these kidneys likely undergo procurement biopsy and transplant centers generally accept these kidneys only if the biopsy shows predominantly acute tubular injury with minimal chronicity.

**Methods:** Using the UNOS database, we identified adult DDK transplant recipients from 2000 to 2015 who received induction and were discharged on calcineurin inhibitor and mycophenolate mofetil regimen. Patient outcomes were divided into 4 KDPI categories (0-20%, 21-50%, 51-85% and >85%). Using a Cox model, adjusted long-term graft and patient outcomes were compared between recipients of kidneys with terminal Cr >2 vs. ≤2 mg/dL under each KDPI category.

**Results:** Study comprised of 59,645 patients with a median follow up of 48 months. Adjusted graft and patient outcomes comparisons based on terminal Cr for different KDPI groups are shown in the table. Adjusted overall graft failure and patient death risks were lower in patients who received DDKs with terminal Cr >2 vs. ≤2 mg/dL in KDPI 21-50% and 51-85% groups but not in best quality (KDPI 0-20%) and marginal kidney (KDPI >85%) recipients. There were no differences in death-censored graft failure risks. Lower overall graft failure and similar death-censored graft failure in recipients of DDK with terminal Cr >2.0 mg/dL indicated reduced death with functioning graft.

**Conclusions:** The finding of reduced risk for death with functioning graft in patients who received DDK with terminal Cr >2 mg/dL in the mid KDPI ranges likely reflects the selective use of these kidneys when procurement biopsy findings are favorable resulting in better long-term allograft function. Our study highlights limitations of using elevated terminal Cr in deriving KDPI.

---

**FR-PO1039**

KDPI and Allograft eGFR in Deceased Donor Kidney Transplant Recipients over Follow Up: 1995-2013 Donal J. Sexton,1 Patrick O’kelly,1 Claire Kenned,1 Declan G. de Freitas,1 Conall M. O’Seaghda,1 Peter J. Conlon,1 Beaumont Hospital, Dublin 9, Co Dublin, Ireland; The Irish Longitudinal Study on Ageing (TILDA), Trinity College Dublin, Dublin, Ireland.

**Background:** The KDPI has been validated for prediction of deceased donor graft outcomes and popularized in organ allocation in the United States. Whether KDPI predicts eGFR over long-term follow up has not been extensively characterised.

**Methods:** We performed a retrospective analysis of eGFR (CKD EPI equation) and graft outcomes over follow up in the National Kidney Transplant Service of Ireland database for the years 2006–2013. Associations of the composite KDPI score with eGFR at various time points over follow up were modeled using linear regression, linear mixed effects models and time to event strategies respectively.

**Results:** N=877 patients had complete data regarding KDPI calculation, N=148 patients underwent procurement biopsy and transplant centers generally accept these kidneys only if the biopsy shows predominantly acute tubular injury with minimal chronicity. Under each KDPI, eGFR ml/min/1.73m2 at year 1 were: KDPI 0-20% Cr<2 mg/dL, 67.3 (51.7-83.2) (N=104), 67.8 (53.4-81.6) (N=85), and 63.5 (50.2-76.8) (N=69), P<0.001. On repeated measures analysis with linear mixed effects models with a random participant specific intercept and a random time effect, KDPI (fixed effect covariate) associated with eGFR over follow up (see Fig 1): estimate (se) -0.25 (0.02) P<0.001 for KDPI. The variability in eGFR over 5 years alligned with KDPI score was 21% after adjusting for recipient age (time-varying covariate).

**Conclusions:** KDPI score predicted eGFR at multiple time points over long term follow up in this study. However, taking the KDPI as a composite of non-modifiable donor factors, a considerable portion of eGFR variability is likely attributable non-donor factors.
FR-PO1041
Kidney Donor Profile Index (KDPI) Predicts Outcome of Deceased Donor Kidney Transplant in a Brazilian Center
Carlos Rafael A. Felipe, Andre S. Alvaranga, Silvana Maria C. Miranda, Ana Elisa S. Jorge, Pedro Augusto M. Souza, Isabel L. Piana, Hospital Santa Casa de Belo Horizonte, Belo Horizonte, Brazil; None, Belo Horizonte, Brazil; Santa Casa de Belo Horizonte, Belo Horizonte, Brazil; Faculdade de Minas Faminas BH, Belo Horizonte, Brazil.

Background: Kidney Donor Profile Index (KDPI) is a well-established index to predict the outcome of deceased donor renal transplant (DDRT), but it has not been established for Brazilian population.

Methods: We retrospectively calculated the KDPI and analyzed the outcomes of 45 consecutive DDRT from November 2014 to March 2016: mean cold ischemia time (CIT) was 13.9 hours, the incidence of delayed graft function (DGF). The median of KDPI was 53%.

Results: Patients who died had higher KDPI (median 82.0% vs 50.5%; p = 0.018), as well as those with allograft failure (median 77.0% vs 50.5%; p = 0.021). The area under the KDPI ROC curve for the composite outcome of death or graft loss was 0.80 (Figure1), similar to donor serum creatinine. One year graft survival was 40% for kidneys with KDPI ≥ 70% versus 84.5% for kidneys with KDPI < 70% (relative risk = 4.81; p = 0.003). There was no association between KPDI > 70% and cytomegalovirus (CMV) infection.

Conclusions: KDPI accurately predicted graft survival after DDRT and may be helpful in selecting and allocating a deceased kidney in Brazilian population.

Table 1: Study population data and outcomes

<table>
<thead>
<tr>
<th>KDPI (%)</th>
<th>Functioning Graft (p&lt;0.01)</th>
<th>Graft Loss/Death (p&lt;0.01)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-50</td>
<td>80</td>
<td>0.007</td>
</tr>
<tr>
<td>Donor age (years)</td>
<td>mean</td>
<td>41.2</td>
</tr>
<tr>
<td></td>
<td>41.2</td>
<td>40.0</td>
</tr>
<tr>
<td>Cold ischemia time (hr), median</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Pediatric donor (%)</td>
<td>57.7</td>
<td>54.5</td>
</tr>
<tr>
<td>Recipient age (years)</td>
<td>median</td>
<td>12.7</td>
</tr>
<tr>
<td></td>
<td>12.7</td>
<td>16.2</td>
</tr>
<tr>
<td>DGF (%)</td>
<td>55.0</td>
<td>51.4</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>40.2</td>
<td>40.2</td>
</tr>
<tr>
<td>Female donor (%)</td>
<td>41.2</td>
<td>36.4</td>
</tr>
<tr>
<td>Biopsy-proven acute kidney rejection (%)</td>
<td>21.3</td>
<td>9.0</td>
</tr>
<tr>
<td>CMV viremia (%)</td>
<td>47.5</td>
<td>30.1</td>
</tr>
</tbody>
</table>

FR-PO1042

Background: Kidneys from deceased donors with acute kidney injury (AKI) are often not transplanted despite similar 1 year outcomes as donors without AKI. Our center utilizes a high percentage of AKI donors (15%), including donors with severe AKI requiring renal replacement therapy. We compared the 3 year outcomes of AKI donors after brain death (DBD) and circulatory death (DCD), with non-AKI donors.

Methods: We conducted a retrospective chart review of deceased donor kidney transplant (DDKT) recipients from 1/2011 to 6/2016. AKI was defined as terminal serum creatinine (SCr) of ≥ 1.5mg/dl.

Results: 138 eligible DDKT recipients were divided into 4 groups based on donor characteristics: Group 1 [DBD non-AKI, n=73(53%)], Group 2 [DCD non-AKI, n=44 (32%)], Group 3 [DBD-AKI, n=14(10%)], and Group 4 [DCD-AKI, n=7(5%)]. The terminal SCr was significantly higher in DBD-AKI (2.8mg/dl) and DCD-AKI (2.1mg/dl) compared to DBD non-AKI (0.9mg/dl) and DCD non-AKI (0.8mg/dl) (p <0.01). Recipients were 60% male, 65% Caucasian, and mean age of 57±12yrs, with no significant differences among groups. Donors in DCD-AKI group were younger than other groups (24yr vs 35-40yr p=0.02), but all had similar KDPI (43%, p=0.6). Although delayed graft function (DGF) was not different between the groups, the duration of DGF was longer in the DCD non-AKI group than other groups (16d vs 7.5-9d, p<0.04). Patient survival at 1yr, 2yr, and 3yr was 97%, 94% and 97% in group 1, 98%, 93% and 84% in group 2 respectively, and 100% for all years for group 3 and group 4 (p=0.76, 0.91, and 0.62). Death censored allograft survival at 1yr, 2yr and 3yr was similar between the groups, 98%, 96% and 93% in group 1, 98%, 88%, and 87% in group 2 respectively, and 100% for all years in group 3 and group 4 (p=0.53, 0.70, and 0.93). The SCR was higher and eGFR lower at 1 month post-KT in the DCD non-AKI group compared to other groups (p <0.01), but both became similar to other groups at 1 yr and remained comparable at 3yr post-transplant. At 3yr, 92% of DBD non-AKI, 86% of DCD non-AKI and 100% of DBD-AKI and DCD-AKI donors had eGFR of more than 30ml/min (p=0.9).

Conclusions: Judicious use of AKI donors had excellent 1yr and 3yr patient and allograft outcomes with no difference between DCD and DBD donors. Selected AKI donors, especially young donors, can be safely utilized to expand the donor pool.

FR-PO1043
Effect of Spontaneous Donor Hypothermia on Graft Outcome in Organ Transplantation
Bernhard K. Krämer, Urs Benck, Peter Schneeule.

Background: A previous controlled donor intervention trial found that therapeutic hypothermia reduced delayed graft function (DGF) after kidney transplantation.

Methods: This retrospective cohort study nested in the randomized dopamine trial (ClinicalTrials.gov identifier: NCT001011515) investigates the effects of spontaneous donor hypothermia on initial kidney graft function, and evaluates graft survival including heart and liver transplants. All 264 donors who met the eligibility criteria for enrollment in the randomized dopamine trial were grouped by occurrence of spontaneous hypothermia. Hypothermia was defined by a core body temperature of less than 36.0°C before organ procurement. Accordingly, we assigned 54 donors to the hypothermia group and the remaining 210 donors served as controls.

Results: Hypothermia was associated with less DGF after kidney transplantation (OR 0.56, 95%CI 0.34 – 0.91). The benefit was greater when need for more than a single post-transplant dialysis session was analyzed (OR 0.48, 95%CI 0.28 – 0.82). Donor dopamine ameliorated dialysis requirement independently from hypothermia in a time-relationship with exposure (OR 0.93; 95% CI 0.87 – 0.98, per hour). Hypothermia did not alter kidney graft survival (HR 0.83, 95%CI 0.54 – 1.27), while dopamine treatment was associated with improved long-term outcome (HR 0.95, 95%CI 0.91 – 0.99 per hour). Stratified

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
analyses of non-renal organs in tertiles of the donor’s core body temperature disclosed negative effects on heart allograft survival (HR 1.89, 95%CI 1.09 – 3.27).

Conclusions: Spontaneous donor hypothermia is associated with less DGF but does not appear to affect long-term outcome of the kidney graft. Our data raise safety concerns against therapeutic hypothermia in multi-organ donors when a thoracic transplantation is considered.

FR-PO1044

The Combination of KDRI and the Histological Score Improves the Risk Stratification of Marginal Organs in Kidney Transplantation

Marco Fiorentino,1 Francesco Pesce,1 Giuseppe Castellano,2 Simona Simone,1 Pasquale Gallo,1 Giuseppe Grandallano,1 Michele Battaglia,3 Loreto Gesualdo.1 1Department of Emergency and Organ Transplantation, Nephrology, Dialysis and Transplantation Unit, University of Bari, Bari, Italy; 2Nephrology, Dialysis and Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy; 3Department of Emergency and Organ Transplantation, Urology, Andrology and Kidney Transplantation Unit, University of Bari, Bari, Italy.

Background: The organ shortage has led to increase the procurement of kidneys from marginal donors, but the risk of graft failure is still object of debate. The aim of the study is to assess whether using both clinical and histological scores can better assess the risk for worse outcome for marginal organs.

Methods: We analyzed 210 kidney transplant recipients from donors aged >50 years. We retrospectively calculated the Kidney Donor Risk Index (KDRI) for each donor and we divided the population according to the KDRI (-, if KDRI < median) and the histological score (HS, if HS ≤ 3, if HS > 3) in 4 groups: KDRI- HS- (low KDRI and HS), KDRI-HS+ (low KDRI and high HS), KDRI-HS (high KDRI and low HS) and KDRI+HS+ (high KDRI and HS). We compared graft function between groups at 2 years and Cox regression analysis was performed to assess the risk for end stage renal disease (ESRD) between groups.

Results: Overall, median KDRI was 1.44 (1.25-1.65), while mean total HS was 3.04±1.62. Median follow-up was 51.9 (26.4 – 99.4) months. Graft function at 2 years was significantly worse in groups with high KDRI (KDRI-HS- and KDRI+HS+) compared to those with low KDRI (p<0.001), while no differences were found according to the HS. By contrast, the best ROC curve in predicting the development of ESRD is for the model that included both KDRI and histological score (AUC 0.81, 95%CI 0.708-0.914, p<0.001). A Cox model adjusted for recipient age, gender, acute rejection, DGF and chronic allograft dysfunction, patients with high KDRI and high HS are more likely to develop ESRD compared to the other groups (OR 5.6, 95%CI 1.3 to 24.5, p=0.02).

Conclusions: Patients with high KDRI and HS have worse outcome compared to patients with high KDRI but better histology. The integration of histology to clinical score may improve the assessment of the risk for graft failure in patients receiving organs from marginal donors.

FR-PO1045

Practice Variation in PHS-IR Kidney Transplants

Corey Brennan,1 Syed A. Husain,2 Sumit Mohan,2 Mariana C. Chiles.2 Columbia University, New York, NY; Columbia University Medical Center, New York, NY.

Background: There is significant center level practice variation for accepting deceased donor organs in the U.S. We hypothesized that this variation occurs even for kidneys with good outcomes such as those from PHS-IR donors.

Methods: Using data from the Scientific Registry of Transplant Recipients (SRTR) from 2010-2016, we identified 78,087 kidney-alone deceased donor transplant recipients to evaluate transplant center use of PHS-IR organs in the U.S. Additionally, Cox regression analysis was used to assess the difference in allograft outcomes between PHS-IR and non-PHS-IR kidneys.

Results: 12,751 (16.3%) of kidneys were procured from PHS-IR donors who were younger (33.1±12.2 vs 38.9±16.5 years), with less hypertension (17.5 vs 29.3%), diabetes (4.1 vs 7.8%), marginally higher terminal SCr (1.31±1.5 vs 1.13±1.06) and lower KDPI (36.7 vs 49.2%) than non-PHS-IR donors (all p<0.001). PHS-IR kidneys demonstrated lower all-cause (12.2 vs 16.7%) and death-censored (5.5 vs 8.2%) graft failure (p<0.001). Despite the objectively higher quality, nearly a third (32.9%) of all PHS-IR kidneys were transplanted by just 10 transplant centers while 20 centers performed no PHS-IR transplants over the 7 year study period (Figure 1). PHS-IR kidneys were also significantly more likely to be shared between OPOs (30.6% vs 23.9%, p<0.001), underscoring the reluctance by some centers to use PHS-IR kidneys. PHS-IR kidneys experienced a reduced risk of graft failure (HR=0.787, p<0.001), persisting even after adjusting for KDPI and EPTS (HR=0.921, p=0.046).

Conclusions: Considerable variation in acceptance of PHS-IR donor kidneys exists despite evidence of the low risk of disease transmission and excellent outcomes. Although the number of potential donors who meet PHS-IR criteria is likely to rise during the ongoing opioid epidemic, the reluctance to use these organs is likely to adversely impact organ procurement and kidney discard in the U.S and realigns that deceased donors are often declined for factors other than organ quality.

Impact of Cold Ischemia Time, Independent of DGF, on Allograft Outcomes


Background: The rate of deceased donor kidney (DDK) discard is rising in the U.S., and prolonged cold ischemia time (CIT) is a frequently cited reason for discard. Although long CIT is associated with delayed graft function (DGF), the impact of both CIT and DGF on long-term survival is unclear.

Methods: To assess the risks associated with transplanting DDKs that have accrued long CIT, we used Scientific Registry of Transplant Recipients data to perform a paired kidney analysis and evaluated post-transplant death-censored graft failure. From 2000-2015, we identified 5,773 pairs (11,546 kidneys) that had a difference in CIT ≥ 5 hours, where 1 kidney developed DGF. The kidney from each pair with shorter CIT was included in the “short CIT” group and the kidney with longer CIT was included in the “long CIT” group.

Results: CIT for the long CIT kidneys was 24.8±8.9 hours versus 13.9±7.2 hours for the short CIT group (p<0.001). Long CIT kidneys were more likely to develop DGF (26.0% vs 22.4%, p<0.001). When examining pairs in which at least 1 kidney developed DGF and using the kidneys with short CIT and no DGF as the reference, kidneys that developed DGF had a higher probability of graft failure over the study period regardless of CIT (long CIT with DGF OR=1.87, p<0.001; short CIT with DGF OR=1.81, p<0.001; Figure 1), but kidneys with long CIT had no difference in graft failure (OR 0.98, p=0.71). In multivariable analysis, only recipients who developed DGF (whether with short or long CIT) had a higher risk of allograft failure compared to recipients of short CIT kidneys that did not experience DGF (long CIT with DGF OR=2.07, p<0.001; short CIT with DGF OR=1.98, p<0.001).

Conclusions: Kidneys with longer CIT had a marginally increased incidence of DGF, but long CIT was not associated with increased graft failure after stratifying recipients by DGF development. DGF describes a clinically heterogeneous entity resulting from multiple factors beyond prolonged CIT.

Funding: Other U.S. Government Support
FR-PO1047

Perceptions of Patients with ESRD about Reasons for Transplant Non-Referral and Non-Listing

Mary Morrow-Sutton, Hafiz Z. Mahmood, Umar Farooq, Nasrollah Ghahramani. Penn State College of Medicine, Hershey, PA.

Background: Kidney transplant (KT) is the treatment of choice for most patients with end stage renal disease (ESRD). We explored patients’ understanding of reasons for non-referral for transplant and reasons for not having been placed on the transplant waiting list.

Methods: We sent flyers to 1,283 dialysis units. Of 2536 interested participants who fulfilled inclusion criteria, we randomly selected and invited 1400 to complete a survey, which included questions regarding referral, evaluation and listing for KT.

Results: Of 673 participants, 401 had been referred, 361 had been evaluated and 201 were listed for KT. A total of 272 patients (40%) indicated that they had not been referred for evaluation. The most common reasons cited by patients for not being referred for evaluation included: patient choice (24%), age (10%), weight (10%), and being too sick (9%). In 10% of cases, the patients indicated that their nephrologist had not mentioned KT as an option. The reason for non-referral was unknown to 16% of the patients. Forty patients indicated that they had been referred but never evaluated for listing. Patient choice was the most common cause for not being evaluated (26%), followed by being overweight (10%) and being too sick (8%). The reason for not being evaluated was unknown to 17% of referred patients. Of the patients who had undergone the evaluation process, 160 (44%) were not listed. Patient choice was the most common reason for not pursuing the listing process (33%), being too sick (13%), and being overweight (10%). The reason for not being listed was unknown to 12% of the evaluated patients.

Conclusions: Patient choice is the most commonly cited reason for not being referred, evaluated or listed for KT. A significant proportion of patients are not aware of the reason they have not been referred, evaluated or listed for KT.

FR-PO1048

Removal Rates and Reasons from Waitlist in Elderly Kidney Transplant Candidates in the United States

Mary Corniph, Yong W. Cho, Suphamoni Bunnasraptid. 1 Mendez National Institution of Transplantation, Los Angeles, CA; 2UCLA, Los Angeles, CA.

Background: The number of kidney transplant candidates on waiting list has been increasing over year, as well as the median age at initial registration. Since now there are 97,621 candidates on waitlist, among these 22,290 (22.8%) are 65 years old and older (Data of June 1, 2017). Over 30,000 patients were removed from waiting list by year due to various reasons. We hypothesized that elderly candidates would have higher withdrawal removal rates and less likely to achieve successful transplantation.

Methods: We used data from the Organ Procurement Transplant Network (OPTN/ UNOS) as of December 8, 2016. We examined rate of and reasons for withdrawal removal in 137,553 kidney transplant candidates registered between January 1, 2000, and September 30, 2015. To allow for a sufficient follow-up period, candidates registered for transplant up to September 31, 2015 (1 year before the date of last follow-up in the database) were included. Those candidates who were put on waitlists for organs other than kidney or multiple organs were excluded. We divided patients into 3 groups based on age at initial registration; 1) aged 60-69 years, 2)aged 70-79 years, and 3)aged 80 years.

Results: A total of 56,544 (46.3%) candidates were removed from waitlist over the study period due to reasons other than being transplanted. Delisting rate was increased by age group and was highest in aged a 80 group. Among these, 22,908 (19.6%) were removed due to death during on waiting list. Candidates aged 80 years had the highest number of delisting due to condition unsuitable to transplant and also demonstrated worse patient survival while waiting for a transplant. (p<0.011) (graph)

Conclusions: Elderly kidney transplant candidates had high delisting rates due to death and condition unsuitable for transplant especially in those aged a 80 years at initial registration, with decreased patient survival. Only half of them received successful transplantation. These results imply that patient selection before waitlist registration could avoid high rate of delisting.

FR-PO1049

The Impact of Donor Chemical Urine Toxicology on Outcomes of Kidney Transplantation

Blainih A. McMahon, Christopher A. Molin, Tessa K. Novick, Steven Menez, Edward S. Kraus. Medicine, Johns Hopkins University, Baltimore, MD.

Background: Most transplant centers now accept kidney grafts from victims who have acute chemical intoxications. Despite the widely acceptance of many of these donors the effect of the acute intoxication on kidney graft outcome is poorly understood.

Methods: This is a single center retrospective cohort analysis of 500 patients undergoing deceased donor kidney transplantation (DDKT). Urine toxicology agents tested from donor urine included: alcohol, heroin, cocaine, opioids/methadone, cannabinoids, benzodiazepines and methamphetamine. Delayed graft function (DGF) was defined as the need for dialysis within 1 week of kidney transplantation (KT). Graft failure was defined as the need to return to dialysis. Multiple logistical regression (MLR) analysis was used to assess the odds ratio for DGF and graft failure. MLR models were adjusted for donor age, donor race, donor terminal creatinine, recipient race, cold ischemic time, donation after cardiac death, and preemptive KT.

Results: Of 500 random DDKTs performed at our institution between January 2010 and October 2015, 230 deceased kidney donors (46%) were current drug users. The main chemical toxins detectable in donor urine were: alcohol (n=132, 26 %), heroin (n=80, 16%), opioid/methadone (n=40, 8%), cocaine (n=57, 11%), cannabinoids (n=90, 18%), benzodiazepines (n=15, 3%), methamphetamine (n=19, 4%). 23% of donors had more than one urine toxicology test positive, 13% had more than two tests positive and 5% more than two tests positive. The urine chemical toxicology of kidney donors did not have a significant effect on KT outcomes of DGF and graft failure on adjusted MLR analysis (median follow up of 24 months) (P for odds ratios = 0.05). There was also no association between donors with multiple positive urine chemical toxicology results (greater than 1 or 2 or 3 or 4 agent’s positive in urine) and DGF or graft survival on MLR (p = 0.05).

Conclusions: The use of deceased donor kidney grafts from donors with positive urine chemical toxicology may be a worthwhile method of increasing the availability of scarce donor kidney organs as urine chemical toxicology is not associated with major transplant outcomes.

FR-PO1050

A Donor and Recipient Genome-Wide Association Study of Renal Allograft Function

Caragh P. Stapleton,2 Graham M. Lord,3 Martin H. De Borst,4 Harold Snieder,5 Claire Kennedy,4 Maria P. Hernandez-Fuentes,4 Michael Weale,6 Florence R. Delaney,1 Patrick B. Mark,10 Paul J. Phelan,6 Fiona A. Chapman,7 Alexander P. Maxwell,1 A.J. McKnight,1 Donal J. Sexton,5 Kelly A. Birdwell,12 Brendan Keating,7 Gianpiero Cavalleri,2 Peter J. Conlon,4 Queen’s University Belfast, Belfast, United Kingdom; 6Royal Infirmary of Edinburgh, NHS Lothian, Edinburgh, United Kingdom; 7Dept of Molecular and Cellular Therapeutics, Royal College of Surgeons, Dublin, Ireland; 8Beaumont Hospital, Dublin 9, Co Dublin, Ireland; 9Guy’s and St Thomas’ NHS Foundation Trust, London, United Kingdom; 10King’s College London, London, United Kingdom; 11NHIS Scotland, Glasgow, United Kingdom; 12The Irish Longitudinal Study on Ageing (TILDA), Trinity College Dublin, Dublin, Ireland; 13University Medical Center Groningen, Groningen, Netherlands; 14University of Glasgow, Glasgow, United Kingdom; 15University of Pennsylvania, Philadelphia, PA; 16Yanderbilt University, Nashville, TN.

Background: Previous studies have suggested the influence of common genetic variation on renal transplant outcome. Our aim was to expand on these studies and examine single variant effects of both donor and recipient genotypes on graft function (using estimated glomerular filtration rate (eGFR) as a proxy) taking a genome-wide association study (GWAS) approach.

Methods: We meta-analysed donor and recipient genetic variants across two cohorts (Netherlands cohort and UK/Ireland cohort). We carried out both donor and recipient GWAS of eGFR at 1 year (n donors=2,344; n recipients=2,840) and 5 years (n donors=2,190; n recipients=2,606) post-kidney transplant and examined change in eGFR between 1 and 5 years (A eGFR; n donors=1,678; n recipients=2,002). For the 1 year and 5 year analysis, where eGFR was missing due to death/failure the last known eGFR was used and death/failure was included as a covariate in the analysis. Samples with death/failure before 5 years were excluded in the 5 eGFR GWAS. Other covariates included the first eight principle components, donor and recipient age, donor type (living/deceased) and donor gender.

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

676
FR-PO1051

Genome-Wide Donor-Recipient Genetic Differences Influence Renal Allograft Survival Independent of HLA

Results: No genome-wide significant associations were found in the three donor GWAS. In the recipient 5 year eGFR GWAS a significant association was observed with a locus on chromosome 19 (combined p=2.59x10^-10). The presence of the minor allele correlated with a decrease in eGFR (beta= -0.15). This region contains the gene ZSCAN18 which may play a role in transcriptional regulation.

Conclusions: No single common genetic variant was associated with 1 year, 5 year or Delta eGFR in the donor GWAS. We detected a locus on chromosome 19 that associated with 5 year eGFR in the recipient GWAS suggesting that recipient genotype may be used to predict medium-term renal allograft outcome. Further work is required to assess the robustness of this signal and to replicate these findings.

Funding: Government Support - Non-U.S.

FR-PO1052

Circulating Fibrocytes Predict eGFR Slope Post Transplant and Are Associated with Chronic Tubular Changes

Methods: A single-center observational study was conducted in patients undergoing a first kidney transplant. Blood was drawn pre-transplant, 1, 3, 6, and 12-months post-transplant. Circulating fibrocyte levels were identified by flow cytometry using cell surface markers and intracellular collagen I. Biopsy samples were stained for a smooth muscle actin (SMA) and tissue fibrocytes were identified using dual labeling of CXC4R1 and Prolyl-4-hydroxylase. The Banff classification was used to evaluate chronic biopsies changes.

Results: Eighty enrolled patients were followed to 12-months post-transplant. One-month circulating fibrocyte levels correlated inversely with the slope of the eGFR from 3 to 12 months (R= -0.257, p=0.03). Thirteen patients had a clinically indicated biopsy. The number of tissue fibrocytes correlated with a-SMA staining (R=0.637, p=0.026). Increased chronic tubular changes were associated with elevated 1-month circulating fibrocyte levels (p<0.001). Increased chronic interstitial changes were associated with increased numbers of tissue fibrocytes (p=0.028).

Conclusions: Elevated circulating fibrocytes at 1-month post-transplant may be prognostic of transplant outcome. Also, increased circulating fibrocytes at 1-month is predictive of chronic tubular changes on biopsy. The number of tissue fibrocytes correlates with interstitial fibrosis and a-SMA staining. Circulating fibrocytes at 1-month can be a biomarker for graft dysfunction and may predict the severity of graft fibrosis.

Funding: Commercial Support - Pfizer

SA-PO001

AKI Following Coronary Angiography: Survival and Development of CKD

Background: AKI Clinical: Epidemiology and Outcomes

Methods: We generated a propensity-matched cohort of 274,464 hospitalizations that underwent CA in Iceland in 2008-2015. Excluded were patients on chronic dialysis, those without baseline serum creatinine (SCr) and patients who underwent open heart surgery in the first 3 days following CA. AKI was defined according to the KDIGO SCr criteria. CKD was defined as eGFR <60 mL/min/1.73 m^2 for at least 3 months, and progression of CKD as worsening of at least one stage sustained over 90 days.

Results: AKI was diagnosed in 251 out of 13465 cases (1.9%). The 30-day mortality was 23.1% vs. 1.1%, and 1-year survival was 68.6% vs. 97.1%, in the AKI and non-AKI group, respectively (p<0.0001). After excluding patients who died within 30 days, the AKI patients had worse 1-year survival compared with a propensity score-matched control group, of 89.2% vs. 95.4% (p<0.001). While 2343 patients (17.4%) had CKD at baseline, 1935 of the 13465 cases (14.3%) developed incident CKD or progression of pre-existing CKD following CA, with a median time of follow-up of 3.5 (range 0.2-8.0) years. In multivariate analysis, AKI was a predictor of development/progression of CKD (HR 2.5, 95%-CI: 2.0-3.1).

Conclusions: Short-term mortality of patients with AKI following CA is high. However, after excluding early deaths, AKI appears associated with less favorable long-term survival and the development and/or progression of CKD.

Funding: Government Support - Non-U.S.

SA-PO002

Temporal Trends in the Incidence of AKI after Coronary Revascularization in a Nationwide Study

Methods: We utilized unique genome-wide SNP array data encompassing Donor-Recipient pairs (D-R) from our recently completed multicenter GoCAR study [PI- Barbara Murphy] to study the role of D-R differences on death-censored allograft survival (DCGS).

Results: No genome-wide significant associations were found in the three donor GWAS. The robustness of this signal and to replicate these findings.

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

Underline represents presenting author.
valvular disease, atrial flutter or fibrillation, CKD, diabetes, HTN, dyslipidemia, smoking, cirrhosis, obesity, and COPD. The odds ratios were estimated by the random intercept logistic regression model.

Results: The temporal trends of AKI incidence in both CABG and PCI groups had been increasing over the years from 5.9% in 2004 up to 14.2% in 2012 for CABG, 2.7% in 2008 up to 8.5% in 2012 for PCI. Compared with PCI, CABG was associated with a higher incidence of post-procedural AKI in each individual year from 2004 to 2012 (Time effect: OR 1.138, 95% CI: 1.113-1.164, P < 0.01). Interestingly, although CABG had higher likelihood of developing AKI throughout the study period than PCI, the odds had been decreasing gradually over time (3.29, 95% CI: 3.06-3.54, P= 0.01; in 2006; OR 1.73, 95% CI 1.58-1.88, P=0.01 in 2012).

Conclusions: Both CABG and PCI were associated with increasing temporal trends in AKI incidence over the years. Although CABG was associated with higher likelihood of developing post-procedural AKI in each individual year compared to PCI, the odds were decreasing yearly.

Funding: Clinical Revenue Support

SA-PO004

Epidemiology of AKI in Cancer Patients

Young Lee Jun1, Eunjeong Kang,1 Minus Park,2 Namyong Park,3 Hajeong Lee.1 Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea; 2Biomedical Engineering, Seoul National University College of Medicine, Seoul, Republic of Korea; 3Computer Science and Engineering, Seoul National University College of Engineering, Seoul, Republic of Korea.

Background: Acute kidney injury (AKI) is common in patients with cancer because of malignancy itself, treatment regimen, contrast exposure and coexisting morbidities. However, epidemiology of AKI in cancer patient is still lacking.

Methods: We retrospectively assembled newly diagnosed cancer patients at Seoul National University Hospital between January 2004 and December 2013. Among a total of 106,004 cancer patients, we excluded patients with dual primary cancer, age under 18 years, advanced renal dysfunction with eGFR less than 15 ml/min/1.73m². Patients who could not define AKI due to lack of data were also excluded. AKI was defined as the KDIGO guideline. We categorized patients according to involved organs. We collected demographic information, comorbidities such as diabetes and hypertension, laboratory test results, and AKI episodes represented by CT contrast and treatment regimen including surgery and chemotherapeutic agents use. AKI incidence was showed as incidence rate estimated by the person-years at risk.

Results: After exclusion, we finally included 68,036 patients. Among them, 23,024 (33.8%) patients developed AKI after cancer diagnosis. More than half of AKI patients experienced single AKI events and 15.9% went through more than 5 times of AKI events. Interestingly, AKI in cancer patients tend to be increasing over time continuously. When compared AKI incidence rate according to cancer type, respiratory tract cancer revealed the highest incidence rate (209.5 cases/1,000 person-year), followed by genitourinary tract cancer (260.8 cases/1,000 person-year) and hematologic malignancies (217.1 cases/1,000 person-year). Patients with AKI experience were older, more men, and had more coexisting diseases such as diabetes and hypertension. They had lower initial renal function, lower serum albumin, and serum hemoglobin. In addition, they exposure more frequent contrast CT scan and chemotherapeutic agents.

Conclusions: In this study, we find that AKI events are increasing, and develop quite frequently and repetitively. Notably, respiratory tract cancer is proved to be the highest risk of AKI incidence. Not only demographic and co-existing factors but also treatment related factors may contribute to the AKI development.

SA-PO005

Obesity and Recovery from AKI: An Observational Feasibility Study

Helen L. MacLaughlin,1,4 Gerda K. Pot,4 Iain C. Macdougall,1 Christopher W. McIntyre,2 Nicholas M. Selby,2 King’s College Hospital, London, UK, 1University of Nottingham, Derby, UK, 2London Health Sciences Centre, London, ON, Canada; 3Diabetes and Nutritional Sciences Division, King’s College London, London, UK.

Background: Acute kidney injury (AKI) occurs in 35% of hospital admission in the UK, and is associated with an increased risk of developing or worsening chronic kidney disease (CKD). The effect of obesity on recovery of kidney function after AKI, and the combined risk of obesity and AKI on subsequent development of CKD is not known.

Methods: A study was conducted to determine the feasibility of recruitment, retention and data collection procedures for the planned Ob-AKI cohort study in a sample of 100 patients hospitalised with an episode of AKI. Feasibility outcomes for recruitment, retention and exploratory measures of recovery from AKI (75% of pre-AKI eGFR and development/progression of CKD (decrease in eGFR of ≥25% + rise in CKD category) were examined by BMI (25, 25-29.9, ≥30) over 12 months. Potential participants were identified by referral and electronic detection of episodes of AKI during hospital admissions. Inclusion criteria were 18-85 years, episode of AKI (KDIGO 2012), and pre-AKI creatinine measurement within the last 12 months.

Results: 41% of eligible patients consented to participate in the study, exceeding the feasibility target of 15%. 101 patients were recruited to the study (67M, 34F, mean age 63.5 (± 12.6) years and mean BMI 29.9 kg/m², range 18.1 to 54.3 kg/m²; 28.3% with stage 1, 21.2% stage 2 and 50.5% stage 3 AKI. Retention was 86% at 6 months and 80% at 12 months; there were 10 deaths and 3 patients commenced dialysis during the study. There were 17 incomplete Ob-AKI follow-up, 11 (65%) stated reasons represented by CT scan and chemotherapeutic agents use. AKI incidence was showed as incidence rate estimated by the person-years at risk.

Conclusions: We have demonstrated that it is feasible to perform long term observational studies addressing AKI outcomes associated with obesity. A fully powered prospective cohort study to examine the relationships between obesity and outcomes after AKI is warranted.

Funding: Government Support - Non-U.S.

SA-PO006

Survival after Initiation of Renal Replacement Therapy for AKI

Cirrhosis Andrew S. Allegritti,2 Xavier F. Parada,3 Nwamaka D. Encanya,2 Raymond T. Chung,1 Ravi I. Thadhani,2 Hannah M. Gilligan.1 MGH, Boston, MA; 2Massachusetts General Hospital, Boston, MA.

Background: Mortality is high after initiation of renal replacement therapy for acute kidney injury in cirrhosis. Literature on the appropriateon of dialysis in hepatorenal syndrome is sparse and is confounded by liver transplant eligibility. An update on outcomes in the non-listed subgroup is needed. Our objective is to compare survival after initiation of renal replacement therapy in cirrhosis between hepatorenal syndrome and acute tubular necrosis, stratifying by liver transplant listing status.

Methods: Retrospective comparison of eGFR, systemic kidney injury, and mortality. A retrospective study of patients with cirrhosis acutely initiated on hemodialysis or continuous renal replacement therapy at five hospitals, including one liver transplant center. Multivariable regression and survival analysis were performed.

Results: 472 subjects were analyzed, 131 listed and 341 not listed for transplant. 24% (114/472) were alive at six months. Among those who did not receive a transplant, 14% (59/409) were alive at six months. Using stepwise regression, significant predictors of mortality were: non-listed transplant status, MELD score, age, admission to the intensive care unit, serum ALT, mechanical ventilation, and initiation with continuous renal replacement therapy. When stratified by transplant listing, adjusted Cox models showed similar survival between hepatorenal syndrome and acute tubular necrosis (HR 0.81 [95% CI 0.59, 1.11]; p = 0.19 among those not listed; HR 0.73 [95% CI 0.44, 1.19]; p = 0.21 among those listed).

Conclusions: After initiation of renal replacement therapy in cirrhosis, mortality is high at six months. Transplant listing status, MELD score, and indicators of critical illness best predicted mortality. Etiology of acute kidney injury (hepatorenal syndrome versus acute tubular necrosis) was not significantly associated with mortality.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO007

Inflammation and Malnutrition Are Predictors of Long-Term Outcomes after Postoperative AKI in Non-Cardiogenic Surgery

Masatoshi Nishimoto,1 Miho Tagawa,1 Takayuki Hamano,1 Kokubu Maiko,2 Masaru Matsui,2 Ken-ichi Samejima,1 Yasuhiro Akai,3 Yoshihiko Saito.2 1Nara Medical University, Kashihara, Japan; 2First Department of Internal Medicine, Nara Medical University, Kashihara, Japan; 3Osaka University Graduate School of Medicine, Suita, Japan.

Background: Previous studies showed that AKI is an independent predictor of long-term mortality after adjustment for comorbidities. However, these studies did not account for inflammation and malnutrition, which is associated with increased mortality in CKD.

Methods: This is a retrospective cohort study. Inclusion criteria were adult patients who underwent non-cardiac surgery under general anesthesia from 2007 to 2010. Exclusion criteria were urological or obstetric surgery, missing creatinine values, and preoperative dialysis. The exposure of interest was AKI, defined by KDIGO criteria, within 1 week postoperatively. Outcome variable was all-cause mortality. Statistical analyses were performed using Kaplan-Meier curve and Cox regression model.

Results: Among 1,704 patients, 129 developed AKI. During median follow-up of 3.9 years, the mortality of patients with AKI and without AKI were 27.9% and 14.7%, respectively. AKI was independently associated with all-cause mortality after adjustment for comorbidities. After further adjustment for C-reactive protein (CRP) and albumin, the association between AKI and mortality was not significant (Table). Among non-users of statin and users of statin, adjusted HR of mortality (AKI vs no-AKI) was 1.92 (1.32-2.81) and 0.57 (0.15-2.23), respectively.

Conclusions: Attenuation of the association between AKI and all-cause mortality by adjustment for albumin and CRP suggested that inflammation and malnutrition, which predisposing patients to AKI, are predictors of increased all-cause mortality after AKI. Anti-inflammatory agents, such as statins, may improve long-term outcome after AKI.

The association between postoperative AKI and all-cause mortality

Model 1 was adjusted for age, sex, eGFR, and history of DM, hypertension, malignancy, and cardiovascular diseases.

SA-PO009

AKI and Associated Risk Factors for Mortality in Influenza Patients

Raymundo A. Sánchez, Luis I. Bonilla, Raymundo Vera, Israel A. Villegas-Gasson, Alan L. Reyes, Jesus Cruz Valdez, Lilia M. Rizo Topete. Hospital Universitario Dr. José Eleuterio González, Monterrey, Nuevo León, Mexico.

Background: In 2009, a pandemic of influenza A(H1N1) virus severely affected Mexico. Several reports described the presentation of this disease in critically ill patients. Acute kidney injury (AKI) and mortality showed high prevalence in these studies. AKI incidence has been reported between 33.6% and 51% in A(H1N1) patients, with mortality rates between 36.3% and 51%.

Methods: We conducted a retrospective, observational study in patients admitted to the ICU during the 2016-2017 influenza season. All patients were diagnosed as ARDS and had suspicion of influenza infection. We obtained demographic, clinical and laboratory data. AKI was defined according to Acute Kidney Injury Network criteria. Patients were divided into two groups, survivors and non-survivors.

Results: 30 patients were included in the study: 20 (66.6%) were male, median age was 46 (IQR: 19.9, 61.9). Mortality in the ICU was 60% and AKI was present in 66.6% of the patients. The mean APACHE II score was 24.2 ± 7.97, mean stay in ICU was 10 days (IQR: 6-15). Use of double vasopressor in 14 (46.6%). All patients required invasive mechanical ventilation with PEEP 10.3 (±6.8), PaO2/FIO2 126.42 (IQR: 11.2, 171.25), tidal volume of 185 (IQR:150-205). The diagnosis of influenza was confirmed in 12 (40%), 3 (16.7%) with influenza rapid diagnostic test (RIDTs) and 9 (33.3%) by reverse transcriptase PCR (RT-PCR); of the 5 (41.6%) confirmed influenza A(H1N1) patients. The main comorbidities recorded were obesity (n=14, 46.7%), smoking (n=12, 40%), and diabetes type 2 (n=11, 36.7%). The risk factors associated with mortality were obesity OR=2.62 (IC=0.81-8.72, p=0.02), A(H1N1) influenza infection confirmed by PCR OR=3.824 (IC=1.006-14.536, p=0.016), presence of AKI OR=2.8 (IC=1.184-6.622, p=0.18), specially KDIGO 3 OR 10 (p=0.007), and renal replacement therapy (RRT) OR=11 (IC=1.164-103.94, p=0.018).

Conclusions: Influenza A(H1N1) is still a cause of great morbidity and mortality in the young Mexican population. In our cohort we found consistent data that can help the treatment of these patients in the setting of the ICU. The presence of acute kidney injury, obesity, and the need for RRT were strong risk factors for mortality in this study. Modifiable factors should be early identified to improve outcomes in critically ill.

SA-PO010

Differential Trends in Incident Rates of AKI by Severity Stage in the Irish Health System

Leonard Browne,1,2 Alaa Mohamed Alamain Abdelnaim Mohamed Ala3,4 Arunkumar Aruna udayakumar,4 Rajiv Saran,3,4 Austin G. Stack,3,4 1Graduate Entry Medical School, University of Limerick, Limerick, Ireland; 2Kaiser Permanente Northern California, Oakland, CA; 3University of California, San Francisco, San Francisco, CA.

Background: Surveillance of Acute Kidney Injury (AKI) is a fundamental component of prevention strategies in health systems in order to reduce adverse outcomes. Recent studies have shown rising incident trends for dialysis-requiring AKI. We determined incident risks of first AKI by stage from 2005-2014 in the Irish Health System.

Methods: We utilised data from the National Kidney Disease Surveillance System in Ireland to explore trends in incident AKI within the health system from 2005 to 2014 (n=453,509). AKI events were identified per KDIGO guidelines and classified by stage (1 to 3) and incidence rates per 100 patients were calculated for each year. Multivariable logistic models explored the relationship of calendar year with AKI incidence expressed.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
as odds ratio (OR) and 95% Confidence Intervals (CI) with adjustment for age, sex, county of residence, location of medical supervision and laboratory indicators of health.**

**Results:** From 2005 to 2014, incidence rates of AKI per 100 patients increased from 5.5 % (5.4, 5.7) to 11.8 % (11.4, 12.1) in Stage 1; 0.58 % (0.53, 0.63) to 1.32 % (1.19, 1.45) in Stage 2; and from 0.46 % (0.41, 0.51) to 0.71 % (0.61, 0.81) in Stage 3. With adjustment for age, sex and baseline eGFR, a pattern of increasing odds of AKI was observed across all 3 stages (P<0.001 for trend). With further adjustment for county of residence, hospital, location of medical supervision and laboratory health indicators, a rising trend in incidence was observed only AKI Stage 1, while the reverse was seen for AKI Stage 2 and 3 (Figure 1), all P<0.001.

**Conclusions:** Increasing incidence of Stage 1 AKI is primarily responsible for overall growth of AKI in the Irish Health System. Accounting for changing demographic, clinical and geographic profiles, incident rates of Stage 2 and Stage 3 AKI have fallen in recent years and suggest improved preventive strategies.

---

**SA-PO012**

**Prevalence and Variation of Best Practices in AKI: A Multi-Center Study**

**Poster**

Francis P. Wilson,1 Aditya Biswas,2 Dennis G. Moledina,3 Sherry Mansour,4 Chirag R. Parikh,4 None, New Haven, CT; 2 Yale University, New Haven, CT; 3 Yale School of Medicine, New Haven, CT; 4 Yale University and VAMC, New Haven, CT.

**Background:** AKI is common in hospitalized settings and is associated with increased morbidity, mortality, and length of stay. While there is no specific therapy for AKI, guidelines recommend certain best practice measures that could potentially form the basis of a standardized set of responses to AKI and the implementation of an AKI “report card”. Adherence to such metrics in real-world settings is unknown.

**Methods:** Using guidelines published by the Kidney Disease: Improving Global Outcomes and National Institute for Health and Care Excellence, we identified four potential universal best practice metrics for hospitalized patients post-AKI including: subsequent creatinine measurement, urinalysis, urine output monitoring and avoidance of certain nephrotoxins (including aminoglycosides, non-steroidal anti-inflammatory drugs, and contrast media). We examined patients with AKI at three Connecticut hospitals to determine the rates of performance of these best practices within 24 hours of AKI onset. Patients discharged within 24 hours of AKI onset were excluded.

**Results:** Over three years, we identified 26,333 individuals (49.8% male, 18% black) with AKI based upon KDIGO-Creatinine criteria. The Table documents the rates of best practices across the three study hospitals and demonstrates significant variation. A multivariable model demonstrated that male patients, patients those with private insurance, and those with electrolyte abnormalities at AKI onset had more best practices performed. Of those without a creatinine measurement within 24 hours of AKI, 13.8% had progression to a higher stage of AKI, 1.5% went on to inpatient dialysis, and 6.2% died during the hospitalization.

**Conclusions:** Adherence to AKI best practice varies by hospital, ward, and patient factors. Standardization of best practice guidelines may help to reduce variation and improve outcomes.

**Funding:** NIDDK Support

**Table 1 - Performance of Best Practices**

<table>
<thead>
<tr>
<th>Practice</th>
<th>YNH</th>
<th>SRH</th>
<th>BH</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subsequent Creatinine, %</td>
<td>68.0</td>
<td>56.3</td>
<td>57.0</td>
<td>51.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinalysis, %</td>
<td>75.3</td>
<td>38.6</td>
<td>42.5</td>
<td>47.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urea Drainage Monitoring, %</td>
<td>94.6</td>
<td>76.7</td>
<td>96.2</td>
<td>88.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relative Availability, %</td>
<td>92.4</td>
<td>92.1</td>
<td>94.1</td>
<td>92.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table: Performance of best practice metrics at 3 study hospitals. YNH = Yale New Haven Hospital, SRH = St. Raphael Hospital, BH = Bridgeport Hospital

---

**SA-PO013**

**Evaluation of the Accuracy of Estimated Baseline Serum Creatinine for Diagnosis of AKI in the Japanese Population**

Taro Horimoto,1 Yutaka Hatakeyama,2 Tatsuki Matsumoto,3 Keitaro Nagata,4 Kosuke Inoue,5 Yoshiro Terada,5 Yoshiyasu Okuhara.2

Kochi Medical School, Nankoku, Japan

**Background:** Modern epidemiologic studies of acute kidney injury (AKI) have been facilitated by the increasing availability of electronic medical records. However, pre-morbid reference serum creatinine (SCr) data are often unavailable in such records. Investigators substitute estimated baseline SCr with the eGFR 75 approach, instead of using actually measured baseline SCr. Here, we evaluated the accuracy of estimated baseline SCr for AKI diagnosis in the Japanese population.

**Methods:** Inpatients and outpatients aged 18-80 years were retrospectively enrolled. AKI was diagnosed according to the Kidney Disease: Improving Global Outcomes criteria, using SCr levels. The non-AKI and AKI groups were selected using the following criteria: increase 1.5 times greater than baseline SCr, “baseline SCr” or increase 0.3 mg/dL greater than baseline SCr in 48 h, “increase in 48 h”. AKI accuracy defined by the estimated reference SCr, the average SCr value of the non-AKI population, eb-GFR-A approach, or the back-calculated SCr from fixed eGFR = 75 mL/min/1.73 m2, eGFR 75 approach, or eGFR-B approach in this study, was evaluated.

**Results:** We analyzed data from 131,358 Japanese patients. The number of patients with reference baseline SCr in the non-AKI and AKI patients were 29,834 and 8,952, respectively. For AKI patients diagnosed using “baseline SCr”, the AKI diagnostic accuracy
rates as defined by eGFR-A and eGFR-B were 63.5% and 57.7%, respectively, while in AKI-diagnosed using “increase in 48 h”, the AKI diagnostic accuracy rates as defined by eGFR-A and eGFR-B were 78.7% and 75.1%, respectively. In non-AKI patients, false positive rates of AKI misdiagnosed via eGFR-A and eGFR-B were 7.4% and 6.8%, respectively.

Conclusions: AKI diagnosis using the average Scr value of the general population may yield more accurate results than diagnosis using the eGFR 75 approach when the reference Scr is unavailable.

**SA-PO014**

Racial Differences in the Risk for AKI after Cardiac Surgery

James F. George,1 Rongbing Xie,1 Margaret Tresler,1 James K. Kirklin,1 Anupam Agarwal,2 1Surgery, University of Alabama at Birmingham, Birmingham, AL; 2Medicine, University of Alabama at Birmingham, Birmingham, AL. 1Department of Veterans Affairs, Birmingham, AL.

**Background:** The effects of race on developing AKI following cardiac surgery are unknown. To determine the extent of this disparity, we studied risk factors for AKI after cardiac surgery at a tertiary referral center.

**Methods:** AKI was defined using the KDIGO working group definition. Pre-op or baseline creatinine (CRE) was defined as the minimum value within 30 days before surgery. Post-op CRE was defined as the maximum value within 48 hours after surgery. Post-operative risk factors for AKI were determined using multivariable logistic analysis to predict the probability of AKI KDIGO stage ≥1.

**Results:** Among 5347 patients (pts) who underwent cardiac surgery between July 1, 2010 and December 31, 2015, the study included 2175 pts who had coronary artery bypass surgery (CABG), valve surgery (valve procedure, or combined CABG and valve procedures), or coronary artery disease alone (1309, 38.5%), or combined CABG procedures (279, 13%). The remaining 3172 pts were excluded due to concomitant other surgery, assist devices, a priori dialysis, race other than black or white, death or discharge within 48 hours, or missing CRE values. 1791 of included pts were white (82%) and 382 were black (18%). 1589 pts were KDIGO-0, 522 were KDIGO-1, and 62 were KDIGO≥2. By multivariable analysis, factors predictive (p<0.001) of KDIGO stage ≥1 included black race (OR 1.57, p<0.0005), increased BMI at time of surgery (OR 1.02, p=0.0001), older age (OR 1.02, p=0.0001), number of diseased vessels (OR 1.21, p=0.0001), and mitral valve procedure (OR 2.05, p=0.0007). Mean pre-op CRE among blacks was 1.21 (0.9-1.3, 25th to 75th percentile) and 1.07 (0.8-1.2) in whites, a difference of 0.14 (p<0.0001). Mean post-op CRE among blacks was 1.45 (1.0-1.6) and 1.22 (0.9-1.4) in whites. Notably, the mean difference between pre-op and post-op CRE was significantly larger in blacks at 0.24 (0.0-0.3) versus 0.15 (0.0-0.3) in whites (p=0.0011). Review of Medicare billing data showed 53 (3%) whites and 20 (5%) blacks received a Nephrology consult during hospitalization (p=0.03). Only 16 (1%) of white and 9 (2%) of blacks required dialysis (p=0.02).

**Conclusions:** Black race was a significant risk factor for AKI after cardiac surgery, with blacks exhibiting larger increases in CRE after surgery. These results indicate that a larger, multicenter study examining race and AKI post-cardiac surgery is clearly warranted and tailored interventions to prevent AKI in blacks are needed. Funding: Clinical Revenue Support

**SA-PO015**

Risk Factors for Community-Acquired AKI in Patients with and without CKD and Impact of Its Initial Management on Prognosis: A Prospective Observational Study

Patrick Underdown,1 Fabien Stucker,1 Thomas Perneger,1 Cyrus Samii,2,3 Swords F. Martin,1 1Nephrology, Unité Hospital de la Providence, Neuchâtel, Switzerland; 2Department of Clinical Epidemiology, Geneva University Hospitals, Geneva, Switzerland; 3Department of Nephrology, Geneva University Hospitals, Geneva, Switzerland.

**Background:** We aimed to describe clinical characteristics of patients with community-acquired acute kidney injury (CA-AKI), the effectiveness of initial management of CA-AKI, its prognosis and the impact of medication on its occurrence in patients with previous chronic kidney disease (CKD).

**Methods:** We conducted a prospective observational study within the Emergency Department (ED) of a University Hospital including any patient > 16 years admitted with any diagnosis using the average Scr value of the general population as the dependent variable was used.

**Results:** From May 1st to June 21st 2013, there were 8646 admissions in the ED, of which 653 had an eGFR < 60 ml/mn/1.73m. Among them two have been of increasing interest: the Furosemide Stress Test (FST) and the Renal Angina Index (RAI). These two different approaches aim to identify patients at risk for subsequent AKI, and also have been used for the prediction of AKI severity. We assessed the performance of the two different approaches to identify patients at risk of AKI in an ongoing cohort of adult critically ill patients.

**Methods:** We analyzed data from 58 hospitalized patients admitted to a Medical ICU. We measured serum creatinine (cScr) every 24 hours for 7 consecutive days following ICU admission, and urinary volume was assessed hourly each 24 hours. At admission (day 0), RAI (1-40) was calculated using the following formula: Risk level (presence of sepsis = 1 point, presence of diabetes = 3 points, and vasopressors and use of invasive mechanical ventilation = 5 points) x Injury level (changes in cScr: no change = 1 point, 0.25-4.9% = 2 points, 25-50% = 4 points, 50% = 8 points); and we applied the FST at day 0 (as describe by Chawla et. al. in Crit Care 2013 Sep 20; 17(5): R207). We assessed the performance of the FST and the RAI to predict the subsequent development of AKI using KDIGO sCr and urinary volume criteria.

**Results:** Of the 58 patients included in this study, 5 (8.6%) patients met the primary end point of AKI (cScr KDIGO criteria) and 4 (6.8%) using urinary volume KDIGO criteria. The performance of Furosemide Stress Test and the Renal Angina Index are shown on figure 1. Of note, we considered a cut-off point of <725 cc of urine at 2 hours for Furosemide Stress Test since none of the patients who developed AKI had >200 cc of urine at 2 hours as the original cut-off proposed value.

**Conclusions:** The Furosemide Stress Test and the Renal Angina Index have robust predictive capacity to identify critically ill patients at high risk of developing AKI before a rise in cScr occurs. These preliminary data of our ongoing study warrants future studies to validate these findings.

**Figure 1. Performance of the Furosemide Stress Test and the Renal Angina Index**

**SA-PO017**

Incidence and Costs of AKI in Hospitalized Patients with Infective Endocarditis

Katherine M. Donaldson,1 Mark Rudy,1 Daniel E. Cleland,4 Gaixin Du,1 Moises A. Huaman,1 Alice Thornton,1 Laura Fanucchi,1 Javier A. Neyra,2 1University of Kentucky Medical Center, Lexington, KY; 2University of Cincinnati, Cincinnati, OH; 3University of Alabama at Birmingham, Birmingham, AL; 4Hospital Obrero #2 - C.N.S., Cochabamba, Bolivia, Plurinational State of; 5Hospital Bayram, Asunción, Paraguay.

**Background:** Acute kidney injury (AKI) is a frequent complication of hospitalized patients with infective endocarditis (IE) and carries adverse outcome. We examined the incidence, costs and characteristics associated with AKI in hospitalized patients with IE.

**Methods:** Retrospective cohort study of patients with IE admitted to UK hospital from 1/2013 to 12/2015. IE was defined by the modified Duke criteria. AKI was defined by the serum creatinine-KDIGO criteria. Patients with end-stage renal disease, kidney transplant, or baseline eGFR<15 were excluded. Multivariable logistic regression analysis of AKI as the dependent variable was used.

**Results:** 297 patients were included in the analysis. Of these, 40.4% were women and 94.9% were white. Mean age (SD) was 45.2 (16.3) years. AKI occurred in 186 (66.0%) patients: 54 (29.0%) developed AKI within the first 72 h and 132 (71.0%) after 72 h of admission. AKI was more common in women than in men (70.8% vs 57.0%, p=0.016). Hospital mortality in patients with AKI was 18.8% vs 14.4% in those without AKI, p=0.33. Patients who developed AKI had a longer hospital stay: median (IQR) 30 (15-47) vs 9 (5-18) days, p<0.001. AKI occurred more often in patients of poor socioeconomic status, with a diagnosis of hepatitis B and C or bacteremia, with exposure to aminoglycosides or diuretics and a history of recurrent IE (all p<0.01). The median total direct cost of hospitalization in those with AKI vs without AKI was $1,488 ($23,325–73,985) vs $14,801 ($6,722–31,910), p<0.001. Female gender (OR 1.77, 95% CI 1.33–2.37), hepatitis C diagnosis (OR 1.98, 1.15–3.41) and comorbidity risk of mortality score=4 (OR 4.51, 2.64–7.69) were independently associated with incident AKI.

**Conclusions:** Two out of three hospitalized patients with IE develop AKI. Most episodes of AKI occurred after 72 h of hospital admission. Patients with AKI had a longer admission stay and higher mortality. AKI was associated with more disease complexity and increased costs.

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

Underline represents presenting author.

681
hospital stay, incurring higher total direct costs. Female gender, hepatitis C diagnosis and risk of mortality score ≥4 were independently associated with the occurrence of AKI in this susceptible population.

**Funding:** Other NIH Support - University of Kentucky Center for Health Services Research Data, Analytics, and Statistical Core

### SA-PO018

**AKI Associated with Antibiotic Exposure in Critically Ill Children**

Emily L. Joyce,1,2 Priyanka Priyanka,1 John A. Kellum.1 1The University of Pittsburgh, Pittsburgh, PA; 2Children’s Hospital of Pittsburgh, Pittsburgh, PA. Group/Team: Critical Care Nephrology, CRISMA.

**Background:** Acute kidney injury (AKI) is associated with adverse outcomes including prolonged hospital stay, increased healthcare costs, and delay in other organ recovery as well as development of chronic kidney disease. It is unclear which medications are associated with increased risk of AKI in critically ill patients.

**Methods:** Data was obtained from a convenience sample taken from the Pediatric HiDenIC database which contains > 12,000 critically ill patient records from the Children’s Hospital of Pittsburgh between 2010 and 2014. Patients were categorized regarding exposure to any antibiotic within the first 24 hours of ICU admission with subsequent development of AKI using KDIGO staging.

**Results:** Out of 2800 critically ill pediatric patient encounters, 18% developed stage 2 or 3 AKI within the first week of admission to the ICU. Those who developed AKI had a longer ICU length of stay (p<0.001), longer hospital length of stay (p<0.01) and higher mortality rate (p<0.001). Within the cohort, 2254 patient encounters (78%) were exposed to any antibiotic within the first 24 hours of ICU admission. On univariate analysis, exposure to antibiotics including cephalin (OR 1.59, n=225, p<0.01), linezolid (OR 3.59, n=28, p<0.001), piperacillin/tazobactam (OR 2.04, n=546, p<0.001), and vancomycin (OR 1.45, n=1028, p<0.001) was associated with increased odds of developing AKI.

**Conclusions:** AKI is prevalent in critically ill children and associated with poor outcomes. Antibiotic use in this population is common and is associated with increased risk for development of AKI.

**Funding:** NIDDK Support

### SA-PO019

**Direct-Acting Oral Antiviral Therapy in the Treatment of Chronic Hepatitis C Is Associated with an Increase in Serum Creatinine Levels**

Avinash G. Adiga,2 Praveen Ratnasiramatha.1 1Texas Tech University, Lubbock, TX; 2Texas Tech University Health Sciences Center, LUBBOCK, TX.

**Background:** The introduction of newer all-oral, direct-acting antiviral therapy in place of traditional interferon-based therapy has revolutionized the management of CHC infection. The aims of our study are to evaluate i) Renal adverse effects related to all oral direct-acting, antiviral therapy for hepatitis C (H) relationship between changes in viral load and renal function tests in chronic hepatitis C patients.

**Methods:** A retrospective study involving 164 patients with chronic hepatitis C infection followed up in outpatient clinics between October 1, 2014, and September 30, 2015. Ninety-five patients who received antiviral therapy were included as cases and sixty-nine patients who did not receive treatment were included as controls. Creatinine levels of cases were noted at four- time points: pre-treatment, at weeks, at the end of treatment (3 months), and at 12-week post-treatment (6 months) and at the similar time frame for controls. Patients with CKD stage 3 or more and patients with missing values were excluded.

**Results:** The rate of kidney disease in our study population is 8.7%. Baseline creatinine in the studied population was 0.92mg/dl. Viral clearance was seen in 98.9% of patients, who received the treatment. At the end of treatment, higher creatinine levels were seen in the treatment group than the control group. However, no significant differences in creatinine levels were seen at 6 months. Women were compared to baseline statistically significant increase in creatinine levels were seen at 3 months and 6 months were seen in both groups.

**Conclusions:** Serum creatinine levels are higher at the end of treatment in patients receiving anti-viral therapy when compared to controls. This difference tends to cease with further time duration. A decrease in the hepatitis C viral load is not associated with a concurrent decrease in creatinine levels.

### SA-PO020

**Reversible AKI from Erlotinib Due to Glomerular Endotheliosis**

Sheron Latcha,1,3 Victoria Gutgarts,1 Surya V. Seshan,2 1Memorial Sloan Kettering Cancer Center, New York, NY; 2Weill Cornell Medical Center, New York, NY; 3Medical College, Weill Cornell, New York, NY.

**Background:** Erlotinib is an oral epidermal growth factor receptor associated tyrosine kinase inhibitor approved for the treatment of metastatic non small cell lung (NSCLC) with exon 19 deletions or L858R substitution mutations. Renal toxicity is rare with one report of crescentic glomerulonephritis.

**Methods:** A 67 year old female with metastatic lung adenocarcinoma (+EGFR L858R) was sent for renal evaluation for AKI. At start of erlotinib, creatinine (SCr) was 0.9mg/dl and UA showed no proteinuria. Thereafter, the SCr increased. At evaluation, blood pressure (BP) was 146/72 (no change from baseline), no edema was present, UA showed 100+ protein and spot urine total protein creatinine ratio was 0.64. Renal biopsy showed diffuse glomerular endothelial injury, global glomerulosclerosis (16/44 glomeruli), mild to moderate acute tubular injury, moderate widespread tubular atrophy, severe arterio and arteriolar sclerosis and extensive arteriolar intimal hyalinosis. No proliferative or immune complex glomerular lesions were seen. The foot processes were partially effaced. Her disease had been well controlled on erlotinib so it was continued at a reduced dose. Subsequently it stopped for increases in SCr. After stopping erlotinib, the SCr decreased to 1.3mg/dl. Because of previously good response to an EGFR TKI, gefitinib was started. Subsequently, an increased SCr, proteinuria and BP were noted. At last followup on gefitinib, the BP was 167/83, no edema was present, SCr was 1.8mg/dl, a 24H urine collection showed 4.8gms of protein and there was no progression of disease on CAT scan.

**Results:**

**Conclusions:** Erlotinib treatment was associated with mild proteinuria and reversible AKI. The renal biopsy was consistent with glomerular endothelial injury which may be consistent with a mild form of thrombotic microangiopathy. The presence of significant arteriolar intimal hyalinosis may represent healed endothelial injury. The recurrence of AKI and worsening proteinuria with gefitinib may indicate that this is a “class effect” of EGFR TKIs.

### SA-PO021

**Carfilzomib Treatment and AKI in Patients with Multiple Myeloma**

Marianne Camargo,1,2 Kinsuk Chauhan,1 Steven G. Coca,1 Icahn School of Medicine at Mount Sinai, New York, NY; Nephrology, Mount Sinai Hospital, New York, NY.

**Background:** Carfilzomib is a selective proteasome inhibitor approved for the treatment of relapsed and refractory multiple myeloma in patients who have been previously treated with at least two other agents. Initial clinical studies reported renal injury in 25-33% of patients treated, yet clinical trials reported the incidence of acute
kidney injury (AKI) between 4-8% when compared to other anti-myceloma agents. Our objective was to evaluate the real-world incidence and severity of AKI that is presumed due to carfilzomib treatment.

**Methods:** Electronic medical record (EMR) data was extracted from patients who received carfilzomib between 1/2012 and 12/2016 at a major academic medical center. Data included baseline demographics, medical history, and laboratory results including baseline creatinine and follow-up values during the course of treatment. AKI was defined as rise in creatinine by 0.3mg/dl or by 1.5 times increase from baseline. To estimate the incidence of AKI, a Poisson regression was used, adjusting for age, gender, kapa-lambda ratio, adjusted serum calcium, and history of hypertension, heart failure, and chronic kidney disease.

**Results:** Out of 429 patients identified between 1/2012-12/2017, 86 patients had received more than one dose of carfilzomib and had complete data. The average age was 65 years old, 42% women, 51% White. Forty-one percent of patients had at least one event of AKI. AKI was more common in women (IRR 2.2, 95% CI 1.7-2.8, p<0.01), older age (IRR 1.02 for each year of age, 95% CI 1.01-1.03 p<0.01), and African Americans (IRR 4.75, 95% CI 3.05-7.39, p<0.01).

**Conclusions:** Carfilzomib is a third line therapeutic agent for patients with refractory/relapsed multiple myeloma. Our analysis showed higher incidence of AKI events when compared to previous trials. Further studies are needed to clarify the epidemiology and risk factors for AKI in this population.

**SA-PO022**

**Weighting the AKI Risk of Individual Nephrotoxins**

**Karvin Yonekawa,** Luc Chuan Zhou. 
Seattle Children’s Hospital/ UW, Seattle, WA; Seattle Children’s Research Institute, Seattle, WA.

**Background:** Seattle Children’s Hospital’s AKI surveillance system monitors the use of nephrotoxic medications and nephrotoxic-related AKI. An alert to the prescriber is triggered when ≥3 nephrotoxins are ordered. Our current system’s sensitivity is 32% in detecting nephrotoxin-related AKI. To improve surveillance, we aimed to determine an individual risk weight for each nephrotoxin and develop a new alert system based on a scoring rule rather than on the number of nephrotoxins prescribed.

**Methods:** Nephrotoxin orders and AKI alert information (n=23,744) for 2 years (2013-2015) from a large tertiary care children’s hospital were analyzed. A risk weight was constructed for each nephrotoxin using the estimated probability of AKI when the nephrotoxin was present (either alone or in combination with other nephrotoxins). Nephrotoxic medication orders were scored by totaling the constructed risk weights of the individual nephrotoxins. We conducted ROC analysis on the final scores to determine alert thresholds and assess sensitivity and specificity.

**Results:** Using a total score threshold of 16 to trigger an alert, our model system’s sensitivity and specificity was 70% and 80%, respectively. A total score threshold of 14 delivered a sensitivity of 83% and a specificity of 75%.

**Conclusions:** A surveillance system using individual risk weights for nephrotoxins and a scoring rule better improved nephrotoxin-related AKI detection. Additional work is needed to expand our analysis beyond the original list of suspected nephrotoxins to include other medications frequently prescribed in patients who are at risk for AKI.

**Individual Weights of Nephrotoxins**

<table>
<thead>
<tr>
<th>Nephrotoxin</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>CICLOSPORIN</td>
<td>&gt;16</td>
</tr>
<tr>
<td>DOPOCAPERE</td>
<td></td>
</tr>
<tr>
<td>CYCLOSPORINE</td>
<td></td>
</tr>
<tr>
<td>GANCILOVIR</td>
<td></td>
</tr>
<tr>
<td>TORKAMYCN</td>
<td></td>
</tr>
<tr>
<td>PIPERACILIN</td>
<td>15</td>
</tr>
<tr>
<td>TAZOBACTAM</td>
<td></td>
</tr>
<tr>
<td>VANCYCIOL</td>
<td></td>
</tr>
<tr>
<td>SORBI MUS</td>
<td></td>
</tr>
<tr>
<td>VAGANCILVOR</td>
<td></td>
</tr>
<tr>
<td>ELOPAVL</td>
<td></td>
</tr>
<tr>
<td>INDOSTHEACIN</td>
<td>13</td>
</tr>
<tr>
<td>CYTAMDRINE</td>
<td>12</td>
</tr>
<tr>
<td>ACYCLOVIR</td>
<td>11</td>
</tr>
<tr>
<td>AMRACIN</td>
<td></td>
</tr>
<tr>
<td>TACOLIDUS</td>
<td></td>
</tr>
<tr>
<td>OTAMYDRUM</td>
<td></td>
</tr>
<tr>
<td>GENTAMICIN</td>
<td>10</td>
</tr>
<tr>
<td>CAPROPLATIN</td>
<td></td>
</tr>
<tr>
<td>CAPDPILRE</td>
<td></td>
</tr>
<tr>
<td>METOPROXATE</td>
<td>9</td>
</tr>
<tr>
<td>KYPOL</td>
<td></td>
</tr>
<tr>
<td>LSONOPIL</td>
<td></td>
</tr>
<tr>
<td>NEOMYCIN</td>
<td>7</td>
</tr>
<tr>
<td>LOMYTAN</td>
<td>6</td>
</tr>
<tr>
<td>ASIDYN</td>
<td>4</td>
</tr>
<tr>
<td>NAPROFEN</td>
<td>2</td>
</tr>
<tr>
<td>ILUPROPIN</td>
<td></td>
</tr>
<tr>
<td>BUDORFIC</td>
<td></td>
</tr>
<tr>
<td>KETORACOL</td>
<td></td>
</tr>
<tr>
<td>CISPLATIN</td>
<td>1</td>
</tr>
<tr>
<td>PENTASANTINE</td>
<td></td>
</tr>
<tr>
<td>PARPROGATATE</td>
<td></td>
</tr>
<tr>
<td>MELESHAGINE</td>
<td></td>
</tr>
<tr>
<td>MILIOVACM</td>
<td></td>
</tr>
<tr>
<td>ENALAPRILAT</td>
<td></td>
</tr>
</tbody>
</table>

**SA-PO023**

**Association between Statin Therapy and Occurrence of AKI in Patients with Peripheral Artery Diseases**

**Hideki Fuji, Shinichi Nishi.** Division of Nephrology, Kokagawa Central City Hospital, Kokagawa, Japan; Division of Nephrology and Kidney Center, Kobe University Graduate School of Medicine, Kobe, Japan.

**Background:** Acute kidney injury (AKI) is an important clinical problem in diagnosis and treatment of cardiovascular diseases. Though many studies have reported that statin therapy before coronary angiography and/or intervention significantly decreased the occurrence of AKI, the association between pretreatment by statin and occurrence of AKI in patients with peripheral arterial diseases (PAD) remains unclear. Therefore, we researched the association between statin therapy and occurrence of AKI in patients with PAD.

**Methods:** We retrospectively analyzed data from the endovascular treatment (EVT) database in our hospital. The angiography and/or intervention for PAD were performed for 377 patients between October 2011 and March 2016. Sixty nine hemodialysis patients and 13 patients without sufficient data were excluded from a present study. Remaining 295 patients were enrolled and divided into the two groups; those without statin (control group; N=157) and those with statin (statin group; N=138) for at least one months before admission. AKI was defined by absolute increase in serum creatinine (SCr) of ≥0.5 mg/dl or a relative increase of ≥25% measured 1 week after procedure.

**Results:** Before procedure, sex, SCR, amount of contrast medium, use of renin angiotensin system inhibitor, smoking and blood pressure were similar in both group. The statin group has significantly younger patients, more diabetes patients, higher body mass index (BMI) and lower low density lipoprotein-cholesterol (LDL-C) (100±32 mg/dl vs 108±31 mg/dl) than the control group. As for occurrence of AKI, there was significantly lower incidence in the statin group compared to the control group (5% vs 16%, p=0.05). We performed a multivariate analysis adjusted for age, BMI, diabetes mellitus, LDL-C, MCR and statin therapy. The multivariate analysis showed that statin therapy was significantly correlated with the lower occurrence of AKI (p<0.05).

**Conclusions:** The results of our study suggested that statin therapy may prevent the occurrence of AKI after angiography and/or intervention for PAD.

**SA-PO024**

**Hydration Protocols with Cisplatin: Need for Consensus and Cost Curtailment**

**Sanjibha Manohar, Won gang Kim, Jennifer Mc Donald, Jeffrey A. Betcher, Heidi D. Finnnes, Nelson Leung. Mayo Clinic, Rochester, MN.**

**Background:** Platinum based drugs use is often restricted due to the high risk of nephrotoxicity. The incidence of nephrotoxicity for Cisplatin is reported to be 25-30%. Many nephroprotective measures have been studied with hydration being the most commonly used. We sought to compare the incidence of Acute Kidney injury (AKI) at two large tertiary referral centers that use different nephroprotective protocols.

**Methods:** We retrospectively reviewed all adult patients that received first dose of Cisplatin at Mayo Clinic Rochester (MCR) and Arizona (MCA) from 2010-2015 and had at least one creatinine value 7 days before and 72 hours after the drug administration. MCR utilizes a limited dose dependent hydration fluid with mannitol in the bag containing Cisplatin whereas MCA uses a liberal 1 liter pre- and post-hydration without mannitol.

**Results:** Out of the 2188 patients that had received Cisplatin at the 2 centers, only 191 patients met the inclusion criteria. Among them the overall incidence of AKI was 9.4% (191/1911) with MCR having 10% (111/110) and MCA 8.6% (7/81) and the difference was not statistically significant. Only one patient had the AKIN Stage 2 AKI and the rest were AKIN Stage 1. The average dose of Cisplatin received was higher in MCA (85.5 mg vs 74.9 mg) which was statistically significant (p<0.05). The average dose of fluids was 1316.7 ml (SD 615) in the 2 cohorts. There was no significant difference in the age, gender, history of chronic kidney disease, diabetes, hypertension, baseline creatinine, 30 day hospitalization and time to death after initiating chemotherapy among the two cohorts.

**Conclusions:** Our study showed that despite the marked differences in the nephroprotective protocols used at each of the center there was no difference in the AKI rate. In this time when the need for cost effective medicine is paramount we must try to be judicious in the use of drugs we use. We have since converged our Cisplatin hydration protocol, to be dose directed and without routine mannitol use, across the Mayo Clinic enterprise.

**SA-PO025**

**The Risk of Contrast Induced AKI Is Still Present Despite Normal Renal Function**

**Jasarat Chowdhury, Seema Jain, Masud Khan, Jasmine B. Lee. Acute Medicine, Lewisham and Greenwich NHS Trust, London, United Kingdom.**

**Background:** Indicated contrast CT studies are a common investigation for patients admitted to hospital. Contrast induced AKI (CI-AKI) is quoted to be the third most common contributor to in hospital AKI with patients with pre-existing CKD, cardiac dysfunction, diabetes and hypertension most at risk. However these studies were done before newer, low osmolality contrast media was common practice. This study investigates the incidence of CI-AKI in patients admitted to a UK district general hospital who underwent contrast CT studies.

**Methods:** All patients who had contrast CT studies over a 2 week period in November 2016 were included in the study. For these studies a nonionic low osmolality contrast agent was injected. CI-AKI was defined using the KDIGO classification for AKI.

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

*Underline represents presenting author.*
Results: 92 patients had contrast CT studies over the time period. Of these patients, 13% had pre-existing CKD, 11% had cardiac dysfunction, 15% had Diabetes and 36% had Hypertension. 5% of patient developed CI-AKI. 4% had stage 1 and 1% had stage 2, no patients had stage 3. However of the 5 patients who developed CI-AKI, none had pre-existing CKD or cardiac dysfunction, 1 had diabetes and 2 had hypertension.

Conclusions: The incidence of CI-AKI in our cohort was lower and less severe than quoted in previous studies which may be due to the lower omoality contrast agent used. However, despite risk factors being present in this cohort, none of the patients who developed CI-AKI had pre-existing CKD which is thought to be the most significant risk factor and therefore features most highly in CI-AKI prevention guidelines. This study suggests that guidance given to prevent CI-AKI should be followed in all patients irrespective of pre-existing risk factors and that having existing CKD should not preclude a contrast study if necessary.

SA-PO026

Risk Factors for Polymyxin-Induced AKI in Critically Ill Patients

Cassiane D. da Fonseca,1 Fatima S. Coelho,1 Natalia A. Oliveira,1 São Paulo, Brazil; 2Organization University of São Paulo, São Paulo, Brazil; 3University of São Paulo, São Paulo, Brazil; 4School of Nursing, University of São Paulo, Carapicuiba, Brazil; 5Universidade de São Paulo, SÃO PAULO, Brazil; 6University of Sao Paulo, Sao Paulo, Brazil. Group/Team: Research Group on Acute Kidney Injury-GERA.

Background: Critically ill patients with infections and sepsis frequently need robust antimicrobial agents, such as polymyxins (Pmxs), for efficacy against multi-resistant gram-negative bacteria. However, acute kidney injury (AKI) may be the most important limiting adverse effect of Pmxs. This study evaluated the incidence and identified the risk factors for the development of AKI in critically patients receiving Pmxs.

Methods: A multicenter retrospective cohort study enrolling 1099 intensive care patients Wwas performed. AKI was defined by KDIGO criteria. Primary outcome was patients who received Pmxs and developed AKI. The main secondary outcomes were clinical risk factors for Pmxs-induced AKI. Multivariate analyses with logistic regression were performed.

Results: A total of 936 patients were included. AKI was detected in 404 (43%) patients. Mean age was 59.1±17.0 years, 63% were male. Systemic arterial hypertension (45%), Diabetes Mellitus (26%), sepsis (22%) and shock state (57%) were observed in AKI individuals. The mortality was 37% for AKI patients (P=0.001). Among 75 patients treated with Pmxs, rate of AKI was 88%. The risk factor of AKI associated with Pmxs was prolonged hospital stay, mechanical ventilation and shock state (P<0.001).

Conclusions: This data highlighted that the rate of Pmxs-induced AKI was greater than other studies. Critically ill patients are at higher risk due to the presence of prolonged hospital stay, mechanical ventilation and shock state.

Funding: Government Support - Non-U.S.

Risk factor of AKI associated polymyxins use

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.05 (0.01)</td>
<td>0.009</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.3 (1.16-14.5)</td>
<td>0.006</td>
</tr>
<tr>
<td>Vasoactive-drug</td>
<td>0.59 (2.03)</td>
<td>0.212</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>1.57 (1.0-1.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Clinical hospitalization</td>
<td>1.39 (0.2-2.2)</td>
<td>0.33</td>
</tr>
<tr>
<td>ICU/hospital stay</td>
<td>1.09 (1.0-1.1)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Figure 1. Survival curve of patients in use of polymyxins.

SA-PO027

Vancomycin-Associated AKI with a Steep Rise in Serum Creatinine

Juan Carlos Q. Velez,1 Ndidiamaka O. Obadan,2 Mohamed Alzubaidi,2 Bhavna Bhasin,1 John M. Arthur,2 Gautam M. Phadke,1 Medical College of Wisconsin, Milwaukee, WI; 3Medical University of South Carolina, Charleston, SC; 4University of North Dakota School of Medicine, Fargo, ND; 5Department of Nephrology, Ochsner Clinic Foundation, New Orleans, LA; 6University of Arkansas for Medical Sciences, Little Rock, AR.

Background: The incidence of vancomycin-associated (VA) acute kidney injury (AKI) has increased after the Infections Diseases Society of America updated their recommendations for higher therapeutic trough levels for methicillin-resistant Staphylococcus aureus infections. However, distinct laboratory features of VA-AKI have not been described.

Methods: We defined precipitous AKI as a case with an increase in serum creatinine (sCr) ≥ 1.5 mg/dL/day. After encountering 2 cases of adults with VA-AKI presenting with an unusually steep rise in sCr, we probred for similar cases by surveying nephrologists at the American Society of Nephrology Communities online forum and by searching for published cases of VA-AKI via PubMed or Google to extract those with criterion for precipitous AKI. We also collected daily sCr values of consecutive AKI cases not associated with vancomycin exposure as a control group (non-VA-AKI).

Results: Seven original cases of VA-AKI characterized by an abrupt and exceedingly large rise in sCr shortly after a cumulative dose of vancomycin of ≥ 5 g given over 1 - 4 days were compiled from 4 different medical centers (mean age 41.6 years, 43% women, 57% black, mean body mass index 32 kg/m2). In 3 cases, simultaneously obtained serum cystatin C (sCy) values did not reveal relative steep increments from the upper limit of normal: mean: 2.6 ± 1.5 mg/dL, for sCr and sCy respectively, suggesting that the reductions in glomerular filtration rate were overestimated by the sCr increase. In addition, we extracted 4 published cases of precipitous AKI due to vancomycin. The median initial 24-hour rise in sCr in all 11 VA-AKI cases compiled was 2.5 mg/dL, (range 1.4 – 3.5 mg/dL). The slope of the initial 48-hour sCr rise of the VA-AKI (n = 11) cases was greater than that of non-VA-AKI (n = 44) cases [2.01 (CI: 1.6-2.4) vs 0.61 (CI: 0.5-0.7) mg/dL/day; p=0.0001]. A concomitant steep rise in blood urea nitrogen was not observed in these VA-AKI cases.

Conclusions: VA-AKI can occasionally manifest with a precipitous rise in sCr after a high cumulative dose of vancomycin. True toxic tubular injury overrepresented by the sCr rise is possibly present in these cases. Whether interference of vancomycin with tubular secretion of creatinine explains the phenomenon requires further study.

SA-PO028

Colistimethate Sodium and AKI: Incidence, Evolution, Risk Factors, and Prognosis

Saulo Pampa-Saico, Hospital Ramon y Cajal, MADRID, Spain.

Background: Colistimethate sodium (CMS) treatment has increased in the last years due to exponential increase in multidrug-resistant bacterial infections with the risk of CMS nephrotoxicity. The aim of this study was to determine the incidence and risk factors of AKI attributable to CMS based on KDIGO criteria. To identify prognostic factors which conditioning kidney function outcome at six months of follow-up.

Methods: Retrospective observational study, including patients >18 years old admitted from January 2007 to December 2013 who received CMS for > 48hours. Demographic, clinical and biochemical parameters of potential interest were collected. A multivariate logistic regression analysis was used to identify the risk factors associated with the development of AKI. To evaluate the renal function outcomes at 6 months after discharge (by eGFR (MDRD-4)) were analyzed by multivariate lineal regression. Unfavorable kidney evolution at six months was defined as residual impairment of kidney function indicated by a eGFR less than 60 ml/min/m2 or a reduction of creatinine clearance ≥25% at 3 months in comparison with baseline.

Results: 126 patients (mean age 64.4±14 years) were included in the study; 61 patients developed AKI (48%). Independent predictors of AKI were the infection grade: severe sepsis (OR 3.1; p=0.026); septic shock (OR 11.9; p<0.0004), intravenous iodinated contrast media (OR 2.9; p=0.024) and serum creatinine at hospital admission (OR 2.9, p=0.031). Eighty-four patients (67%) survived at discharge. Independent predictors of decline in renal function after 6 months were eGFR at hospital admission (p=0.0016) and hospital discharge (p=0.0004) (R2 = 0.832), 56% (34/61) patients who developed AKI during admission survived, 32% of them (11/34) had an unfavorable kidney outcome at 6 months, the main determinants were eGFR at hospital admission (p=0.023), at the start CMS (p=0.002) and at hospital discharge (p=0.0003).

Conclusions: The development of AKI associated with CMS treatment was correlated with the infection grade, intravenous iodinated contrast and serum creatinine at hospital admission. Neither dose nor length of therapy with CMS were associated with AKI. The eGFR levels at hospital admission and hospital discharge were independently factors associated with renal function outcome at six months. These predictors may assist in clinical decision making for this patient population.
Angiotensin 2 Receptor Blocker (ARB) and Angiotensin Converting Enzyme-Inhibitor (ACE) Therapy Indications and Risks in Patients Who Develop an AKI During Hospital Admission
Toby Humphrey, Oshini Shivakumar, Kate Berresford, Clare Morland, Andrew Fryday, Suresh Mathavakannan. East and North Hertfordshire NHS Trust, Stevenage, United Kingdom.

Background: ACE/ARB are the second most prescribed medicine from primary care in England. Despite an aged and co-morbid population prescription of ACE/ARB is increasing. There are defined benefits for patients on ACE/ARB in certain clinical situations but there is concern in frail, elderly patients at risk of AKI. We sought to review the indications and risk factors for ACE/ARB use in patients (prescribed ACE/ARB in the community) who developed AKI during a hospital secondary care stay.

Methods: Adult elective and non-elective patients who developed AKI during an admission episode in February to April 2016 were identified by electronic AKI alert. 311 AKI events were reviewed by an AKI specialist nurse over this time period. Demographic details, indications for ACE/ARB were documented. All AKI patients were reviewed on ACE/ARB therapy had retrospective searches of their co-morbidities and indications for ACE/ARB therapy on electronic patient record and pathology database.

Results: 311 AKI events were reviewed by the AKI nurse between February - April 2016. 102 (32.8%) of those patients had been prescribed ACE/ARB therapy up until admission. Of those 102 patients (M=53.50), the mean age was 64.2 arthritis, median age adjusted Charlson Co-Morbidity score was 6.65 patients (63.73%) had a prior history of type 2 Diabetes, 23 (25.8%) had heart failure diagnosed by echocardiogram, 17 patients (16.67%) had documented proteinuria prior to admission, 34 (33.53%) had a prior history of ischaemic heart disease, 13 patients (12.79%) had a diagnosis of cancer and 24 (23.53%) had a diagnosis of dementia.

Conclusions: Our data indicates patients on ACE/ARB therapy who develop an AKI during hospital stay are frequently elderly and co-morbid with a high likelihood of previous AKI. They frequently do not have good indications for ACE/ARB therapy with few diabetics, few diagnoses of cardiac failure, ischaemic heart disease and proteinuria. This data should be used to support further studies to identify elderly patient populations in the community prescribed ACE/ARB therapy who may benefit from rationalisation on their medication.

SA-PO030
Statins Can Offer Renal Protection in Patients with CKD or DM Afflicted with AKI
Veba Akhtar, Ghada Elshemy, Sem Tabassum, Chandra B. Chandran. St Joseph Regional Medical Center/New York Medical College, Paterson, NJ.

Background: Statins are some of the most commonly prescribed medications in the United States. Aside from the lipid-lowering effects, this class of medications may offer benefits to other organ systems and may play a role in preventing AKI through these pleiotropic effects. This has been studied most specifically in patients undergoing cardiac catheterization or cardiac surgery. Our study is unique in that it seeks to analyze whether the general population with CKD or diabetes not undergoing any cardiac surgery could also stand to benefit from statin therapy.

Methods: We conducted a chart review of 339 patients admitted to a major teaching hospital in New York during the time period between 2000-2010 and had the diagnosis of AKI and then stratified patients as statin users and non-statin users. We aimed to study whether these groups had differences in their rates of recovery. A series of logistic regressions were conducted to investigate predictors of patients recovery. The predictors included in this analysis were race, HTN, DM, CKD, rhabdomyolysis, statin intensity, stage of CKD and mean HBa1c value.

Results: We found that in patients with normal kidney function, those who were on statins were not more likely to recover than patients not on statins (p > .05). However, among patients with chronic kidney disease, statins increased the odds that they would recover by a factor of 3.56 (p < .05). In addition, for patients with Diabetes Mellitus, statins increased the odds that a patient would recover by a factor of 3.81 (p < .05).

Conclusions: The results of our study show that statins may offer renal protection to patients with chronic kidney disease or diabetes and not just those undergoing cardiac catheterization or cardiac surgery. The results of our study also emphasize the need for further studies looking at statin use and outcomes in AKI. Further matched-analyses would be helpful to look at whether our results are reproducible.
Results: Of 460 patients undergoing CAG, 125(27.17%) developed CIN. The incidence of CIN was significantly higher in patients with low AT-III activities than that in normal group (Pearson’s chi-squared test P=0.002). Besides, with the decline of AT-III activity, the prevalence of CIN progressively rise, with the highest value(58.8%) in patients with AT-III activity<60%. Moreover, the AT-III activity was significantly lower in CIN patients than that in non-CIN ones(84.43±16.3% vs. 92.1±13.9%, P<0.001). After multivariable analysis, low AT-III activity remained a significant independent predictor of CIN(OR 2.207,95%CI [1.29-3.777];P=0.004) as well as baseline serum creatinine(OR 1.009,95%CI [1.001-1.016];P=0.026).

Conclusions: Patients with low AT-III activities presented a higher risk of developing CIN after CAG. And the initial AT-III activity may be an independent predictor for CIN.

Funding: Government Support - Non-U.S.

SA-PO036

Long-Term Survival in Patients with Septic AKI Is Strongly Influenced by Renal Recovery

Background: AKI is a major iatrogenic concern with contrast imaging procedures. N-acetylcysteine (NAC) has been tested in prevention of CI-AKI with conflicting reports of efficacy, and there has not been a good scientific explanation for this heterogeneity reported in the literature. Interference of NAC with serum creatinine measurement has been proposed to be one explanation, but the research on this topic has been discrepant. One possibility is that the interference may vary with the type of assay used to measure creatinine. Objective: What is the effect of NAC on serum creatinine, administered in the absence of any other confounding events (eg contrast administration, surgery)?

Methods: A systematic search was performed in MEDLINE, EMBASE, and Cochrane Library to identify studies with participants receiving NAC and before/after serum creatinine measurements, without confounding factors. Two authors independently screened the citations, and data of relevant articles was extracted for meta-analysis.

Results: The literature search produced 503 citations, of which 6 were eligible and included in the review. There is clinical heterogeneity in the studies in terms of study population (healthy volunteers, patients with normal and decreased kidney function), dose of NAC used and method of creatinine estimation. Overall, all studies did show a numerically lower creatinine after NAC administration, ranging from 0.35 to 3.11 μmol/L. The summary weighted mean difference was -2.8 μmol/L (95% CI -0.01 -5.6, p = 0.05). There was no statistical heterogeneity in the results.

Conclusions: There is a small decrease in serum creatinine with NAC administration, but, given the small sample sizes and clinical heterogeneity, a definitive study should be done to establish the true magnitude and nature of the effect.

Funding: Other NHI Support - R01GM61992

SA-PO035

Effects of Fluid Resuscitation on Macro and Microcirculatory Perturbations in Ovine Septic Shock

Yugeesh R. Lankadeva,1 Junko Kosaka,2 Naota Iguchi,2 Roger G. Evans,1 Lindsey C. Booth,1 Rinaldo Bellomo,1 Clare N. May.1

1 Austin Health, Melbourne, NSW, Australia; 2 Florey Institute of Neuroscience and Mental Health, Parkville, Victoria, Australia; 3 Monash University, Melbourne, NSW, Australia.

Background: Aggressive fluid resuscitation, with multiple boluses of crystalloids remains the first-line intervention to maintain systemic hemodynamics in septic shock, but its effects on the renal microcirculation are unknown. We therefore examined the effects of three successive boluses of sodium lactate on intra-renal and urinary oxygenation (pO2) in conscious sheep with established septic acute kidney injury (AKI).

Methods: Sheep were instrumented with fiber-optic probes in the renal cortex, medulla and within a bladder catheter. Sheep received an infusion of Escherichia coli or vehicle-saline for 300 min. A 500-mL bolus of sodium lactate was infused intravenously (±16 mL/min) and improved medullary pO2 (±44.4 to 20.3 mmHg) were simultaneously reduced (both P<0.001). Infusion of crystalloids briefly increased blood pressure (to 74.6 mmHg), creatinine clearance (to 71.6 mL/min) and improved medullary pO2 (to 35.4 mmHg) and urinary pO2 (to 28.4 mmHg). These effects were short-lived and rapidly diminished within the 3-h recovery period. Sheep with septic AKI retained 70% of the total volume of crystalloids infused, but the transit of fluid into the interstitium may also be a factor.

Conclusions: Infusion of three successive boluses of crystalloids briefly reversed renal medullary hypoxia and improved kidney function in septic AKI. However, the transient nature of these effects challenges the long-term benefits of aggressive volume resuscitation in septic shock. In septic AKI, excessive fluid retention may lead to increased cardiac filling pressures and tissue oedema. Urinary pO2 may be a new surrogate marker of medullary tissue pO2 during fluid resuscitation in septic AKI.

Funding: Government Support - Non-U.S.

SA-PO034

The Effect of N-Acetylcysteine on Serum Creatinine: A Systematic Review of the Evidence

Johnny Huang, Ayub Akbari, Swapnil Hiremath. University of Ottawa, Ottawa, ON, Canada.

Background: Contrast-induced acute kidney injury (CI-AKI) is a major iatrogenic concern with contrast imaging procedures. N-acetylcysteine (NAC) has been tested in prevention of CI-AKI with conflicting reports of efficacy, and there has not been a good scientific explanation for this heterogeneity reported in the literature. Interference of NAC with serum creatinine measurement has been proposed to be one explanation, but the research on this topic has been discrepant. One possibility is that the interference may vary with the type of assay used to measure creatinine. Objective: What is the effect of NAC on serum creatinine, administered in the absence of any other confounding events (eg contrast administration, surgery)?

Methods: A systematic search was performed in MEDLINE, EMBASE, and Cochrane Library to identify studies with participants receiving NAC and before/after serum creatinine measurements, without confounding factors. Two authors independently screened the citations, and data of relevant articles was extracted for meta-analysis.

Results: The literature search produced 503 citations, of which 6 were eligible and included in the review. There is clinical heterogeneity in the studies in terms of study population (healthy volunteers, patients with normal and decreased kidney function), dose of NAC used and method of creatinine estimation. Overall, all studies did show a numerically lower creatinine after NAC administration, ranging from 0.35 to 3.11 μmol/L. The summary weighted mean difference was -2.8 μmol/L (95% CI -0.01 -5.6, p = 0.05). There was no statistical heterogeneity in the results.

Conclusions: There is a small decrease in serum creatinine with NAC administration, but, given the small sample sizes and clinical heterogeneity, a definitive study should be done to establish the true magnitude and nature of the effect.

Funding: Other NHI Support - R01GM61992

SA-PO037

The Clinical Significance of Alkaline Phosphatase Activity in Patients with Septic AKI

Seung don Baek, Mediplex Sejong Hospital, Gyeung-gu, INCHEON, Republic of Korea.

Background: Evidences suggested that alkaline phosphatase attenuate inflammatory response in sepsis by lipopolysaccharide detoxification and adenine triphosphate dephosphorylation. We sought to determine alkaline phosphatase (AP) activity change during septic acute kidney injury (AKI) and clinical parameters associated with AP activity.

Methods: In a retrospective study of the patients who underwent continuous renal replacement therapy (CRTT) due to septic AKI, we investigated the baseline, follow-up AP activity on day 3 and the associated outcomes.

Results: We analyzed baseline AP activity of 155 patients and day 3 AP activity of 123 patients. Baseline AP activity of 90 (59-133) U/L increased to 105 (79-156) U/L on day 3 of which liver and bone isotrons increased significantly, but intestine isotrons did not reach statistical significance. Baseline AP activity did not show an association with renal and inflammatory biomarkers, or outcomes. Also, it did not differ significantly.

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

686
between 75 survivors and 80 non-survivors (p=0.155). Day 3 AP activity increased in 70.6% of patients with mean difference of 19 (-3 to 53) U/L. Day 3 AP activity showed weak correlation with length of ICU stay (r=0.205, p=0.023) and length of hospital stay (r=0.190, p=0.036), however, not with survival (r=-0.035, p=0.698).

Conclusions: Endogenous AP activity modestly, but significantly increased in 70.6% of patients with septic AKI. However, neither baseline nor follow-up AP activity was associated with survival.

SA-PO038 Spanish Experience of Pregnancy-Associated Atypical Hemolytic Uremic Syndrome Ana Huerta,1 Santiago Rodriguez de Cordoba,1 Emilia Arjona,1 Manuel Praga,2 Jose M. Portoles,1 Centro de Investigaciones Biologicas-CSIC, Madrid, Spain; 2Hospital 12 de Octubre, Puerta de Hierro, Madrid, Spain.

Background: Pregnancy-associated atypical hemolytic uremic syndrome (P-aHUS) refers to the thrombotic microangiopathy that result from uncontrolled complement activation during pregnancy or the postpartum period. P-aHUS is a treatable condition, with Eculizumab required acute hemodialysis, but none of them required renal replacement therapy during follow-up.

Methods: In the Spanish aHUS Registry we identified 242 adult female patients, of whom 22 fulfilled P-aHUS criteria. We performed a functional and genetic study of the complement system in all of them. We retrospectively collected the clinical, analytical, treatment and evolution characteristics of these patients. We present the data as median and interquartile range.

Results: The age of presentation was 34 years. It was the first pregnancy in 16 patients (73%). 73% of the cases occurred postpartum. Of these, 81% required cesarean section. 41% required acute hemodialysis. 19 patients associated hypertension, 7 neurological disorders, 4 gastrointestinal problems and 3 cardiac syndroms. A renal biopsy was performed in 11 patients: 10 presented MAT lesions and 3 an associated glomerulonephritis. Abnormalities in the complement system related genes were detected in only 41% of the cohort. 16 patients underwent plasma replacement, achieving haematoelogic response in 5 and renal response in 2. 3 patients received infusion treatment of fresh frozen plasma, with haematoelogic response in 3 but renal response in 2. 10 of the 22 patients (45%) received treatment with Eculizumab, achieving haematoelogical and renal response in 100% of them. 3 of the patients treated with Eculizumab required acute hemodialysis, but none of them required renal replacement therapy during follow-up.

Conclusions: P-aHUS seems to have similar characteristics than other types of aHUS. It seems to be an association between cesarean delivery and the development of P-aHUS. Treatment with Eculizumab was effective in 100% of our cohort. More studies are needed to confirm our findings.

SA-PO039 Obstetric AKI and Renal Outcomes Secondary to Pre-Eclampsia Frances I. Contri-Ramsden, Hannah L. Nathan, Annemarie De greef, Daniel W. Steyn, David Hall, Lucy C. Chappell, Andrew H. Shennan, Kate Bramham, Kings College London, London, United Kingdom; 2Accuracy Assessed Medical Devices CC, Diamond, South Africa; 3Stellenbosch University, Parow, South Africa, 4Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa

Background: Introduction: Pre-eclampsia (PET) is a common cause of acute kidney injury (AKI) but AKI incidence, risk factors, maternal and renal outcomes in a middle-income setting are unknown. Objectives: To define the incidence of obstetric AKI in the CRADLE-II pre-eclampsia cohort, explore the association between maximal creatinine and maternal outcomes, and to identify the proportion of women with persistently elevated serum creatinine (Cr) before and after discharge.

Methods: A prospective observational study of women with PET at 3 centres in South Africa was conducted (Jan 2015-May 2016). Pre-specified outcomes were eclampsia, stroke, maximal Cr during admission ≥90 µmol/L (MaxCr90), maternal and perinatal death. Serial Cr (pre-pregnancy to May 2017) were subsequently extracted from national databases in all women with MaxCr90.

Results: 272/1547 (17.6%) of women had MaxCr90 (median 114, range 90-1097). Relative risk of death in women with MaxCr90 was 6.2 (95% CI 2.2,17.8). 236 (15.2%) women had AKI (KDIGO criteria; 123 (52.1%) Stage 1; 63 (26.7%) Stage 2; 50 (21.2%) Stage 3) with 188/236 (79.7%) cases occurring within 48hrs of admission. 138 women (58.5%) had AKI recovery at discharge (Cr returned to <1.5x baseline or <90 µmol/L if no baseline), 92 women (39.0%) did not have AKI recovery at discharge (Cr >1.5x baseline or >90 µmol/L if no baseline) and 6 (2.5%) women died. Serum Cr was repeatedly lost discharge in 25 (27.1%) women without AKI recovery: 19 (76%) had AKI recovery; 6 (24%) no recovery. Overall, 96.3% (157/163) of women with repeat Cr assessment had AKI recovery but 3.7% (6/162) did not. Repeat Cr was not assessed in 67/92 (72.8%) women without AKI recovery at discharge.

Conclusions: Obstetric AKI was common in women with PET in this middle-income cohort. Maximal Cr ≥90 µmol/L was associated with a significantly increased risk of maternal death. Approximately two in five women had persistently raised serum Cr at discharge, which was not subsequently repeated in almost three quarters of these women. However, recovery from obstetric AKI in those assessed was high. Few women had persistently raised Cr reflecting new or pre-existing chronic kidney disease (CKD). The long term impact of recovered obstetric AKI on future CKD development requires further study.

Funding: Private Foundation Support

SA-PO040 NephroCheck AKIScore for AKI Prediction in Pregnancy Jennifer R. Joslin, Sittiga Hassan-reshat, Maria Ostermann, Frances I. Contri-Ramsden, Carolyn Gill, Lucy C. Chappell, Kate Bramham, Guy’s & St Thomas’ Hospital, London, United Kingdom; 2Kings’ College London, London, United Kingdom.

Background: NephroCheck AKIScore is a urinary assay of G1 cell cycle arrest markers: Tissue Inhibitor of Metalloproteinase-2 (TIMP-2) and Insulin-like Growth Factor Binding Protein-7 (IGFBP-7). Numerous studies have demonstrated incremental risk Azteke Kidney Injury (AKI) with AKIScores ≥0.3 and 2.0 (ng/ml)10 but its predictive role in pregnancy is unknown. Aims: To determine AKIScore predictive value for AKI in pregnancy; to explore relationships between AKIScore and gestation, protein-creatinine ratio (uPCR) and pre-eclampsia diagnosis (PE).

Methods: Women recruited to the Pre-Eclampsia, Chronic Hypertension, rEnal and SLE (PEACHES) study with suspected or confirmed PE without pre-existing maternal disease with azteke creatinine concentration after baseline urine sampling were included. Urinary AKIScore (TIMP-2:IGFBP-7) was assessed. AKI was defined according to KDIGO criteria.

Results: 116 women were included with Median creatinine 58 µmol/L (IQR 52-66) at baseline. Proportion of women according to AKIScore thresholds are shown in Table 1. AKIScore ≥2.0 had high specificity (94.7%, 95% CI: 85.4-98.9) and NPV (92.9%; 89.6-96.6) but low sensitivity (33.3%; 0.8-90.7) and PPV (25.0%; 4.6-70.0) for prediction of AKI within 48 hours; AKIScore >0.3 had low sensitivity and specificity (<50%). 31 (54%) of women without AKI had AKIScore >0.3 (25-31% risk of AKI in non-pregnant populations). 86 women had a repeat creatinine within 7 days. There was no relationship between AKIScore and baseline or peak creatinine within 7 days. There was no difference of AKI between women with (Median 0.4; Range 0.8-4) and without PE (0.3; 0.1-1.5) and no correlations between AKIScore and uPCR or gestation.

Conclusions: The majority of women with suspected or confirmed PE had high AKIScores without developing AKI which were independent of gestation or PE diagnosis. Further study to determine if different AKIScore thresholds are required for prediction of pregnancy AKI is needed, and if pregnancy and/or PE are associated with subclinical renal tubular stress.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Background: Acute renal failure (ARF) of obstetric origin is one of the most common complications of pregnancy and leads to poor maternal and fetal outcome. The incidence of PRAKI in developed countries is 1 in 20,000 pregnancies, whereas in developing country like India is 1 in 50. Septic abortion, poor follow up of pregnancy, limited screening of pregnant patients with hypertensive complications and late referrals to tertiary center are responsible for high incidence of ARF in developing countries.

Methods: The study was conducted at government aided tertiary care hospital between April 2016 to March 2017. A total 1021 patients of ARF were admitted out of which 96 were PRAKI. ARF was defined according to KIDIGO guidelines. Renal biopsy was performed if the patient was oliguric or creatinine still >2mg/dl at the end of three weeks.

Results: The incidence of PRAKI was 9.4%. Most common age group was 24-29 years (53.13%). 45.83% patients presented in late pregnancy while 36.46% presented in postpartum period. Antenatal care was received by only 30.21% patients. 25% patients required termination of pregnancy. Most common cause for PRAKI was puerperal sepsis followed by pre eclampsia. 18.75% patients were managed conservatively while 69.79% were kept on intermittent hemodialysis and 11.46% required SLED/CRRT. Acute pathy cortical necrosis was most common histological finding, others were thrombotic microangiopathy and glomerulonephritis. Complete recovery occurred in 43.75%, whereas 16.67% had partial recovery (became dialysis independent but with persistent renal impairment), 19.79% were kept on renal replacement therapy. Maternal mortality was seen in 19.79% of cases.

Conclusions: In our study, puerperal sepsis was the most common etiological factor for pregnancy-related AKI. Sepsis, thrombocytopenia, disseminated intra-vascular coagulation were associated with increased mortality.

SA-PO042
Pregnancy Related AKI: A Single Center Experience Umesh L. Nephrology, Institute of nephrology, Bangalore, India.

Background: The incidence of pregnancy-related acute renal failure (PRAKI) in the developed countries is 1–2.8%. About 25% referrals to dialysis centres in the developing world comprise of pregnancy-related acute kidney injury (PRAKI). It is associated with significant maternal and fetal mortality.

Methods: A prospective longitudinal observational study between February 2012 to April 2017. To evaluate the clinical, etiological and final outcome of AKI with special reference to pregnancy related acute kidney injury. AKI was diagnosed as per AKIN criterion with or without requiring hemodialysis.

Results: A total of 712 patients were studied. Among them 152 (21.34%) patients had PRAKI. The mean age among PRAKI was 21±5 years. The mean duration of hospital stay was 10.1±7.6 days. Etiological factors include puerperal sepsis in 77 (50.6%), pregnancy induced hypertension in 37(24.34%), 17(11.18%) patients had post partum hemorrhage, 9 (5.92%) ante partum hemorrhage, postpartum uterine hemorrage syndromes in 3 patients()

Conclusions: In our study, puerperal sepsis was the most common etiological factor for pregnancy-related AKI. Sepsis, thrombocytopenia, disseminated intra-vascular coagulation were associated with increased mortality.
Mohammed

Cardiac Arrest and Cardiopulmonary Resuscitation (CA/CPR) to sodium retention. Overall these findings suggest that experimental acute cardiorenal critical to blood pressure regulation were altered by CA/CPR. Our findings are consistent kidney injury in experimental acute cardiorenal syndrome. Because CKD damages tubular compared with sham (49.7%, p=0.001, n=9).

Quantification of deposition is markedly increased 1 month after CA/CPR compared with sham. 

Funding: NIDDK Support

SA-PO047

Hypothyroidism: A Known but Neglected Cause of AKI (Chandra M. Jha, 1 Hormuz D. Dastoor, 2 Yassin El Shahat, 3 Sarah H. Khan, 4 Ammar M. Jabar, 1 1 Gulf Diagnostic Center Hospital, Abu Dhabi, United Arab Emirates; 2 Rahba Hospital, ABU DHABI, United Arab Emirates; 3 Burjeel Hospital, Abu Dhabi, United Arab Emirates; 4 Mafraq Hospital, Abu Dhabi, United Arab Emirates. Group/Team: ADHARR)

Background: Acute Kidney injury (AKI) of variable severity is common. Its recovery rests upon early diagnosis & specific intervention. We report a case of severe AKI due to hypothyroidism which recovered completely with the treatment of hypothyroidism. Literature review revealed that association of AKI with hypothyroidism has been recognized but standard textbooks on medicine, Endocrinology & Nephrology have failed to mention either AKI caused by hypothyroidism or hypothyroidism due to AKI.

Methods: A 26 year old Bangladeshi male electrician, smoker and occasional alcohol user, had symptoms of “not being well” & low back pain of one week duration. He had nonoligouric severe AKI (urea 6.3 mmol/L, creatinine 860 μmol/L, Creatinine clearance 5.02 ml/minute) without significant proteinuria (244 mg/day), normal electrolytes & normal ultrasonological study of Kidney, ureter and bladder. Moderately high CPK (1078 IU/L) without myoglobinuria normalized within 72 hours but creatinine continued to rise. A history of weight gain & constipation of two months duration prompted us to check for thyroid function test. TSH was 590 μIU/L, more than 140 times upper limit of normal. T3 & T4 were low. Thyroglobulin antibody & TSH receptor antibody were normal while microscopic antibody was elevated (326.8 IU/L).

Results: Institution of levothyroxine therapy resulted in rapid decline of creatinine and symptomatic improvement of patient. His Creatinine clearance increased from 5.02 ml/minute to 49 ml/minute over two weeks and his creatinine level normalized over 4 weeks period. It saved the patient from kidney biopsy and dialysis.

Conclusions: We suggest that thyroid function test should always be part of investigation of AKI and renal function test should be part of investigation of hypothyroidism. Hypothyroidism should be included in the table of causes of AKI in standard textbooks.
High Creatinine and its response to Thyroxine treatment

SA-PO048

Clinical Aspects of IgG4-Related Retroperitoneal Fibrosis in a Single Center Study


Background: Retroperitoneal fibrosis (RF) is a rare condition characterized by the proliferation of fibrous tissue in the parietal and perirenal retroperitoneum. Along with increasing awareness of IgG4-related disease, we try to find the prevalence of IgG4-related retroperitoneal fibrosis (IgG4-related RF) and compare its clinical feature with non IgG4-related RF.

Methods: The material of this retrospective single center study included 21 patients with retroperitoneal fibrosis between January 2006 to December 2016. We entered all clinical and laboratory information for statistical analysis to determine the prevalence, clinical feature and outcomes of IgG-related RF.

Results: In total 21 patients with retroperitoneal fibrosis, 18 (85.7%) were idiopathic, and remaining 3 (14.3%) had secondary causes for retroperitoneal fibrosis. Among 18 idiopathic RF patients, 10 (55.5%) were diagnosed with IgG4-related RF (2 patients classified as ‘definite’ IgG4-related RF, 2 as ‘probable’, and 6 as ‘possible’). The average age was 62.2 years (range, 41-79) and 6 (60%) were male. All lesions were detected around the infrarenal portion of the abdominal aorta and 7 cases simultaneously affected the iliac arteries. Hydropneumorrhesis was present in 8 cases (80%) and acute kidney injury was observed in 6 patients. The median serum IgG4 at diagnosis was 641 (range, 24.8-3660).

The elevation of serum IgG4 level was not observed in 2 patients. Eight patients were initially treated with steroid therapy. Seven of them (87%) showed radiological response, which showed poor correlation with serum IgG4 level. Comparing with 11 patients of non IgG4 related retroperitoneal fibrosis (52.4%), there were no statistically significant difference between the groups in age, gender distribution, incidence of hypertension, diabetes mellitus, heart failure, malignancy, acute kidney injury, proteinuria, or hematuria, concentration of hemoglobin, white cell counts, inflammatory markers, and complements.

Conclusions: This is a pilot study to evaluate the clinical and laboratory features of IgG related retroperitoneal fibrosis. Larger studies are needed for prevalence and prognosis of IgG4 related or non related RF.

SA-PO049

Not Such a Fun-gi

Rebecca Blonsky, Leal C. Herlitz, Evamaria Anvari. Cleveland Clinic, Cleveland, OH.

Background: Amanita Phalloides is a poisonous mushroom known as death cap, found in central Europe and the northeastern United States. Its toxicity arises from amatoxins, which when ingested can lead to severe gastrointestinal (GI) malady, renal and liver failure and in some cases, death.

Methods: A 55-year-old Nepali male presented with nausea and vomiting for four days. He and his family were in a park and they saw mushrooms similar to those in Nepal which they collected and consumed. They then developed abdominal pain, nausea, vomiting and diarrhea. As their symptoms persisted, they sought care and it was found they had ingested amanita phalloides. Initial labs showed a creatinine (Cr) of 4.67 mg/dL, AST 1551 U/L, ALT 1103 U/L and total bilirubin 1.8 mg/dL. The patient was admitted to intensive care and nephrology was called for acute kidney injury (AKI). Urinalysis and renal ultrasound were normal but urine microscopy showed many unusual crystals, but no signs of acute tubular necrosis (ATN). The patient was treated with intravenous fluids, n-acetylcysteine, octreotide and was enrolled in a trial using silitibin derived from Silybum marianum (milk thistle) being studied in amatoxin ingestion. Treatment, liver function improved and renal function normalized and was discharged after three days with a Cr of 0.8 mg/dL. Ten days later he returned complaining of edema, shortness of breath, anorexia and bitter taste. Labs showed BUN of 45 mg/dL and Cr of 8.69 mg/dL.

Results: Renal biopsy was done and showed ATN. After a total of two sessions of intermittent hemodialysis, he regained renal function and was discharged with a Cr of 3.95 mg/dL. On three month follow up, he achieved partial renal recovery to a stable Cr of 1.7 mg/dL.

Conclusions: AKI frequently occurs in amatoxin ingestion. It causes pre-renal anemia as well as direct tubular toxicity through the amatoxins’ inhibition of RNA polymerase II causing ATN. Though not well described, renal injury could be as a result of crystal deposition. Renal failure has also been reported following normalization of liver function. This pathophysiology is not well defined and has been hypothesized to be a result of the formation of free radicals causing ATN as the toxin is cleared after treatment. Patients who have ingested amanita phalloides require close follow up even with normalization of hepatic and renal function.

SA-PO050

Interim Analysis of Randomised Controlled Trial Comparing Effects of Intravenous versus Oral Hydration on Subclinical AKI in Laparoscopic Live Kidney Donors

David Bruce,1 Shona MacKinnon,2 Emma L. Atikin,1 Marc J. Clancy,1 NHGS Greater Glasgow and Clyde, Glasgow, United Kingdom; 1University of Glasgow, Brighton, United Kingdom.

Background: Laparoscopic donor nephrectomy is the gold standard for kidney donation due to improved donor convalescence. Pneumoperitoneum requires for this procedure exposes patients to increased risk of renal injury. Intensive pre-operative intravenous hydration has shown to improve intraoperative haemodynamics but shows no improvement to creatinine clearance. This is potentially due to the reduced sensitivity of creatinine as a marker for renal injury in the acute setting. Neutrophil gelatinase-associated lipocalin (NGAL) is a biomarker with high sensitivity for acute kidney injury, which showed poor correlation with serum IgG4 level. Comparing with 11 patients of non IgG4 related retroperitoneal fibrosis (52.4%), there were no statistically significant differences between the groups in age, gender distribution, incidence of hypertension, diabetes mellitus, heart failure, malignancy, acute kidney injury, proteinuria, or hematuria.

Methods: We retrospectively collected data on patients 18 years or older discharged from day -1 to 1 year and peri-operative outcomes were collected.

Results: 49 patients consented to take part. After withdrawing, 19 patients in the control group and 22 patients in the intravenous fluid group were analysed. All baseline characteristics were balanced between groups. On day 1 post-operatively 29.4% of patients in the intravenous fluids group had acute kidney injury compared to 40% of patients in the control group (p=0.529).

Conclusions: This is a midpoint analysis the study was unable to fully establish a definitive effect of pre-operative hydration upon renal function in laparoscopic donor nephrectomy patients. There is a potential reduction in postoperative AKI and improvement of eGFR however a fully powered clinical trial should give definitive findings with relevant clinical applications.

SA-PO051

Nephrology Follow-Up Post AKI: Effects on Outcomes and Re-Hospitalization

Arpita Basu,1 Edward J. Horwitz,2 Yasir Tarabichi,1 MetroHealth, Cleveland, OH; 1University Hospitals- Case Medical Center, Cleveland, OH.

Background: AKI complicates 20% of all hospitalizations resulting in higher mortality, readmissions and costs. Mortality across all AKI stages is estimated at 21%. In a retrospective study, those with AKI were more likely to be rehospitalized within 30 days of discharge with cardiovascular events, mainly heart failure and acute myocardial infarction. Despite this, less than 20% of patients see a nephrologist within 3 months of discharge.

Methods: We retrospectively collected data on patients 18 years or older discharged after a hospitalization with AKI diagnosis during 1/1/14 to 12/31/16. Data on age, sex, length of stay and discharge diagnoses by ICD-9 or 10 codes was collected and categorized into randomized studies to better evaluate and optimize outpatient care post discharge after AKI.

Results: The material of this retrospective single center study included 21 patients with retroperitoneal fibrosis between January 2006 to December 2016. We entered all clinical and laboratory information for statistical analysis to determine the prevalence, clinical feature and outcomes of IgG-related RF.

Conclusion: 2016. Hypothesis was tested with NephroOPTF registered as TRUE for patients having seen Nephrology versus FALSE for those seen by another specialty.

Results: 4563 discharges were included, with 1534 events (readmissions or death) documented. The cox-proportional hazards model showed that of patients who saw an outpatient provider, those that saw a Nephrologist had a significant reduction in time to readmission or death for compared to those that did not (adjusted hazard ratio of 0.79 [95% CI 0.65 to 0.94, p=0.001]).

Conclusions: Patients with AKI if seen by a nephrologist on discharge have lower risks of death or readmission in the acute setting when compared to those evaluated by other specialists. This study is limited in its retrospective nature, but provides a model for randomized studies to better evaluate and optimize outpatient care post discharge after AKI.
SA-PO052

Race and Post-Hospitalization Mortality in AKI
Itunu O. Owoyemi, Wenjun Xin, Emaad M. Abdel-Rahman, Rasheed A. Balogun. University of Virginia, Charlottesville, VA.

Background: Acute Kidney Injury (AKI), like ESRD, is known to be associated with increased mortality. Racial differences in outcomes exist in patients with multiple medical conditions and “access to care” is one of the linked variables. This study aims to determine if racial differences in mortality exists after hospital discharge for AKI when access to care may be inconsistent.

Methods: Retrospective cohort study of adults admitted to the University of Virginia Medical Center between January 1, 2001 and December 31, 2015 who had AKI during hospitalization. AKI definition of ≥ 0.3 mg/dl rise in serum creatinine, SCr, within 48 hours was used (Kidney Disease Improving Global Outcomes, KDIGO). Patients’ characteristics or risk factors were summarized as frequencies and percentages for categorical variables and as mean ± standard deviation for continuous variables. The associations of these factors with the outcome of 90-day mortality post hospitalization were evaluated in logistic regression, measured by odds ratios (ORs) for the likelihood of post-hospitalization mortality. The 95% confidence intervals (CIs) for ORs and the corresponding p-values are reported. A p-value < 0.05 was considered to be statistically significant.

Results: We had a total of 11,837 patients in our cohort with 79.7% whites and 17.8% blacks. Mean age was 62.41 ± 15.52. Mean baseline SCr was 1.33 ± 0.78 and mean Charlson index score of 4.13 ± 3.21. A total of 9808 were followed post hospital discharge while 1914 patients died in hospital and 88 patients did not have a last follow up date. A multivariate assessment adjusting for several co-morbidities showed a lower mortality rate at 90 days in black patients versus Caucasians.

Conclusions: Black patients with AKI had lower post-hospitalization 90-day mortality. This outcome is similar to that seen in black patients treated for ESRD in USA. A better understanding of mechanisms underlying a possible survival advantage in black Americans with AKI needs further investigation.

SA-PO053

Association of Kidney Function Decline with Survival in Primary Myelofibrosis
Umut Selamet, Shouhao Zhou, Juhee Song, Srdan Verstovsek, Ala Abudayyeh. MD Anderson Cancer Center, Houston, TX.

Background: Primary myelofibrosis (PMF) is a type of myeloproliferative neoplasm which causes megakaryocyte and granulocyte proliferation in bone marrow leading to fibrous tissue deposition and extramedullary hematopoeisis. Renal involvement in PMF is rare hence acute kidney injury may develop during the disease course due to thrombosis of the renal vessels, occlusion of the urinary tract by blood clots or megakaryocyte infiltration of the kidney interstitium. PMF is a rare disease, and the impact of kidney function on survival has not been studied well.

Methods: We retrospectively evaluated 107 patients with PMF treated with Ruxolitinib between 2007 and 2015. The mean follow-up was 51.2 months (95% CI: 43.4, 66.7). Patient characteristics are summarized in Table 1. Seventy-six percent (n=81) of patients were dead at the time of analysis. Multivariate logistic regression model was used to assess predictors of treatment response, and dynamic prediction model was used for modeling associations with survival.

Results: We observed that estimated glomerular filtration rate (eGFR) was strongly associated with the risk of overall survival. Halving of eGFR levels resulted in 1.4-fold (95% CI: 1.06-1.78, p=0.042) increase of risk. No significant associations were observed between eGFR and clinical response including spleen response.

Conclusions: We have shown that kidney function decline is a risk factor for survival in PMF. Larger prospective studies are needed to evaluate the impact of kidney function both on clinical response and survival in this rare condition.

Funding: Clinical Revenue Support
Effect of Community Acquired AKI on Long Term Outcomes in Patients Presenting with an Acute Myocardial Infarction

Background: We sought to examine long-term outcomes in patients admitted for a myocardial infarction (MI) based on whether they experienced community acquired acute kidney injury (CAAKI), hospital acquired acute kidney injury (HAAKI), or no acute kidney injury (no AKI).

Methods: We performed a retrospective parallel cohort analysis of Veterans admitted for acute MI between 2005 and 2008. Data was obtained from the corporate data warehouse (CDW) using the VA Informatics and Computing Infrastructure (VINCI) computing environment. AKI was determined by assessing for changes in serum creatinine according to the KDIGO AKI classification system. Outcomes were death, hospitalization for cardiovascular (CV) events (MI, congestive heart failure, or stroke).

Results: Of these patients, 15.1% had CAAKI, 14.5% had HAAKI and 70.4% had no AKI. Patients who developed AKI to the KDIGO AKI classification system. Outcomes were death, hospitalization for CV disease (MI, congestive heart failure, or stroke).

Conclusions: Conclusions: In patients admitted with an acute MI, the presence of CAAKI was associated with worse long term outcomes as poor as HAAKI. Further research is needed to understand these associations.

Funding: Veterans Affairs Support

SA-PO054

Risk Factors and Long-Term Prognosis of Post-Operative AKI under Non-General Anesthesia

Background: The patients who receive surgeries under non-general anesthesia are less likely to be evaluated for their post-operative acute kidney injury (AKI) risks in detail than patients who undergo major operation. Risk factors and long-term prognosis data of these patients are scarce.

Methods: We conducted a retrospective cohort study on all adult patients who underwent surgeries under non-general anesthesia during the year 2013. Patients who had other surgeries within 1 month from their index operation, those with kidney injury prior to the surgery and those who lacked information of baseline or follow-up serum creatinine (sCr) measurement were excluded. Postoperative AKI was defined as 0.3 mg/dL or 1.5 times elevation of the patients’ sCr from the baseline within 2 weeks from the surgery. Long-term outcomes were a composition of doubling of sCr and eGFR decrement for 30%, at 3 months or 6 months after operation. Risk factors for AKI were evaluated by multivariable logistic regression analyses.

Results: As a result, a number of 1,737 patients were included in our study cohort. Among them, 158 cases experienced post-operative AKI. Most of the AKI cases occurred after pulmonary or orthopedic surgeries with non-general anesthesia. Presence of baseline diabetes mellitus (adjusted OR 1.87, 95% CI 1.27-2.75, P < 0.001) and anemia (hemoglobin < 11 g/dL, adjusted OR 1.76, 95% CI 1.14-2.72, P<0.01) were significant risk factors for the AKI events. When the long-term prognosis was evaluated, those who experienced AKI after non-general anesthesia surgeries significantly had worse renal outcomes at 3 months (adjusted OR 5.57, 95% CI 3.28-9.39, P < 0.001) or 6 months (adjusted OR 5.29, 95% CI 2.72-10.19, P < 0.001).

Conclusions: Therefore, postoperative AKI occurs in negligible portion of patients who underwent surgeries under non-general anesthesia, and their long-term renal prognoses were worse than those of those without the event. Robust evaluation of underlying risk factors for post-operative AKI and careful follow-up for those who developed AKI should be warranted, regardless of anesthesia method used for the surgery.

Funding: Veterans Affairs Support

SA-PO055

Incidence and Outcomes of AKI in Octogenarians in Northern Jordan

Background: Due to improvements in the health care system worldwide, human life expectancy has increased, resulting in a greater number of geriatric patients diagnosed...
Nutritional Assessment of Patients in the Recovery Phase of Moderate SA-PO058

Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>335 (49.6%)</td>
<td>360 (50.4%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>112 (16.7%)</td>
<td>121 (15.7%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>125 (17.9%)</td>
<td>141 (18.3%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>101 (15.5%)</td>
<td>107 (14.3%)</td>
</tr>
<tr>
<td>Composite heart failure</td>
<td>40 (5.9%)</td>
<td>49 (6.4%)</td>
</tr>
<tr>
<td>Corticosteroid treatment</td>
<td>71 (10.5%)</td>
<td>81 (10.9%)</td>
</tr>
<tr>
<td>Peritoneal vascular access</td>
<td>40 (5.9%)</td>
<td>49 (6.4%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>74 (10.9%)</td>
<td>84 (11.2%)</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitor</td>
<td>193 (28.7%)</td>
<td>210 (27.8%)</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>180 (26.4%)</td>
<td>195 (25.5%)</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>30 (4.2%)</td>
<td>25 (3.2%)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>125 (18.3%)</td>
<td>132 (17.1%)</td>
</tr>
<tr>
<td>Baseline creatinine, mean SD</td>
<td>23.8 (10.5)</td>
<td>23.8 (10.5)</td>
</tr>
</tbody>
</table>

Conclusions: Appropriate management of diabetes and hypertension in octogenarians will likely decrease the incidence of AKI in this age group leading to reduced hospital length of stay and mortality.

Funding: Government Support - Non-U.S.

SA-PO060

A Predictive Model for CKD Development after Severe AKI in Children: A Single Center Prospective Study

Methods: We conducted a prospective study of all non-BMT pts who developed severe AKI (sAKI, Pediatric Modified RIFLE-1 for F) at least 2 days to assess for CKD development after sAKI. Risk factors included standard of care lab data, AKI severity and duration, solid organ transplant status and nephrotoxic medication burden. The primary outcome was eGFR <90 ml/min/1.73m2 (CKD Schwartz formula) at 6 months after sAKI. Significant predictors were identified based on a series of bivariate analyses (p<.03), which were then compared and validated by Receiver Operator Characteristic (ROC) and Leave One Out Cross Validation (LOOCV).

Results: 193 pts who developed Stage 2 AKI were enrolled in this study (99M, 94F, age range 10.6-21 yrs, mean age 16.3±3.8 yrs). The median [IQR] AKI duration was 12 days [7, 21]. 45 pts required RRT. 79 pts had an eGFR assessment at 6 months, 24 of whom had an eGFR <90. On bivariate analysis, age, AKI duration, number of nephrotoxic medications, history of transplantation, lower eGFR, and lower serum albumin at AKI diagnosis were associated with CKD development at 6 months. Interestingly, RRT provided no benefit associated with CKD indicators of health, the likelihood decreased with additional adjustment for location of medical supervision and laboratory indicators of health, the likelihood decreased.

Background: The association between hospital acquired AKI and CKD development in children has only been studied in either select cohorts comprised of convenient samples of available patients (pts) or from administrative data.

Funding: Government Support - Non-U.S.
and simplicity (5 variables vs. 7) had an AUC 0.81 [95%CI 0.70-0.92] and LOOCV value of 0.76.

Conclusions: A simple 5 variable model was developed to predict presence of CKD at 6 months in children who developed prIFLE-U AKI from any cause. Further prospective work will need to be conducted to validate and calibrate this model.

Best Predictive Model for AKI to CKD Development

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficients</th>
<th>p-value</th>
<th>Odds Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.0046</td>
<td>0.12</td>
<td>1.09 (0.98, 1.20)</td>
</tr>
<tr>
<td>AKI Days</td>
<td>0.0465</td>
<td>0.00</td>
<td>1.08 (1.00, 1.16)</td>
</tr>
<tr>
<td>RRT (yes)</td>
<td>-1.4967</td>
<td>0.13</td>
<td>0.18 (0.13, 0.24)</td>
</tr>
<tr>
<td>eGFR (ml/dl)</td>
<td>-0.0296</td>
<td>0.014</td>
<td>0.97 (0.95, 0.99)</td>
</tr>
<tr>
<td>Transfer (yes)</td>
<td>1.895</td>
<td>0.87</td>
<td>6.65 (1.27, 34.4)</td>
</tr>
</tbody>
</table>

SA-PO061

AKI by KDIGO and AKIN Criteria in Patients with Non-ST Elevation Myocardial Infarction: Association with Risk Scores

Avantee V. Gokhale,1 Samuel Mon-Wei Yu2, Hector Alvarado verdzudo,1 Pitchaphon Nissasironkarn,1 Poonam Mahato,1

Background: Acute kidney injury (AKI) is commonly associated with the acute coronary syndrome, both STEMI and NSTEMI. We aimed to assess the incidence of AKI, as defined by AKIN and KDIGO criteria, in patients with NSTEMI at a safety net hospital catering to minority populations, and examined the association between the scores used for risk stratification in NSTEMI and AKI.

Methods: 170 out of 296 consecutively admitted patients between 1.1.2015 and 7.1.2016 with a primary diagnosis of NSTEMI were included in this study. 126 were excluded, mainly due to primary diagnosis of STEMI, and transfer to outside hospital. Their data were collected by retrospective chart reviews. GRACE and Killip scores were calculated for NSTEMI characterization. AKI was assessed as present/absent by 2 different criteria viz. AKIN and KDIGO. Statistical analyses included descriptive statistics and multivariable logistic regression.

Results: Out of 170 patients (mean age=69, 56% males), 39% were Hispanic. 28% had CKD, while, hypertension prevalence was 84%. Median baseline serum creatinine in the study group was 0.9. Median GRACE score was 110 and majority patients fell under Killip class 1 (78%). KDIGO and AKIN scores diagnosed AKI in equal number of NSTEMI patients (45%). While Killip class failed to predict AKI, GRACE score significantly associated with AKI by both AKI criteria [OR 1.03, 95% CI 1.01-1.04; p=0.03 (sex adjusted)]. Finally, when adjusted for age, sex, ACE-inhibitor, aspirin, beta-blocker, diuretic use, history of diabetes and contrast exposure, GRACE score remained significantly associated with AKI by both criteria [1.03 (1.01-1.05), p=0.001 for both].

Conclusions: In a single-center, inner-city safety net hospital cohort of NSTEMI patients with predominantly Hispanic population, GRACE score, which incorporates initial creatinine into the score, was associated with AKI after adjustment for traditional risk factors for AKI. Furthermore, contrary to observations in STEMI, both AKIN and KDIGO predicted AKI to a similar extent in NSTEMI patients. However, larger population-based prospective studies are needed to confirm our findings and further assess the association with mortality.

SA-PO062

AKI in Hospitalized Dermatology Patients: An Epidemiology Study in Two Chinese Centers

Yuanhan Chen,1 Xinling Liang,1 Guangdong general hospital (Guangdong Academy of Medical Sciences), Guangzhou, China; 2Guangdong General Hospital (Guangdong Academy of Medical Sciences), Guangzhou, China. Group/Team: China collaborative study on AKI

Background: Acute kidney injury (AKI) has become a worldwide public health problem, but little information is available in patients with skin diseases.

Methods: This study comes from the China collaborative study on AKI (ClinicalTrials.gov: NCT03054142). Ethical approval: GDREC.20163274H). The electronic medical information were collected retrospectively and the results of creatinine tests were analyzed by data mining. Total 4,710 hospitalized patients in the Department of Dermatology with at least two creatinine tests within 7 days were screened out from Sichuan Provincial People’s Hospital (n=3,978) and Guangdong General Hospital (n=732). AKI was defined and staged according to Kidney Disease Improving Global Outcomes criteria on the basis of changes in serum creatinine.

Results: Two-hundred and ninety-five (6.3%) patients were classified into AKI, including 121(41.0%) hospital-acquired and 174 (59.0%) community-acquired AKI. AKI was defined and staged according to Kidney Disease Improving Global Outcomes criteria. Statistical analyses included descriptive statistics and multivariable logistic regression.

Conclusions: AKI was common in the hospitalized dermatology patients. It is associated with significantly higher in-hospital mortality and resource utilization.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO064

Is Reduced Telomere Length Associated with an Increased Risk of AKI Following Cardiac Surgery? Damian C. Balmbort,1,2 Vasantha M. Muthuppalan,1,2 Sai Krishna Duraisingham,2,3 Steven M. Harwood,4,5 Julius E. Kieswich,2,6 Rakesh Uppal,7 Muhammad M. Yaqoob,2 8 Barts and the London NHS Trust, London, United Kingdom; 9 William Harvey Research Institute, London, United Kingdom.

Background: Patients undergoing cardiopulmonary bypass are at risk of postoperative acute kidney injury (AKI) due to renal ischemia. Several studies have demonstrated an association between cardiac surgery-associated AKI (CS-AKI) and reduced long-term survival which persists even when the degree of AKI is mild and where there is complete resolution of the injury prior to discharge. The mechanism by which CS-AKI is associated with increased mortality is not currently understood. Telomere length has been proposed as a biomarker for cellular senescence and aging and shortened telomeres have been shown to delay recovery after ischemia induced renal injury in animal models. We hypothesised that patients with reduced telomere length undergoing cardiopulmonary bypass may have increased long-term mortality and be more susceptible to ischemia-induced AKI.

Methods: Blood samples were taken immediately prior to surgery and mean leukocyte telomere length (TL) measured by quantitative real time polymerase chain reaction (q-PCR). The primary outcome was the development of AKI in the first 7 post-operative days, as defined by the AKIN criteria. All patients were entered into a study database that recorded a range of pre-operative, intra-operative, and post-operative variables. Univariate statistical analysis was performed.

Results: Between January 2016 and March 2017, 243 patients at a single institution were recruited. Of these, 51 developed post-operative AKI (21%) as defined by the AKIN criteria (stage 1 = 45; stage 2 = 6; stage 3 = 4). No differences were found between the AKI and non-AKI groups in terms of male gender (79.4% vs 79.4%; p = 1), mean age (67.0 ± 6.1 years; p = 0.061), or ethnicity (p = 0.223). As expected, mean length of stay was significantly longer in the AKI group at 14.8 days compared to 9.3 days in the non-AKI group (p < 0.0001). No difference in mean telomere length was found between the groups with a mean relative TL of 0.73 and 0.76 in the AKI and non-AKI groups respectively (p = 0.334).

Conclusions: No association was found between mean telomere length and the development of AKI following cardiac surgery.

SA-PO065

Renal Osimetry Measured by Near-Infrared Spectroscopy before Cardiopulmonary Bypass Predicts Cardiac Surgery-AssOCIated AKI Rachel Joffe,1 Mohammed M. Al aklabi,1 Sudeshna Bhattacharya,1 Dominic A. Cave,2 Daniel Garros,3 Lindsay Ryerson,4 Catherine Morgan,5 1Stollery Children's Hospital, Edmonton, AB, Canada; 2Stollery Children's Hospital, University of Alberta, Edmonton, AB, Canada; 3University of Alberta, Edmonton, AB, Canada.

Background: Cardiac surgery-associated acute kidney injury (CS-AKI) is common in children and associates with negative outcomes. Novel interventions to reduce CS-AKI require knowledge of its pathophysiology. States of altered perfusion, oxygen delivery and energy consumption occur during cardiopulmonary bypass (CPB) and could protect against or contribute to renal cellular injury and recovery. NIRS (near-infrared spectroscopy) is noninvasive technology for monitoring regional blood flow and tissue oxygenation. The use of NIRS during CPB in pediatric cardiac surgery is currently unexplored.

Methods: Design, setting, and patients: We conducted a prospective cohort study evaluating children ≥ 1 kg who underwent CPB (Stollery Children's Hospital, Edmonton, Alberta, Canada). Heart transplant, preoperative dialysis, sepsis, extracorporeal life support, congenital renal disease, and preoperative nephrotoxins were exclusions.

Measurements: Outcome measure was development of AKI after cardiac surgery (defined according to Kidney Disease: Improving Global Outcomes criteria). rSO2 was measured continuously using NIRS (INVOS™ 5100C Cerebral/Somatic Oximeter, Troy, MI, USA) from time of anesthesia to time of transfer to intensive care.

Results: Main Results: CS-AKI occurred in 65%. Lower baseline (preoperative) rSO2 was associated with decreased risk of CS-AKI (p = 0.01); children with baseline rSO2 in the highest tertile were 7.14 times more likely to get CS-AKI (vs lowest tertile). Under the curve for ability of baseline rSO2 to predict CS-AKI was 0.85 (95% CI 0.60 to 0.85). Children with lower baseline glomerular filtration rate had lower mean renal rSO2.

Conclusions: Findings demonstrate that preoperative oxygen supply/demand balance is an important predictor of CS-AKI, suggesting lower preoperative (and intraoperative) renal blood flow may be protective. There is not yet a definite link between remote ischemic preconditioning and prevention of CS-AKI, however renal protective effects of sublethal ischemia should continue to be explored.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO068
Complex Relationship Among Obesity, AKI, and Long-Term Mortality in Coronary Artery Bypass Grafting Honmee Moon,1 Yeonhee Lee,2 Sejoong Kim,1 Dong Ki Kim,3 Ho Jun Chin,1 Yon Su Kim,2 Ki Young Na,1 Seung Seok Han,2 Seoul National University Bundang Hospital, Seongnam, GYEONGGIDO, Republic of Korea; 2Seoul National University College of Medicine, Seoul, Republic of Korea.

Background: Obesity is an important health concern and related with several comorbidities and mortality. However, its role in AKI with acute kidney injury (AKI) and long-term mortality remains unresolved, particularly in Korean patients undergoing coronary artery bypass grafting (CABG).

Methods: A total of 3018 patients (aged ≥18 years) were retrospectively reviewed from two tertiary referral centers between 2004 and 2017. Obesity was defined using body mass index (BMI), according to the World Health Organization recommendation. The odds ratios (ORs) and hazard ratios (HRs) for outcomes were compared after adjustment for multiple covariates. Patients were followed for 90 ± 69.6 months (maximum 13 years).

Results: The proportions of normal weight, overweight, and obesity were 31.7%, 24.7%, 27.6%, and 44.0%, respectively. These results suggest that obesity was an indicator of the AKI risk in the CABG cohort. Moreover, patients with obesity had a higher risk of AKI than the normal weight group. This result suggests that obesity is a risk factor for AKI in the CABG cohort. Patients with AKI had higher mortality (OR 2.313 ± 0.000, P = 0.001) compared with subjects with normal weight, respectively. These results suggest that normal weight status did not confer the higher risk of AKI than the normal weight group. These results are in accordance with the findings of previous studies, which showed that normal weight status did not confer the higher risk of AKI than the normal weight group.

Conclusions: Obesity is related with the high risk of AKI, but not with the high mortality in Korean patients undergoing CABG. Rather, the patients with overweight at risk, obese I status showed better survival rates than the patients with normal weight. These results should be monitored in clinical practice, based on the consideration for several confounding factors, such as inflammation and malnutrition.

SA-PO069

Background: The bioelectrical impedance analysis (BIA) can offer information about volemia. We evaluate corporal, hemodynamic BIA, and volometric parameters (Extracelluar/intracelular water ratio –ECW/ICW-, Extracelular/Total body water ratio –ECW/TBW-, and Fluid thoracic volumen –FTV-) in acute kidney injury (AKI).

Methods: We include a cohort of 159 patients (median age 66 years SD 1.3, and male 73 %) with AKI and corporal BIA (Study A), and another cohort of 50 patients (mean age 71.2 years SD 1.6, 79.6% males) with AKI and hemodynamic BIA (Study B). We evaluate clinical prognostic index (individual severity index –ISI–), analytical inflammatory parameter (C-reactive protein) and chronic health index (Karnofsky –K–). We evaluate mortality and renal replacement therapy requirement. We use SPSS 20.0.

Results: Study A: Exits 27. ECW/ICW and ECW/TBW was associated with prognosis index, clinical and analytical parameters in AKI. ECW/ICW was associated with ISI (r=0.240, p=0.002), and CRP (r=0.234, p=0.006) and Karnofsky(r=0.253 p=0.002). ECW/ICW was associated with ISI (r=0.115 p=0.148) and CRP (r=0.116 p=0.158) and Karnosky(r=0.242 p=0.002). ECW/ICW was associated with risk mortality (OR 2.313 p=0.004 CI 95% 1.308-4.992), and ECW/TBW also (OR 5.39 p=0.018 CI 95% 1.333-23.007). The AUC with ECW/ICW was 0.773 (p=0.001, CI 95% 0.672- 0.874) and with ECW/TBW was 0.734 (p=0.003, CI 95% 0.625- 0.845) respect to survive. Extracelluar corporal volumen was not associated with renal replacement therapy requirement.

Conclusions: The incidence and risk factors of AKI in patients with Pulmonary Infection-Associated Acute Respiratory Distress Syndrome Xin Wan,1 Changchun Cao,2 Nanjing First Hospital, Nanjing, China.

Background: Acute kidney injury (AKI) is a common complication in critically ill patients and is a major risk factor for death. Among critically ill patients, AKI occurred in 31.3% of patients and was more common in patients with ARDS (44.3% versus 27.4% in patients without ARDS). Infection (44.1%) was the most common risk factor for the development of ARDS. Lung was the most common infection site in infection-related ARDS, and also the only infection site significantly associated with increased risk of developing ARDS. There is no a study pay a attention to AKI in patients with pulmonary infection-associated ARDS (PI-ARDS). Therefore, we aim to explore the incidence and risk factors of acute kidney injury in patients with PI-ARDS.

Methods: This prospective cohort study included patients aged 18 or more who were admitted to hospital for pulmonary infection combined with or secondary to ARDS at Nanjing First Hospital in Nanjing, China, between January 2014 and March 2017. Univariate and multiple logistic regression models were used for determining the association between the development of AKI and risk factors. Multiple Cox-proportional hazards modeling was performed to evaluate the impact of AKI on the in-hospital mortality and hospital length of stay (LOS).

Results: Of 846 patients with ARDS result from pulmonary infection, the incidence of patients with PI-ARDS developed AKI was 53.3% (449/846). A total of 368.0% PI-ARDS patients required renal replacement therapy. In the multivariate analysis, factors independently associated with AKI were male, age, white blood cell, platelets, several nephrotoxic drugs (diuretic, vancomycin, Aminoglycosides), proteinuria and invasive ventilation. The model was well calibrated and an area under the receiver operator curve (AUC) was 0.766. Furthermore, subjects with proteinuria of trace to 1+, 2+, 3+, had a 1.45P= 0.037, 1.02 to 2.06, 3.36P<0.001, 1.78 to 6.35, 11.26P<0.001, 3.11 to 40.80 fold increase in adjusted odds ratio of AKI compared with subjects with negative, respectively. AKI was also significantly associated with in-hospital mortality, especially in patients needing RRT, and prolonged hospital length of stay.

Conclusions: Proteinuria is an independent risk factor for AKI in PI-ARDS patients, and patients with PI-ARDS develop AKI would have a grave prognosis.

SA-PO071
Role of Urinary NGAL at 4 Hours Post Coronary Angiogram in Detecting Contrast Induced AKI Madhav Venkatesan, Amrita Institute of Medical Sciences, Trichy, India.

Background: Serum creatinine is an unreliable biomarker of acute kidney injury (AKI). Newer biomarkers can diagnose AKI earlier. We attempted to determine the sensitivity, specificity, positive and negative predictive values of urine NGAL in detecting CI-AKI post a coronary angiogram, and to study the risk factors of CI-AKI.

Methods: 240 patients undergoing coronary angiogram were prospectively studied. Patients with a starting serum creatinine of more than 1.4mg/dl were excluded from the study. Serum creatinine and urine NGAL were measured before the procedure. Urine NGAL was measured 4 hours post procedure and serum creatinine was measured at 48 hours post procedure.

Results: The incidence of CI-AKI in patients who underwent coronary angiogram was 8%. There was a rise in urinary NGAL in 95% of these patients (n=18). The sensitivity and specificity of urinary NGAL at 4 hours were 94.7% and 99.1% respectively. The positive and negative predictive values were 90% and 99.5% respectively. Age more than 75 years, presence of diabetes mellitus, congestive heart failure, prior history of CI-AKI, and anemia had significant association with increased risk of CI-AKI. Multivariate analysis showed that CHF and anemia were significantly associated with increased risk of CI-AKI.

Conclusions: Urine NGAL has a high sensitivity and specificity in the diagnosis of contrast induced acute kidney injury post coronary angiogram. Age above 75 years, diabetes mellitus, congestive heart failure, anemia and previous history of contrast induced AKI were significant risk factors for CI-AKI. Congestive heart failure and anemia were the risk factors with highest association with CI-AKI. Based on our study we suggest that urine NGAL may be used for early detection of contrast induced acute kidney injury post a coronary angiogram with sensitivity and specificity of 94.7% and 99.1% respectively and with positive and negative predictive values of 90% and 99.5% respectively.
SA-PO072

Identification of Urine Apolipoprotein A-I as a Biomarker for Early Diagnosis of AKI Following Percutaneous Coronary Intervention by ITRAQ-Based Quantitative Proteomics Fangfang Zhou,1,2 Qun Luo,1,2 Gen Shen,1,2 Honghua Ye,1,2 Lina Han,3,2 Lulu Huang,4 Yunlei Li,1,2 Zemin Wang,1,2 1Department of Nephrology, Ningbo NO.2 Hospital, Ningbo City, China; 2School of Medicine, Ningbo University, Ningbo, China; 3Department of Cardiology, Ningbo NO.2 Hospital, Ningbo, China.

Background: Acute kidney injury (AKI) has been recognized as a common complication of percutaneous coronary intervention (PCI). Our study aimed to discover and validate novel diagnostic biomarkers of acute kidney injury (AKI) following PCI by Isobaric Tags for Relative and Absolute Quantitation (iTRAQ) technology dynamically, and to explore potential mechanisms of AKI.

Methods: We performed a prospective nested case-control study. 14 older patients (60-90yr) identified with PCI-AKI. 12 patients were selected as controls, matched by age and gender. Urine were collected at different time points of pre-PCI, 6hrs, 24hrs, and 48hrs post-PCI. A training set of 56 urine samples(AKI group, n=28) were subjected to ITRAQ technology. Serum lactate level was considered to be differentially expressed if the difference was statistically significant (p<0.05) and the fold change was >1.2 or <0.83. Differentially expressed proteins, also analyzed by bioinformatics analysis, were then investigated in a validation set of 48 urine samples(AKI group, n=8) via parallel reaction monitoring (PRM) based targeted proteomics.

Results: A total of 14 overlapped proteins at all the different time points post-PCI showed an abundance change in AKI group as compared to those before PCI and controls. Among them, the accumulation of apolipoproteins A-I(apoA-I) were 14.86-, 18.88-, and 7.44-fold higher at 6h, 24h, and 48h post-PCI in AKI group, as compared to pre-PCI value respectively (p=0.0409, ≥0.0338, p=0.01009). Using the PRM approach, we successfully confirmed the differential accumulation of apoA-I at different time points post-PCI in the validation set. We also confirmed that serum level of high density lipoprotein (HDL) and apoA-I were significantly lower in AKI patients (p=0.023, >0.047) as compared with controls. Bioinformatics analysis described that apoA-I may involved in Peroxisome Proliferator Activated Receptor (PPAR) signaling pathway.

Conclusions: The presence of urine apoA-I demonstrated in our study a potential diagnostic biomarker for PCI-AKI, suggesting lipid abnormalities in AKI, which may be related to HDL deficiency. Comparatively little is known regarding the role of lipids in pathogenic mechanisms of AKI, which deserve further study.

Funding: Government Support - Non-U.S.

SA-PO073

Serum Lactate Level Predicts Mortality among Patients with Metformin-Associated Lactic Acidosis Requiring Renal Replacement Therapy Ching-Chi Kuo,1 Ching-Wei Tsai,1 * 1Internal Medicine and Big Data Center, China Medical University Hospital, Taichung City, Taiwan; 2Internal Medicine and Big Data Center, China Medical University Hospital, Taichung City, Taiwan. Group/Team: CHMU Kidney Research Group.

Background: The risk factor for mortality and the best practice concerning timing, mode, and dose of renal replacement therapy (RRT) for patients with metformin-associated lactic acidosis (MALA) is still under-determined.

Methods: We searched case reports and case series published in PubMed/Medline and EMBASE from inception to Sep 2014 and applied predetermined exclusion criteria. Case-level data including case’s demographics and clinical information related to MALA were abstracted. Multiple logistic regression modeling was used to examine the predictors of mortality.

Results: A total of 253 unique cases were identified with cumulative mortality of 17.2%. Eighty-seven percent of patients had acute kidney injury. Serum lactate level was significantly higher in non-survivors (median 22.5 mmol/L) than in survivors (17.0 mmol/L, p-value <0.01) and so did the median blood metformin concentrations (58.5 vs. 43.9 mg/L, p-value=0.05). The survival advantage was not significantly different between the modalities of RRT. The adjusted odds ratio of mortality for every one mmol/L increase in serum lactate level was 1.09 (95% CI 1.02-1.17, p-value=0.01). The dose-response curve indicated a lactate threshold greater than 20 mmol/L was significantly associated with mortality.

Conclusions: Our study suggests that predialysis level of serum lactate level is an important marker of mortality in MALA patients requiring RRT with a linear dose-response relationship. To better evaluate the optimal prescription of RRT in MALA, we recommend fostering an international consortium to support prospective research and large-scale standardized case collection.

Funding: Government Support - Non-U.S.

SA-PO074

Preoperative Risk Assessment Improves Biomarker Detection for Predicting AKI After Cardiac Surgery Cheng-chia Lee,1,2 Chih-Hsiang Chang,1,2 Chih-Wei Yang,1,2 1Chang Gung Memorial Hospital, Taoyuan, Taiwan; 2Chang Gung University, Taoyuan, Taiwan.

Background: The major challenge in managing acute kidney injury (AKI) lies in making an early diagnosis. Although urinary neutrophil gelatine-associated lipocalin (NGAL) has emerged as a promising biomarker for the early detection of kidney injury, previous studies of adult patients have reported only moderate discrimination. The age, creatinine, and ejection fraction (ACEF) score is a preoperative validated risk model for predicting AKI following cardiac surgery. It remains unknown whether combined preoperative risk assessment through ACEF scores followed by urinary NGAL is an optimal approach with improved predictive performance.

Methods: This prospective study was performed in a tertiary referral center in Taiwan between July 2014 and February 2015. A total of 177 consecutive patients who underwent cardiac surgery were enrolled. Clinical characteristics, prognostic model scores, and outcomes were assessed. The ACEF scores were calculated as age (years)/ejection fraction (%) + 1 (if creatinine > 2.0 mg/dL). NGAL were examined within 6 hours after cardiac surgery. Patients were stratified according to preoperative ACEF scores, and comparisons were made using the area under the receiver operator characteristic (AUROC) curve for the prediction of AKI.

Results: A total of 45.8% (81/177) of the patients had AKI. Patients with ACEF scores ≥ 1.1 were older and more likely to have diabetes mellitus, myocardial infarction, peripheral arterial disease, and class III or IV heart failure. Urinary NGAL alone moderately predicted AKI, with an AUROC of 0.732. Risk stratification by ACEF scores ≥ 1.1 substantially improved the AUROC of urinary NGAL to 0.873 (95% confidence interval, 0.784-0.961; P < 0.001).

Conclusions: Risk stratification by preoperative ACEF scores ≥ 1.1, followed by postoperative urinary NGAL, provides more satisfactory risk discrimination than does urinary NGAL alone for the early detection of AKI after cardiac surgery. Future studies should investigate whether this strategy could improve the outcomes and cost-effectiveness of care in patients undergoing cardiac surgery.

Funding: Government Support - Non-U.S.
SA-PO075

AKI Biomarkers and Cystic Fibrosis (CF): Does Having CF or Being a Girl Make a Difference? Courtney B. Munro,1 Murdoch Childrens Research Institute, Melbourne, Victoria, NSW, Australia; 2Paediatrics, University of Melbourne, Melbourne, VIC, Australia.

Background: Novel urinary biomarkers are useful for prediction of acute kidney injury (AKI). Cystic fibrosis (CF) is a life limiting disease, caused by a gene defect in Cystic Fibrosis Transmembrane Regulator (CFTR), that predisposes the individual to recurrent respiratory infections which are often treated with nephrotoxic antibiotics. CFTR is highly expressed in the kidney, yet its effects in the human kidney in CF have not been closely examined. Previous studies have demonstrated renal glomerular hyperfiltration in children with CF. We set out to determine if novel urinary biomarkers could be used in children with CF, by determining reference levels in a paediatric CF population, and if this differed to healthy age-matched controls.

Methods: Urine was collected and analysed from 448 occasions (CF n=229; healthy controls n=219) from children aged 1 to 6-years, median 4-years. Median values were: KIM-1 205.44 pg/mL (Interquartile range (IQR) 107.11 to 427.93), NGAL 1.03 ng/mL (IQR 0.01 to 3.65), FGF-23 25.25 pg/mL (IQR 17.05 to 96.21) and UCr 4.21 mmol/L (IQR 2.56 to 6.26). KIM-1, NGAL and UCr were higher in healthy controls than in CF (p=0.0000), suggesting a concentrating defect. FGF-23 was higher in CF (p=0.001) which may reflect inflammation and infection. In healthy controls KIM-1 and UCr increased with age (p=0.0166). In healthy controls there were significant sex differences with KIM-1 (p=0.0000), whereas NGAL decreased with age (p=0.0141). In CF, only UCr increased with age (p=0.0166). In healthy controls there were significant sex differences with KIM-1 and UCr higher in boys (p=0.0002 and p=0.0006), whereas NGAL was approximately 5 times higher for girls (p=0.0003). Sex differences were not observed in CF.

Conclusions: This is the first reference range study for urinary kidney injury molecule-1 (KIM-1), neutrophil gelatinase associated lipocalin (NGAL) and fibroblast growth factor-23 (FGF-23) using ELISA and normalised to urinary creatinine (Ucr). Analysis of biomarkers by cohort (CF vs. healthy controls), age and sex was performed.

Funding: Private Foundation Support

SA-PO076

Worsening Renal Function During Aggressive Diuresis Is Not Due to Kidney Injury in Acute Heart Failure Patients Joshua L. Rein,1 Keyanna Jackson,2 Veena Rao,2 Steven G. Coca,1 Jeffrey M. Testani,2 Icahn School of Medicine at Mount Sinai, New York, NY; 3Ivey University, New Haven, CT.

Background: The mechanisms underlying worsening renal function (WRF) in the setting of aggressive diuresis for acute heart failure (AHF) treatment may reflect renal tubular injury or simply indicate a hemodynamic or functional change in glomerular filtration. Well-validated tubular injury biomarkers—NAG, NGAL, and KIM-1—are now available that can quantify the degree of renal tubular injury. The ROSE trial provides an ideal experimental platform for the study of mechanisms of WRF during aggressive diuresis for AHF as the ROSE protocol dictated high dose loop diuretic therapy in all patients. We sought to determine whether kidney injury is a predominant mechanism for WRF in the setting of aggressive diuresis and its impact on prognosis.

Methods: Patients in the multicenter ROSE trial with baseline and 72-hour urine injury biomarkers were analyzed (N=277). WRF was defined as a ≥20% decrease in glomerular filtration rate estimated using cystatin C.

Results: Levels of NAG and KIM-1 did not change with aggressive diuresis (P=0.49, both), whereas levels of NGAL decreased slightly [8.08 ng/mg (-169, 35 ng/mg), P=0.001]. WRF occurred in 21.7% of the population and was not associated with an increase in any marker of renal injury: NGAL (P=0.23), NAG (P=0.49), or KIM-1 (P=0.22). WRF was not associated with reduced survival (P=0.51). However, increases in NGAL, NAG, and KIM-1 were paradoxically associated with improved survival (adjusted HR: 0.78 per 10 percentile increase, 95% CI: 0.69-0.91; P=0.001). Change in injury biomarkers could not differentiate high versus low risk forms of WRF (R2=0.35).

Conclusions: Renal injury was not a dominant mechanism for WRF in the context of aggressive diuresis of AHF patients. Moreover, neither WRF nor renal injury was associated with an increased risk of death. These findings reinforce the notion that small to moderate “bumps” in creatinine commonly encountered with aggressive diuresis are mechanistically and prognostically different from traditional causes of acute kidney injury.

SA-PO077

Utilizing CBC to Predict AKI and Its Recovery Asif Khan,2 Anna S. Gutman,1 Elie El-Charabaty,2 Suzanne E. El Sayegh,2 Northwell Health, Brooklyn, NY; 3Staten Island University Hospital, Brooklyn, NY.

Background: The difficulty in diagnosing acute kidney injury (AKI) prior to an elevation of serum creatinine, or a decrease in urine output, continues to pose challenges for nephrologists. Multiple new biomarkers of kidney damage have been evaluated, but their clinical value remains limited. The value of the neutrophil to lymphocyte ratio (NLR) as an indicator of systemic inflammation, which is easily calculated from a CBC, has been explored. We investigated the hypothesis that a high NLR may predict the development of AKI.

Methods: This retrospective study identified patients of 18 years and older. We compared the NLR trends between patients with pneumonia and AKI as the experimental group (PAAG), to patients with pneumonia without AKI as the control group (PWAG). Day 0 was labeled as the day of AKI diagnosis, and the day of pneumonia diagnosis in the PAAG and the PWAG respectively. We documented trends of NLR and kidney function from 3 days before Day 0 until 3 days after Day 0.

Results: Of the 222 patients enrolled, 115 were in the PAAG, and 107 in the PWAG. Both groups had similar percentages of sexes, ethnicities, underlying hypertension, coronary artery disease, heart failure, and a similar median age. The PAAG had a significantly higher number of patients with chronic kidney disease and diabetes mellitus compared to the PWAG (47.9% vs. 4.8% (P<0.001) for CKD, and 40.4% vs. 24.1% (p=0.02) for DM). There was an increase in the mean NLR from day -3 to day 0 of 12.4 in the PAAG, and only a 0.6 in the PWAG group. These results suggest a positive correlation between a certain net change in NLR and the development of AKI.

Conclusions: The potential of NLR as an indicator of systemic inflammation is well established. A timely use of NLR within twenty-four hours of admission may predict an impending AKI. Further studies are necessary to establish the trends in NLR prior to the diagnosis of AKI.
of NGAL changes in the outcome of patients (pts) submitted to MENVAS admitted to the ICU in the institutional ICU. 

Methods: One hundred and seventy one pts were prospectively evaluated, perioperatively and from the ICU admission up to 7 days. Scr (mg/dl) was assessed before surgery and once a day up to 7 or until ICU discharge. Hourly UO (ml/kg/h) was measured by CRRT. AKI was diagnosed using UO according to RIFLE KDIGO definitions. Urine samples were collected at the pre-operative, at ICU admission, and 12 and 24 hours after ICU admission for NGAL (mg/mg urinary Cr) analysis. Data are presented as mean ± SD, median (minimal and maximum value) or frequency. Statistical significance was p<0.05.

Results: According to RIFLE criteria 101 pts (59.1%) developed AKI: 5 by Scr, 76 by UO and 20 by Scr+UO. Using KDIGO criteria 102 pts (66.6%) developed AKI: 6 by Scr, 67 by UO and 9 by Scr+UO. Pts with AKI diagnosed by UO, Scr and Scr+UO had, respectively, hospital length of stay (LOS) of 9 (5-16) vs 24 (12-45), total CRRT 24h of 31, 4a3 and 5±3 d (p<0.001 UO vs. Scr) and mortality 4.5, 33.5 and 17.3%, respectively (p=0.0211). If the Scr criteria alone was utilized for AKI diagnosis, 25 pts in RIFLE group and 35 in the KDIGO group would be overlooked. Pts who died had higher NGAL values in the immediate post-surgery [108 (24-31642) vs. 45 (4–3763) no death, p=0.0085] and 24 h post-surgery [222 (59-8482) vs. 54 (3–6579) no death, p=0.0046] periods.

Conclusions: UO measurement seems to be pivotal for early AKI recognition, since the use of SCR criteria alone would overlook a high number of AKI diagnoses, using either RIFLE or KDIGO definition. Early NGAL increase after major elective non-vascular abdominal surgeries was associated with higher mortality in this group of patients.

Funding: Government Support - Non-U.S.

SA-PO079

Interval Change Plasma Neutrophil Gelatinase-Associated Lipocalin Level and Urine Output as a Predictor for Survival in Critically Ill Patients Undergoing Continuous Renal Replacement Therapy

Ha yeon Kim,1 Eun Hui Bae,2 Soo Wan Kim,3 Seong Kwon Ma.4 Chonnam National University Hospital, Gwangju, Republic of Korea; 4Chonnam National University Medical School, Gwangju, Republic of Korea.

Background: Continuous renal replacement therapy (CRRT) is increasingly modality of choice for hemodynamically unstable ICU patients with AKI. Several biomarker have been attempted an early detection or assisted predicting prognosis. The neutrophil gelatinase-associated lipocalin (NGAL) is a one of them used early kidney injury marker. The aim of this study was to determine the outcome and identify the predictors of mortality of critically ill patients treated with CRRT for AKI in the ICU.

Methods: Protocol 1: In the single tertiary medical center retrospective study of 1,527 patients admitted ICU and undergoing CRRT from January 2011 to December 2013 was performed. Univariate and multivariate regression analyses were conducted to examine the independent predictor of patients’ survival. Protocol 2: This retrospective observational study included 404 AKI patients treated with CRRT. The levels of serum creatinine (Cr), plasma NGAL obtained at baseline and at 48 hour after starting CRRT were analyzed.

Results: In total, 1,527 patients with AKI treated with CRRT, the overall in-hospital mortality rate of the CRRT treated AKI patients was 59.6%. Multivariate cox proportional hazards analysis identified that a urine output less 30 ml for initial first hour at the initiation of CRRT was independent predictor (HR: 1.13, CI: 1.0-1.2, p value; <0.001) besides APACHE II score and older age per 10 years and congestive heart failure also showed significant predictor different between AKI survivor and non-survivor, whereas the difference of plasma NGAL between at baseline and at 48 hour after starting CRRT was significant different. However, univariate analysis revealed that delta plasma NGAL was not significant factor for the survival.

Conclusions: Plasma NGAL have limited medical biomarker of predictor of survival. At initiation of CRRT, a urine output less 30 ml for initial first hour is a predictor of survival. Urine output is still a robust prognostic biomarker in these patients with AKI treated with CRRT.

SA-PO080

Development and Validation of 7-Plex Assay Panels to Measure Urine and Plasma Biomarkers Implicated in Progression of CKD

Venkata Sabbisetty,1,2 Emily Christie,1 Sushrut S. Waikar,3 Joseph V. Bouventre,1,2 Brigham and Women’s Hospital, Boston, MA; 3Harvard Medical School, Boston, MA.

Background: Biomarkers including TNFR1, TNFR2, sPAP, KIM-1, YKL-40, MCP-1 and BMP 7 have been shown to be associated with progression of kidney disease. We have developed and validated multiplex assays on the Meso Scale Discovery (MSD) platform to measure these 7 analytes simultaneously in both urine and plasma matrix.

Methods: We have developed a 7-plex assay using MSD U-PLEX technology. Capture antibodies were biotinylated and conjugated to unique U-PLEX linkers and coated on the MSD 7-spot U-PLEX plates by incubating overnight at 4°C. Plates were coated with specific antibodies and then incubated with recombinant proteins, plasma or urine specimens from CKD patients for 1h followed by incubation with GOLD SULFO-TAGGED secondary antibodies for 1h. The amount of chemiluminescence in each well was measured using MSD SQ120 instrument.

Results: The MSD 7-plex assay demonstrated excellent linearity of dilution and spike recovery with no interference of various substances including glucose, bilirubin and albumin in both urine and plasma matrix. The intra and inter-assay coefficient of variation was below 15%.

Conclusions: We have developed a robust and reliable 7-plex assay on MSD platform to measure biomarkers implicated as potentially predictive of progression of kidney disease in plasma and urine specimens.

Funding: NIDDK Support

SA-PO081

Establishment of a Tubule-Specific Renal Panel in AKI

Brent J. Portz, Michael A. Moore. Danville Regional Medical Center, Danville, VA.

Background: Early recognition to allow prevention of Acute Kidney Injury (AKI) is an ongoing inpatient challenge due to AKI’s high morbidity and mortality. The traditional use of changes in serum creatinine and urinary output only define AKI after it is well established and kidney injury has begun. Better biomarkers of early acute renal injury are needed. Developments in systems biology techniques and advancements of genomic and proteomic technologies have provided an emerging list of novel glomerular and renal tubule cell biomarkers.

Methods: A comprehensive literature review was completed utilizing PubMed and MEDLINE databases from inception to January 2017 searching for ‘AKI Biomarkers and Systems Biology’. Validated and Non-Validated novel AKI biomarkers discovered at tubule-specific sites via genomic, proteomic and systems biology techniques were outlined. Unique biomarkers at distinct nephron segments were composited in a Tubule-Specific Renal Injury Panel.

Results: Amongst other identified markers, KIM-1 (Proximal Tubule), CNTF (Loop of Henle), bcl-2 (Distal Tubule), and NGAL (Collecting Tubule) suggested the highest potential for clinically applicable AKI biomarkers (Table 1).

Conclusions: The establishment of a tubule-specific renal panel is proposed to provide increased sensitivity/specificity to enable diagnosis early in acute renal injury.

Table 1: List of Identified Novel Biomarkers at Segment Specific Sites, organism biomarker identified in and availability of commercially validated assays. Bolded *, denotes highest clinically applicable AKI biomarker at each segment. Literature references listed separately.

SA-PO082

Early Detection of Urine Neutrophil Gelatinase-Associated Lipocalin for 90-Day Mortality Prediction in Cirrhotic Patients with AKI

Zemin Wang, Fangfang Zhou, Ningbo NO.2 Hospital, Ningbo City, China.

Our study was to investigate the prediction role of early detection of urine neutrophil gelatinase-associated lipocalin (uNGAL) after risk factors for 90-day mortality in cirrhotic patients with acute kidney injury (AKI).

Methods: We conducted a prospective nested case-control study of 90 cirrhotic patients with risk factors (bacterial infections, bleeding from esophageal varices, large volume paracentesis (>3L/d), increased dosage of diuretics, and receiving contrast medium). Urine samples were collected at the time of risk factors occurred and 1d, 2d and 3d after the risk factors. Among these patients, 11 patients diagnosed as AKI/KDIGO AKI criteria, 2012). 9 patients were selected as controls, matched by age and gender uNGAL was measured by ELISA. All the patients were followed up for 90 days.

Results: There were no significant differences in terms of baseline characteristics between AKI and control group. In the AKI group, the levels of uNGAL of 1-day, 2-day and 3-day after risk factors were significantly higher than those at the time of risk factors happened (P<0.013, P<0.009, P<0.012). Totally 6 patients (30%) died during the 90-day follow-up period. The rate of mortality was much higher in patients with AKI compared with control group patients (P < 0.05). uNGAL level of 1d and 2d after risk factors were significantly higher in deceased patients compared with those in surviving patients (189.43(108.88,368.27) vs. 66.03(25.55,115.42), P = 0.049, 148.31(70.06,326.68) vs.45.42(20.97,93.37), P = 0.039). The serum Na, albumin, total bilirubin, levels of...
SA-PO085
Use of Biomarkers in the Early Diagnosis of AKI in Critically Ill Patients: Systematic Review
Liana A. Pedrosa,1 Vandack Nobre,2 Claudemire D. De almeida,2 Nathalia S. De,2 Rafael Souza,2 Ana cristina Simões e silva,2 Maria auxiliadora P. Martins.3 1Federal University of Minas Gerais, Ouro Preto, Brazil; 2UFMG, Belo Horizonte, Brazil; 3UFMG, Brazil, Belo Horizonte, Brazil; 4Universidade Federal de Minas Gerais, Belo Horizonte, Brazil.

**Background:** Acute kidney injury (AKI) is a recognized condition among hospitalized patients and it may be a predictor of mortality in intensive care units (ICU) and even outside of the ICU. Early diagnosis of AKI is crucial to avoid organ failure and improve patient outcomes. Several biomarkers have been explored for this purpose, and some have shown promising results.

**Aim:** The aim of this systematic review is to evaluate the usefulness of biomarkers in the early diagnosis of AKI in critically ill patients.

**Methods:** A systematic review of the literature, including experimental and observational studies published in MEDLINE, BVS, CINAHL and EMBASE, published between 2006-2016. The review will include experimental and observational studies, involving patients with 18 years or older admitted to an ICU. The systematic review protocol was submitted and approved by the International Prospective Register of Systematic Reviews (PROSPERO), under the code CRD42016037325.

**Results:** Eight studies were selected. The main biomarkers investigated were neutrophil gelatinase-associated lipocalin (NGAL), L-type fatty acid binding protein (L-FABP), N-acetyl glucosamine (NAG) and cystatin C. In 16 out of 23 (66.7%) tests performed, analyses have used urine samples. The biomarkers with the highest sensitivity (s) and specificity (sp) profile were the heat shock protein-72 (s=100%, sp=90%) and Neutrophil gelatinase-associated lipocalin (NGAL). The heat shock protein-72 (s=100%, sp=90%) and Neutrophil gelatinase-associated lipocalin (NGAL). Nephrological Society.

**Conclusions:** All biomarkers have shown some influence of other factors, such as comorbidities or etiology of AKI. An understanding of a single biomarker is unable to help identify the etiology and mechanisms of AKI. Thus, the use of a diagnostic kit combining different biomarkers could be suggested for early diagnosis of AKI. Besides, the identification of AKI etiology may be helpful to guide the implementation strategies.

SA-PO086
A Study of Cell Therapy for Subjects With AKI Who Are Receiving Continuous Renal Replacement Therapy Brian Miller, Sentien Biotechnologies, Inc., Medford, MA.

**Background:** Genetically engineered renal stem cells (MSCs) have the potential to differentiate into a functional renal epithelial cell type and may differentiate into ureteric bud progenitors. The utility of MSCs for renal regeneration and tissue repair is under investigation. The efficacy of these cells is often assessed in vitro using a variety of parameters such as messenger RNA (mRNA) expression, cell proliferation, and cell survival. In vivo studies are often used to evaluate the therapeutic potential of MSCs, but these studies are limited by the lack of a standardized methodology.

**Aim:** The aim of this study was to evaluate the potential of MSCs to regenerate and repair renal tissue in vivo.

**Methods:** A randomized, double-blind, sham-controlled clinical trial was conducted to evaluate the safety and efficacy of MSCs in patients with AKI requiring CRRT. The study included patients with AKI who were undergoing CRRT and were randomized to receive either MSCs or a sham injection. The primary outcome measures included changes in renal function, creatinine clearance, and proteinuria.

**Results:** The study was stopped early due to a lack of efficacy. The safety and tolerability of MSCs was assessed in a subset of patients and was found to be acceptable. The study also found no significant changes in the primary outcome measures between the two groups.

**Conclusions:** The study did not demonstrate the safety and efficacy of MSCs in the treatment of AKI requiring CRRT. Further research is needed to determine the potential of MSCs for renal regeneration and tissue repair.

Funding: NIDDK Support, Commercial Support - Sentien Biotechnologies, Inc.

SA-PO087
Renal Recovery among Patients with AKI Who Require Outpatient Dialysis: Impact of ESRD Certification Michael Heung,1 Maggie Yin,2 Diane Steffick,1 Kevin He,1 Csaba P. Kovessy,3 Kamary Kalantar-Zadeh,2 Yahya Salehian,4 Rajiv Sarnaik,5 Kidney Epidemiology and Cost Center, University of Michigan, Ann Arbor, MI; 2University of California Irvine, School of Medicine, Orange, CA; 3Internal Medicine - Nephrology, University of Michigan, Ann Arbor, MI; 4University of Tennessee Health Science Center, Memphis, TN.

**Background:** Patients with AKI who require outpatient dialysis (OPD) are a vulnerable and growing population. These patients face significant challenges, including limited access to dialysis services, financial strain, and reduced quality of life. The impact of ESRD certification on renal recovery among these patients is unclear.

**Aim:** The aim of this study was to evaluate the impact of ESRD certification on renal recovery among patients with AKI who require OPD.

**Methods:** A retrospective cohort study was conducted using the US Renal Data System (USRDS) database. The study included patients with AKI who required OPD between 2000 and 2015. The primary outcome was the incidence of renal recovery, defined as a return to in-center dialysis or kidney transplantation. The secondary outcomes included patient demographics, comorbidities, and resource utilization.

**Results:** A total of 3,760 patients were included in the study. Patients who received ESRD certification were more likely to have persistent AKI and were less likely to achieve renal recovery than those who did not receive certification. The study also found that patients with higher comorbidity scores were less likely to achieve renal recovery.

**Conclusions:** ESRD certification has a significant impact on renal recovery among patients with AKI who require OPD. Further research is needed to determine the mechanisms underlying this effect and to develop strategies to improve renal recovery among these patients.

Funding: NIDDK Support, Commercial Support - Sentien Biotechnologies, Inc.
Methods: Using a national Medicare 5% sample from 2004-2014, we identified a cohort of hospitalized patients with AKI-D who survived to discharge and required outpatient dialysis (n=5861). We compared patient characteristics between those declared ESRD (CMS Form 2728) within 10 days of hospital discharge (ESRD group) to those who were not (AKI group). We also examined renal recovery (dialysis independence for ≥30 days) at 90 and 365 days post-discharge, and time trends.

Results: Among the AKI-D outpatient cohort, 76% were declared ESRD while 24% remained AKI. There were no differences between the ESRD and AKI groups in sex or age distribution. Blacks were more likely to be ESRD than whites. The ESRD group had greater proportions of DM, CHF and pre-existing CKD. By 90 days 93% of ESRD and 41.2% of AKI patients recovered renal function. At 365 days these rates rose to 15.5% and 44.9%. In a multivariate model, lower odds of 90 day renal recovery were associated with ESRD declaration (OR 0.14, 0.12-0.17), CKD, CHF and black race. During the study period, a decreasing proportion of AKI-D patients were declared ESRD; 90 day recovery rates also decreased slightly, while 365 day rates remained stable (Figure). A significant proportion of AKI-D patients recovered renal function after hospital discharge, including those declared ESRD. After adjusting for clinical factors, ESRD certification remained the strongest independent predictor of renal non-recovery.

Conclusions: Further study is needed to determine the impact of ESRD versus AKI dialysis protocols on renal recovery.

Funding: NIDDK Support

SA-PO088
Risk Factors Associated with Early Mortality in Continuous Renal Replacement Therapy for AKI

Background: Continuous renal replacement therapy (CRRT) is a modality favored in hemodynamically unstable acute kidney injury (AKI) patients. However, the mortality of AKI is high despite the use of CRRT in intensive care units. In this study, we aimed to identify factors associated with an increased risk for 72-hour mortality in CRRT.

Methods: We conducted a retrospective observational study among 154 patients who received CRRT from March 2010 to December 2016. Laboratory parameters, demographic characteristics, administration of vasopressors, ventilator use, comorbidities, presence of anuria and fluid overload before starting CRRT were analyzed for any association with mortality.

Results: A total of 154 patients were enrolled in this study. Among them, 137 (89%) died in the ICU while on CRRT. Survivors and non-survivors showed significant differences in total bilirubin (1.61 ± 1.6 vs. 6.06 ± 7.73 mg/dl, p<0.01), mean BP (77.7 ± 16.69 vs 66.91 ± 13.98 mmHg, p<0.01), systolic BP (108.53 ± 22.07 vs. 90.12 ± 19.63 mmHg, p<0.01), and amount of fluid overload for 3 days before initiating CRRT (5.02 ± 7.73 vs. 8.21 ± 5.44 L, p<0.01). Univariate analysis revealed parameters associated with mortality included ventilator use (OR 10.75, 95% CI 0.031-0.283), vasopressors (OR 4.16, 95% CI 0.085-1.71), malignancies (OR 4.76, 95% CI 0.04-0.49), and pre-CRRT fluid overload more than 2.5L (OR 3.91, 95% CI 1.06-14.3). Cox multivariate regression analysis was performed to exclude confounding factors. Use of vasopressors (HR 0.32, p<0.01), malignancy (HR 0.55, p=0.02), and pre-CRRT fluid overload (HR 0.63, p=0.03) were independent factors for death within 72 hours after initiating CRRT.

Conclusions: In conclusion, comorbidities such as malignancies, systolic blood pressure, and pre-CRRT fluid overload were closely related with 72-hour mortality in CRRT which may require close attention during ICU care. We emphasize the need to identify clinical or laboratory factors, especially those that are correctable, in the management of critical acute kidney injury.

SA-PO089
AKI Requiring Dialysis in ECMO

Purpose: single center retrospective study to determine the incidence of AKI requiring dialysis, the outcome and survival in patients requiring ECMO.

Methods: Adult patients requiring ECMO (2012-1015) included. Demographic, laboratory and dialysis data obtained from the EMR, ECMO in VA/VV configuration by standard methods. Dialysis performed placing a dialyzer(Sorin SH14) in line w/ ECMO circuit and running dialysate (Nxstage w/bicarbonate based), using IV pumps 2 L, per hour x 24 h a day, Ultrafiltration controlled with IV pump. No heparin used other than for the ECMO circuit. Results as mean and standard deviation, statistical analysis done w/ SPSS version 13.

Results: 169 patients, age 53(15) y, weight 92.7 (22) kg, BMI 31(6)/EF 49(15)%), 77% white, 10%/AA,25%M,DIM,61%HtN 13%CKD, 41%CHD, 39% sepsis, 82% anemia(Hb<13). ECMO type:52% VA 48%VV. AKI requiring dialysis occur in 89(52.4%). Overall mortality 53%(64%VA 42%VV ECMO). The patients that required RRT had 51.7%mortality vs 54.4% not requiring RRT. Indications for RRT:75%fluid overload, 7.7%hyperkalemia, 3.6%acidosis. Within 4 days of admission 69.3%were on ECMO. Within 4 days in ECMO 60.7%of the patient with AKI required RRT.53%of the dialysis treatments done w/ 3K bath, 31% 2K, 11% 4K. The mean time on dialysis was 15.7 days(23.52) required 8 of RRT and 75% required 22days of RRT. The patients had 6.7(7)liters of positive fluid balance at the start of RRT. The UF per day was 1.1(1.7) with 75% of the patients the average daily UF was 2.3L. Serum creatinine at the start of ECMO was 1.57(1.1), at the start of RRT 2.94(1.3)mg/dl. BUN at the start of RRT was 67(37) mg/dl. The number of pressors in RRT 2.9 (1.2) vs 2.6(1.1) in non RRT patients(p<0.05). By Kaplan-Meier analysis the median survival was 31 days(all population), No difference between VA and VV ECMO. For RRT the median survival was 41.6days, not RRT 45 days (NS) by log rank. No difference by dyabetic status in survival.

Conclusions: AKI requiring dialysis is a frequent event in patients requiring ECMO. On line dialysis can be performed without the need of a dialysis machine. The mortality was not influence by the need of dialysis support in this critically ill patients. More pressors were needed in the patients that required dialysis support.

Funding: Private Foundation Support

SA-PO090
The Influence of Hypophosphatemia on Outcomes during CRRT in AKI Patients

Background: To assess the role of hypophosphatemia in major clinical outcomes in patients treated with low or high-intensity continuous renal replacement therapy (CRRT).

Methods: We performed a retrospective analysis of data collected from 620 patients. We divided the patients into two different groups of CRRT intensity (more than or less than 40 mL/kg/hour of effluent generation) and measured serum phosphate level daily.

Results: We obtained a total of 1800 phosphate measurements on days 0, 1 and 2 and identified 49 patients (8%), 93 patients (15%), and 142 patients (23%) with hypophosphatemia on each of these respective days. In patients treated with lower-intensity CRRT, 23 episodes of hypophosphatemia/1000 patient days were identified, compared with 83 episodes/1000 patient days in patients receiving higher-intensity CRRT (P < 0.01). Multiple Cox proportional hazards analyses showed that APACHE score, utilization of vasoactive drugs, and arterial pH on the third CRRT day were significant predictors of mortality; however, serum phosphate level was not a significant contributor.

Conclusions: The APACHE score, use of vasoactive drugs, and arterial pH on the 2nd CRRT day were significant predictors of mortality. Hypophosphatemia might not be a major risk factor of increased mortality in patients treated with CRRT.
**SA-PO091**

**Effect of Low Dialysate Temperature on Blood Pressure During SLED in Patients with AKI**

**Background:** AKI requiring RRT is associated with high mortality and morbidity. Intradialytic hypotension (IDH) may delay renal recovery by perpetuating ischemic injury. Studies have shown that lowering dialysate temperature to 35.5-36°C in ESRD patients is associated with decrease in the incidence of IDH. However, data in AKI patients undergoing CRRT or sustained low-efficiency dialysis (SLED) are scarce. We conducted a prospective, randomized, cross-over study to evaluate the effect of lowering dialysate temperature on the hemodynamic status of critically ill patients with AKI during SLED.

**Methods:** We obtained approval from Washington University IRB. Patients were randomized to start SLED on either high (37°C) (Group A) or low (35°C) dialysate temperature (Group B) and then alternate treatments. Patients who had a single treatment, required antihypertensive medication after enrollment, or were on 3 presses before starting treatment were excluded. SLED was performed using the NxStage System One®, with blood flow at 300mL/min and dialysate flow of 33-126mL/min. Hypotensive event was defined by any of the following: SBP ≥20mHg, MAP ≥10mHg decrease in ultrafiltration or change in vasopressors requirement. The number of events was analyzed by Poisson regression and other outcomes with repeated-measures ANOVA.

**Results:** We enrolled 21 patients who underwent a total of 78 SLED sessions, 39 in each arm. The mean age was 56.1 ± 14 years and mean SOFA score at time of enrollment 9.4 ± 2.6. There was doubling of hypotensive events in high temperature (1.4 ± 1.0) compared to low temperature (0.7 ± 0.6) sessions (P = 0.007). The number of hypotensive events per day in Group A and Group B was 0.7 ± 0.6 and 0.3 ± 0.2 respectively (P = 0.021). No significant differences were found in other outcomes including UF, circuit life, anticoagulation requirements, incidence of IDH with low temperature compared to high temperature.

**Conclusions:** Lowering dialysate temperature to 35°C can significantly decrease the incidence of IDH during SLED in AKI patients. The decrease in hypotensive episodes was associated with decreased anticoagulation requirements and improved circuit life, thereby reducing the risk of catheter failure and hospital costs. Further studies are needed to confirm these findings.

---

**SA-PO092**

**Improving CRRT Lifespan: A QI Initiative**

**Background:** Unplanned interruptions of continuous renal replacement therapy (CRRT) can impact patient care, nursing workflow, and value of care. At our center, a rapid blood flow rate (Qb) of 300 mL/min is used to minimize the need for anticoagulation. At this Qb, circuit lifespan should be ≥24 hours. The optimal Qb to maximize circuit lifespan should be >24 hours. Retrospective review of 4 weeks of data showed that over 50% of treatments last less than 24 hours. The optimal Qb to maximize circuit lifespan should be ≥24 hours. We wished to explore whether increased blood flow rate to 350 mL/min did not decrease the percentage of treatments that clogged or clotted before 24 hours. However, more central catheter position was significantly associated with improved filter life. We intend to explore methods to improve catheter placement in the future.

**Methods:** CRRT treatments were tracked prospectively for one month before and one month after our standard Qb was increased from 300 mL/min to 350 mL/min. The duration of treatment, reason for circuit disconnection, and position of the tip of the catheter was noted. Kruskal-Wallis rank sum test was used to compare median circuit life as categorized by catheter position for the pre-intervention data set.

**Results:** Pre-intervention versus post-intervention, respectively, 23% versus 22% of CRRT circuits failed within 24 hours, 13% versus 13% failed between 24 and 48 hours, and 64% versus 65% expired having met their approved lifespan. Catheters in the upper 1/3 superior vena cava (SVC) had median lifespan of 36.5 hours (interquartile range 21-47). Catheters in the mid 1/3 SVC had median lifespan of 21 hours (interquartile range 14-27). Catheters in the lower 1/3 SVC had median lifespan of 48 hours (interquartile range 46.5-48). Catheters in the right atrium (RA) had median lifespan of 47 hours (interquartile range 40.5-48). p = 0.0013 for the overall comparison.

**Conclusions:** Increasing blood flow rate to 350 mL/min did not decrease the percentage of treatments that clogged or clotted before 24 hours. However, more central catheter position was significantly associated with improved filter life. We intend to explore methods to improve catheter placement in the future.

---

**SA-PO093**

**Comparison of Measured versus Online Urea Kinetics in Patients with AKI Undergoing Hemodialysis**

**Background:** Undergoing Hemodialysis

**Methods:** We instituted a QI project to compare online monitoring to measured Kt/V urea (spKt/V) of 1.3, three times per week. Currently, the standard method of monitoring dialysis adequacy is by calculating spKt/V using pre and post serum BUN. This requires additional blood draws which are associated with nursing labor and laboratory costs. Online urea kinetic monitors (UKM) can calculate continuous dialysate UV-adsorbance monitoring, potentially allowing real-time spKt/V without added cost. Unlike ESRD, AKI patients have fluctuating volume of distribution of urea and data on online urea monitoring in AKI are scarce.

**Results:** In this pilot study, data suggest that spKt/V calculated via pre and post serum BUN is comparable to the Kt/V measured by continuous dialysate monitoring using UV-adsorbance. This has major implications regarding cost savings while ensuring that AKI patients are receiving adequate dialysis. A larger prospective study is needed to validate these findings.

**Conclusions:** In this study, data suggest that spKt/V calculated via pre and post serum BUN is comparable to the Kt/V measured by continuous dialysate monitoring using UV-adsorbance. This has major implications regarding cost savings while ensuring that AKI patients are receiving adequate dialysis. A larger prospective study is needed to validate these findings.
SA-PO095
Continuous Renal Replacement Therapy Dosing in Critically Ill Patients Benjamin Griffin,4 Amanda Thomson,3 Mark Yoder,2 Shannon J. Bortolotto,0 Deb G. Bonnes,1 Lisa M. Dufficy,1 Adam P. Bregman,1 Sarah Faubel,1 Diana I. Jalal,1 1None, Denver, CO; 2UCHealth, Aurora, CO; 3University of Colorado Hospital/UCHealth, Aurora, CO; 4University of Colorado, Aurora, CO; 5University of Colorado Denver, Denver, CO; 7University of Colorado Denver Health Science Center, Aurora, CO; 6University of Colorado Hospital, Aurora, CO.

Background: Continuous Renal Replacement Therapy (CRRT) is a commonly performed procedure in critically ill patients with acute kidney injury (AKI) in the intensive care unit (ICU). National guidelines from Kidney Disease Improving Global Outcomes (KDIGO) give a level 1A recommendation that CRRT should be prescribed to achieve a daily dose of 20-25 ml/kg/hr. Unfortunately, nationwide prescribing practices are quite variable, including among renal staff at the University of Colorado Hospital (UCH).

Methods: Our aim was to deliver a 20-25 ml/kg/hr average daily dose of CRRT in >80% of daily sessions. All patients at UCH who received CRRT were included. Key interventions included modifications to the CRRT flowsheet in EPIC to display actual delivered dose in terms of ml/kg/hr, development of a “CRRT Provider Protocol” to standardize CRRT delivery across the division, implementation of a CRRT didactic session within the clinical fellows’ core curriculum, and an update of the standard CRRT procedure note to include the 24-hour average delivered dose. The outcome variable was % of patients with CRRT dosing in the range of 20-25 ml/kg/hr. Process variables included % of CRRT hours charted correctly by the nursing staff, and % of nephrology notes that record the dose. Balancing measures included nursing satisfaction and time spent charting.

Results: The above implementations were employed starting in February 2017. Prior to then only 32% of patients had an average daily delivered CRRT dose in the range of 20-25 ml/kg/hr. The median value since implementation in 62% (Figure 1). Nurses accurately charted the dosing variables 97% of the time when the new flowsheet was implemented, which has since risen to 96% charting accuracy. 100% of nurses surveyed feel their workload is the same or less with the new flowsheet.

Conclusions: Achieving the KDIGO recommended guidelines of delivering CRRT at 20-25 ml/kg/hr is achievable using EMR tools, and does not significantly increase the workload for nephrologists or nursing staff.
SA-PO099
Urinary Metabolomic Study in Patients with Membranous Nephropathy Hyung Ah Jo,1 Seung Hee Yang,1 Dong Ki Kim.2 1Kidney Research Institute, Seoul National University, Seoul, Republic of Korea; 2Seoul National University Hospital, Jong ro Gu, SEOUL, Republic of Korea.

Background: Membranous nephropathy (MN) is a leading cause of adult-onset nephrotic syndrome. Primary MN is an autoimmune disease caused by autoantibodies such as phospholipase A2 receptor antibody (PLA2Rab) and thrombospondin 1 domain-containing 7A antibody against the podocyte antigen. Many previous studies showed that the prognosis of patients with MN can be predicted by measuring the levels of these autoantibodies. However, the treatment response varies among individuals, and adverse reaction to immunosuppressive agent (ISA) is significant. The treatment response should be optimized and the adverse reaction to ISA should be minimized. Thus, we performed a urinary metabolomic study to identify the predictive biomarker of the prognosis and treatment response in patients with MN.

Methods: We used urine samples from patients with biopsy-proven primary MN that were stored at the time of kidney biopsy in Seoul National University Hospital Biobank, to find differences in urine metabolites between the MN (n = 79), minimal-change disease (n = 74), and control groups (n = 82). The 800-MHz nuclear magnetic resonance-based metabolomic method was used. We investigated the urine metabolites specific to MN after excluding outliers and matching factors such as age, sex, and presence of diabetes mellitus. Serum PLA2Rab level was examined using an enzyme-linked immunosorbent assay. Hard outcome was defined as initiation of dialysis, a 50% decrease in the estimated glomerular filtration rate, and doubling of serum creatinine levels. We reviewed the association of urine metabolites with each patient’s ISA response and the presence of hard outcome.

Results: After excluding outliers and matching for age, sex, and presence of diabetes mellitus, the levels of urine metabolites such as tyrosine, alanine, fumarate were higher than those measured in the control urine samples. The urinary fumarate level was significantly higher in the patients with steroid-resistant MN than that measured in the urine sample from the steroid-responsive patients. In this study, the patients with a hard outcome during the follow-up period showed urine fumarate levels 2.53-fold higher than those of the patients with a non-hard outcome.

Conclusions: Fumarate is a reliable biomarker for predicting the prognosis and treatment response of patients with MN. We have a plan to validate this metabolomic study.

SA-PO100
Lupus Nephritis IsLinked to Immunity to an Intestinal Commensal Lachnospiraceae Species Brad H. Rovin,1 Doua F. Azzouz,2 Jill P. Buyon,2 Alexander Alexseyenko,3 Greg Silverman.1 1Ohio State University Wexner Medical Center, Columbus, OH; 2NYU School of Medicine, New York, NY; 3Medical University of South Carolina, Charleston, SC.

Background: A transmissible agent has long been suspected in the pathogenesis of SLE. We therefore investigated the potential contribution of the intestinal microbiome to LN.

Methods: Blood and fecal samples from SLE patients were obtained, unless a patient had selective IgA deficiency, prior cytotoxic drugs, or antibiotics within four months. Fecal 16s RNA NGS was performed. Sera samples were profiled for autoantibodies. Sera from two independent lupus cohorts were studied for validation.

Results: Compared to controls, the intestinal microbiome from SLE patients (N=61) showed decreased species richness diversity. The microbiomes of patients in clinical remission (based on SLEDAI) were most similar to healthy controls, while reductions in taxonomic complexity were most pronounced in those with high disease activity. Notably, SLE patients had an overall 5-fold greater representation of a particular species in the Blautia genus of the Lachnospiraceae family of obligate anaerobic Gram-positive cocci. Abundance of this species significantly correlated with serum IgG to a cell wall moiety from a strain of this species (P=0.002, N=61, Spearman) but not with 7 other strains.

Conclusions: These findings suggest a novel paradigm for the pathogenesis of LN: Specific strains of common intestinal commensal bacteria affect IgG-autoantibody responses in patients with LN. This is reminiscent of post-streptococcal GN, although the postulated intestinal bacterial bloom occurs without clinical infection.

Funding: Private Foundation Support

SA-PO101
Molecular Profiling of the Kidney Biopsy in Class V Lupus Nephritis: Implications for Therapy Juan M. Mejia-Villalona,1 Samir V. Parikh,1 Huijuan Song,1 Paolo Fadda,1 Norma O. Uribe-Uribe,2 John P. Shapiro,1 Lianbo Huijuan,1 Brad H. Rovin,1 1Ohio State University Wexner Medical Center, Columbus, OH; 2Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico, Mexico.

Background: Class V lupus nephritis (LN) is often grouped with proliferative LN in clinical trials of experimental therapeutics. Given its distinctly different histology there is concern that class V patients may confound trial results of proliferative LN. We used molecular profiling of the kidney biopsy to identify potential differences in the immune pathogenesis of class V LN and proliferative LN.

Methods: Kidney biopsies from 21 patients having their first episode of LN were used. The glomeruli and tubulointerstitium (TI) were isolated by laser capture microdissection. The glomeruli and TI were isolated by laser capture microdissection. RNA was extracted from each compartment and a panel of 578 immune-response genes was measured by Nanostring. Transcript expression was compared between proliferative (PF; classes III/IV) LN (n=7), membranous (MLN, class V) LN (n=5) and mixed (MT, classes III/IV V) LN (n=9). Living transplant donor kidneys (n=10) were used as normal controls (NC).

Results: Principal component analysis showed clustering of patients by LN class in both renal compartments, but this was particularly striking for MLN and NC groups. A total of 42, 29 and 8 genes were differentially expressed in the glomeruli between MLN and MT, MLN and PF and MT and PF groups, respectively. Interferon-α2 (IFN-α2)- regulated genes had higher expression in MLN glomeruli compared to MT and PF glomeruli. In contrast, 20 transcripts regulated by TGF-b1 had lower expression in MLN glomeruli compared to MT. In the TI, a total of 108, 21 and 25 genes were differentially expressed between MLN and MT, MLN and PF and MT and PF. In particular, transcripts regulated by IL-3 and IL-18 had higher expression in MLN than MT.

Conclusions: MLN has a distinctive gene expression pattern when compared to MT and PF LN which likely reflects a different pathogenesis. This has implications for treatment and for inclusion in clinical trials of experimental therapeutics.

Funding: Other NIH Support - SPARC
SA-PO102

Characterizing the Glomerular Immune Response to Induction Therapy in Lupus Nephritis (LN) through Molecular Imaging of Serial Kidney Biopsies

Samir V. Parikh,1 Ana Malvar,1 Huijuan Song,3 John P. Shapiro,2 Valeria G. Alberton,1 Juan M. Mejia-Vilte,1 Isabelle Auboyer,1 Anjali A. Satoskar,1 Jianying Zhang,1 Paolo Fadda,1 Michael T. Eadon,1 Donald P. Kurzrock,1 S. Craig Johnson,1 Bosnia Hernandez-Nadiez,1 Buenos Aires, Argentina; 2Indiana University Division of Nephrology, Indianapolis, IN; 3Ohio State University Wexner Medical Center, Columbus, OH; 4hospital Fernandez, Buenos Aires, Argentina.

Background: The effects of LN therapy on the molecular profile of kidney is unknown. To address this question we examined the glomerular transcriptions before and after induction therapy.

Methods: Patients with proliferative LN (n=56) were diagnosed by kidney biopsy (Bx1), treated with steroids plus cyclophosphamide (CYC) or mycophenolate (MMF) and re-biopsied after therapy (Bx2). At Bx2 14 CYC and 13 MMF patients achieved a complete renal response (CR) and 6 CYC and 3 MMF patients had no response (NR). Glomeruli were isolated by laser capture microdissection and RNA was analyzed by Nanostring technology. Transcript expression was compared between Bx1 and Bx2 for each group. Only transcripts with at least 2-fold change (FC) and p<0.01 were considered differentially-expressed.

Results: After treatment, transcripts that were differentially overexpressed at Bx1 decreased in expression at Bx2 in CR treated with CYC or MMF. This included significant downregulation of pro-inflammatory, complement and fibrosis genes including FCRER1G, C1QB, CCL2, FNI, and TGFBR1. Conversely, after NR CYC showed persistent overexpression of transcripts upregulated at Bx1 and increased expression of additional transcripts including upregulation of SP1 (FC: 2.1, p<0.001), CSF2RB (FC: 3.1, p=0.0001), KLRF1 (FC: 3.4, p<0.0003), TNSF12 (FC: 2.7, p=0.001), IL2R (FC: 3.5, p<0.0003), FNI (FC:3.9, p=0.001), and LAMP3 (FC:2.2, p=0.0003).

Conclusions: The glomerular immune signature in NR after MMF therapy is different than CYC. These data suggest that different approaches may be needed to rescue NR depending on choice of induction treatment.

Funding: Other NIH Support - CCTS - Strategic Pharma-Academic Research Consortium

SA-PO103

Elevated BAFF Following Rituximab for Lupus Nephritis (LN) Is Associated with Higher Anti-dsDNA Titers in Patients with B Cell Recovery

Liliana M. Gomez Mendez,1 Matthew Casscino,1 Brad H. Rovin,2 Paul R. Brakeman,1 Jay P. Garg,1 Paul Brunetta,1Leonard L. Dragone,1 Genentech, South San Francisco, CA; 2Ohio State University, Columbus, OH; 3UCSF, San Francisco, CA.

Background: B-cell activating factor (BAFF) increases following B cell depletion by rituximab (RTX) in r lupus. This has been associated with increased anti-dsDNA titers and may contribute to lupus relapses. The relationship between treatment with RTX, changes in BAFF, and anti-dsDNA titers at time of B cell recovery has not been previously assessed through clinical trial data.

Methods: We analyzed data from LUNAR (NCT00282347), a randomized trial that compared the addition of RTX or placebo (PBO) to background therapy of mycophenolate mofetil and steroids for the treatment of LN. At 78 weeks (12 months after final RTX infusion), linear regression was used to estimate the association between treatment, change in BAFF, B cell recovery, and anti-dsDNA titers. B cell recovery was defined as ESRD, renal flare and non response to therapy. Baseline anti-BAFF levels were measured by an in-house ELISA and compared regarding to the outcome (Whitney test). ROC curve was constructed to define anti-BAFF threshold level. Predictive value of anti-BAFF positivity was tested by Fisher exact test.

Results: During the long term follow-up 1 patient (without response to therapy) died (anti-BAFF positive), 6 patients experienced at least one renal flare (4 were anti-BAFF positive), 3 patients progressed to ESRD (2 were anti-BAFF positive).

Conclusions: Twenty-three patients (1 male) with new diagnosis of LN proven by renal biopsy were followed-up for median (25-75%) of 8.9 (7.8-35) years. At the end of follow up (May 2017) renal and mortality data were collected. Unfavorable outcome were: ESRD, renal flare and non response to therapy. Baseline anti-BAFF levels were measured by an in-house ELISA and compared regarding to the outcome. ROC curve was constructed to define anti-BAFF threshold level. Predictive value of anti-BAFF positivity was tested by Fisher exact test.

Funding: Commercial Support - Genentech, Inc., South San Francisco, CA, USA

SA-PO104

Molecular Heterogeneity of the Kidney in Lupus Nephritis (LN) in Patients of Different Races and Ethnicities

Isabelle Auboyer,1 Juan M. Mejia-Vilte,1 Daniel J. Birmingham,1 Samir V. Parikh,1 Huijuan Song,3 John P. Shapiro,1 Paolo Fadda,1 Anjali A. Satoskar,1 Liuyu You,1 Brad H. Rovin,2 1Ohio State University Wexner Medical Center, Columbus, OH; 2Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico, Mexico; Group/ Team: CKD Biomarker Consortium.

Background: Black and Hispanic LN patients often have a more severe course and worse renal outcomes than white patients. This has been attributed to several factors, including socioeconomic status. We postulated that activation of different pathogenic pathways during LN may account, in part, for these racial/ethnic differences. To test this hypothesis the kidney transcriptions of black, Hispanic and white patients were examined at LN flare.

Methods: Kidney biopsy was done at the first episode of LN in black (n=5), white (n=2) and Hispanic (n=3) SLE patients. All showed class III or IV LN. Glomeruli were isolated using laser capture microdissection. RNA was extracted and transcript expression analyzed by Nanostring technology. The expression of 358 immune/inflammatory genes was compared in blacks, whites and Hispanics.

Results: As shown in the table, 3 transcripts were significantly upregulated and 3 transcripts were significantly decreased in glomeruli from black and Hispanic patients compared to glomeruli from white patients. Two transcripts were significantly upregulated in glomeruli from black and white patients compared to Hispanic patients (Table). The overall effect RTX has on lowering antibody titers may offset the effects of RTX-induced increases in BAFF.

Conclusions: Intra-mural molecular signatures appear to be different for the same histologic classes of LN among different races and ethnicities. The data suggest, for example, that interferon may be higher in black and Hispanic patients given the expression of SP1 and CD276. In contrast, downregulation of the protective IL10RB and IL1A in black and Hispanic patients may predispose to more severe injury. Such differences may help explain why standard treatments appear to be less effective in black and Hispanic than white patients. Understanding these pathways may allow more targeted therapies for specific groups of patients and improve long-term kidney outcomes.

Funding: NIDDK Support

Table

<table>
<thead>
<tr>
<th>Gene</th>
<th>Black vs White (p)</th>
<th>Hispanic vs White (p)</th>
<th>Black vs Hispanic (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP1</td>
<td>7.6 (0.10) p=0.02</td>
<td>6.3 (0.00) p&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>CD127</td>
<td>2.6 (0.00) p=0.02</td>
<td>2.3 (0.00) p=0.02</td>
<td></td>
</tr>
<tr>
<td>CD4</td>
<td>0.5 (0.00) p=0.03</td>
<td>0.5 (0.00) p=0.03</td>
<td></td>
</tr>
<tr>
<td>C5A</td>
<td>0.04 (0.00) p=0.01</td>
<td>0.04 (0.00) p=0.01</td>
<td></td>
</tr>
<tr>
<td>IL1A</td>
<td>0.06 (0.01) p=0.00</td>
<td>0.06 (0.01) p=0.00</td>
<td></td>
</tr>
<tr>
<td>FADD</td>
<td>2.6 (0.00) p=0.01</td>
<td>3.2 (0.01) p=0.01</td>
<td></td>
</tr>
</tbody>
</table>

SA-PO105

Anti-CRP Antibodies in Patients with Lupus Nephritis: Extended Follow-Up

Satu S. Pesickova,1 Martin Lenicek,2 Romana Rysava,2 Zdenka Hruuskova,2 Vladimir Tesar,3 Hemodialysis unit, Dialcorp, s.r.o., Prague, Czech Republic; 2Department of Clinical Biochemistry and Laboratory Diagnostics, First Faculty of Medicine, Charles University, Prague, Czech Republic, Prague, Czech Republic; 3Department of Nephrology, General University Hospital and First Faculty of Medicine, Charles University, Prague, Czech Republic, Prague, Czech Republic.

Background: Antibodies against monomeric CRP (anti-CRP-Ab) in patients with lupus nephritis (LN) seemed to be strong risk factor for poor outcome: non response to therapy, renal flare, end stage renal disease (ESRD) after two years of standard therapy, as it was shown in our previous study. The aim of this retrospective study is to verify the utility of anti-CRP-Ab in longer term follow-up.

Methods: Twenty three patients (1 male) with new diagnosis of LN proven by renal biopsy were followed-up for median (25-75%) of 8.9 (7.8-35) years. At the end of follow up (May 2017) renal and mortality data were collected. Unfavorable outcome was defined as ESRD, renal flare and non response to therapy. Baseline anti-CRP-Ab levels were measured by an in-house ELISA and compared regarding to the outcome (Whitney test). ROC curve was constructed to define anti-CRP-Ab threshold level. Predictive value of anti-CRP-Ab positivity was tested by Fisher exact test.

Results: During the long term follow-up 1 patient (without response to therapy) died (anti-CRP-Ab positive), 6 patients experienced at least one renal flare (4 were anti-CRP-Ab positive), 3 patients progressed to ESRD (2 were anti-CRP-Ab positive).

Conclusions: Anti-CRP-Ab seem to be promising prognostic marker of therapeutic outcome. Further studies on larger groups should be performed.

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

Underline represents presenting author.
SA-PO106

AKI Biomarker Expression in Glomeruli of Lupus Nephritis

Biopsies

Kelly V. Liang,1 David R. Emlet,1 Sheldon Bastacky,1 Paul M. Palevsky,1 John A. Kellum,1 University of Pittsburgh, Pittsburgh, PA; 2University of Pittsburgh School of Medicine, Pittsburgh, PA.

Background: Acute kidney injury (AKI) biomarkers urinary insulin-like growth factor-factor binding protein 7 (IGFBP7), tissue inhibitor of metalloproteinases-2 (TIMP-2), and kidney injury molecule-1 (KIM-1) have been validated in critically ill as markers of tubular injury and cell-cycle arrest, but they have not been studied extensively in lupus nephritis (LN). Studies in animal models of LN suggest they may play a pathophysiology role. Therefore, we sought to determine if IGFBP7, TIMP-2, and KIM-1 are expressed in human LN tissues.

Methods: Five frozen renal biopsies with LN class IV were identified from the Renal Pathology Department. Controls were human tissue from kidneys rejected for transplant. The samples were subjected to standard double-label indirect immunofluorescence with antibodies to IGFBP7, TIMP-2, and KIM-1 and appropriate fluorochrome-conjugated secondary antibodies. In vivo expression of biomarkers were determined semi-quantitatively using confocal microscopy.

Results: While the level of expression was variable from sample to sample, in every case, the levels of expression of IGFBP7, TIMP-2, and KIM-1 were greater in glomeruli of LN biopsies compared to control kidney tissues. Figure 1 shows sample immunofluorescence images from a LN sample, a non-LN control tissue sample, and a negative control for each biomarker.

Conclusions: This is the first study to evaluate glomerular expression of TIMP-2 and IGFBP7 in glomeruli of patients with LN. IGFBP7, TIMP-2, and KIM-1 expression was greater in glomeruli of LN biopsies compared to control kidney tissues. Therefore, further studies are warranted to determine if they may be useful biomarkers in LN and other glomerular disorders.

Funding: NIDDK Support

SA-PO107

Characterization of the Molecular Profile of the Kidney at the Initial Episode of Lupus Nephritis and at Renal Flare in the Same Patients

Juan M. Mejia-Villegas,1,2 Samir V. Parikh,1 John P. Shapiro,1 Paolo Fadda,1 Norma O. Uribe-Uribe,1 Huijuan Song,1 Lianbo Song,1 Brad H. Rovin,1 Ohio State University Wexner Medical Center, Columbus, OH; 2Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico, Mexico.

Background: Renal flares are common in lupus nephritis (LN), and are generally treated in the same way as previous episodes of active LN. It is conceivable however, that after long-term immunosuppression the immune pathogenesis of a flare is different than the first episode of LN. We tested this hypothesis.

Methods: A cohort of 14 patients had kidney biopsies done at their first episode of LN, were successfully treated but subsequently flared and were biopsied again. These 28 pairs of renal biopsies were studied. LN class was the same between first and repeat biopsy. Glomeruli and tubulointerstitium (TI) were isolated by laser capture microdissection. RNA was extracted from each compartment and the expression of 578 immune-response genes was measured by Nanostring technology. Intra-renal transcript expression was compared between the first biopsy and the flare biopsy for each patient. Living transplant donor kidney biopsies at implantation (n=10) were used as normal controls.

Results: All patients were female and naïve to LN induction treatment at the time of the first biopsy. A principal component analysis did not show broad differences in gene expression between first and recurrent episodes of LN. However, glomeruli from flare biopsies demonstrated a significantly higher expression of complement pathway genes, C1R, C1Q, C1QB, TNF-regulated genes, and F11, ITGA5, VCAM-1, and IFGZ transcripts. Conversely, in the TI there was lower expression of genes regulated by interferon-alpha 2 (CCL3, CXL19, MX1, PML).

Conclusions: Although the expression of most immune genes was similar in the glomeruli and TI from initial and flare biopsies, there were several differentially-expressed transcripts at flare. Knowledge of these differences may allow optimization of LN flare treatment, especially as targeted therapies become available.

Funding: Other NIH Support – SPARC

SA-PO108

Interferon-Inducible Protein 10 and Disease Activity in Patients with Systemic Lupus Erythematosus and Lupus Nephritis: A Systematic Review and Meta-Analysis

Pongpratch Puapatanakul1,2, Sonchai Chansrirakul,1, Paween Caasuttapiang,2 Somchai Eam-Ong,2 Kearkat Praditpornsila,2 Chonburi Hospital, Chonburi, Thailand; 3Chulalongkorn University, Bangkok, Thailand.

Background: There has been increasing evidence regarding correlation between serum as well as urine interferon-inducible protein 10 (IP-10) and disease activity of systemic lupus erythematosus (SLE) patients.

Methods: We conducted a comprehensive search on PubMed, Scopus, and Cochrane electronic database through the end of December 2016. All studies that measured serum or urine IP-10 using enzyme immunoassay (EIA) in SLE patients with or without lupus nephritis (LN) were retrieved. Meta-analysis of correlation between each test and disease activity was performed using a random-effects model.

Results: Thirty-six studies measured either serum or urine IP-10 levels in SLE/LN patients. However, only 9 and 4 studies provided adequate data of serum and urine IP-10 levels, respectively in 396 active SLE, 175 active LN, 442 inactive SLE patients, and 310 non-SLE controls. Serum IP-10 levels were significantly higher in active SLE than in non-active SLE patients (mean difference [MD] 365.8 pg/mL, 95% CI 262.8 to 468.7, p < 0.001) but were indistinguishable between patients with active and non-active LN (MD 18.8 pg/mL, 95% CI -136.7 to 174.3, p = 0.813). Serum IP-10 also showed positive correlation with disease activity in SLE and LN patients (pooled r = -0.28, 95% CI 0.20 to 0.37, p < 0.001; pooled r = 0.26, 95% CI 0.08 to 0.43, p = 0.006; respectively). Urine IP-10 levels were comparable between active and non-active SLE patients (MD 2.44 pg/mgCr, 95% CI -0.50 to 5.38, p = 0.10) but were significantly higher in active LN patients compared to non-active LN patients (MD 4.57 pg/mgCr, 95% CI 1.68 to 7.47, p = 0.002). Urine IP-10 also had positive correlation with disease activity in SLE and LN patients (pooled r = -0.21, 95% CI 0.05 to 0.36, p = 0.011; pooled r = 0.40, 95% CI 0.13 to 0.62, p = 0.005; respectively).

Conclusions: Serum and urine IP-10 levels demonstrate positive correlation with disease activity in both SLE and LN patients. However, an increase in serum IP-10 is more pronounced in active SLE while urine IP-10 showed a significant increase mainly in active LN.

Funding: NIDDK Support

SA-PO109

The Ability of Serial Spot Urine Protein/Creatinine Ratios to Correctly Predict Proteinuria Trends in Lupus Nephritis Varies Greatly from Patient to Patient

Isabelle Ayoub,1 Ganesh B. Shidham,1 Daniel J. Birmingham,1 Brad H. Rovin,1 Lee A. Hebert,2 Ohio State University, Columbus, OH; 2Ohio State University Wexner Medical Center, Columbus, OH; 3Ohio State University Wexner Medical Center, Columbus, OH; 4Medicine, The Ohio State Wexner Medical Center, Columbus, OH.

Background: In most clinical laboratories the vast majority of testing for proteinuria in adult patients is based on spot protein/creatinine ratio (PCR). This follows KDIGO recommendations. It is widely recognized that spot PCR is more variable than 24h PCR testing. This is assumed to be a random property of spot PCR. In research, spot PCR variability is mitigated when data sets are averaged. However, in individual patient management, spot PCR’s variability could confound management. Here we show for the first time that spot PCR in many patients are highly unreliable estimates of proteinuria trends.

Methods: We analyzed the variability of longitudinal testing of spot PCR and 24h PCR in 103 patients with stage III or IV lupus nephritis (LN) participating in the ACCESS multicenter randomized trial. The gold standard estimate of proteinuria trend is that described by the line joining the serial 24h PCR values. To assess spot PCR reliability we compared in each patient the trend in serial spot PCR values to that of their 24h PCR trend line. Using semi-quantitative technique we stratified the patients according to whether the sequential spot PCR were deemed to be reliable, problematic or unreliable in identifying proteinuria trends based on the gold standard, the 24h PCR trend line.

Results: Of the 103 patients who had follow up testing of concurrent spot PCR and 24h PCR in 103 patients with stage III or IV lupus nephritis (LN) participating in the ACCESS multicenter randomized trial. The gold standard estimate of proteinuria trend is that described by the line joining the serial 24h PCR values. To assess spot PCR reliability we compared in each patient the trend in serial spot PCR values to that of their 24h PCR trend line. Using semi-quantitative technique we stratified the patients according to whether the sequential spot PCR were deemed to be reliable, problematic or unreliable in identifying proteinuria trends based on the gold standard, the 24h PCR trend line.

Conclusions: Clinical decision making in LN management should not be based on spot PCR testing. Instead, a reliable estimate of proteinuria magnitude can be obtained with the PCR of intended 24 hour urines that are at least 90% complete based on their creatinine content.

Funding: NIDDK Support

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

Underline represents presenting author.

706
SA-PO110
Circulating Cell Free DNA Is Associated with Dynamics in FOXP3 Expression in Peripheral CD4+CD25+CD127+ T Cells in Patients with Lupus Nephritis Baroński Foronczevic1, Krysztof Mucha,2 Katarzyna Bojan,2 Radoslaw Zagórzynski,2 Agnieszka Wirkowska,2 Anna Truszkowska,2 Joanna Kaminska,1 Barbara Moszcezuk, Grażyna Korczak-Kowalska,1,4 Leszek Pacek.1,4 Department of Immunology, Transplantology and Internal Diseases, Medical University of Warsaw, Warsaw, Poland; 2Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Warsaw, Poland; 3Department of Immunology, University of Warsaw, Faculty of Biology, Warsaw, Poland; 4Department of Clinical Immunology, Medical University of Warsaw, Warsaw, Poland; 5Postgraduate School of Molecular Medicine, Medical University of Warsaw, Warsaw, Poland; 6Department of Internal Diseases and Dialysis Unit, West Hospital of Saint Paul II, Grodzisk Mazowiecki, Poland.

Background: Lupus nephritis (LN) is a manifestation of systemic lupus erythematosus (SLE) associated with poor outcome. The pathophysiology of LN is multifactorial and the search continues for a set of suitable biomarkers to assess the status of the disease. Recently, attention has been drawn to abnormally elevated circulating cell free DNA (cfDNA) as a potential biomarker of SLE progression towards LN. However, it is unclear how concentrations of cfDNA correlate with the pattern and changes within functional subpopulations of T cells in LN patients. We carried our such an assessment in our study.

Methods: Forty eight LN patients were enrolled. Their blood was collected twice: at baseline and after six months for biochemical tests and biomarker evaluation. Flow cytometry was used for analysis of T cells populations for the expression of CD4, CD25, CD127 and intracellular FOXP3. cfDNA was isolated by use of QIAamp Circulating Nucleic Acid Kit (QIAGEN, Hilden, Germany).

Results: We found significant associations between cfDNA concentrations at baseline and also cfDNA change over six months with the changes in intracellular FOXP3 content in subpopulation of CD4+ (CD25+CD127+) T cells.

Conclusions: CD4+ (CD25+CD127+)FoxP3+ subpopulation of T cells has been proposed to act as a suppressor of autoimmunity. The exact biomarker potential of this subpopulation of T cells in autoimmune diseases, including LN, has not been fully explored. Our study suggests that this particular subpopulation of T cells may become useful as an attractive indicator of disease activity in LN, which warrants further investigation.

Funding: Government Support - Non-U.S.

SA-PO111
Urinary VCAM-1 and ICAM-1 as Biomarkers for Active and Chronic Kidney Injury in Lupus Nephritis Shihika Wildawski,1 Xiaoan Zhang,1 Juan M. Mejia-Vilet,2 Anthony S. Alvarado,2 Tibor Nadasy,1 Brad H. Rovin,3 1The Ohio State University, Columbus, OH; 2Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico, Mexico; 3for the CKD Biomarkers Consortium, Bethesda, MD.

Background: Urine levels of the adhesion molecules VCAM-1 and ICAM-1 may reflect active kidney disease in patients with lupus nephritis (LN), but it is unknown if these can serve as biomarkers of kidney pathology. This study investigated the relationship of urine (u)VCAM-1 and uICAM-1 to renal histology in LN.

Methods: uVCAM-1 and uICAM-1 were measured by ELISA at the time of kidney biopsy in 129 LN patients. SLE patients without kidney involvement (non-renal [nr] SLE, n=35) served as controls. Urine analyte levels were normalized to urine creatinine concentration, log-transformed and then examined in relation to ISN/RPS histologic class and specific histologic lesions using ANOVA, nonparametric Wilcoxon ranked-sum testing and linear regression as appropriate.

Results: uVCAM (R=0.57, p<0.0001) and uICAM (R=0.52, p<0.0001) correlated with proteinuria. Mean uVCAM and uICAM levels from LN patients were 5.4 and 2.2 fold higher, respectively than levels from nrSLE (R=0.0001). Significance was maintained when classes II-V LN were compared individually to nrSLE. In proliferative LN, uVCAM and uICAM levels positively correlated with biopsy activity index (R=0.32, p=0.0007 and R=0.26, p=0.0145 respectively). uVCAM and uICAM levels were elevated in patients whose biopsies had karyorrhexis/fibrinoid necrosis (p<0.006; p=0.02, uVCAM; uICAM), hyaline deposits (p=0.006; p=0.02, uVCAM; uICAM) and PMN infiltrates (p <0.003; p=0.03, uVCAM; uICAM). Only uVCAM was elevated in the presence of cellular crescents (p=0.0002), and uICAM reflect interstitial inflammation. Conversely, uICAM was negatively associated with biopsy chronicity index (R=0.32; p=0.0026), and was significantly lower in patients whose biopsies showed glomerular sclerosis and fibrous crescents (p=0.03; p=0.002). uICAM did not reflect interstitial fibrosis or tubular atrophy.

Conclusions: uVCAM-1 and uICAM-1 are biomarkers for glomerular injury in LN. uVCAM-1 levels reflect glomerular inflammation while uICAM-1 levels indicate chronic glomerular damage.

Funding: NIDDK Support

SA-PO112
Early Renal Response Biomarkers in Lupus Nephritis: Data from the AURION and AURALN Trials Robert B. Huizinga,1 Brad H. Rovin,2 James A. Tumlin,3 Matt Truman,1 Neil Solomon,1 Aurinia Pharmaceuticals, Victoria, BC, Canada; 2Ohio State University Wexner Medical Center, Columbus, OH; 3University of Tennessee College of Medicine, Chattanooga, TN.

Background: During treatment of lupus nephritis (LN) early biomarkers of clearance (CR) and no response (NR) to therapy are needed to confirm that patients destined to not respond to their current treatment. Changes in complement and proteinuria after 8 weeks of therapy were shown to predict renal response at 6 months in the ALSM LN trial. To validate these biomarkers their performance was tested in the recently completed AURION and AURALN trials.

Methods: Data was taken from the AURION 10 patient open-label study of voclosporin (VCS) 23.7 mg po BID, MMF and steroids in active LN, and from the AURLA 265 patient randomized double-blind study of voclosporin in active LN. In AURIA patients were dosed with voclosporin 23.7 mg po BID, 39.5 mg po BID or placebo, MMF and steroids. First morning voids (FMVs), 24 hour urine collections C3, C4 and anti-dsDNA were collected throughout. Normalization of C3 or C4 at week 12 and 25% reduction in Week 8 UPVR (25%/UPCR) were used as predictors of CR at 24 and 48 weeks.

Results: In AURION, a 25%/UPCR was 71% and 75% sensitive in predicting CR at weeks 24 and 48, but specificities were 33% and 25% respectively. Similar sensitivities (99% and 90%) for predicting 24 and 48 week CR were seen for a 25%/UPCR, specificity remaining low (33% and 33%). In AURION C3 or C4 normalization at week 12 was not sensitive (29 and 23%), but specific (100% and 75%) for predicting 24 and 48 week CR. Similarly in AURLA, C3 or C4 were not sensitive, but C3 was 80% and 81% specific while C4 was 77% and 76% specific for predicting 24 and 48 week CR. Change in anti-dsDNA has similar specificities as C3 or C4 but lower sensitivity for predicting CR at 24 and 48 weeks.

Conclusions: As active lupus nephritis flares cause damage within the renal matrix, a more rapid way of predicting CR at 24 or 48 weeks is needed. A rapid predictor should demonstrate both high sensitivity and specificity providing clinicians confidence for changing therapy earlier rather than waiting for 24 or 48 weeks. Use of a 25% reduction in Week 8 UPVR plus C3 normalization at week 12 provides clinicians a sensitive (99%) and specific (80%) method of predicting CR at 24 weeks. This same combination also provides clinicians a sensitive (90%) and specific (81%) method of predicting CR at 48 weeks. Future clinical trials should consider the use of this methodology.

Funding: Commercial Support - Aurinia Pharmaceuticals

SA-PO113
Accurately Representing the Heterogeneity of IgA1 O-Glycosylation in Patients with IgA Nephropathy Matthew B. Renfro1, Audra A. Hargett,2 Stacy J. Hall,1 Bruce A. Julian,3 Jan Novak,3 1UAB, Birmingham, AL; 2University of Alabama at Birmingham, Birmingham, AL; 3University of Alabama at Birmingham, Birmingham, AL.

Background: Patients with several autoimmune disorders, chronic inflammatory diseases, and some infectious diseases exhibit abnormal glycosylation of serum immunoglobulins and other glycoproteins. The biological functions of these modifications in health and disease continue to be a significant area of interest in biomedical research. Specifically, the task of defining site-specific glycoprotein heterogeneity is recognized as an area that still needs a considerable amount of effort to fully understand the role of glycan heterogeneity in biological processes and disease pathogenesis.

Methods: We have developed robust workflows for the analysis of the IgA1 clustered O-glycan heterogeneity in clinical samples from patients with IgA nephropathy (IgAN). IgA1 was isolated from serum of healthy controls and patients with IgAN, followed by determination of all available glycans for each sample's specific O-glycosylation profile. Each patient’s monomeric, polymeric, and circulating immune complex IgA1 were analyzed separately to determine if there was a difference in the glycan signature of the specific type of IgA1. The HR-MS profile of both the IgAN patients and healthy controls was also tested using existing ELISA test for Gd-IgA1.

Results: IgAN is the leading cause of glomerulonephritis in the world with as many as 20-40% of patients progressing to end stage renal disease. Patients with IgA nephropathy have increased levels of nephritogenic circulating immune complexes that contain the immunoglobulin, IgA1. We and others have shown that IgA1 in patients with IgAN have altered O-glycan heterogeneity. This work demonstrates the progress we have made in characterizing the differing patterns of IgA1 O-glycan heterogeneity in patients with IgAN. IgA1 was isolated from serum of healthy controls and patients with IgAN, and all samples were analyzed to determine each samples' specific O-glycosylation profile. Each patient’s monomeric, polymeric, and circulating immune complex IgA1 were analyzed separately to determine if there was a difference in the glycan signature of the specific type of IgA1. The HR-MS profile of both the IgAN patients and healthy controls was also tested using existing ELISA test for Gd-IgA1.

Conclusions: The detailed characterization of glycoprotein site occupancy and glycan heterogeneity is required for a better understanding of the biological roles of individual glycoproteins and to determine the impact of the glycosylation on the proteins functionality. Our current results will demonstrate our ability to reliably provide quantitative comparison of individual sites of glycosylation across a range of O-linked glycosylation sites in order to determine a protein’s Glycan Signature and how that signature relates to the proteins function. This work is supported by the NIH (GM098539).

Funding: NIDDK Support, Other NIH Support - GM098539, DK078244, DK082753

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

707
SA-PO114

Assessment of the Impact of Serum Levels of Gd-IgA1-Specific IgG Autoantibodies on the Prediction of the Course of Disease in Czech Patients with IgA Nephropathy

Dita Maixnerova,1 Stacy D. Hall,2 Colin Reily,1 Michaela Neprasova,1 Jelena Skibova,1 Miloslav Suchanek,2 Eva Honsova,1 Ruhbell T. Brown,3 Jan Novak,1 Vladimir Tesar.1 University of Alabama at Birmingham, Birmingham, AL; 3University of Chemical Technology Prague, Prague, Czech Republic; 1Institute of Clinical and Experimental Medicine, Prague, Czech Republic; 2Dept. of Nephrology, General Teaching Hospital, 1st Faculty of Medicine, Charles University, Prague, Czech Republic.

Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis, often leading to end-stage renal disease. The diagnosis and assessment of disease severity requires renal biopsy. Due to its inherent risks, non-invasive approaches would be very helpful.

Methods: We examined 94 patients with biopsy-proven IgAN who were assessed at the time of diagnosis for renal function, proteinuria, microscopic hematuria, and hypertension, and followed-up clinically since then. Using serum samples collected the time of diagnosis, we determined levels of galactose-deficient IgA1 (Gd-IgA1) and IgG autoantibodies specific for Gd-IgA1 (IgGAb) using lectin and immunodetection methods. Discriminant analysis and logistic regression model were used for statistical analyses.

Results: Clinical data (serum creatinine and eGFR), serum biochemical markers (Gd-IgA1, IgGAb) and histological scoring (Oxford MEST system) were used to develop a formula predicting the risk of disease progression at the time of biopsy. We observed higher levels of IgG autoantibodies in IgAN patients with progressive renal insufficiency at diagnosis compared to IgAN patients with stable renal function at the onset. We confirmed the association of IgG autoantibodies with the progression of Czech patients with IgAN.

Conclusions: Elevated serum levels of IgGAb may serve as marker of disease activity and/or decline of renal function and, thus, unfavorable predictor of disease progression in patients with IgAN. Longer clinical follow-up of this group and further evaluation of these findings are needed. The authors (JN, CR, BAJ) have been supported in part by grants DK106341, DK079337, DK078244, DK082753, GM098539 from the National Institutes of Health and a gift from the IGA Nephropathy Foundation of America and the authors (DM, VT) by grant LH151168 and PRVOUK-P25-LF1/2.

SA-PO116

Renal Immune Deposits of Patients with IgA Nephropathy Are Enriched for IgG Autoantibody Specific for Galactose-Deficient IgA1

Manish K. Saha,1 Dana Rizk,1 Stacy D. Hall,1 Ruhbell T. Brown,1 Lea Novak,3 Bruce A. Julian,3 Jan Novak,1 1UBA, Birmingham, AL; 3University of Alabama, Birmingham, AL; 1University of Alabama at Birmingham, Birmingham, AL.

Background: Patients with IgA nephropathy (IgAN) have circulating immune complexes (ICs) consisting of galactose-deficient IgA1 (Gd-IgA1) bound by Gd-IgA1-specific IgG autoantibodies. Some ICs deposit in the kidney, inciting injury. Renal biopsy examination by routine immunofluorescence reveals IgA, usually with C3 and variably with IgG. We assessed whether patients with IgAN have Gd-IgA1-specific IgG autoantibodies in renal biopsy tissue.

Methods: Frozen renal biopsy specimens from patients with IgAN with (n=5) or without (n=10) IgG glomerular co-deposits (determined by routine immunofluorescence) and a patient with membranoproliferative glomerulonephritis (MPGN, disease control) were used. Tissues were washed with PBS to remove interstitial and blood IgG. IgG from immunodeposits was then extracted by acidic buffer (5 % acetic acid, 1 % SDS, 50 mM NaCl, 50 mM Tris-HCl pH 8.0). Extracts were plated onto nitrocellulose membranes and probed with patient serum samples (1:100). Immunofluorescence was performed using frozen tissue specimens stained with fluorochrome-labeled antibodies specific for IgA, IgG, and C3.

Results: IgG was isolated from washes and extracts of all biopsy specimens, as determined by ELISA and confirmed by western blotting. This finding, suggesting that routine immunofluorescence has low sensitivity and underestimates IgG in immunodeposits, was confirmed by high-resolution confocal microscopy. Line intensity analysis confirmed co-localization of IgA and IgG. Moreover, IgG autoantibodies specific for Gd-IgA1 were detected in extracts of all biopsy specimens from patients with IgAN, but not MPGN. IgG was present at low amounts in MPGN.

Conclusions: IgG autoantibodies specific for Gd-IgA1 were detected in renal immunodeposits of patients with IgAN, even in those without IgG by routine immunofluorescence. These findings support the pathogenic significance of Gd-IgA1 autoantibodies in IgAN.

Funding: Other NIH Support - National Institutes of Health Grant T32DK075545

SA-PO117

Proteomics of Glomeruli with IgA Nephropathy Reveals the Concomitant Abnormalities of Cytoskeleton in the Podocytes

Hiroki Yamaguchi,1 Shin Goto,1 Yoshitoshi Hirao,1 Bo Xu,1 Keiko Yamamoto,2 Suguru Yamamoto,1 Yoshikatsu Kaneko,1 Tadashi Yamamoto,2 Ichiji Narita.1 1Nigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; 2Biofluid Biomarker Center, Institute for Research Collaboration and Promotion, Nigata University, Niigata, Japan.

Background: Previous, extensive molecular research had been carried out to disclose the mechanism of glomerular injuries in IgAN, however, comprehensive analysis targeted human glomeruli have been rarely reported. To investigate the molecular network of IgAN, we conducted quantitative proteomic analysis of dissected glomeruli of patients with IgAN.

Methods: We enrolled 12 IgAN patients (mean eGFR, 90.9 ml/min/1.73m²; mean urinary protein, 0.61 g/day; crescentic lesion in kidney biopsy < 10%), and 4 nephrectomized patients due to ulrogical cancers as normal samples (Nor). The glomerular samples were collected by laser microdissection and digested peptides were subjected to LC-MS/MS analysis. Their MS/MS spectral data were searched against SwissProt database. Finally, we performed label-free quantitation using Normalized Spectral Index and extracted proteins which were significantly and distinctively expressed in glomeruli of IgAN or Nor. These proteins were assigned to web-accessible program, DAVID to discover enriched functional related-protein groups.

Results: A total of 3143 proteins were identified with peptide FDR < 1%, and 394 and 563 proteins were selected as expressed differentially in IgAN and Nor respectively. Functional annotation clustering on the glomerular proteins in IgAN ranked several metabolic and biosynthesis pathways as top categories, while that on the glomerular proteins in Nor gave higher enrichment scores to cytoskeletal proteins rich in the podocytes. Especially, the abundance of Actinin-alpha-4, synaptopodin, and RhoA-specific GEF were significantly lower in IgAN. Between the IgAN groups divided by the level of urinary protein (0.5 g/day), the expression of synaptopodin was significantly lower in the group with higher proteinuria.

Conclusions: These results suggest that mesangial inflammation in IgAN could cause the cytoskeletal abnormalities in podocytes, resulting to significant proteinuria and glomerular injury.

SA-PO118

Gut Microbiota in IgA Nephropathy: What Is the Possible Association with Clinical Manifestations?

Wen Tang, Peking University Third Hospital, Beijing, China.

Background: Few study have investigated the microbiota in IgA nephropathy (IgAN) and their association with clinical disease progression factors. In the present study, we investigated the microbiota in IgAN patients with relative normal renal function and further examined the association between clinical risk parameters of IgAN and microbial groups.

Methods: Fecal microbiota was studied in nineteen new diagnosed IgAN and fifteen matched healthy control. Microbiota composition and functional capacity were characterized using sequencing of the 16S rRNA gene on Illumina MiSeq platform. Patients’ clinic parameters were also collected to investigate their association with the microbiota.

Results: The proportion of Bifidobacterium was higher but Bacteroides was lower in the patients with IgAN as compared to healthy control. Additionally, CCA (canonical correlation analysis) analysis (Figure 1) revealed that Bifidobacterium was positively associated with serum IgA level and 24 hour proteinuria. Lachnoclostridium was positively associated with present of hypertension. Bacteroides and Prevotella were negatively associated with them. Escherichia-Shigella was positive with urinary red blood cell count.

Conclusions: This study has for the first time revealed the association between microbiota and the factors associated with IgAN progression, which found that Bifidobacterium was positive associated with disease progressive factors. Further research are need to understand the potential role of the Bifidobacterium in the IgAN.

Funding: Government Support - Non-U.S.
The glomerular size differs in each patient. Although it is assumed that the glomerular size should change according to the type of kidney disease and the hemodynamic state of the glomeruli, no clinical studies have investigated the impact of these factors on the glomerular size.

**Methods:** PAM-stained images of paraffin-embedded kidney sections were imported into a vertical slide system. The glomerular size was automatically calculated by manually outlining the glomerular tuft area on the display. We measured a total 18,673 glomeruli (with the exception of for globally sclerosed glomeruli) from 677 patients who underwent kidney biopsy in our hospital. All measurements were performed by a technical assistant in a blinded manner. In the present study, we especially focused on the glomerular sizes of patients with IgA nephropathy (IgAN) (n=212), diabetic nephropathy (DMN) (n=107), benign nephrosclerosis (BN) (n=78), and secondary focal segmental glomerulosclerosis (sFSGS) (n=53), and minimal change nephrotic syndrome (MCNS) (n=28). We also analyzed the glomerular sizes in patients with each stage of CKD.

**Results:** As shown in Figure, in CKD stages 1 and 2, the glomerular sizes of patients with diabetic nephropathy, benign nephrosclerosis, and secondary FSGS were significantly larger in comparison to patients with IgAN or MCNS (p<0.05). In DMN and sFSGS, the sizes are similar in all CKD stages, while those in BN gradually decreased with the progression of the CKD stage. Conversely, the glomerular sizes of patients with IgAN gradually increased with the progression of the CKD stage.

**Conclusions:** The changes in glomerular size depend on the individual kidney disease. The pattern of the changes that occur with the progression of CKD should also differ according to the kidney disease.

**SA-POI18**

Plasma CX3CL1: A Biomarker Predicts Renal Inflammation and Progression of IgA Nephropathy

Ran Lu, Shuiming Luo, Takehiko Shuwan, Shuiming Huazhong University of Science and Technology, Wuhan, China.

**Background:** Plasma biomakers of IgA nephropathy (IGAN) are still relatively unknown to date. This study was to investigate whether CX3CL1 was associated with pathology and renal outcome in IGAN.

**Methods:** 229 patients with IGAN diagnosed by renal biopsy between 2012 and 2014 at Huazhong University of Science and Technology Tongji hospital, were included in the study. Follow-up time was up to 42.5 months. Renal outcome was defined as composite endpoints, including ESRD and doubling of plasma creatinine. Plasma CX3CL1 level was measured by ELISA. Inflammatory cells including CD4+, CD8+, CD20+ and CD68+ cells in renal biopsy tissues were detected by immunohistochemistry. The two single nucleotide polymorphisms (SNPs) of CX3CL1, rs3732378 and rs3732379, were assessed with IGAN leukocyte.

**Results:** Plasma CX3CL1 levels correlated with serum creatinine (r=0.344, p<0.001), estimated glomerular filtration rate (eGFR) (r=0.370, p<0.001), and albumin (r=0.002, p=0.249). In renal biopsy specimens, the density of CD68+ cells was significantly associated with plasma CX3CL1.

**Conclusions:** Plasma CX3CL1 correlates with IGAN pathology and prognosis. CX3CL1 may be a risk factor for progression of IGAN.

SA-POI19

The Change in the Glomerular Size According to the Type of Glomerular Disease and the Renal Function

Toshiyuki Inamasu, Masaki Uehara, Takafumi Yamakawa, Takehiko Kawaguchi, Department of Nephrology, National Hospital Organization, Chiba-East Hospital, Chiba, Japan.

**Background:** The glomerular size differs in each patient. Although it is assumed that the glomerular size should change according to the type of kidney disease and the hemodynamic state of the glomeruli, no clinical studies have investigated the impact of these factors on the glomerular size.

**Methods:** As shown in Figure, in CKD stages 1 and 2, the glomerular sizes of patients with diabetic nephropathy, benign nephrosclerosis, and secondary FSGS were significantly larger in comparison to patients with IgAN or MCNS (p<0.05). In DMN and sFSGS, the sizes are similar in all CKD stages, while those in BN gradually decreased with the progression of the CKD stage. Conversely, the glomerular sizes of patients with IgAN gradually increased with the progression of the CKD stage.

**Conclusions:** The changes in glomerular size depend on the individual kidney disease. The pattern of the changes that occur with the progression of CKD should also differ according to the kidney disease.

**SA-POI120**

Transcriptomic analysis of BTBRob/ob and eNOS-/-db/db mouse models reveals podocyte markers that are differentially regulated in the presence of obesity and hyperglycemia.

**Background:** There is no data available on the transcriptomic changes that occur in the presence of obesity and hyperglycemia in the context of kidney disease. This study aimed to identify novel podocyte markers that are differentially regulated in the presence of obesity and hyperglycemia.

**Methods:** Transcriptional analysis of kidney tissue from BTBRob/ob and eNOS-/-db/db mice was performed using RNA sequencing. The transcriptomic data was analyzed using bioinformatic tools to identify novel podocyte markers that are differentially regulated in the presence of obesity and hyperglycemia.

**Results:** Transcriptomic analysis revealed a set of podocyte markers that are differentially regulated in the presence of obesity and hyperglycemia. These markers were found to be upregulated in the presence of obesity and hyperglycemia, and were found to be expressed in the podocyte cell type.

**Conclusions:** The results of this study provide novel insights into the transcriptomic changes that occur in the presence of obesity and hyperglycemia in the context of kidney disease. These findings may provide new therapeutic targets for the treatment of obesity and diabetes-associated kidney disease.
SA-PO121
High Protein Diet Accelerates Development of Diabetic Nephropathy in db/db Mice; Siase A, Norgaard,1 Dorte B. Sorensen,2 Elisabeth D. Galsgaard,1 Fredrik Wulffhagen Sand,3 Henrik Søndergaard;1 1Liver Disease Pharmacology, Novo Nordisk A/S, Maaloev, Denmark; 2Diabetes & Cardiovascular Pharmacology, Novo Nordisk A/S, Måløv, Denmark; 3Veterinary Disease Biology, University of Copenhagen, Copenhagen, Denmark; 4Diabetes Complications Pharmacology, Novo Nordisk A/S, Måløv, Denmark.

Background: Diabetic and obese db/db mice are widely used in diabetic nephropathy (DN) research. However, this model only mimics the early changes in human DN with mild albuminuria and mesangial expansion (ME) as primary readouts. Both in humans and in diabetic models, a high protein diet (HPD) has been reported to affect the progression of nephropathy. Here, the objective was to explore if a HPD could accelerate nephropathy in db/db mice with the perspectives to study more advanced stages of DN (e.g. interstitial fibrosis) and improve the therapeutic window.

Methods: 32 diabetic (C57BLKS-Lepr+/−) and 20 non-diabetic (C57BLKS-Lepr−/−) were fed either regular chow diet (21 kcal% protein) or HPD (60 kcal% protein) from 6 weeks of age (WoA) until termination at 21 WoA. In-life readouts were: body weight, blood glucose (BG), %HbA1c and albuminuria. At termination the kidneys were weighed and processed for histology and qPCR analysis. ME was scored on a scale from 0 to 3, on blinded PAS stained sections.

Results: Feeding db/db mice HPD instead of regular chow was well tolerated and all db/db mice were diabetic throughout the study (BG>16.6 mM) although mildly reduced compared to db/db mice fed regular chow. HPD increased albuminuria more than 10-fold at 21 WoA and kidney size at termination compared to db/db mice fed regular chow. The ME score revealed a significant increase in db/db mice on HPD compared to regular chow (p<0.001). Further, histopathological assessment of renal lesions (e.g. fibrosis) and gene expression profiling of the kidney by qPCR will be performed to extend these findings. No changes were found in db−/− mice given HPD for either of the readouts.

Conclusions: Feeding db/db mice HPD instead of regular chow seems to accelerate the development of diabetic nephropathy without affecting lean non-diabetic mice. Thereby, HPD could potentially improve the overall quality of this model through an accelerated disease progression and an increased therapeutic window. Further histopathological assessment of the kidney will reveal if HPD additionally enhances other readouts associated with advanced nephropathy e.g. fibrosis.

Funding: Commercial Support - Novo Nordisk A/S, Government Support - Non-U.S.

SA-PO122
Linagliptin Treatment versus RAAS Inhibition Alone Improves Murine Diabetic Nephropathy; Anna Batskovska,1 Monica Sanchez avila,2 Kelly L. Hadkins,3 Charles E. Alpers,3 1University of WA, Seattle, WA; 2University of Washington, Seattle, WA; 3University of Washington Medical Center, Seattle, WA.

Background: Linagliptin (LIN) and other DPP4 inhibitors have proven effects as treatments for diabetes (DM), but the renal benefit is not well understood. We explore effects of LIN, and LIN in combination with the ARB, losartan (LOS), on diabetic nephropathy (DN) in a murine model. The mouse is shown to mimic morphologically advanced human DN and type II DM. Administration of lepin (LEP) is shown to reduce body weight by 20-40%, return mice to normoglycemic levels, and improve functional and structural characteristics of DN.

Methods: Cohorts of female mice (n=12) were treated with LIN (83mg/kg in chow), LOS (100mg/mL in drinking water), combined LIN/LOS or LEP. 6 weeks starting at 18 weeks of age. We collected 6-hour fasting glucose and protein excretion measurements for all mice at 18 and 24 weeks. Baseline structural characteristics for WT and OB mice were determined by sacrificed untreated mice at 18 weeks. Glomerular abnormalities assessed at 24 weeks include expansion of silver stained mesangial matrix by computer morphometry, and podocyte density using the p57 marker of mature podocytes. Renal function was assessed by measurement of urine albumin/creatinine ratio (UACR) and measurement of 8-OHdG in urine as a marker of DNA/RNA damage.

Results: LIN-treated mice exhibited reduced mesangial expansion (13.6% silver positive matrix per glomerular cross section) compared to untreated mice (18.4%) at 24 weeks (p<0.02). Treatment with LOS, or LIN/LOS resulted in statistically significant reduced UACR when paired 18 and 24 week urine samples were analyzed (p=0.032, 0.035 respectively). An ELISA assay for 8-OHdG in urine showed all treatment groups decreased significantly levels compared to untreated controls at 24 weeks (WT 28.2, 24wk OB 93.1, 24wk OB LIN 35.4, 24wk OB LIN/LOS 30.5, 24wk OB LOS 41.4, 24wk OB LEP 39.6 ng 8-OHdG/mg Cre, p<0.001). LEP-treated mice had restored podocyte density, but no significant difference was detected between other treatment groups and untreated controls.

Conclusions: Our results suggest that DPP4- and RAAS-inhibition may ameliorate features of DN via independent of restored podocyte density.

Funding: Commercial Support - Boehringer Ingelheim

SA-PO123
Omentin1 Ameliorates Hyperglycemia or Hypoxia-Induced Podocyte Dysfunction by Activating AMP-Activating Protein Kinase Hidetoshi Kobayashi, Fumihiko Furuya, Yoshio Ishii, Kenichiro Kitamura. University of Yamanashi, Chuo, Japan.

Background: Increased albuminuria is associated with the loss of capillary wall permeability in podocytes and is one of the risk factors for end stage kidney disease (ESKD). Omentin1 is an adipokine and has anti-inflammatory and anti-atherogenic properties. The aim of this study is to elucidate whether serum omentin1 levels are associated with the progression of diabetic kidney disease (DKD) and to explore the molecular mechanisms by which omentin1 induces anti-diabetic properties.

Methods: One hundred twenty-five diabetes patients were followed up for 7 years. Logistic regression models were used to evaluate the association of serum omentin1 levels with progression of DKD. To explore the protective function of omentin1, we focused on the AMPK pathway in podocytes. We exposed cultured podocytes to hyperglycermia or hypoxia and analyzed the kinase activities and the expression of downstream pathway in the presence or absence of omentin1.

Results: During the observation, progression either to the next albuminuria level in 16 patients or to ESKD occurred in 5 patients. In these progressors of DKD, baseline serum omentin1 was significantly low compared with non-progressors. Multiple regression analysis revealed that a significant inverse association between serum omentin1 levels and the progression of DKD. In cultured podocytes, omentin1 administration was associated with increased activity of AMPK, and AMPK activation reduced podocyte permeability to albumin and podocyte dysfunction under hyperglyceremia or hypoxia, as evidenced by zona occludens1 translocation to the membrane. These omentin1-induced activation of AMPK pathways are mediated through the adiponectin receptor1 (AdipoR1) in podocyte since it was diminished by siRNA-mediated knockdown of AdipoR1. These effects seemed to be caused by reduction of oxidative stress, as AdipoR1 and AMPK activation both reduced oxidative NOx4 and NADPH oxidative NOx4 in the podocytes.

Conclusions: Decreased serum omentin1 levels predict the progression of DKD in diabetes patients. In our vitro findings demonstrated that omentin1-bound AdipoR1 is one of the key regulator of albuminuria and progression of DKD, likely acting through the AMPK pathway to modulate oxidative stress in podocytes.

SA-PO124

Background: Angiopoietin-like protein 2 (Angptl2) is an adipokine which was secreted by adipose tissue or macrophages and that its circulating level was closely related with diabetic patients with ESKD. In murine podocytes, Angptl2 induced the activation of focal adhesion kinase (FAK) via integrin α5β1-integrin-linked kinase and translocation of zona occludens-1 in the membrane and alubumin permeability.

Conclusions: Increased serum Angptl2 levels predict the progression of DKD in diabetes patients. In our vitro findings suggest that Angptl2 is a key regulator of albuminuria, likely acting through the FAK pathway.

SA-PO125
Role of Wnt-β Catenin Pathway in Mediating Salutary Effects of Paricalcitol in Experimental Diabetic Nephropathy; Sharma S. Prabhakar, Madhura Bose. Texas Tech University Health Sciences Center, Lubbock, TX.

Background: Diabetic nephropathy (DN) remains the most frequent cause of end stage renal disease but its pathogenesis remains unclear and consequently the treatment is not optimal. Many investigations including ours have shown renoprotective effects of paricalcitol (PAR) in DN. The aim of the current studies is to examine the role of Wnt-β catenin signaling in the beneficial effects of PAR in DN.

Methods: Obese ZSF rats, an established model of DN (type 2 diabetes), were treated with PAR (0.2 μg sc. twice a week) for 10 weeks from 21 weeks of age while control rats received none. Urine and blood samples were collected at the start and end of study. At 31 weeks rats were sacrificed, kidneys harvested and homogenates of one kidney in each rat were used to study expression of Wnt proteins and other pathogenic mediators by immunoblotting while the other kidney was used for RNA isolation and Next Gen
Sequencing (NGS) analysis. Kidney RNA seq data from ZSF obese and PAR treated rats were collected. The results were significantly different. Thus, 15% of genes and 2 fold change were filtered and mapped to canonical pathways in the IPA Knowledge Base. The dataset was filtered and a student t test was used to identify the genes most significantly altered following PAR treatment.

Results: The overexpression of COMP-Ang1 was confirmed not only in glomeruli but also in pancreatic and hepatic capillaries, which corrected the diabetes-induced dysregulation of tissue Ang2/Ang1 balance. Untreated db/db mice had substantial hyperglycemia (BG, 576±33mg/dL; HbA1c, 11.3±1.3%) and developed progressive increases in albuminuria and glomerular mesangial matrix expansion, associated with increased renal PAI-1, a1(IV) collagen and fibronectin expression compared with db/m mice at 18wks of age. Treatment with COMP-Ang1 yielded a significant reduction of glycemia (BG, 241±19mg/dL; HbA1c, 7.2±1.5%) and slowed the progression of albuminuria and glomerulosclerosis in db/db mice by 70% and 61%, respectively. Furthermore, renal expression of NF-κBp65, Nox2 and p47phox and pancreatic albuminuria and glomerulosclerosis in db/db mice by 70% and 61%, respectively. Treatment of db/db mice with compound II for 10 weeks enhances insulin sensitivity, decreases glucose uptake in myocytes, and SHIP2 overexpression abrogates its insulin-mimetic properties. Treatment of SHIP2-Tg mice for 12 days with compound II reduces SHIP2 activity in kidney, skeletal muscle and liver and enhances insulin sensitivity. Treatment of db/db mice with compound II for 10 weeks enhances insulin sensitivity, decreases SHIP2 activity in the kidney and tends to reduce urinary albumin excretion.

Conclusion: Compound II inhibits the activity of SHIP2, enhances glucose uptake, and improves insulin sensitivity. Compound II and SHIP2-Tg mice show a trend of reduced albuminuria. This highlights the potential of SHIP2 as a drug target to treat diabetic kidney injury and insulin resistance. The data also propose that compound II and its derivatives have potential to be used for developing new insulin sensitizing drugs.

Funding: Private Foundation Support

SA-PO128

A Novel SHP2 Inhibitor Reduces the Catalytic Activity of SHP2 in Kidney, Muscle, and Liver and Enhances Insulin Sensitivity

Sanna H. Lehtonen,2 Zydruke Polianskyte-pruse,2 Tuomas A. Tolvanen,3 Sonja Lindfors,2 Kanta Kon,2 Hong Wang,3 Vincent Dumont,2 Per-Henrik Groop,1 Tsutomu Wada,1 Hiroshi Tsuchi,2 Toshiyasu Sassaoka,2 Folkhälsan Institute of Genetics, Folkhälsan Research Center, University of Helsinki, Helsinki, Finland; 3Department of Pathology, University of Helsinki, 00290 Helsinki, Finland; University of Toyama, Toyama, Japan; Division of Nephrology, Helsinki University Hospital, Helsinki, Finland.

Background: The expression of lipid phosphatase SHIP2 is elevated in kidney, muscle and adipose tissues in experimental models of diabetes. Thus, SHIP2 is a potential therapeutic target to treat diabetic kidney injury and insulin resistance. To date, only few SHIP2 inhibitors have been developed. In this study, we performed screening of chemical libraries. The most potent SHIP2 inhibitors were validated by expression of recombinant SHIP2 protein, cell lines and isolated animal tissues.

Results: Virtual screening of chemical libraries containing 8860 molecules revealed compound II as a potential SHIP2 inhibitor. Compound II inhibits the catalytic activity of recombinant SHIP2. Treatment of SHIP2 phosphatase domain with an IC50 value of 75 μM. It also inhibited the activity of SHIP2 in cultured podocytes, myocytes and hepatocytes. Compound II increases glucose uptake in myocytes, and SHIP2 overexpression abrogates its insulin-mimetic properties. Treatment of SHIP2-Tg mice for 12 days with compound II reduces SHIP2 activity in kidney, skeletal muscle and liver and enhances insulin sensitivity. Treatment of db/db mice with compound II for 10 weeks enhances insulin sensitivity, decreases SHIP2 activity in the kidney and tends to reduce urinary albumin excretion.

Conclusion: Compound II inhibits the activity of SHP2, enhances glucose uptake, and improves insulin sensitivity. Compound II and SHIP2-Tg mice show a trend of reduced albuminuria. This highlights the potential of SHIP2 as a drug target to treat diabetic kidney injury and insulin resistance. The data also propose that compound II and its derivatives have potential to be used for developing new insulin sensitizing drugs.

Funding: Private Foundation Support

SA-PO129

Phenotype Agglomeration Analysis of Clinical and Histological End Points of Diabetic Kidney Disease Defines Modules with Improved Transcriptional Associations

Paolo Guarneri,1 Jonathan Hill,2 Vijí Nair,2 Jennifer L. Harder,2 Junke Wang,1 Julie Hawkins,1 Steven S. Pullen,1 Robert G. Nelson,1 Carine Boustany,2 Behzad Najafian,2 Michael Maurer,4 Matthias Kretzler2,4 Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT; 2University of Michigan, Ann Arbor, MI; 3National Institutes of Health, Phoenix, AZ; 4University of Washington, Seattle, WA; 5University of Minnesota, Minneapolis, MN.

Background: Diabetic kidney disease (DKD) is the primary cause of end stage renal disease worldwide. While the structural and functional determinants of DKD have been studied extensively in various populations, comprehensive aggregation of longitudinal phenotypic measures with molecular mechanisms is lacking.

Methods: We collected an extensive set of clinical and histological endpoints from a cohort of 70 Pima Indians with type 2 diabetes. We performed annual research examinations that included measurement of glomerular filtration rate (GFR, iothalamate) and had 2 research kidney biopsies performed 10 years apart. We developed a method in which missing values were interpolated with the mean, normalized and log transformed, if applicable. For inter-related traits only the most representative measurement was selected. The remaining traits were then clustered across samples balancing silhouette coefficients with minimum cluster size. A single composite trait – eigentrait – was then generated by averaging its components. Weighted gene co-expressed network analysis was used to define modules with eigentrait expression, associated with either measured traits or eigentrait. Enriched biological functions were determined using Ingenuity Pathway Analysis on composite genes of significantly associated modules.

Results: We identified 7 eigentraits defining modules of mixed clinical and histological endpoints. A highly robust module included the slope of GFR, glomerular basement membrane thickening and mesangial expansion, and was associated in the first biopsy with immune cell migration while in the second biopsy with extracellular matrix synthesis, thereby supporting a role for inflammation in the initiation of DKD.

Funding: Commercial Support - SCT

SA-PO112

Phenotypic Analysis in Human “Neo-Islets” Composed of Equal Numbers of Mesenchymal Stem and Pancreatic Islet Cells Durably Corrects Hyperglycemia in Diabetic NOD/SCID Mice

Christof Westenfelder,1 Anna Gooch,1 Zhuama Hu,1 Ping Zhang,1 University of Utah and VA Medical Centers, Salt Lake City, UT.

Background: Globally, individuals with autoimmune Type 1 Diabetes mellitus (T1DM) continue to depend for survival on insulin injections. While pancreas and intraphepatic pancreatic islet transplants can produce insulin-independence and ameliorate serious complications, both therapies depend on potentially toxic anti-rejection drugs. Furthermore, the scarcity of pancreas donors, islet transplant failures, and the inability to adequately culture expand insulin-producing β-cells significantly limit the general availability of such and other cell-based interventions. Encapsulation of islets to protect them from allo- and auto-immune destruction has shown both promise and failures. We report here that Gene-drive VECTOR Cells (GVCs, 2017) that contain and express “Neo-Islets” (NI) are immune protected and correct autoimmune diabetes in NOD mice. Furthermore, we are conducting an FDA-approved Pilot Study with canine NI’s in insulin-dependent dogs using identical technology. As there remains a critical need for curative therapies of T1DM, we engineered human NI’s and tested their ability, in a preclinical model, to reestablish euglycemia in streptozocin (STZ)-diabetic NOD/SCID mice.

Methods: We generated ex vivo islet-sized NIs in which culture-expanded islet cells were aggregated in cell clusters with equal numbers of MSCs. NIs (5x10^6/kg b.wt) or vehicle were administered i.p. to groups (n=6 each) of STZ-diabetic NOD/SCID mice.

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

Underline represents presenting author.

711
Conclusions: Phenotype agglomeration analysis provided a means of distilling biologically meaningful signals from a complex collection of traits in Pima Indians with DKD.

Funding: Commercial Support - Boehringer Ingelheim

SA-PO130

Children's Hospital Colorado, Aurora, CO; Joslin Diabetes Center, Boston, MA; Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, ON, Canada; Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada, Quebec City, QC, Canada; None, Oakville, ON, Canada; Sinai Health System, Toronto, ON, Canada; Universal Health Network, Toronto, ON, Canada; University Health Network, Toronto, ON, Canada, Canada.

Background: Central adiposity is considered an important cardio-renal risk factor in the general population and in type 1 diabetes (T1D). We sought to determine the relationship between central adiposity and renal hemodynamic function in adults with longstanding T1D with and without diabetic nephropathy (DN).

Methods: Patients with longstanding T1D (n=75, duration >50 yrs) and age/sex-matched healthy controls (HC, n=75) were studied. The T1D cohort was stratified into 50 DN Resistors (eGFR >60mL/min/1.73m² and <30 mg/day urine albumin) and 25 with DN. Renal hemodynamic function (glomerular filtration rate [GFR], effective renal plasma flow [ERPF], renal blood flow [RBF], renal vascular resistance [RVR], filtration fraction [FF], glomerular pressure [P_GFR], derived from Gomez' equations. Fat and lean mass were quantified by DXA.

Results: In healthy controls, measures of adiposity did not associate with GFR, ERPF, RBF, RVR and FF. In T1D, trunk fat mass inversely correlated with GFR (r: -0.46, p=0.0001), ERPF (r: -0.31, p=0.01) and positively with RVR (r: 0.53, p=0.0003). In analyses stratified by DN status, greater central adiposity related to lower GFR (P<0.05) in both DN and DN resistors, but the relationships between central adiposity, ERPF, PAH and GFR were not significant in HC. In T1D, trunk fat mass inversely correlated with GFR (r: -0.46, p=0.0001), ERPF (r: -0.31, p=0.01) and positively with RVR (r: 0.53, p=0.0003). In analyses stratified by DN status, greater central adiposity related to lower GFR in both DN and DN resistors, but the relationships between central adiposity, ERPF, PAH and RVR were attenuated and/or reversed in DN compared to DN resistors. GFR across tertiles of trunk fat percentage are shown in Fig 1.

Conclusions: The adiposity-renal hemodynamic function relationship may be modified by the presence of T1D and of DN, requiring further study of the mechanisms by which adiposity influences renal hemodynamic function in health and disease.

SA-PO131
Policy Impact on Diabetes Detection in Vulnerable Populations - Karen Cartwright, David N. van der Goes, University of New Mexico, Albuquerque, NM.

Background: Earlier detection of type 2 diabetes is associated with improved management of diabetes. Populations with barriers to care are more likely to have type 2 diabetes and are more likely to be diagnosed at an advanced stage of the disease. US residing Hispanics are not only more likely to be diagnosed with diabetes than their non-Hispanic counterparts, but they are also more likely to die of a diabetes-related cause. Before the ACA, Hispanics were the most likely to be uninsured or underinsured in all states. After the ACA, in states which expanded Medicaid, the uninsured rate for Latinos was reduced to 9% compared to 7% for non-Hispanic whites. However, in states which did not adopt Medicaid expansion, 24% of Latinos are uninsured compared to 10% of non-Hispanic whites. California went further by expanding coverage to non-citizens, which increased the number of non-citizens covered by about 31%. In this project, we analyze the change in self-reported diabetes among non-citizen Hispanic women in expansion and non-expansion states.

Methods: In a multivariate regression framework, we use the 2011-2015 NHIS to analyze the change in self-reported diagnosis of diabetes among Hispanic non-citizen women before and after the ACA Medicaid expansion. Less than 5% of Hispanic women in the South lived in states that expanded Medicaid, while approximately 97% of Hispanic women in the West lived in states that expanded Medicaid under the ACA. We use a difference-in-difference model with our second difference comparing the Southern US to the Western US.

Results: Non-citizen Hispanic women living in Medicaid expansion states saw an 80% (1.81 OR; CI 1.11-2.93) relative increase in self-reported diabetes (compared to non-citizen Hispanic women in non-expansion states). Comparing the same group’s changes in self-assessed health and BMI showed no change. This indicates the change in self-reported diabetes in unlikely due to changes in health status, but instead due to improved detection of diabetes.

Conclusions: This investigation supports the argument that expanding health coverage is associated with improved health knowledge. One of the most vulnerable groups in the US, non-citizen Hispanic women, seems to have benefited from Medicaid coverage expansion. Improved detection of diabetes in this population creates an opportunity to better manage this condition and improve health outcomes, survival odds, and health equity.

SA-PO132
Systems Biology Identified Molecular Pathways and Biomarkers Associated with Diabetic Kidney Disease Progression - Skander Mulder, Viji Nair, Wenjun Ju, Kelli M. Sas, Hiddo J. Lambers Heerspink, Matthias Kretzler, University Medical Center Groningen, Groningen, Netherlands; University of Michigan, Ann Arbor, MI.

Background: Diabetic kidney disease (DKD) is the leading cause of end-stage kidney disease (ESKD). Understanding of molecular pathways involved in the initiation and progression of DKD facilitates precision development and drug target identification. We aim to identify molecular pathways associated with progressive loss of kidney function in early and advanced stages of DKD.

Methods: We included 810 patients with early DKD from the DIRECT-2 trial (eGFR 61 ± 11ml/min/1.73m² and normoalbuminuria) and 911 patients with advanced DKD from SUN-Macro (eGFR 33 ±10 and macroalbuminuria). Baseline urine proteomics, serum metabolomics and proteins were mapped to intra-renal transcriptional profiles of DKD biopsies from the European Renal CDNA Biobank (ERCN, n=19). All molecular features were associated with the primary end point of 30% eGFR decline or ESKD (n=288), and subsequently with the secondary endpoint of eGFR slope < -3ml/year (n=704). Ingenuity pathway analysis identified significantly enriched canonical pathways and disease networks in associated features.

Results: The systems biology integration identified canonical pathways significantly enriched in molecular features associated with renal end points in early (3 pathways), advanced (1) and both stages (5) of DKD, respectively (Figure 1). These pathways include novel (Intrinsic Prothrombin Activation) and known DKD associated pathways (NAD biosynthesis and LXR/RXR activation). Antibody based assay results confirmed 11 (10 serum, 1 urine) biomarkers to be predictive for endpoints, including MMP7, TNFR1 and Endostatin representing the 5 enriched pathways in both early and late DKD.

Conclusions: By integrating intra-renal transcriptomic data with unbiased proteomics and metabolomics we identified stage-specific and shared molecular pathways, as well as their representing biomarkers, that are associated with DKD progression in early and late stages of DKD. Our work sets the stage for investigations of these biomarkers and molecular pathways for prognostic and interventional purposes.

Funding: Government Support - Non-U.S.

SA-PO133
Identification of Novel Genetic Factors Linked to Diabetic Nephropathy - Paolo Guarneri, Chengxiang Qiu, Julie Hawkins, Jonathan Hill, Weiling Ni, Matthew Palmer, Yong G. Yue, Steven S. Pullen, Carine Boustandy, Katalin Susztak, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT; University of Pennsylvania, Philadelphia, PA.

Background: Diabetic nephropathy (DN) is serious kidney condition and the leading cause of chronic kidney disease in the USA contributing to 30-40% of all end-stage renal disease cases. In order to provide a better insight into its molecular mechanism, genetic determination and finally identify novel targets, we first generated a novel dataset from a report we analyzed a cohort of 250 patients undergoing nephrectomy and then we integrated the results with public domain data from genome-wide association studies (GWAS).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Patients in the study were genotyped using high density Arrayx arrays and phenotyped using collected clinical records. Each matched kidney specimen was histologically assessed and RNA-seq transcriptionally profiled separating tubules from glomeruli.

Results: Our analysis identified several genes associated with kidney function decreased collagen (glomerular filtration rate), many also responsible for the progression of interstitial fibrosis and/or associated with lymphocytic infiltration. Cell type specific gene signatures used with deconvolution algorithms revealed that several immune cells, mostly T lymphocytes, are active since the early stages of the disease. Our distinctive gene expression enabled the first human kidney specific splicing analysis and helped focus on genes for which expression in kidney is genetically determined either in tubules, in glomeruli or both. We completed the expression to genotype to trait associations by performing a Bayesian co-localization analysis between our results with those available from GWAS and then matched the direction of the expression change with the effect on the trait.

Conclusions: In this study we generated a high resolution tissue and disease specific transcriptome database which allowed the study of genes and processes implicated in DN.

Funding: Commercial Support - Boehringer Ingelheim

SA-PO134
Fluorescence Lifetime Imaging Microscopy Reveals Gradual Accumulation of Collagens and NADH Lifetime Decrease in Human Kidney Glomeruli with Diabetic Disease Progression

Eugenia Dobriniskikh,1 Kammi J. Henriksen,1 Moshe Levi,1 The University of Chicago, Chicago, IL; 2University of Colorado Denver, Aurora, CO; 3University of Colorado, Denver, Aurora, CO.

Background: Diabetes mellitus is a heterogeneous group of diseases which is a leading cause of renal cell and tissue damage, fibrosis and eventual renal failure. In view of recent therapies aimed at the pathogenesis of fibrosis generation and progression, sensitive and quantitative techniques for recording fibrosis becomes necessary.

Methods: We have applied the Two Photon Excitation (TPE), Second Harmonic Generation (SHG) and Fluorescence Lifetime Imaging Microscopy (FLIM) for label-free imaging of kidney sections from kidney biopsies from human diabetic subjects. We have applied the phasor approach for FLIM analysis, which allows for the visual determination of collagens and other extracellular matrix components localization, and metabolic state of the kidney (free to bound NADH ratio) taking advantage of the specific autofluorescence characteristics of these molecules.

Results: In kidney biopsies obtained from diabetic humans, compared to biopsies obtained from nondiabetic subjects, we have determined that there is a strong SHG signal in the kidney sections suggesting collagen synthesis, which indicates presence of fibrosis. FLIM shows grade发生变化 of different types of collagens in the glomerulus and tubulointerstitial areas with the diabetes progression, which suggests different organization of extracellular matrix. NADH signal decreases and its lifetime shifts to the shorter lifetime in diabetic’s kidneys that corresponds to different metabolic state of the tissue. FLIM also might determine relative degree of the disease progression based on the ratio of NADH lifetimes in different regions in diabetic compared to nondiabetic control kidneys.

Conclusions: TPE-SHG and FLIM imaging is a sensitive technique for label-free imaging, which can show metabolic state and ECM accumulation with the disease progression of the kidney based on the autofluorescence of the ECM components and NADH.

Funding: NIDDK Support

SA-PO136
Type 1 Interferon Is Associated with Kidney Dysfunction in Type 2 Diabetes

James Conway,1 Felix H. Eichinger,1 Brad A. Godfrey,2 Vijji Nair,3 Anna Reznichenko,2 Tim Slidel,1 Clemens D. Cohen,1 Brandon W. Higgs,1 Carol P. Moreno Quin,1 Matthias Kretzler3 MedImmune, Gaithersburg, MD; 2AstraZeneca, Malmö, Sweden; 3University of Michigan, Ann Arbor, MI; 4Klinikum München, München, Germany.

Background: Type 1 interferon (IFN) is linked to the pathogenesis of autoimmune and inflammatory diseases known as interferonopathies. A portion of patients show aberrant Type I interferon signaling, which is regulated by a gene called interferon regulatory factor 3 (IRF3), but this has not been thoroughly investigated in type 1 diabetes.

Methods: We applied Two Photon Excitation (TPE), Second Harmonic Generation (SHG) and Fluorescence Lifetime Imaging Microscopy (FLIM) for label-free imaging of kidney sections from kidney biopsies from human diabetic subjects. We have applied the phasor approach for FLIM analysis, which allows for the visual determination of collagens and other extracellular matrix components localization, and metabolic state of the kidney (free to bound NADH ratio) taking advantage of the specific autofluorescence characteristics of these molecules.

Results: In kidney biopsies obtained from diabetic humans, compared to biopsies obtained from nondiabetic subjects, we have determined that there is a strong SHG signal in the kidney sections suggesting collagen synthesis, which indicates presence of fibrosis. FLIM shows grade发生变化 of different types of collagens in the glomerulus and tubulointerstitial areas with the diabetes progression, which suggests different organization of extracellular matrix. NADH signal decreases and its lifetime shifts to the shorter lifetime in diabetic’s kidneys that corresponds to different metabolic state of the tissue. FLIM also might determine relative degree of the disease progression based on the ratio of NADH lifetimes in different regions in diabetic compared to nondiabetic control kidneys.

Conclusions: TPE-SHG and FLIM imaging is a sensitive technique for label-free imaging, which can show metabolic state and ECM accumulation with the disease progression of the kidney based on the autofluorescence of the ECM components and NADH.

Funding: NIDDK Support

SA-PO137
Integrated Score from Glomerular Structure and Molecular Profiles Predicts ESRD in Diabetic Kidney Disease (DKD)

Vijji Nair1, Jennifer L. Harder,2 Paolo Guarnieri,2 Jonathan Hill,2 Brad A. Godfrey,2 Carine Boustany,1 Behzad Najafi,1 Michael Maurer,1 Robert G. Nelson,2 Matthias Kretzler3 University of Michigan, Ann Arbor, MI; 2Boehringer Ingelheim, Ridgefield, CT; 3University of Washington, Seattle, WA; 4University of Minnesota, Minneapolis, MN; 5National Institutes of Health, Phoenix, AZ.

Background: DKD progression is the major cause of ESRD and increases mortality risk globally. We used systems biology tools to identify predictors of DKD progression through the integration of kidney structural changes with transcriptional profiling.

Methods: Glomerular specific gene expression profiling and quantitative morphometric analyses were performed on protocol kidney biopsies from 70 Pima Indians with type 2 diabetes (tubalitis) compared to 25 healthy controls. Microarray (PM006) and histopathological scores were measured and regression analysis was used to identify predictors of ESRD.

Results: Structural and molecular changes were associated with a score of 271. A score of 271 or more predicted a 7-fold increased risk of ESRD.

Conclusions: An integrated score that combines both structural and molecular changes is highly predictive of ESRD in type 2 diabetes.

Funding: Commercial Support - MedImmune, AstraZeneca, Novo Nordisk, Eli Lilly, Gilead

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

Underlines represent presenting author.
Hospital Maastricht, Maastricht, Netherlands; 3University of Washington, Diabetic and Obesity Induced Kidney Disease - Experimental

Atrasentan Treatment Combined with RAAS Inhibition Increases in Podocytes

Further evaluation of these pathways could provide early intervention targets and novel biomarkers with predictive clinical utility.

Funding: NIDDK Support, Commercial Support - Boehringer Ingelheim

SA-POI140

Exogenous miRNA-23a/27a Attenuates Diabetes-Related Muscle Atrophy and Renal Fibrotic Lesions

Bin Wang,1 Aiqing Zhang,2 Faten Hasounah,1 Xiaohan Wang,3 Emory University, Atlanta, GA; 1Institute of Nephrology, Zhongshan Hospital, Southern University, Nanjing, China; 4Department of Pediatric Nephrology, The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China.

Background: Muscle atrophy is a frequent complication of diabetes mellitus. The microRNA-23a, -27a and -24-2 are located together in a gene cluster on chromosome 8. MiR-23a and miR-27a are known to regulate proteins that are involved in the atrophy and fibrosis process. We hypothesized that treatment with miR-23a/27a would both reduce chronic muscle wasting and renal fibrosis through exosome-mediated muscle-kidney crosstalk.

Methods: We generated an adeno-associated virus (AAV) that overexpresses miR-23a/-27a/-24-2 precursor RNA (and a AAV-GFP control) and injected it into the tibialis anterior (TA) muscle of STZ-induced diabetic mice. After 3 months, mice were killed and muscles and kidneys were analyzed for protein markers of atrophy and fibrosis. In Vivo X-treme camera system was used to track GFP migration to kidney in vivo.

Results: Injection of AAV-miRs into muscle increased miR-23a and miR-27a. The levels of muscle signaling proteins were decreased in metabolic memory experiments by ≥60% (p<0.05 for all) in diabetic animals compared to controls. Therefore, the benefit of combined A plus L treatment in reducing proteinuria, muscle loss and attenuates renal fibrosis lesions via exosome-mediated muscle-kidney crosstalk.

Funding: Other NIH Support - National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under Award Number R01 AR060268

SA-POI141

Dietary Acid Reduction with Either Fruits and Vegetables or Oral Bicarbonate Reduces Oxidative Stress and Improves Kidney Injury in Stage 1 CKD

Nimrit Goraya,1,2 Lauren N. Sager,3 Jan Simoni,4 Donald E. Wesson,1,5 Biostatistics, Baylor Scott & White, Temple, TX; 2Internal Medicine, Baylor Scott and White Health, Temple, TX; 3Diabetes Health and Wellness Institute, Dallas, TX; 4Internal Medicine, Texas A and M School of Medicine, Temple, TX.

Background: Chronic kidney disease stage 1 (GFR > 90 ml/min/1.73 m², CKD 1) patients with macroalbuminuria (urine albumin-to-creatinine ratio > 200 mg/g creatinine) are at increased risk for CKD progression with higher morbidity, mortality, and costs. Dietary acid (H+) induces nephropathy progression in animal models of CKD, mediated in part through angiotension II (AII)-induced oxidative stress. We tested the hypothesis that dietary H+ reduction with base-producing fruits and vegetables (F+V) or oral NaHCO3 (HCO3) prevents further kidney injury in CKD 1.

Methods: Seventy-one macroalbuminuric, non-diabetic CKD 1 subjects had systolic blood pressure (SBP) reduced to < 150 mm Hg with regimens including ACE inhibition and were then randomized to receive F+V (n=23) in amounts to reduce dietary potential acid load by half, oral NaHCO3 (n=24) or no additional intervention (Usual Care, n=24). Creatinine-based eGFR and spot urine levels of the following, factor per g creatinine, were measured at baseline and yearly for five years: albumin (Ua/b), an index of kidney injury, angiotensinogen (UAGT), an index of kidney angiotensin II, and isostetramine (Ua/b), an index of oxidative stress.

Results: Baseline eGFR, Ua/b, UAGT, and Us iso were not different among the groups. The five-year mean (mean, 95% confidence limit or CI) of Us was lower than Usual Care (406 mg/g, CI=376-435) in both F+V (332 mg/g, CI=312-352) and HCO3 (368 mg/g, CI=336-400), consistent with lower kidney AII. The five-year course (mean, 95% confidence limit or CI) of Us was lower than Usual Care (1.24 ug/g, CI=1.19-1.29) in both F+V (1.10 ug/g, CI=1.05-1.15) and HCO3 (1.11 ug/g, CI=1.07-1.14), consistent with less oxidative stress in both dietary reduction groups. There was no significant change in eGFR over the five years in any of the three groups.

Funding: None

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

Underlines represent presenting author.

714
**SA-PO14**

**Changes in Protein Intake among Adults with and without CKD:**

**Methods:** Using the National Health and Nutrition Examination Surveys (NHANES) 2003-2008 (T1) and 2009-2014 (T2), we estimated changes in protein intake over time and the percentage of adults consuming above the RDA average recommended amount of protein (56 g/day for men, 46 g/day for women), overall and by CKD status. We included adults ≥19 years old, excluded those pregnant or lactating, those with missing data on CKD status, diabetes status, or protein intake. The final analytic sample yielded 12,302 adults for T1 and 12,306 adults for T2 to allow for T1-T2 comparisons. We calculated the percentage of the population exceeding protein intake recommendations remained high in 2003-2008 and 2009-2014. There is much room for improving in reducing protein intake and potentially slowing disease progression in those with CKD. In ongoing work we also examine types of protein (e.g., animal, dairy, plant) and how their intake varies by CKD status.

**SA-PO143**

**Osteoprotegerin Is a Strong Independent Marker of Cardiovascular Mortality in Patients with CKD Stage 3 to 5**

**Methods:** We studied 459 patients, 61.4% male, 47.3% diabetic. The prevalence of muscle weakness (sarcopenia), but the EWGSOP and FNIH advocate HGS cut offs as part of their definition (OR 0.89, p=0.007) and being a non-diabetic (OR 0.31, p=0.001) whereas gender is not a significant factor. In addition, 66.7% of patients with no comorbidities were weak, compared to 93.8% with highest co-morbidity score, p=0.001.

**Conclusions:** There is currently no agreed universal definition for muscle wasting (sarcopenia), but the EWGSOP and FNIH advocate HGS cut offs as part of their definition. The prevalence of muscle weakness varies according to cut off; and whether age and gender matched normative data is used. In addition, patient characteristics in terms of age and co-morbidity also determine the prevalence of muscle weakness.

---

**SA-PO144**

**Differences in Prevalence of Muscle Weakness (Sarcopenia) in Haemodialysis Patients Determined by Hand Grip Strength According to Variation in Sarcopenia Guidelines**

**Poster/Saturday**

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

Underline represents presenting author.

---

**SA-PO145**

**Effect of Statin Therapy on Markers of Thrombosis and Inflammation in ESRD**

**Methods:** Medical records of prevalent hemodialysis patients as of 30Jun2016 were reviewed. Statins group included patients taking statins ≥6 months prior to 1Jan2016 and continued statins until 30Jun2016. No statins group included patients never taking statins or who stopped taking statins >6 months prior to 1Jan2016. Basic demographic, comorbidity, and laboratory data was tabulated. Independent t-test was used to compare differences in protein intake between patients taking statins versus no statins.

**Results:** 224 patients were prevalent as of 30Jun2016. Exclusion consisted of 20 new patients, 98 with active infection or hospitalization, 5 on omega-3, 6 on steroid, 9 on statins ≥6 months, 7 started statins after 31Dec2015, 3 stopped statins between 1Jan-30Jun2016, and 5 received blood transfusion. In remaining 71 patients, 36 patients (24 males, 11 diabetics) aged 61±17 years never used or discontinued statins ≥6 months prior to 1Jan2016 while 35 patients (22 males, 22 diabetics) aged 70±13 years (p=0.018) taking statins ≥6 months prior to 1Jan2016 and continued statins until 30Jun2016. In statins group, 2 were on low intensity, 26 were on moderate intensity, and 7 were on high intensity statins. No statins group had higher mean cholesterol (159±34 vs 134±40 mg/dL) and LDL level (94±28 vs 73±34 mg/dL) compared to statins group. After controlling for age and diabetes (P<0.02), mean MPV was significantly higher in statins group (11.2±1 vs ≤80) and non-statin group (10.4±1.2) (P=0.013) whereas WBC to MPV ratio and ferritin levels were similar.

**Conclusions:** Our findings suggest that statin therapy in hemodialysis population is not associated with lower but rather higher MPV. Moreover, WBC to MPV ratio and
ferritin levels are unaffected by the use of statins. Lack of statins impact on markers of oxidative stress and inflammation and end stage renal disease may explain lack of mortality benefit observed in previous literature.

SA-PO146
Exercise Capacity Predicts Mortality and Morbidity in Patients across the CKD Trajectory
Sharlene A. Greenwood, Ellen M. O’Connor, Helen L. MacLaughlin, Ian C. Macdougall, King’s College Hospital, London, United Kingdom; King’s College London, London, United Kingdom.

Background: Exercise capacity is reduced in patients with chronic kidney disease (CKD). Low exercise capacity has been shown to be an independent predictor of mortality in patients with end-stage renal disease. We analysed the value of exercise capacity, characterised as the incremental shuttle walk test (ISWT) for predicting mortality and morbidity in a cohort of 438 patients (male 54%) from across the CKD trajectory (124 haemodialysis patients, 126 kidney transplant recipients, 31 peritoneal dialysis patients, 157 non-dialysis patients) over a 12-year period from 2005 to 2017 (median follow-up of 34 months).

Methods: Survival status was determined for 438 patients with CKD who were referred to an outpatient renal rehabilitation programme for which the ISWT and other clinical data had been determined. Chi-square and Kaplan-Meier survival analyses were performed. Risk of mortality was investigated independent of modality, BMI, diabetic status, age, gender, ethnicity, and smoking status using Cox proportional hazards model.

Results: There were a total of 108 combined events (death, cerebrovascular accident and hospitalisation for chronic heart failure) during the follow-up period. ISWT (>270m; p<0.001 by Kaplan-Meier) was a strong predictor of mortality and morbidity. Deficit in functional ability, Sit to Stand 60 test (>18 complete transfers; p<0.001 by Kaplan-Meier), Timed Up and Go 3m test (>8.05s; p<0.001 by Kaplan-Meier), the Duke’s Activity Status Index (>23.45; 0.003 by Kaplan-Meier) were also strong predictors of survival. On multivariate analysis, ISWT contributed significantly to the minimal explanatory model relating clinical variables to mortality and morbidity (overall x2 37.4, p=0.001). Patients who were able to walk >270m had a 2.3-fold (Hazard Ratio 2.3; 95% confidence interval: 1.1 to 4.7) independent greater risk of a combined event (P = 0.02).

Conclusions: Exercise capacity is strongly predictive of mortality and morbidity in patients across the CKD trajectory. Exercise training interventions to improve clinical outcome in patients with CKD should be explored.

SA-PO147
Randomized Controlled Clinical Study to Prevent Decline in Renal Function and Nutritional Status in Predialysis Patients Using Ketonaolide Supplementation
Anita Saxena, Amit Gupta, Trisha Sachan, Chandra M. Pandey, Department of Nephrology, Lucknow, India; Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India; Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.

Background: Low protein diet is a means to protect residual renal function and to slow down progression of CKD to end stage renal disease. Study was conducted to evaluate effect of combined therapy of very low protein diet (vLPD) and ketonaolide on renal function of predialysis patients and compliance to very low protein diet.

Methods: Prospective randomized controlled study. Forty patients divided into two groups, Group 1, vLPD of 0.6 g/kg/day and 35 kcal/kg/day energy. Biochemical investigations, included serum albumin, hemoglobin, sodium, potassium, calcium, phosphorus, and blood glucose were done at baseline (visit 1) and at 10 months (Visit 2). Dietary intake was taken by dietician. Nutritional status was assessed using SGA.

Results: At baseline, the GFR was higher in controls (51.14±15.1 ml/min) compared to ketonaolide group (47.79±13.2 ml/min). GFR declined in the control group from 51.14±15.1 ml/min at baseline to 35.52±9.4 ml/min over a period of 10 months. In ketonaolide group the GFR remained stable after 10 months 47.65±13.26 ml/min (47.79±13.2 at baseline). Serum albumin was preserved at 4.03±0.52 g/dl after 10 months (4.1±0.43 g/dl at visit 1) in ketonaolide group compared to controls at visit 1. Serum albumin decreased in control group from 3.9±0.9 g/dl at visit 1 to 3.09±0.38 after 10 months (visit 2). GFR (p = 0.023) and serum albumin (p = 0.000) were significantly higher in ketonaolide vLPD group compared to controls at visit 2. Group 1 patients were noncompliant to vLPD as protein intake was 0.6±0.24 g/kg/day instead of 0.4 g/kg/day but GFR remained stable at 47.7±11 ml/min over 10 months. Energy intake was low 19.48±6.84 kcal/kg/day and 16.15±6.85 kcal/kg/day in group 1 and 2 respectively compared to RDA.

Conclusions: Ketonaolide supplementation preserves nutritional status and prevents decline renal function.

SA-PO148
The Effect of a Renal Specific Oral Nutritional Supplement on Nutritional Status in Non-Dialytic CKD
Wen-Yi Cheng, Shang-Jyh Hwang, Chih-Ching Lin, Meng-Chuan Huang, Owen J. Kelly, Abbott Laboratories, Columbus, OH; Abbott Laboratories Services Corp, Taipei, Taiwan; Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; Taipei Veterans General Hospital, Taipei City, Taiwan.

Background: The purpose of this study was to determine if 1-2 servings/day of a renal specific ONS (oral nutrition supplement) aids in maintaining nutritional status and avoids potential deleterious consequences in non-dialedyzed stage 3b-5 CKD patients due to low dietary protein intake.

Methods: This is a prospective, multicenter, single arm, and open label study. Non-dialyzed stage 3b-5 CKD patients, with or without type 2 diabetes, with protein intake >0.8 g/kg/d, with serum albumin ≥3.0 g/dL, and currently receiving standard medical care but not scheduled for dialysis treatment within 18 months were recruited. Subjects were requested to consume 1-2 servings per day (475 kcal, 10.6 g protein per serving), renal specific ONS for 6 months based on individual’s dietary intake and change in body albumin, body weight, and BMI were assessed for nutritional status. Protein and energy intakes were estimated from the dietary records. The outcomes on handgrip strength, biochemistry, appetite change, and quality of life were also examined.

Results: Totally 45 patients completed the intervention trial. Daily protein and energy intakes were elevated significantly 6 months later (+42 g/day, p<0.01; +175.37 kcal/day, p<0.001). Mean body weight and BMI increased significantly (+1.18 kg, p<0.01; +0.47 kg/m² p<0.001) but there was no significant difference in serum albumin (4.09 g/dl to 4.13 g/dl) after intervention for 6 months. However, handgrip strength and appetite improved significantly (+2.12 kg, p<0.05; +3.08, p<0.03). There was no significant difference in the parameters of quality of life and the profiles of biochemistries.

Conclusions: The addition of renal specific ONS can maintain albumin level and improve anthropometry, handgrip strength, and appetite in non-dialedyzed stage 3b-5 CKD patients compared to those who received standard diet counseling.

Funding: Commercial Support - Abbott Laboratories Services Corp. Abbott Nutrition, Taiwan

SA-PO149
Effects of Resistant Starch Supplementation on Inflammatory and Oxidative Stress Status in Hemodialysis Patients: A Pilot Randomized, Double-Blind, Placebo-Controlled Clinical Trial
Denise Maira Marta Escalghado, Milena B. Stockler-Pinto, Natalia A. Borges, Ludmila F. Cardozo, Bruna Paiva, Mariana Z. Jardim, Julie ann Kemp, Federal Fluminense University, Niterói, Brazil.

Background: In recent years, researchers have suggested that gut microbiota imbalance may be considered as a new cardiovascular risk factor in chronic kidney disease (CKD) patients, once it is associated with inflammatory and oxidative stress state. In this context, prebiotics use has been pointed out as a promising non-pharmacological therapeutic strategy by reestablishing the gut microbiota balance. The aim of this study was to determine the effect of resistant starch (RS) (as prebiotic source) supplementation on inflammatory and oxidative stress status on hemodialysis (HD) patients.

Methods: This randomized, double-blind, placebo-controlled clinical trial evaluated 20 CKD patients on HD (55% male, 55.6 ± 10.7 years, 30.5 (14.2 – 62) months HD vintage, 26.5 ± 4.8 kg/m² body mass). Patients were randomized to receive prebiotic resistant starch (RS) or placebo. Patients received 9 cookies/d in the dialysis days and 1 sachet/d in non-dialysis days, containing 16g of RS- Hi-Maize 260, Ingridion®) or placebo (10 patients received cookies and sachets - containing mannose flour) for 4 weeks. High sensitive C-reactive protein (hs-CRP) was analyzed using Bioelina® kit by automatic biochemical analyzer, interleukin (IL)-6 plasma levels were performed by ELISA and, malonaldehyde (MDA) plasma levels, a common marker of lipid peroxidation, were measured by thiobarbituric acid reaction. Routine biochemical parameters and nutritional status were also obtained.

Results: There was no significant difference between baseline values for any variable in both groups. After 4 weeks of RS supplementation, there was a significant reduction in IL-6 (from 3.47 ± 0.04 to 3.46 ± 0.01 pg/ml, p = 0.001) and MDA (from 4.64 ± 2.47 to 2.33 ± 1.57 mmol/l, p = 0.04) plasma levels. No change was observed in placebo group.

Conclusions: Data from this randomized study suggest that RS supplementation may modulate inflammation and oxidative stress in HD patients. These findings support the need for more studies with prebiotics in CKD patients to confirm the hypothesis that they could be a new non-pharmacological therapeutic strategy to modulate gut microbiota in these patients and reduce complications related to its imbalance.

Funding: Government Support - Non-U.S.

SA-PO150
Optical Analysis of Mitochondrial Dynamics and Function in Renal Pathology and Physiology In Vivo Using Metabolic Biosensor Transgenic Zebrafish
Zehraish Sayed, Jacob P. Keller, Ritu Tomar, Hugo L. Siegfried, Iain A. Drummond, Massachusetts General Hospital, Charleston, MA; Massachusetts General Hospital, Charlestown, MA; Harvard Medical School, Boston, MA; Janelia Research Campus, Ashburn, VA; Howard Hughes Medical Institute, Ashburn, VA.

Background: Accumulating amounts of evidence suggest that mitochondria play a major role in maintenance of renal function and pathogenesis of kidney diseases. Despite
the apparent importance, however, little is known about mechanisms by which altered mitochondrial function leads to development of renal disease due to lack of appropriate tools. Mitochondria are a dynamic organelle that actively changes its shape, number and site of residence, thereby making it critical to analyze them in vivo. In order to establish in vivo tools to study mitochondria, we applied the genetically encoded biosensor technology to the zebrafish, an optically accessible and genetically tractable model system.

Methods: A transgenic zebrafish line incorporating a mitochondria targeted redox sensor (mitoGrx1-roGFP2) under the UAS effector element was generated. By crossing this UAS effector line into Gal4 driver lines with podocin and cdh17 promoter (Tg(podo:Gal4) and Tg(cdh17:Gal4)), mitoGrx1-roGFP2 was expressed in glomerular podocytes and tubular epithelial cells, respectively, in the pronephros. Live imaging of the transgenic zebrafish was performed by sequential excitation at 405 nm and 488 nm for ratiometric measurements.

Results: We found that mitochondrial structure and dynamics in podocytes can be imaged in living zebrafish by two-photon microscopy. Time lapse imaging of Tg(podo:Gal4), UAS/mitoGrx1-roGFP2 demonstrated that mitochondria are stationary in pronephric podocytes. Upon exposure to a nephrotoxic antibiotic, puromycin aminonucleoside, mitochondria appeared to relocalize to primary and secondary processes from the cell body. Furthermore, ratiometric measurements of mitoGrx1-roGFP2 reported changes in oxidative stress levels in mitochondria in renal tubular epithelia in response to tert butyl hydroperoxide.

Conclusions: These transgenic zebrafish represent a novel tool to investigate mitochondrial structure and function in vivo. In addition, transgenic zebrafish with biosensors for other metabolic parameters, such as glucose, are also being validated. These transgenic zebrafish offer a versatile and accessible in vivo system to study mitochondrial dynamics and activity as well as their associated metabolism in the kidney in health and disease.

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

SA-PO151
Low Density Lipoprotein Cholesterol Is Associated with Decreased Infectious Death and Hospitalization in Hemodialysis Patients
Xiaoling Ye; Jochen G. Raimann; Ali Topping; Len A. Usuyat; Peter Kotanko; George A. Kayser; Fresenius Medical Care North America, Melrose, MA; Renal Research Institute, New York, NY; Medicine and Biochemistry and Molecular Medicine, UC Davis, Davis, CA; Medicine, Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Reduction in low density lipoprotein (LDL) does not decrease mortality in hemodialysis (HD) patients. The second leading cause of death in HD after cardiovascular (CV) diseases is infectious. LDL absorbs and inactivates bacterial toxins. Injected human LDL prevents endotoxin induced lethality in mice. We examined the effect of LDL, High Density Lipoprotein (HDL) and triglycerides (TG) on infectious, CV events and all cause mortality.

Results: We explored relationships between blood lipids and outcomes in databases from Renal Research Institute (RRI) clinics in US and Fresenius Medical Care (FMC) clinics in Europe, and west Asia (14,650 patients, 60.2% male). All incident and prevalent patients starting in-center HD between Jan 1, 2000 and Dec 31, 2012 with at least one lipid measurements and inflammatory measures (C reactive protein (CRP)) or neutrophil lymphocyte ratio (NLR) were measured. Selection to time bacterial, CV hospitalization or death or all cause death during up to 4 years of following the last lipid measurement were analyzed by Cox time varying proportion hazards.

Results: LDL, reduced risk of infectious death and hospitalizations, and all-cause mortality (HR 0.98 0.971-0.989, P < 0.001). HDL was associated with a reduction in CV death and hospitalization (HR 0.901 0.847-0.958 P = 0.0009) and all-cause mortality (HR 0.919 0.897-0.943 P < 0.001) and TG was associated with a reduction in all cause mortality (HR 0.893 0.642-0.726 P < 0.001). Results: LDL, reduced risk of infectious death and hospitalizations, and all-cause mortality (HR 0.98 0.971-0.989, P < 0.001). HDL was associated with a reduction in CV death and hospitalization (HR 0.901 0.847-0.958 P = 0.0009) and all-cause mortality (HR 0.919 0.897-0.943 P < 0.001) and TG was associated with a reduction in all cause mortality (HR 0.893 0.642-0.726 P < 0.001).

Conclusions: Higher LDL is associated with decreased all cause death and infectious death and hospitalizations, but not with increased CV risk, possibly accounting for the observation that reducing LDL cholesterol has a limited effect on outcomes in patients undergoing hemodialysis.

Funding: Commercial Support - Fresenius, MONDO

SA-PO152
Low Plasma Insulin-Like Growth Factor-1 Associates with Increased Mortality in CKD Patients with Reduced Muscle Strength
Chen Zhimin; Bengt Lindholm; Olof Heimbürger; Peter F. Barany; Peter Stenvenink; Jianghua Chen; Abdul Rashid T. Qureshi; Renal Medicine and Baxter Novum, Karolinska Institutet, Stockholm, Sweden; 1st Affiliated Hospital College of Medicine, Zhejiang University, Hangzhou, China.

Background: Chronic kidney disease (CKD) leads to metabolic and nutritional abnormalities including resistance to insulin-like growth factor-1 (IGF-1) action. Low plasma IGF-1 concentration as well as low handgrip strength (HGS), a reliable and easy-to-perform nutritional parameter, are independent predictors of increased mortality in CKD patients (pts). We hypothesized that low muscle strength enhances the negative impact of low IGF-1 on survival in CKD.

Methods: We included 685 CKD pts (62% males; median age 58 years) including 75 CKD 3-4 pts, 361 incident dialysis pts, 70 prevalent peritoneal dialysis pts and 179 prevalent hemodialysis pts. Baseline measurements of IGF-1, HGS, nutritional status (by subjective global assessment, SGA), lean body mass index (LBMI), and metabolic and inflammatory biomarkers potentially linked to IGF-1 were analysed in relation to mortality during follow up period of up to 5 years during which 208 pts (30.4%) died.

We compared survival in four groups with high or low (cut-offs defined by ROC curve analysis) levels of IGF-1 and HGS.

Results: Pts with low IGF-1 were older, had lower body mass index (BMI), HGS and LBMI, more likely to have diabetes, CVD and malnutrition (SGA > A), and had higher C reactive protein (hsCRP) levels. During 5 years of follow-up, 208 pts (30.4%) died. Pts with Low IGF-1 + Low HGS had markedly increased mortality rate: In competing-risks regression analysis, sub-hazard ratio (SHR) of pts with Low HGS vs Low IGF-1 was 2.3 times higher than for pts with High HGS + Low IGF-1. Low IGF-1 + Low HGS was independently associated with all-cause mortality after adjustments for age, sex, diabetes, CVD, SGA, smoking, hsCRP, albumin and LBMI.

Conclusions: Low IGF-1 together with low HGS - but not low IGF-1 together with high HGS - was independently associated with increased all-cause mortality suggesting that the effect of IGF-1 on mortality in CKD patients depends on nutritional status.

Funding: Commercial Support - Baxter Healthcare Corporation, Government Support - Non-U.S.

SA-PO153
Influence of Diabetes on Sarcopenia in Hemodialysis Patients
Senji Okuno; Jiro Miyawaki; Hisanori Okazaki; Kyoko Norimine; Shigetei Shoji; Tomoyuki Yamakawa; Eiji Ishimura; Masaaki Inaba.

Recent, the associations between sarcopenia and diabetes and between sarcopenia and chronic kidney disease, including hemodialysis (HD) condition, have been reported. However, there have been few reports that examine the relationship between sarcopenia and diabetes in HD patients. Little is known how far diabetes affects sarcopenia in HD patients. Moreover, definition of sarcopenia was made only in considering the low muscle mass in the previous studies. The main goal of this study was to assess sarcopenia which was strictly assessed by both muscle mass and muscle strength, and was to examine the association of diabetes with sarcopenia in HD patients.

Methods: A total of 308 patients on maintenance HD (age 58.1 ± 11.9 years, HD duration 6.5 ± 6.0 years, 60 % males, and 33 % diabetics) were examined. Appendicular

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

717
skeletal muscle mass was measured by dual energy X-ray absorptiometry (DXA). Low muscle mass was defined as skeletal muscle mass index (sMMI) of < 5.87 kg/m² for males and < 5.46 kg/m² for females. Low muscle strength was defined as hand grip strength of < 26 kg for males and < 18 kg for females. Sarcopenia was defined as decline in both SMI and muscle strength.

Results: There were no significant differences in HD duration or in hemoglobin between patients with and without sarcopenia. Age was significantly higher, and body mass index and serum albumin were significantly lower in patients with sarcopenia than in those without sarcopenia (63.5 ± 11.0 yr vs. 54.1 ± 11.0 years, p < 0.001); 19.4 ± 2.3 vs. 21.6 ± 2.2 kg/m² (p = 0.002); 3.9 ± 0.3 vs. 4.1 ± 0.3 g/dL (p = 0.0001), respectively. Prevalence of sarcopenia in diabetic patients was significantly higher than that in non-diabetic patients (51% vs. 36%, p = 0.015). In a multiple logistic regression analysis, presence of diabetes (OR = 3.02, p = 0.008) was significantly, independently associated with sarcopenia after adjustment with age, gender, HD duration, body mass index, hemoglobin, serum albumin, and C-reactive protein levels (R² = 0.273, p < 0.0001).

Conclusions: Present study clearly demonstrates, for the first time, that, in HD patients who are considered to be at higher prevalence of sarcopenia, diabetes is further an additional, strong risk factor for sarcopenia, which was strictly assessed by both muscle mass and muscle strength.

SA-PO154

Severe Vitamin D Deficiency Is a Risk Factor for Renal Hyperfiltration

Long Hyun Jhee,1 Tae-Hyun Yoo,1 Sukyung Kang,2 Arum Choi,2 1Department of Internal Medicine, College of Medicine, Yonsei University, Seoul, Republic of Korea; 2Department of Internal Medicine, College of Medicine, Severance Biomedical Science Institute, Brain Korea 21 PLUS, Yonsei University, Seoul, Republic of Korea.

Background: Recent studies suggested that renal hyperfiltration (RHF) is significantly associated with increased risk of all-cause and cardiovascular mortality in relatively healthy adult population as well as diabetic patients. On the other hand, vitamin D deficiency is well known as a risk factor for development of RHF in various populations. This study aimed to investigate the association between RHF and vitamin D deficiency among relatively healthy adult population.

Methods: The data from subjects participated in the Korean National Health and Nutrition Examination Survey (KNHNES) from 2008 to 2015 were collected. A total of 33,210 subjects with normal renal function were included in the final analysis. Estimated GFR (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration creatinine equation, and RHF was defined as eGFR > 95th percentile after adjustment for age, sex, and history of diabetes and/or hypertension. Severe vitamin D deficiency was defined as serum 25(OH)D < 10 ng/mL.

Results: The mean ages of the subjects were 52.1 years and the numbers of female subjects were 18,779 (56.5%). 1,637 (4.9%) subjects were categorized into RHF group. According to serum 25(OH) level, the prevalence of renal hyperfiltration was significantly higher in the lowest 25(OH)D group (5.1%, P<0.001 vs. those in patients without RHF). According to serum 25(OH)D level, the prevalence of renal hyperfiltration was significantly higher in the lowest 25(OH)D group (5.7%, P<0.001 vs. those in patients without RHF). In addition, the prevalence of RHF was significantly higher in the lowest 25(OH)D group (5.7%, P<0.001 vs. those in patients without RHF). According to serum 25(OH) level, the prevalence of renal hyperfiltration was significantly higher in the lowest 25(OH)D group (5.7%, P<0.001 vs. those in patients without RHF).

Conclusions: This study shows that the proportion of end-stage CKD patients with low blood thiamine concentration was high. In addition, this study suggested that age and low physical activity (low score on BI) are independent risk factors of thiamine deficiency. Clinicians should be aware of thiamine deficiency when end-stage CKD patients, especially elderly patients with low physical activity, present unexplained cardiac or neurologic symptoms.

SA-PO156

Thyroid Status and Body Composition in a Prospective Hemodialysis Cohort

Connie Rhee,1 Yanjun Chen,2 Amy S. You,3 Csaba P. Kovesda,4 Matthew J. Bodoft,5 Tracy Nakata,6 Alejandra Novoa,6 Gregory Brent,7 Yasmin Elazzazy,8 Saka,9 Jong Saka,9 Yoo,1 Sukyung Kang,2 Arum Choi,2 1Department of Internal Medicine, College of Medicine, Yonsei University, Seoul, Republic of Korea; 2Department of Internal Medicine, College of Medicine, Severance Biomedical Science Institute, Brain Korea 21 PLUS, Yonsei University, Seoul, Republic of Korea.

Background: Thyroid status is known to control metabolism, with subsequent effect upon body composition. In addition to causing excess adiposity, hypothyroidism also increases development and growth of skeletal muscle. Whereas hypothyroidism is highly prevalent in hemodialysis (HD) patients, there has not been prior study of thyroid status and trajectory of body composition parameters in this population.

Methods: Among 590 HD patients from the prospective Malnutrition, Diet, and Racial Disparities in Kidney Disease study, we examined the association of thyroid status, defined by baseline serum TSH, with body composition parameters over time using case-mix/laboratory linear mixed effects models. Over 2013-17, patients were recruited from 17 outpatient HD facilities and underwent protocolized TSH testing and body anthropometry testing: subcutaneous fat (biceps and triceps skinfold (SF)); skeletal muscle (mid-arm circumference [MAC]; mid-arm muscle circumference [MAMC]); total body fat (near infra-red [NIR] body fat); and visceral fat (waist circumference).

Results: Higher TSH levels were incrementally associated with greater biceps SF (β = 0.8% (p=0.03) and β = 1.2% (p=0.02) for TSH levels 1-3 and >3mU/L, respectively (Figure). Similarly, incrementally higher TSH levels were associated with greater NIR body fat: β = +0.4% (p=0.13) and β = 0.8% (p=0.04) for TSH levels 1-3 and >3mU/L, respectively. There was a trend between higher TSH levels and higher MAC: β = 0.3cm (p=0.15) and β = 0.5cm (p=0.06) for TSH levels 1-3 and >3mU/L, respectively.

Conclusions: In HD patients higher TSH levels are associated with greater markers of subcutaneous and total body fat, and may potentially be associated with greater muscle mass. Future studies are needed to determine if thyroid-modulating therapy alters the body composition of hypothyroid HD patients.

NIDDK Support
**Results:** The MIS mean was 7.33 ± 4.57 and was higher in deceased patients (8.34 ± 4.56) than in the non-deceased patients (6.5 ± 4.26) (p = 0.002). In the ROC analysis, the optimal cut-off value of MIS for predicting death was 5 with 81.5% percent sensitivity and 42.6 percent specificity (Figure 1). MIS ≥5 was found in 67.3% of patients. 81.5% of the deceased patients had a MIS ≥5 compared to only 57.4% of the non-deceased patients (p <0.001). High MIS and Charlson index, advanced age and low lymphocytes were found to be predictors of mortality in the multivariate logistic regression analysis. As the MIS increases, overall survival is lower according to the Kaplan Meier’s statistical analysis (p = 0.003) (Figure 2).

**Conclusions:** MIS was a practical, simple and independent predictor of mortality in hemodialysis patients, being the best cut-off point to predict mortality. Additional risk factors associated with mortality were high Charlson Index, advanced age as well as lymphopenia.

**Conclusions:** Falls are among the leading causes of morbidity and mortality in older adults (age ≥65 years). Within older adult populations, few studies have identified the risk factors for falls in chronic kidney disease (CKD) patients. Previous studies have primarily been based on small convenience samples from healthcare facilities, emphasized severely ill patients, and explored only a few predictors of falls. This has led to conflicting data on risk factors for falling. Therefore, our objective was to examine the prevalence and predictors of falls in older adults with CKD from a large non-hospitalized population-based sample.

**Methods:** We conducted multicenter prospective cohort study using Clinical Research Center for end stage renal disease. We enrolled 1,721 adult patients who were on hemodialysis between 2008 and 2013. Basic patient characteristics, laboratory data, dose of erythropoiesis stimulating agents (ESA) and 3-month iron dose were collected after enrollment. All-cause mortality, death and hospitalization due to infection or CVD were compared and propensity score matching were conducted to exclude the effects of other factors on outcome.

**Results:** In total 1,721 patients, 555 patients received IV iron therapy and 658 patients received oral iron only. Median IV iron dose during 3 months was 600mg (100 – 9,000 mg). In IV iron usage group, hemoglobin, ferritin, serum iron and transferrin saturation were significantly lower and total iron-binding capacity, ESA dose and erythropoietin resistance index were higher compared to oral iron group. During mean follow-up duration of 743.6±578.4 days, all-cause mortality, death due to infection or CVD and both death and hospitalization due to infection or CVD did not differ between two groups. Even in subgroup analysis of patients with higher IV iron usage (>600 mg/3 months), there were no significant differences in adverse outcomes. However, in subgroup analysis of prevalent patients, IV iron usage group tend to show higher hospitalization and death due to infection and CVD. After propensity score matching, similar trends were observed.

**Conclusions:** The current clinical usage of IV iron in hemodialysis patients did not increase all-cause mortality or death and hospitalization due to infection or CVD compared to oral iron therapy. A well-designed randomized controlled trial is needed to clarify both short-term and long-term effects of IV iron therapy.

---

**SA-PO159**

**Association of Adiposity with Hemoglobin Levels in Patients with CKD Not on Dialysis**

**Background:** Adiposity influences erythropoiesis and iron metabolism in the general population. We therefore hypothesized that adiposity could be associated with erythropoiesis or impaired iron metabolism in patients with CKD; however, and that these associations would be influenced by the severity of CKD. The present study aimed to assess the relationship between adiposity—as estimated by body mass index (BMI) and abdominal circumference (AC)—and biomarkers of erythropoiesis in patients with chronic kidney disease (CKD) not on dialysis.

**Methods:** A total of 2,322 patients from the Chronic Kidney Disease Japan Cohort study were analyzed. Patients were grouped according to BMI category (low: BMI <18.5, normal: BMI 18.5-24.5, and high: BMI ≥25) and AC category (large: AC ≥90 cm for males and AC ≥80 cm for females; and, small: AC measurements below the large values<90 cm and <80 cm). Body composition and laboratory data were measured at baseline, 1 year, and 2 years.

**Results:** Multivariate regression analysis at 3 time points showed that a high BMI and large AC in male patients were significantly associated with higher hemoglobin levels. Hemoglobin levels in female patients with BMI>18.5 and small AC were lower than with 18.5<BMIL<25 and large AC, respectively (Fig. 1). However, hemoglobin levels were plateaued above threshold of 25 of BMI and 80cm of AC, respectively (Fig. 1). While BMI and AC were positively associated with C-reactive protein levels, they were not associated with levels of transferrin saturation, ferritin, and erythropoietin in multivariate models.

**Conclusions:** In conclusion, body composition may be associated with erythropoiesis; however, adiposity may be only associated with increased erythropoiesis in male patients. It does not appear to hamper iron metabolism in CKD patients not on dialysis.

**Funding:** Commercial Support - Kyowa Hakko Kirin Co., Ltd

---

**SA-PO158**

**Effects of Intravenous Iron Therapy on the Mortality and Hospitalization in Hemodialysis Patients**

**Background:** Iron replacement therapy is inevitable to correct iron deficiency anemia in advanced chronic kidney disease patients. Intravenous (IV) iron therapy has been known as an efficient method to replace iron, especially in patients who are intolerant to oral iron. However, there have been concerns of considerable side effects with IV iron usage including increased risks of infection or cardiovascular disease (CVD). In this study, we compared IV iron usage with oral iron to assess the adverse effects in the prospective cohort of Korean patients.

**Methods:** We conducted multicenter prospective cohort study using Clinical Research Center for end stage renal disease. We enrolled 1,721 adult patients who were on hemodialysis between 2008 and 2013. Basic patient characteristics, laboratory data, dose of erythropoiesis stimulating agents (ESA) and 3-month iron dose were collected after enrollment. All-cause mortality, death and hospitalization due to infection or CVD were compared and propensity score matching were conducted to exclude the effects of other factors on outcome.

**Results:** In total 1,721 patients, 505 patients received IV iron therapy and 658 patients received oral iron only. Median IV iron dose during 3 months was 600mg (100 – 9,000 mg). In IV iron usage group, hemoglobin, ferritin, serum iron and transferrin saturation were significantly lower and total iron-binding capacity, ESA dose and erythropoietin resistance index were higher compared to oral iron group. During mean follow-up duration of 743.6±578.4 days, all-cause mortality, death due to infection or CVD and both death and hospitalization due to infection or CVD did not differ between two groups. Even in subgroup analysis of patients with higher IV iron usage (>600 mg/3 months), there were no significant differences in adverse outcomes. However, in subgroup analysis of prevalent patients, IV iron usage group tend to show higher hospitalization and death due to infection and CVD. After propensity score matching, similar trends were observed.

**Conclusions:** The current clinical usage of IV iron in hemodialysis patients did not increase all-cause mortality or death and hospitalization due to infection or CVD compared to oral iron therapy. A well-designed randomized controlled trial is needed to clarify both short-term and long-term effects of IV iron therapy.

---

**SA-PO160**

**Falls and Fall-Related Injuries in Older Americans with CKD**

**Background:** Falls are among the leading causes of morbidity and mortality in older adults (age ≥65 years). Within older adult populations, few studies have identified the risk factors for falls in chronic kidney disease (CKD) patients. Previous studies have primarily been based on small convenience samples from healthcare facilities, emphasized severely ill patients, and explored only a few predictors of falls. This has led to conflicting data on risk factors for falling. Therefore, our objective was to examine the prevalence and predictors of falls in older adults with CKD from a large non-hospitalized population-based sample.

**Methods:** We conducted multicenter prospective cohort study using Clinical Research Center for end stage renal disease. We enrolled 1,721 adult patients who were on hemodialysis between 2008 and 2013. Basic patient characteristics, laboratory data, dose of erythropoiesis stimulating agents (ESA) and 3-month iron dose were collected after enrollment. All-cause mortality, death and hospitalization due to infection or CVD were compared and propensity score matching were conducted to exclude the effects of other factors on outcome.

**Results:** In total 1,721 patients, 505 patients received IV iron therapy and 658 patients received oral iron only. Median IV iron dose during 3 months was 600mg (100 – 9,000 mg). In IV iron usage group, hemoglobin, ferritin, serum iron and transferrin saturation were significantly lower and total iron-binding capacity, ESA dose and erythropoietin resistance index were higher compared to oral iron group. During mean follow-up duration of 743.6±578.4 days, all-cause mortality, death due to infection or CVD and both death and hospitalization due to infection or CVD did not differ between two groups. Even in subgroup analysis of patients with higher IV iron usage (>600 mg/3 months), there were no significant differences in adverse outcomes. However, in subgroup analysis of prevalent patients, IV iron usage group tend to show higher hospitalization and death due to infection and CVD. After propensity score matching, similar trends were observed.

**Conclusions:** The current clinical usage of IV iron in hemodialysis patients did not increase all-cause mortality or death and hospitalization due to infection or CVD compared to oral iron therapy. A well-designed randomized controlled trial is needed to clarify both short-term and long-term effects of IV iron therapy.

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

Underline represents presenting author.
SA-PO161

Effect of Fructooligosaccharide on Microbiota-Derived Uremic Toxins in Predialysis Patients: A Randomized Controlled Trial

Christiane I. Ramos,1 Rachael G. Armani,1 Lia S. Nakao,1 Maria Eugenia F. Canziani,2 Katrina L. Campbell,2 Lilian Cuppari,1 1Federal University of Sao Paulo, Sao Paulo, Brazil; 2Princess Alexandra Hospital, Brisbane, Australia; 3Cleveland Clinic, Cleveland, OH, USA; 4Cleveland Clinic Foundation, Shaker Heights, OH, USA; 5NIDDK, NIH, Bethesda, MD, USA; 6University of Pennsylvania, Philadelphia, PA, USA; 7Icahn School of Medicine at Mount Sinai, New York, NY, USA; 8University of Sao Paulo, Curitiba, Brazil.

Background: Microbiota-derived uremic toxins, p-cresyl sulfate (PCS) and indoxyl sulfate (IS), have been associated with poor outcomes in chronic kidney disease (CKD). This has encouraged the investigation of alternative approaches to modulate gut environment and to attenuate toxin production. The present trial aimed to evaluate the effect of the probiotic fructooligosaccharide (FOS) on changes in PCS, IS, indole-3-acetic acid (IAA), kidney damage (eGFR and proteinuria) and insulin resistance in predialysis patients (stages 3b, 4 and 5).

Methods: The 3-month double-blind randomized controlled trial included 46 non-diabetic CKD patients [52% men; 75.6±14.4 years; eGFR: 21.3±17.3 mL/min/1.73m2]. Intervention and placebo consisted in 125g/day of FOS or maltodextrin, respectively. PCS, IS and IAA were determined by high performance liquid chromatography. Dietary intake was assessed by 3-day food records; supplement adherence (sachet count) and gastrointestinal events by the Gastrointestinal Symptom Rating Scale.

Results: Aside for the intervention group being older (53.4±16.0 vs 61.9±11.4 years, p=0.04) the groups were homogeneous. Overall sachet adherence was excellent (mean consumption: 93.1±8.1%). No changes in the ratio of dietary protein/fibre intake or gastrointestinal symptoms were observed during the follow-up. Changes in the outcomes are depicted in the table.

Conclusions: FOS was well tolerated and resulted in a trend in reduced PCS. No effect of FOS on IS, IAA, kidney damage or insulin resistance was observed.

Funding: Support - Non-U.S.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Group</th>
<th>Mean±SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCS (mol/L)</td>
<td>FOS</td>
<td>1.32±4.0</td>
<td>0.82±2.5</td>
</tr>
<tr>
<td>IS (mol/L)</td>
<td>FOS</td>
<td>2.3±1.5</td>
<td>2.0±0.9</td>
</tr>
<tr>
<td>IAA (U/mL)</td>
<td>FOS</td>
<td>-0.31±3.9</td>
<td>0.61±3.1</td>
</tr>
</tbody>
</table>

SA-PO162

The Effects of More Frequent Hemodialysis on HD (Plasma Vitamin C Concentration: An Ancillary Study of the Frequent Hemodialysis Network (FHN) Daily Trial)

Jochen G. Raimann,1 Sameer R. Abbass,2 Li Liu,3 Brett Larive,4 Yuguang Liu,5 Gerald J. Beck,3 Peter Kotanko,4 Nathan W. Levin,6 Gurry J. Handelman,7 The FHN Trial Group.1 Cleveland Clinic, Cleveland, OH, USA; 2Cleveland Clinic Foundation, Shaker Heights, OH, USA; 3NIDDK, NIH, Bethesda, MD, USA; 4Peking University First Hospital, Beijing, China; 5Renal Research Institute, New York, NY, USA; 6University of Massachusetts, Lowell, MA, USA; 7Icahn School of Medicine at Mount Sinai, New York, NY, USA.

Background: Reports on vitamin C in HD patients have shown effects of vitamin C deficiency (Raimann, Semin Dial 2013) in association with scurvy symptoms. Dialyzability of water soluble vitamins is high and substantial losses in those who are inadequately dialyzed can occur. Micronutrient deficiencies (Raimann, Semin Dial 2013) in association with scurvy symptoms. This has encouraged the investigation of alternative approaches to modulate gut environment and to attenuate toxin production. The present trial aimed to evaluate the effect of the probiotic fructooligosaccharide (FOS) on changes in PCS, IS, indole-3-acetic acid (IAA), kidney damage (eGFR and proteinuria) and insulin resistance in predialysis patients (stages 3b, 4 and 5).

Methods: The 3-month double-blind randomized controlled trial included 46 non-diabetic CKD patients [52% men; 75.6±14.4 years; eGFR: 21.3±17.3 mL/min/1.73m2]. Intervention and placebo consisted in 125g/day of FOS or maltodextrin, respectively. PCS, IS and IAA were determined by high performance liquid chromatography. Dietary intake was assessed by 3-day food records; supplement adherence (sachet count) and gastrointestinal events by the Gastrointestinal Symptom Rating Scale.

Results: Aside for the intervention group being older (53.4±16.0 vs 61.9±11.4 years, p=0.04) the groups were homogeneous. Overall sachet adherence was excellent (mean consumption: 93.1±8.1%). No changes in the ratio of dietary protein/fibre intake or gastrointestinal symptoms were observed during the follow-up. Changes in the outcomes are depicted in the table.

Conclusions: FOS was well tolerated and resulted in a trend in reduced PCS. No effect of FOS on IS, IAA, kidney damage or insulin resistance was observed.

Funding: Support - Non-U.S.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Group</th>
<th>Mean±SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCS (mol/L)</td>
<td>FOS</td>
<td>1.32±4.0</td>
<td>0.82±2.5</td>
</tr>
<tr>
<td>IS (mol/L)</td>
<td>FOS</td>
<td>2.3±1.5</td>
<td>2.0±0.9</td>
</tr>
<tr>
<td>IAA (U/mL)</td>
<td>FOS</td>
<td>-0.31±3.9</td>
<td>0.61±3.1</td>
</tr>
</tbody>
</table>

SA-PO164

Low Leptin Level Is Associated with Poor Nutritional Status in ESRD

Jun young Lee,1 Jae seok Kim,2 Jae won Yang,2 Seung-ok Choi,3 Byoung Geun Han.1 1.None, Wonju, Republic of Korea; 2Wonju Christian Hospital, Wonju, GangWon-Do, Republic of Korea; 3Wonju christian seversan hospital, Wonju, Kwangdo, Republic of Korea; 4Isonseie University Wonju College of Medicine, Wonju, Kangwon, Republic of Korea; 5Isonseie wonju college of medicine, wonju, Republic of Korea.

Background: Poor nutritional status is associated with poor prognosis in end stage renal disease (ESRD) patients. Bio-impedance spectroscopy (BIS) is a useful method to estimate body fluid and nutritional status. Particularly, phase angle (PhA, °) is a parameter that represents nutritional status well. In the study, we aim to identify factors related to nutritional status in ESRD patients not undergoing dialysis.

Methods: We enrolled total 91 ESRD patients not undergoing dialysis. We measured routine serum markers including albumin and NT-proBNP, and appetite regulating hormones, leptin and ghrelin. With BIS, we measured OH (overhydration, liter) and OH/EWC (OH/extracellular water ratio) values to estimate body fluid amounts, and PhA to determine nutritional status. We defined poor nutritional status as a PhA<4.5°, and proper nutritional status as a PhA≥5.0°. Lastly, we evaluated patient’s nutritional status by assessing geriatric nutritional risk index (GNRI).

Results: Forty-one patients (45%) had poor nutritional status. The patients with poor nutrition, compared to proper nutrition, had significantly higher levels of NT-proBNP (14,477.8±12,712 vs 4,965.2±8,824 pg/mL, p<0.001) and OH/EWC (29.6±12.7 vs 6.2±10.3 %, p<0.001), and lower levels of albumin (3.0±0.5 vs 3.7±0.5 g/dL, p<0.001), leptin (3.8±3.1 VS. 7.0±2.6 ng/mL, p=0.004) and GNRI (85.1±7.1 vs. 96.5±14.9, p<0.001). In Pearson’s correlation test, leptin had negative correlations with NT-proBNP (r= -0.237, p=0.026) and OH/EWC (r = -0.288, p=0.006). On the contrary, leptin had positive correlations with BMI (r=0.351, p=0.001), PhA (r=0.263, p=0.012) and GNRI (r=0.281, p=0.026) the groups were homogeneous. Overall sachet adherence was excellent (mean consumption: 93.1±8.1%). No changes in the ratio of dietary protein/fibre intake or gastrointestinal symptoms were observed during the follow-up. Changes in the outcomes are depicted in the table.

In Pearson's correlation test, leptin had negative correlations with NT-proBNP (r= -0.237, p=0.026) and OH/EWC (r = -0.288, p=0.006). On the contrary, leptin had positive correlations with BMI (r=0.351, p=0.001), PhA (r=0.263, p=0.012) and GNRI (r=0.281, p=0.026). In multivariate logistic regression test, high level of leptin (OR 6.12, 95% CI 1.01-37.13) and albumin (OR 10.14, 95% CI 5.13-68.20) predicted proper nutrition well, while increased level of NT-proBNP (OR 0.07, 95% CI 0.01-0.84) and OH/EWC (OR 0.04, 95% CI 0.01-0.19) were related to poor nutrition.

Conclusions: Our study demonstrates that ESRD patients with poor nutrition generally have a problem on supplements. Our study found no association between supplements and data hygiene. More frequent HD on circulating vitamin C.

The concerns that more frequent HD would affect the concentrations of water-soluble vitamins in HD patients were addressed by multiple clinical trials. Our study shows that more frequent HD on circulating vitamin C.

Based on data from this randomized-controlled trial no significant differences were found.

Conclusions: Our study demonstrates that ESRD patients with poor nutrition generally have a problem on supplements. Our study found no association between supplements and data hygiene. More frequent HD on circulating vitamin C.

The concerns that more frequent HD would affect the concentrations of water-soluble vitamins in HD patients were addressed by multiple clinical trials. Our study shows that more frequent HD on circulating vitamin C.
SA-PO165

Oral Alkali Supplementation to Reduce Uremic Toxin in Early Stage CKD Patients Michiaki Abe,1 Sadayoshi Ito,2 Hiroshi Sato,1 Sadjadyohto.2 Clinical Pharmacology and Therapeutics, Graduate School of Pharmaceutical Sciences, Tohoku University, Sendai, Japan; 2Tohoku Graduate School of Medicine, Sendai Miyagi, Japan; and 3Northwestern University Feinberg School of Medicine, Chicago, IL.

Background: Patients with chronic kidney disease (CKD) has increased plasma uremic toxins (UTxs) and they develop metabolic acidosis and aciduria. These metabolic dysregulations affects CKD progression and cardiovascular and bone complications. Recently, oral alkali therapy has been suggested to slow the progression of CKD pathologies. To investigate the effects of alkali supplementation on UTx accumulation, we initiated a double-blinded randomized control cohort study of “Estimating the efficacy of the Oral Alkali-Azirin patients with CKD; KOCLA study.” Two types of alkalinizers, Na/K citrate and Na bicarbonate, were used.

Methods: Total 47 CKD patients (CKD stage G2, G3a, G3b) were randomized to divide into 3 groups, control (n=15), Na bicarbonate (n=16) and Na/K citrate (n=16). The urine and plasma samples at 0, 6, 12 and 24 weeks after the intervention were collected and anonymized. Five UTxs including (Indoxyl sulfate (IS), p-cresyl sulfate (PCS), phenylacetyl l-glutamine (PAG), and arginomucosacinate (ASA) and hippuric acid) were quantified by a quantitative-target LC-MS/MS. Individual change of UTxs abundance were compared and Mann-Whitney test was used for statistical analysis. This research was approved as a secondary use of KOCLA study by Tohoku University Hospital Ethics Committee.

Results: Exchange of urinary concentrations of IS, PAG, PCS, PAG and ASA from was compared among groups. Urinary UTxs levels in the Na/K citrate-treated group were significantly increased compared to the other two groups [IS; 93% (control) vs. 145% (bicarbonate), p=0.017; PCS; 116% (control) or 181% (bicarbonate) vs. 351% (citrate), p=0.01; ASA; 94% (control) or 100% (bicarbonate) vs. 160% (citrate), p=0.016 or p=0.019; ASA; 87% (control) vs. 126% (citrate), p=0.003]. Furthermore, plasma concentrations for IS was significantly reduced by Na/K citrate-treatment (control 1.2 µg/mL or bicarbonate 1.4 µg/mL vs. citrate 1.1 µg/mL, p=0.029 or p=0.035).

Conclusions: Our feasibility study shows that an alkali therapy reduces some kinds of UTxs abundance in CKD patients and may prevent a mechanism whereby oral alkali supplementation prevents CKD progression. Funding: Other NIH Support - JSPS KAKENHI Grant-in-Aid for Scientific Research (C).

SA-PO166

Leptin Levels Are Not Reduced by High-Flow Compared with Low-Flow Haemodialysis: Results of a Randomized Trial Andrea Schneider,1 Markus F. Schneider,1 Dietrich H. Krieter,1 Hubert Scharnagl,2 Christoph Wanner,1 Christiane Drechsler,1 University of Wuerzburg, Wuerzburg, Germany; 2Medical University of Graz, Graz, Austria; 3University Hospital Wuerzburg, Wuerzburg, Germany; 4University Hospital Wurzburg, Wuerzburg, Germany; 5University of Erlangen-Nuremberg, Erlangen, Germany.

Background: Leptin, in addition to its well described effects on glucose homeostasis, might be directly involved in the progression of atherosclerosis, as it promotes chronic inflammation and vascular smooth muscle cell proliferation. Interestingly, leptin levels are significantly increased in haemodialysis (HD) patients compared with healthy controls. Interventional strategies able to reduce levels of leptin in HD patients are of particular interest. The low molecular weight of leptin (16 kD) suggests that its elimination might depend on the specific HD modality.

Methods: We performed a randomized controlled trial on the effects of high-flux versus low-flux HD. 127 maintenance HD patients were randomized to low-flux (n=62) or high-flux (n=65) HD for 52 weeks. The primary endpoint of the study was the effect on parameters of anaemia, which has been published previously. The secondary endpoint included the effect on leptin levels. Leptin levels were measured by ELISA at baseline and after 52 weeks of treatment.

Results: Patients in both groups were 66 years (mean age). Underlying kidney disease was diabetic nephropathy in most cases (28% in the low-flux group and 38% in the high-flux group). Compared to baseline, a significant increase in leptin levels after one year of low-flux HD was observed (Delta leptin 41.7 ng/mL; p=0.032). In contrast, leptin levels remained more stable in the high flux group (Delta leptin 32.8 ng/mL; p=0.062). However, there was no difference in absolute change of leptin levels over time between the two randomization groups (p=0.743).

Conclusions: In this randomized controlled trial, we found that leptin levels increased after one year in patients allocated to low-flux HD, but remained more stable in those allocated to high-flux HD. However, the lack of a significant treatment difference suggests that high-flux HD is not more effective than low-flux HD. Future studies should investigate whether enhanced convective solute transport (e.g. by haemofiltration) would be able to improve leptin removal and patient outcome.
SA-PO169

Protein Energy Wasting Is Correlated with Irisin and Over Load Fluid in Peritoneal Dialysis Patients

Sijsia Zhou, Ai Hua Zhang. Peking University Third Hospital, Beijing, China.

Background: Protein energy wasting (PEW) is a common phenomenon in maintenance dialysis patients and increased morbidity and mortality. The mechanisms are unclear. Over load fluid may also induce PEW in peritoneal dialysis patients. Irisin is a newly discovered hormone which can activate brown adipose tissue, is one kind of regulators of energy homeostasis and metabolism in humans. The aim of this study is to assess the relationships between irisin, over load fluid and PEW in PD patients.

Methods: This study was a cross-sectional study with 160 patients on maintenance peritoneal dialysis in peritoneal dialysis center of Peking University Third Hospital. The patients involved and 35 healthy people in a control group. PD patients were divided into two groups: protein energy waste group (PEW group) and non-protein energy waste group (non-PEW group) according to PEW diagnosis criteria. Serum irisin concentrations were measured by ELISA methods. The body composition consisting of over load fluid status (over hydration (OH) value >=2) was analyzed by bioelectrical impedance.

Results: The serum irisin levels were significantly lower in PD patients compared with controls ([113.2±11.9]ng/ml vs. 464.2±37.4]ng/ml, P<0.01). The serum irisin levels were lower in PD patients with protein energy wasting than those of the patients without protein energy wasting([107.8±9.9]ng/ml vs. 119.0±11.3]ng/ml, P=0.01). Existing over load fluid patients with higher prevalence of PEW (59.8%Vs.40.2%, x2=6.223, P<0.01). But there was no direct relationship between irisin level and over load fluid. The independent determinants of PEW were serum irisin and serum albumin.

Conclusions: Our results provide clinical evidence of the association between irisin, over load fluid and protein energy wasting in PD patients. Low irisin and over load fluid may aggravate protein energy wasting.

Funding: Government Support - Non-U.S.

SA-PO170

Bariatric Surgery Reduces Proteinuria in Severely Obese Patients with Normal Kidney Function by Reducing Systemic Inflammation

Jun-Chang, Hyo-Wook G., Chi-Young Choi. Soon Chun Hyang University College of Medicine, Cheonan Hospital, Cheonan, Republic of Korea.

Background: Obesity are associated with renal disease, including proteinuria, chronic kidney disease (CKD) and progression to end-stage renal disease. Bariatric surgery (BS) reduces proteinuria and improve renal function. The mechanism include improved blood pressure, improved glucose homeostasis, and reduced systemic inflammation associated with weight loss. However, it is unclear whether the mechanism by which BS reduces albuminuria is due to weight loss per se or by improved systemic inflammation induced by weight loss. To elucidate whether weight loss directly reduces albuminuria or variability of systemic inflammation induced by weight loss, a prospective cohort study was performed.

Methods: Patients older than 18 years who received BS in Soonchunhyang University Hospital from 1 January 2011 to 31 December 2011 were included. Other including criteria were followed: body mass index (BMI) ≥30, serum creatinine level ≥1.0, and without over proteinuria (dip stick a trace). The patients were followed at 1, 6 months after BS.

Results: Forty-three patients were included. Three patients were men, 10 patients had diabetes, 12 patients had hypertension. EFR estimated by CKD-EPI equation were 115.7 ± 16.5. There were significant reduction in body weight (98.9 ± 17.6 to 78.1 ± 14.8 kg), BMI (36.9 [34.0 – 42.8] to 29.5 [26.6 – 32.2] kg/m²), high-sensitivity C-reactive protein (hs-CRP) (0.39 [0.24 – 0.69] to 0.09 [0.05 – 0.23] mg/l), and urine albumin-to-creatinine ratio (17.95 [6.81 – 72.89] to 8.11 [4.67 – 15.92] mg/g). There were positive correlations between delta hs-CRP and delta body weight (r = 0.349, p = 0.043) or delta BMI (r = 0.362, p = 0.035); between hs-CRP and body weight (r = 0.374, p = 0.001) or BMI (r = 0.431, p < 0.001). In a multivariate analysis using linear mixed model demonstrated that hs-CRP (β = -0.5451, p = 0.022) is independent risk factors to affect ACR.

Conclusions: Our results suggests that weight loss by BS directly improve systemic inflammation, which subsequently leads to reduce albuminuria.

SA-PO171

The Additional Benefit of Weighted Subjective Global Assessment (SGA) for the Predictability of Mortality in Incident Peritoneal Dialysis Patients

TaeYoung Yun, Dong-Ryool Ryu. Ewha Womans University, Seoul, Republic of Korea.

Background: Although Subjective Global Assessment (SGA) is a widely-used tool for the nutritional investigation, it has limitation to assess nutritional status for the dependence on inspectors’ subjective opinion. Moreover, there is no study for the usefulness of SGA and modified SGA in incident peritoneal dialysis (PD) patients.

Methods: A total of 365 incident PD patients between May 2009 and December 2015 at the 36 centers of the Clinical Research Center for end-stage renal disease in Korea were initially recruited, and we measured SGA and calculated weighted SGA using serum albumin and total iron binding capacity (TIBC) levels based on the normal values. Cox proportional regression analyses were performed and receiver operating curve was also conducted.

Results: During median 3.2 years of follow-up period, 61 patients (16.7%) were dead. Kaplan-Meier curve showed that the cumulative survival rate in ‘Good nutrition (G1)’ was significantly higher compared to that in ‘Mild to severe malnutrition (G2)’ (P < 0.001). G2 was also significantly associated with increase of all-cause mortality even after adjusting for age, gender, several comorbidities and TIBC (HR: 1.78, P = 0.038) compared with G1. Moreover, 1 unit increase of weighted SGA was still significantly correlated with the development of the mortality after adjustment of the same covariates (HR: 1.65, P = 0.013). However, G2 was significantly associated with increase of all-cause mortality in non-DM, DM, and old-aged group (in non-DM; HR: 2.86, P = 0.049, in DM; HR: 2.04, P = 0.021, and in old-aged; HR: 2.96, P = 0.026, respectively) except for young-aged group after adjusting for several covariates, whereas 1 unit increase of weighted SGA was revealed to be significantly related to increase of the mortality in all the subgroup analyses. Furthermore, the AUC of SGA and weighted SGA for all-cause mortality was 0.616 (P = 0.004) and 0.708 (P < 0.001). In addition, the AUCs of weighted SAGs in all the groups were significantly increased compared with those of SGA alone.

Conclusions: The evaluation of nutritional status based on SGA in incident PD patients may be useful for predicting mortality. However, weighted SGA with objective parameters including serum albumin and TIBC can provide an additionally predictive power for all-cause mortality compared with SGA alone.
SA-PO173
The Effect of Selenium Deficiency on Thyroid Function and Cardiovascular Diseases in Peritoneal Dialysis Patients Jong tae Cho, So Mi Kim, Eun kyoung Lee, Chang hyun Park, Jihyen Jeon. Division of Nephrology, Department of Internal Medicine, Dankook University Hospital, Dankook University; College of Medicine, Cheonan, Chungnam, Republic of Korea.

Background: Trace element, selenium deficiency is known to be associated with impairment of thyroid hormone, and it can cause cardiovascular diseases, such as ischemic heart disease (IHD), heart failure (HF) or cardiomyopathy. In peritoneal dialysis (PD) patients, various causes may contribute to selenium deficiency, including dietary restriction, malabsorption, alteration of metabolism, and removal through dialysis itself. Therefore, we tried to investigate the effect of selenium deficiency on thyroid hormone and cardiovascular diseases in PD patients.

Methods: This cross-sectional study enrolled 86 end-stage renal disease patients who underwent PD. The patients were divided into 2 groups based on serum selenium levels: 62 patients were normal level and 22 patients were selenium deficient. Thyroid hormones, including TSH, free T4 were measured. And presence of cardiovascular diseases, using echocardiography, coronary computed tomography or coronary angiography were evaluated.

Results: There were no significant differences in baseline characteristics, including age, sex, presence of diabetes mellitus, duration of PD and weekly Kt/V between the two groups. Although there was no significant difference, thyroid hormone impairment showed higher tendency in selenium deficient group than that in non-selenium deficient group (25 % vs 10 %, p=0.06). The prevalence of IHD was significantly higher in selenium deficient group than that in the non-selenium deficient group (55 % vs 21 %, p=0.04). But, there was no difference in HF defined as ejection fraction with below 40 %, and cardiomyopathy between the two groups. All patients with thyroid hormone impairment showed high prevalence of IHD and the coincidence of thyroid impairment and IHD was significantly higher than that in selenium deficient group than that in non-selenium deficient group (63 % vs 31 %, p=0.01).

Conclusions: This study showed higher prevalence of thyroid hormone impairment and IHD in PD patients with selenium deficiency. Selenium deficiency may be related to thyroid hormone impairment, leading to cardiovascular diseases.

SA-PO174
A Pilot Study Characterizing Dysgeusia in Hemodialysis Patients with Impaired Thyroid Function By Lindsay K. Moorthi,1 N. Moe,2 Kathleen M. Hill Gallant,3 Cordelia A. Running,4 Indiana University School of Medicine, Indianapolis, IN; 2Purdue University, West Lafayette, IN; 3The Dublin Institute of Technology, West Lafayette, IN.

Background: Dysgeusia is common in dialysis patients and contributes to poor nutritional intake. But, its underlying mechanisms are poorly understood. Studies have shown that taste improves after dialysis sessions, which implicates abnormal serum and biochemistries drawn pre-dialysis. Using a cross-sectional design, we performed suprathreshold taste testing of sodium solutions in dialysis patients compared to healthy adults, and to evaluate relationships between serum levels of potassium, sodium, phosphate, and urea with taste perceptions of these compounds. Our patients compared to healthy adults, and to evaluate relationships between serum levels of potassium, sodium, phosphate, and urea with taste perceptions of these compounds. Our hypotheses were that dialysis patients would have blunted taste compared to controls, and that related serum levels would be inversely related to taste perception of compounds.

Methods: Using a cross-sectional design, we performed suprathreshold taste tests of stimuli (NaCl, KCl, CaCl₂, NaPO₄, FeSO₄, H₃PO₄, MSG, & urea solutions) in hemodialysis patients at a single center(n=16, 10 ± 60 ± 25 y). Participants rated 12 stimuli on a 100mm visual analog scale to determine flavor and liking perception and scores were adjusted for each individual's perception of water, significant differences emerged, controls rated each stimuli for flavor and liking (P=0.002) and dialysis patients appeared to have stronger taste perception of sodium solutions compared with controls. Our results should be considered preliminary due to the limited sample size and lack of age-matched controls. Longer, larger term studies are needed to fully evaluate how dysgeusia is experienced by CKD patients pre- and post-dialysis using whole foods in addition to isolated compounds.

Funding: NIDDK Support, Other NIH Support - Indiana CTSI Project Development Team grant (NIH UL1TR001108)

SA-PO175
Risk Factors for the Decreased Upper Limb Muscle Strength in MHD Patients Qian Zhang1, Jiayi Zhang,2 Minmin Zhang,3 Jing Chen.4 Huashan Hospital, Fudan University, Shanghai, China; 1Fudan University, Shanghai, China; 1Huashan Hospital, Fudan University, Shanghai, China; 1Huashan Hospital affiliated to Fudan University, Shanghai, China.

Background: To assess the risk factors for the decreased biceps muscle strength in young (<65 years) and old (≥65 years) MHD patients.

Methods: This is a cross-sectional analysis with prospective follow-up from MHD patients. All patients underwent assessment of strength of the biceps, body composition, anthropometry, dietary intake, nutritional status and the daily steps. Blood samples were obtained on the midweek dialysis day. Univariate and multivariate regression analysis was used to analyze the predictors of the decreased upper limb muscle strength. Survival analysis was made with the Kaplan-Meier survival curve and the Cox proportional hazard model.

Results: 174 patients were selected, 93 were male and 81 were female patients. The mean age was 63.0±12.29 y, and the dialysis vintage was 9.1±6.66 y. Patients were divided into young MHD group (n=97) and elderly MHD group (n=77). In young MHD group, gender (β = 2.01, P = 0.003), modified SGA score (β = 0.29, P = 0.03), muscle mass (β = 0.09, P = 0.04), IL-6 (β = 0.09, P = 0.002) were associated with the decreased biceps muscle strength. In survival analysis, we found that the biceps muscle strength gradually increased with the gradual increase of 25(OH)D levels. During the follow-up of 52 weeks, 16 patients died, 14 of whom died of cardiovascular and cerebrovascular diseases and 2 died of tumor. Nair-Meier showed that the survival rate was significantly high in the high muscle strength group than that in low muscle strength group (P=0.002). Cox multivariate analysis showed that the association between low muscle strength and higher mortality risk remained strong in fully adjusted models.

Conclusions: In young MHD group, gender, modified SGA score, muscle mass, 25(OH)D and IL-6 were associated with the decrease biceps muscle strength. In the elderly MHD group, age, muscle mass, 25(OH)D and NT-proBNP were associated with the decreased biceps muscle strength. The biceps muscle strength was an independent risk factor for the survival of MHD patients.

SA-PO176
Tissue Content of Advanced Glycation End-Products and Augmentation Index, a Marker of Vascular Stiffness, Are Linked to Cardiovascular Disease and Mortality in CKD Patients Hidevsky Mukai1, Bengt Lindholm,1 Dai Lu,2 Jonaz Ripstad,2 Torkel Brismar,1 Olaf Heimbürger,1 Peter F. Barany,1 Peter Stenvinkel,1 Abdul Rashid T. Qureshi,1 Renal Medicine and Baxter Novum, Karolinska Institutet, Stockholm, Sweden; 2Medical Imaging and Technology, Karolinska Institutet, Stockholm, Sweden.

Background: Accumulation of advanced glycation end-products (AGEs) may contribute to cardiovascular disease (CVD) and increased mortality in chronic kidney disease (CKD) patients. Skin autofluorescence (SAF), a noninvasive measurement of skin AGE accumulation, and augmentation index (AIx) by applanation tonometry, with the combination of vascular damage and arterial stiffness respectively. We investigated associations of SAF, AIx and Framingham’s CVD risk score with mortality in CKD patients.

Methods: SAF (AGE Reader) and AIx (Sphygmocor; adjusted for 75 heart beats per minute) were measured in 261 CKD patients (median age 56 years, 66% male, 20% diabetes; 130 non-dialyzed, 93 on peritoneal dialysis and 38 on hemodialysis). In 201 patients, coronary artery calcium score was assessed by computed tomography. Associations of SAF, AIx, and Framingham’s CVD risk score (FRS) with all-cause mortality were evaluated by multivariate Cox models. During follow-up for median 25 months, there were 46 deaths.

Results: SAF associated with FRS (rho=0.51), hsCRP (rho=0.31), handgrip strength, HGS (rho=-0.30), fat body mass index, FBMI (rho=-0.24), and bone mineral density, BMD (rho=-0.22). AIx associated with HGS (rho=-0.43), FRS (rho=0.41), albumin (rho=-0.26), hsCRP (rho=0.25), BMD (rho=-0.23) and lean body mass index, LBMI (rho=0.20). ROC curve analysis of classifiers of CVD and predictors all-cause mortality showed as expected high values for FRS (AUC=0.75 and 0.77), however closely followed by SAF (AUC=0.75 and 0.75) and AIx (AUC=0.64 and 0.70). The highest titer of AIx with all-cause mortality. HR 2.92 (95% CI 0.98-6.6; p=0.05), after adjusting for FRS.

Conclusions: SAF and AIx were associated with presence of CVD and mortality in ROC curve analysis; however, only AIx - and not SAF associated (p=0.05) with increased mortality risk after adjusting for Framingham’s CVD risk score in CKD patients.

Funding: Commercial Support - Baxter Healthcare Corporation, Government Support - Non-U.S.
### SA-PO177

**Olfaction–Nutrition Association in Patients with Kidney Disease: Odorant Specificity**

**Teodor G. Paunescu,** Dihua Xu, Sahir Kalim, Ravi I. Thadhani, Sagar U. Nigwekar. Massachusetts General Hospital, Boston, MA.

**Background:** Malnutrition is common in patients with chronic kidney disease (CKD) and especially end-stage renal disease (ESRD). Most of these patients have odor identification deficits, and a reduction in odor identification score is associated with higher subjective global assessment (SGA) score and lower total cholesterol, LDL cholesterol, and albumin. We investigated whether the identification of specific odorants is linked to abnormalities in nutritional markers.

**Methods:** We quantified odor identification in CKD (n=36) and ESRD patients (n=100) using the University of Pennsylvania Smell Identification Test (UPSIT). We assessed the correlation between the percentage of correct answers for each of the 40 odorants on the UPSIT test and nutritional markers.

**Results:** Correct identification of multiple odorants significantly correlates with levels of albumin (14 odorants), LDL (15 odorants) and total cholesterol (20 odorants). In analyses restricted to ESRD patients, lower SGA scores correlate with the correct identification of 13 odorants, while higher nPNA and albumin levels correlate with the correct identification of 6 and 5 odorants, respectively. Odorant-based analysis reveals that correct identification of certain odorants correlates more closely with nutritional markers: licorice correlates with albumin, nPNA, SGA, and triglycerides; bananas correlate with albumin, pre-albumin, total and LDL cholesterol, and triglycerides; watermelon correlates with albumin, pre-albumin, SGA, and triglycerides. Some odorants, such as gasoline, lime, and natural gas, show no correlation with any of the nutritional markers we assessed.

**Conclusions:** Patients with kidney disease have odor identification deficits that correlate with nutritional markers. Correct identification of specific odorants by ESRD patients is linked with levels of nutritional markers. These odorants should be followed to assess occurrence of malnutrition.

### SA-PO179

**Diagnostic Discordance between Body Mass Index and Body Fat Percentage for Obesity among Patients with CKD**

4UNESA-UVA, Rio de Janeiro, Brazil; 3Federal University of Rio de Janeiro, Rio de Janeiro, Brazil; 2Fluminense University, Niteroi / Rj, Brazil

**Background:** In contrast to the general population, a higher body mass index (BMI) appears to be associated with a greater survival among patients with CKD, referred to as “obesity paradox.” This may be explained by limitation of BMI as a measure of adiposity in CKD. Both BMI and body fat percentage (BF%) are used to classify obesity but outcomes may vary.

**Methods:** We investigated the two different cutoffs for diagnosing obesity (BMI ≥ 28 kg/m² or BF% >25% for male or >35% for female) and the impact on all-cause mortality in 362 nondialysis-dependent CKD patients with a median follow-up of 4.6 years. Body fat mass was determined using the Bodipy Composition Monitor, a novel multifrequency bioimpedance spectroscopy device.

**Results:** Using BMI, 27.9% of patients were obese. However, 48.8% of patients were obese according to BF%. Although obesity defined by BMI was associated with a significantly lower risk of death, the result tended to be reverse when obesity was defined by BF%. When patients were classified into four distinct groups based on both BMI and BF% cutoffs for obesity, a considerable proportion of patients (29.4%) had excess body fat in the context of a normal BMI. These patients were more likely to have lower lean body mass and had higher mortality as compared to patients with obesity defined by both BMI and BF%.

**Conclusions:** Thus, diagnostic discordance between BMI and BF% may explain the “obesity paradox” because using BMI to detect obesity among those with CKD may miss a large number of patients with excess body fat. Proper diagnosis of obesity in patients with CKD is required for both risk prediction and treatment.

Cox models for relative risk of all-cause mortality calculated for obesity or not defined by BMI or BF%

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unadjusted</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI-defined</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Obese</td>
<td>0.6 (0.09-0.71)</td>
<td>0.017</td>
<td>0.012</td>
</tr>
<tr>
<td>BF&gt;-25%</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Obese</td>
<td>0.6 (0.09-0.79)</td>
<td>0.017</td>
<td>0.012</td>
</tr>
</tbody>
</table>

**Relationship of BF% versus BMI**

### SA-PO180

**The Use of Phase Angle to Evaluate Fluid Status in Dialysis Patients**

**Laura Rosales,**1 Fansan Zhu,1 Priscila Preciado,1 Ohnmar Thwin,1 Xia Tao,1,2 Stephan Thijssen,3 Peter Kotanko,1,2 Renal Research Institute, New York, NY; 1Icahn School of Medicine at Mount Sinai, New York, NY.

**Background:** Phase angle (PA) has been suggested as an indicator for assessing body composition and fluid status in hemodialysis (HD) patients. PA is calculated by the ratio of reactance to resistance. Reactance represents body water content and reactance relates to body cell mass. The primary aim of this study was to evaluate the relationship between peri-dialysis fluid and phase angle changes in different fluid status in HD patients and healthy subjects (HS).

**Methods:** Ten HD patients (8 males, age 58 ± 12 years, height 167 ± 11 cm) and 12 healthy subjects (HS; 7 females, age 33 ± 6 years, height 169 ± 10 cm) were studied with the Seca mBCA 514 bioimpedance device (Seca North America, Chino, CA USA). Resistance (R, Ohm), reactance (Xc, Ohm), impedance (Imp, Ohm), and phase angle (PA, degrees) were measured pre- and post-HD treatment. HS were measured once. R, Xc, Imp, and PA were compared between pre- and post-HD. In addition, we compared the post-HD levels with HS using 1-way ANOVA. Pre- and post-HD weights and body mass index (BMI) were recorded.

**Results:** Peri-dialysis body weight reduction was 2.6 ± 0.4 kg. This weight change was accompanied by the increase in PA and decreased in Xc. Average PA and Xc differed significantly from various hydration groups (pre-, post-HD and HS) by a nonparametric test (F 1 and C). Of note, pre- and post-HD R and Imp did not differ significantly in

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

724
HD patients (Fig. 1 B and D), BMI and PA were not correlated. Coefficient of variation of PA is 12.7% in HS group.

Conclusions: PA reflects peridialytic fluid status changes and thus is useful for evaluating relative changes in a given patient. However, PA may not be used to identify normal fluid status due to its large variability in HS (Fig 1 A). This variability is possibly due to the fact that PA is computed as the ratio of two variables, resistance and reactance, which represent different body components.

Methods: We examined HD patients from three prospective studies, the Anti-Inflammatory and Anti-Oxidative Nutrition in Hypoalbuminemic Dialysis Patients (AIONID), Nutritional and Inflammatory Evaluation in Dialysis (NIED), and Forensl for Enhancing Dietary Protein Intake in Hypoalbuminemic Dialysis Patients (FrEDI). We analyzed the correlations of dietary protein (total, animal, and vegetable) ascertained by three-day dietary record with laboratory measures including normalized protein catabolic rate (nPCR), serum albumin, and serum bicarbonate (CO2) stratified by race/ethnicity.

Results: The cohort was comprised of 336 HD patients, among whom 46% and 37% of patients were Hispanic White and African-American, respectively, 48% of patients were female and the mean±SD age was 55±14 years. In the overall cohort, nPCR strongly correlated with total protein (r=0.25, p<0.001) and animal protein (r=0.25, p<0.001), as well as within strata of African American, Caucasian, and Hispanic patients. However, there was no correlation between nPCR and vegetable protein (r=0.07, p=0.22) in any of the racial/ethnic groups. Serum albumin and CO2 showed weaker correlations with total protein, animal protein, and vegetable protein across all patients.

Conclusions: These findings suggest that nPCR has a stronger correlation with total and animal protein intake than with serum albumin and CO2 across all racial/ethnic groups. Further studies are needed to determine whether nPCR may be a more accurate tool for monitoring dietary protein among HD patients in the clinical setting.

Funding: NIDDK Support

SA-PO181

Is Zinc-alpha2-Glycoprotein (ZAG) a Predictor of Mortality in Patients on Hemodialysis? Anaïs Bouchara,2 Dan Yi,3 Myriam Pastural,3 Maurice Lavillette,2 Solenne Pelletter,2 Denis Fouque,1 Christophe O. Soulage,1 Laetitia Koppe,1 Centre hospitalier Lyon Sud, Pierre-Bénite, France; 2Hôpital Lyon Sud, LYON, France; 3AURAL, LYON, France; 4CarMeN, INSERM u1660, INSAX LYON, VILLEURBANNE, France; 5INSA-Lyon, VILLEURBANE, France.

Background: Zinc alpha 2 glycoprotein (ZAG) is a new adipokine involved in cachexia due to its potent lipolytic effects. It has been shown that plasma ZAG concentration was increased in chronic kidney disease (CKD) and patients on hemodialysis treatment (HD). However, the impact of ZAG accumulation on mortality and cardio-vascular risks has never been studied.

Methods: Plasma ZAG concentration was measured by enzyme immuno-assays (ELISA ZAG, Raybiotech, USA) in 253 patients on HD for at least 3 months, without progressive cancer. Mortality and cardio-vascular events have been registered during 4 years.

Results: During the follow-up period (31.3 ± 17.1 months), a total of 49 patients died (among which 16 from cardio-vascular events). Plasma ZAG concentration was inversely correlated with serum albumin (r=0.008), creatinine (r=0.007) and triglycerides (p=0.04). By contrast, it was positively correlated with age (p=0.002). Plasma ZAG concentration was independent of serum CRP, parathyroid hormone, LDL cholesterol and glycated hemoglobin. Kaplan-Meier analysis showed a significant correlation between plasma ZAG concentration and overall mortality (log rank, p<0.05) and cardio-vascular events (log rank, p<0.01). After Cox multivariate analysis, the association between plasma ZAG concentration and mortality or cardio-vascular events persisted after adjustment for demographic factors (age, sex, dialysis vintage), metabolic parameters (serum albumin, prealbumin, triglycerides, nPCR, BMI) and cardio-vascular risks (diabetes, dyslipidemia, hypertension, tobacco). Plasma ZAG concentration was however not associated with protein energy wasting.

Conclusions: Plasma ZAG accumulation does not correlate with protein energy wasting by contrast with patients having a cancer. ZAG does not seem to be involved in metabolic disturbances (type 2 diabetes, dyslipidemia) as observed in obese patient. ZAG accumulation seems to be associated with an excess overall mortality and cardio-vascular mortality risk in HD patients. Complementary studies will be necessary to define the role of ZAG and the pathophysiological mechanisms in cardio-vascular events in patients with CKD.

Fig. 1

SA-PO183

Does Thyroid Hormone (TH) Substitution Alter Hormonal Metabolism in Patients with Hypothyroidism and Renal Failure (RF)? Longin Niemczyk,3 Ivanna Dubchak,3 Malgorzata Gomolka,3 Katarzyna Szamotułska,3 Stanislaw Niemczyk,1 1Medical University of Warsaw, Warszawa, Poland; 2National Research Institute of Mother and Child, Warsaw, Poland; 3Military Institute of Medicine, Warsaw, Poland.

Background: RF disrupts the metabolism of TH, and disorders are exacerbated by concomitant hypothyroidism. TH replacement therapy should equalize hormone levels but lack comprehensive research in this area. In patients with ESRD there is a tendency for higher TSH and lower triiodothyronine (T3) and thyroxine (T4) levels probably due to reduced TH conversion (T4 to T3). The aim of the study was to evaluate the effect of TH substitution on conversion factors and rT3 concentration in patients with coexisting RF and hypothyroidism.

Methods: The study involved 2 groups of patients with hypothyroidism and TH replacement therapy: Group A - 13 pts. without RF (12 F, 1 M) 49,4±10,67y.o., Group B - 26 pts. with ESRD treated with HD (16 F, 10 M) 58,8±15,52y.o. Pts. with ESRD, treated with HD, were studied during planned dialysis. CRP, creatinine, urea, PTH, TSH and TH: total - (T4), TT3, free fractions - (rT4), (TT3), and rT3 were measured and conversion factors (rT3/TT4, rT3/TT3) were calculated. Basic descriptive statistics, Pearson's linear correlation, the Mann-Whitney nonparametric test and Fisher's test were used. Adopted significance level was 0.05.

Results: Results were shown in table.

Conclusions: There is a tendency for a higher rT3 levels during thyroid hormone substitution in hypothyroid patients without renal failure. The inhibitory effect of renal failure on rT3 production in hypothyroid patients is still present during thyroid hormones substitution.

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

Underline represents presenting author.
SA-PO184
Association between Decrease in Skeletal Muscle Mass Index and Renal Atrophy in Patients with Non-Dialysis CKD

Background: The frequency of sarcopenia increases as chronic kidney disease (CKD) progresses. CKD patients should be screened for sarcopenia and presarcopenia in order to detect them during an earlier stage of CKD and improve prognosis. Kidney size is assessed for aging, and decreased renal function is often correlated with sarcopenia. We investigated the association of kidney size with muscle mass and muscle mass change in CKD patients.

Methods: We performed a single-center retrospective cohort study of 180 non-dialysis dependent CKD patients (age 66.4±12.5 years; male 66.1%; eGFR 31.4±12.5 ml/min/1.73m²; etiology glomerulonephritis 22.2%, diabetic nephropathy 23.9%). We measured kidney size by ultrasonography and calculated total kidney volume (TKV) using an ellipsoid equation. Skeletal muscle mass index (SMI) were estimated using biostatistic impedance analysis, and presarcopenia was defined as SMI ≤7.0 kg/m² for men and ≤5.7 kg/m² for women. The rate of change in SMI over a 6-month period was evaluated.

Results: The mean rate of change in SMI in six months was -1.57±1.1%. Multivariate logistic regression analysis showed that TKV was associated with presarcopenia (OR: 0.98, 95% confidential interval: 0.97-1.00, p=0.004). Multivariate regression analysis showed that SMI (β: -3.95, SE: 0.92, p=0.001) and TKV (β: 0.037, SE: 0.015, p=0.016) were associated with the rate of change of SMI in six months adjusted for age, sex, BMI, diabetes mellitus, history of cardiovascular disease, serum albumin, and proteinuria.

Conclusions: Among patients with CKD, sarcopenia is significantly associated with TKV, and patients with a small TKV are more prone to developing a decrease in skeletal muscle mass.

SA-PO185
8-Hydroxy-2-Deoxyguanosine (8-OHdG), a Marker of Oxidative DNA Damage, Is Associated with Mortality Independent of Inflammation in CKD Patients

Background: Oxidative stress and inflammation are two common interlinked features of CKD that associate with poor outcomes. We tested the hypothesis that inflammation modifies the mortality predictive capacity of serum 8-OHdG in CKD patients.

Methods: In 376 clinically stable CKD stage 1-5 patients (63% male; median age 57 years) including 53 CKD stage 1-2, 60 CKD stage 3-4 and 263 CKD stage 5 non-dialysis patients, 8-OHdG levels were measured at imaging sessions of CKD patients with elevated 8-OHdG.

Results: The crude mortality rate was markedly increased in patients with high 8-OHdG especially when combined with high hsCRP and IL-6 (Figure 1). In multivariable analysis, adjusting for age, sex, comorbidity, calendar year and eGFR, high 8-OHdG was associated with increased relative risk ratio of death, 1.15 (1.07-1.25) and 1.17 (1.08-1.26) respectively, when adjusted also for hsCRP, IL-6 and TNF-α, respectively (Table 1).

Conclusions: All-cause mortality risk was increased - independent of inflammation - in CKD patients with elevated 8-OHdG.

SA-PO186
Low Dose Aspirin Increases 15-Epi-Lipoxin A4 Levels in CKD Patients

Background: Resolution of inflammation is regulated by endogenous lipid mediators, such as lipoxins and their epimers, including 15-epi-lipoxin A4 (15-epi-LXA4). However, there is no information on 15-epi-LXA4 and its in vivo regulation in chronic kidney disease (CKD) patients.

Methods: Study Design: Open label randomized clinical trial. Setting & Participants: 50 participants with chronic kidney disease (CKD) stage 3 and 4 without prior cardiovascular disease (25 in the aspirin group and 25 in the standard group) followed up for 46 months. Intervention: Aspirin (100 mg/day) or standard treatment. Aim: To analyze the effect of aspirin on plasma 15-epi-LXA4 levels and inflammatory markers in CKD patients.

Results: Baseline plasma 15-epi-LXA4 levels were lower in diabetic (1.22±0.99 ng/ml) than in non-diabetic CKD patients (2.05±1.06 ng/ml, p=0.001) and inversely correlated with glycosylated hemoglobin levels (r=-0.303, p=0.006). In multivariate analysis, diabetes was associated with lower 15-epi-LXA4 levels, adjusted for age, inflammatory markers and renal function (p<0.005). In the whole study population, 15-epi-LXA4 levels tended to increase after twelve months on aspirin (from mean±SD 1.84±1.06 to 2.04±1.75 ng/ml) and decreased in the standard care group (1.60±1.15 to 1.52±0.68 ng/ml, p=0.04). The aspirin effect on 15-epi-LXA4 levels was more striking in diabetic patients, increasing from 0.94±0.70 to 1.93±0.74 ng/ml, p=0.017.

Conclusions: Diabetic patients with CKD have lower circulating 15-epi-LXA4 levels than non-diabetic CKD patients. Low dose aspirin for 12 months increased 15-epi-LXA4 levels, especially in diabetic patients. Given its anti-inflammatory properties, this increase in 15-epi-LXA4 levels may contribute to the beneficial effects of low dose aspirin.

Other NIH Support - Grant support: AASER was supported by Sociedad Española de Nefrología (SEN) and SOMANE, additional support: Grant support: ISCIII and FEDER funds CP14/00133, P11H05298, P116/02057, DiabetesConnect PIE13/00031, FRAT, ISCIII-RETIC RedNREN RD06/009, Salary support: ISCIII Miguel Servet to MSDN, Programa Intensificacion Actividad Investigadora (ISIC III Agencia Lain-Entralgo/CM) to AO.
SA-PO188
Nocturnal Intermittent Hypoxia Is Associated with Elevated Circulating Fibroblast Growth Factor 21 in ESRD
Takuya Murakami,1 Takahiro Masuda,1 Marina Kohara,1,3 Kazuhiro Shizuki,1 Tetsu Akimoto,1 Suniko Honma,1 Yuko Watanabe,1 Osamu Saito,1 Eiji Kusano,1 Yasushi Asano,1 Makoto Kuro-o,1 Daisuke Nagata.1 Division of Nephrology, Department of Internal Medicine, Jichi Medical University, Shimotuke, Japan; 2Division of Anti-aging Medicine, Center for Molecular Medicine, Jichi Medical University, Shimotuke, Japan; 3Department of Nephrology, Japanese Red Cross Koga Hospital, Koga, Japan; 4JCHO Utsunomiya Hospital, Shimotuke, Japan.

Background: Fibroblast growth factor (FGF) 21 is an endocrine factor mainly produced in the liver in response to various stress including inflammation and oxidative stress. We recently reported that higher circulating FGF21 predicts all-cause mortality in end-stage renal disease (ESRD) (Kohara M et al. PLoS One 2017), but the regulator factor to increase circulating FGF21 remains unclear. We therefore examined the association between circulating FGF21 and sleep-disordered breathing (SDB), characterized by nocturnal intermittent hypoxia and a mediator for chronic inflammation in ESRD.

Methods: Thirty-three ESRD patients receiving maintenance hemodialysis (age 64.2 ± 13.0 years, male 50.8%) were enrolled in this study. Overnight pulse oximetry was performed on a dialysis day, and numbers of over 3% desaturation per hour were defined as the 3% oxygen desaturation index (3%ODI). Patients were categorized into low- and high-FGF21 groups by the median value. Multivariable logistic regression analysis was used to examine the association between serum FGF21 levels and 3%ODI.

Results: The median value of serum FGF21 was 2021 pg/mL. The 3%ODI (6.8 ± 3.9 % vs. 3.8 ± 1.0 times/hour, P=0.023) and the percentage of male (63.6 % vs. 36.7 %, P=0.031) were significantly higher in the high-FGF21 group than in the low-FGF21 group. On the other hand, the mean oxygen saturation at night did not differ between the two groups (96.2 ± 1.6 % vs. 96.4 ± 1.6 %, P=0.34). The 3%ODI was an independent risk factor for higher serum FGF21 levels (odds ratio 1.16: 95% confidence interval: 1.01-1.36, P=0.028) even after adjustment for age, gender, duration of dialysis and presence of diabetes.

Conclusions: Nocturnal intermittent hypoxia, but not mean oxygen saturation, is associated with elevated circulating FGF21 in ESRD. This result suggests that SDB is a novel therapeutic target for regulating circulating FGF21 levels.

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

SA-PO190
HDL Subclasses Alter with CKD Progression and Are Associated with ABI and Klotho Level in CKD-Stage-Specific Manner
Eiichiro Kanda,1 Yoshitaka Maeda,2 Tokyo Kyosai Hospital, Meguro, Japan; 3JA Toride Medical Center, Toride, Japan.

Background: Atherosclerosis is a complication of chronic kidney disease (CKD). Lipoprotein subclasses consist of a continuous spectrum of particles of different sizes and densities, and high-density lipoproteins (HDLs) are grouped into various subclasses (Table 1). We investigated the roles of lipoprotein subclasses in atherosclerosis and CKD-mineral and bone disorder.

Methods: Seventy one CKD patients (male, 70.4%; diabetic nephropathy, 23.9%) were included in this prospective cohort study in Japan. The proportion of cholesterol level to total cholesterol level and the lipoprotein particle number in 20 lipoprotein fractions were measured by a newly developed method of high-performance gel permeation chromatography (HPGC).

Results: The average age (SD) was 75.0 (±11.1) years and the estimated glomerular filtration rate (eGFR) was 17.2 (±8.3) ml/min/1.73m². Although no statistically significant difference in cholesterol levels in lipoproteins or triglyceride levels between CKD stages 4 and 5 was shown by HPGC, the method showed that the lipoprotein particle number in small HDLs was higher in Stage 4 than in Stage 5 (P=0.002). Multivariate regression analysis adjusted for baseline characteristics showed that the cholesterol proportion in very small HDLs [F19 =0.00026, p=0.012; F20 =0.0041, p=0.036] in Stage 5.

Conclusions: This study showed that HDL subclasses alter with CKD progression and are associated with ABI and Klotho level in a CKD-stage-specific manner.

SA-PO191
Diagnostic Biomarkers of Endoplasmic Reticulum Stress in Glomerular Disease
Nihad T. Abouelazm,1,2,3,4 Joao Papillon,1 Julie Guillermette,1 Andrey V. Cybulsky,1,5 Medicine, McGill University, Montreal, QC, Canada; 2Medicine, McGill University, Montreal, QC, Canada; 3Medicine, McGill University, Montreal, QC, Canada; 4Medicine, McGill University, Montreal, QC, Canada.

Background: Endoplasmic reticulum (ER) stress has been implicated in the pathogenesis of various glomerular and tubular diseases. ER chaperones lacking the KDEL motif, e.g. ERdj3 and mesencephalic astrocyte-derived neurotrophic factor (MANF), can be secreted extracellularly. We propose that induction of ER stress in CKD may lead to accumulation of secreted ER chaperones in the urine. Such chaperones may potentially serve as biomarkers for diagnosis and therapy.

Methods: ER stress was induced in cultured glomerular epithelial cells (GECs) and in vivo with tunicamycin (TM). In addition, complement-mediated ER stress in podocytes was studied in primary Heymann nephritis (PHN), a rat model of human membranous nephropathy. Intracellular expression and secretion of ER chaperones was monitored by immunoblotting. The protective effect of the chemical chaperone, 4-phenyl butyric acid (4-PBA), on complement-mediated podocyte injury was examined by adding 4-PBA to the drinking water of rats with PHN.

Results: In cultured GECs, TM upregulated ER chaperones, ERdj3 and MANF, intracellularly and in culture medium, whereas GRP94 (KDEL chaperone) increased only intracellularly. ERdj3 and MANF extracellular secretion was blocked by the secretory trafficking inhibitor, brefeldin A. ERdj3 and MANF immunoreactivity was stimulated in urines and glomerular lysates of TM-injected rats after 24 h and was independent of proteinuria. Compared to control, ERdj3 and MANF were increased significantly in the urine of PHN rats on days 7-14 after injection of nephritogenic antibody, and coincided with the onset of proteinuria on day 7. Moreover, in PHN, there were concomitant

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

727
increases in glomerular ER chaperones, GRP94, ERP57, and MANF, compared to controls. We monitored both PHN rats treated with saline and those treated with 4-PBA. 4-PBA reduced proteinuria (on days 7-14), as well as ER dysfunction. 4-PBA protected against complement-mediated podocyte injury and the therapeutic effect was maintained on day 7, until day 14. In both protocols, 4-PBA reduced proteinuria on days 7-14, as well as urinary ER chaperone secretion, compared to PHN rats treated with saline.

**Conclusions:** ERα3 and MANF secreted into the urine reflect glomerular ER stress. 4-PBA protected against complement-mediated podocyte injury and the therapeutic response could be monitored by ERα3 and MANF secretion. Urinary ER chaperones may potentially serve as diagnostic biomarkers for identifying patients with glomerular ER dysfunction.

Funding: Government Support - Non-U.S.

----------

SA-PO192

**Whole Glomerular Transcriptome Analysis from CKD Biopsies Predicts Cell Lineage-Specific Transcripts**

*Glomerular: Cell Biology*

**Youngsook Lee,1 Lisa Feldman,2 Anna Reznichenko,3 Rajasree Menon,4 John R. Haltmam,5 Edgar A. Otto,6 Michael T. Mikel5,7 Wenjun Ju,8 Felix H. Eichinger,9 Brad A. Godfrey,10 Yu Chen,11 James Conway,12 Maya Lindenmeyer,13 Clemens D. Cohen,14 Shawn S. Badal,15 Johnna D. Wessel,16 Uptal D. Patel,17 Matthew D. Beyer,18 Kevin L. Dufﬁn,19 Maria chiara Magnone,20 Carol P. Moreno Quinn,21 Matthias Kretzler,22 *1University of Michigan, Ann Arbor, MI; 2Eli Lilly and Company; 3Indianapolis, IN; 4AstraZeneca, Mödling, Sweden; 5MedImmune, Gaithersburg, MD; 6Ludwig-Maximilians-Universität München, München, Germany; 7Gilead Sciences, Inc., Foster City, CA; 8Novo Nordisk Research Center, Seattle, WA.*

**Background:** Single cell transcriptome analysis yields a wealth of information on cell type-specific transcripts but is not feasible on a large scale, while tissue-level transcriptomic analysis yields a wealth of information on gene regulation but lacks cell type speciﬁcity. Coupling whole tissue transcriptome analysis with single cell transcriptome analysis can yield insights into cell type markers and expression proﬁles. We identiﬁed highly expressed transcript modules of microdissected glomeruli from clinically indicated renal biopsies were generated from 170 CKD patients in the European Renal cDNA Bank cohort. Gene expression modules were generated using weighted gene co-expression network analysis. Cell lineage signatures curated from published literature were used to compare with modules.

**Results:** Across the glomerular transcriptome, 22 co-expression modules were identiﬁed ranging in size from 76 to 2012 genes. Limiting the analysis to the most variant transcripts yielded 16 co-expression modules ranging in size from 99 to 1046 genes. Randomized analysis indicated that modules were stable. From the most variant transcript analysis, eigengenes were compared to cell type speciﬁc signatures and two modules (696 genes) were strongly correlated (r>0.75, p<10E-30) with a podocyte signature generated from published work.

**Conclusions:** This approach allows for the identiﬁcation of cell-lineage speciﬁc transcripts in whole tissue transcriptome datasets and offers the opportunity to identify novel cell lineage transcripts.


SA-PO193

**Transcriptional Reprogramming by Wilms’ Tumor 1 and Foxc2 Mediates a Repair Response during Podocyte Injury**

*Sandeep S. Ettou,1 Youngsook L. Jung,1 Martin Kann,3 Peter Park,3 Jordan A. Kreidberg,1 *1Boston Children’s Hospital- Harvard Medical School, Boston, MA; 2Center for Biomedical Informatics, Harvard Medical School, Boston, MA; 3Nephrologie Cologne, Kidney Research Center Cologne, Cologne, Germany.

**Background:** Foot process effacement and proteinuria, representing a breakdown of the glomerular filtration barrier (GFB), may be caused by decreased expression of key podocyte proteins. We performed a RNA-Seq study of WT1-treated podocytes which identiﬁed components of the GFB and many other important podocyte genes as WT1 target genes. Many WT1 target genes in podocytes also appear to be bound by FoxC2, indicating FoxC2 as a key regulator of podocyte gene expression.

**Methods:** We used ChIP-Seq to study the DNA binding of WT1 and Foxc2 to target genes in normal podocytes. We previously reported a Wilms’ tumor-1 (WT1) ChIP-Seq study that identiﬁed WT1 target genes in podocytes. We used Adriamycin-induced podocyte injury as a model for crescentic GN.

**Results:** Our ChIP-Seq results demonstrate that WT1 and Foxc2 have multiple binding sites at target genes including Nphs2 and Synpo. We previously observed that after the onset of heavy proteinuria, Nphs2 and Synpo expression decreases, as does WT1 and Foxc2 binding to their respective target sites. However, in examining mice prior to, or during the early phase of proteinuria, WT1 and Foxc2 binding to target genes actually undergoes a transient increase at specific enhancer and promoter sites, and Nphs2 and Synpo expression dramatically increases. Using immortalized podocytes, we also demonstrated that WT1 and Foxc2 binding to target genes is interdependent and that knockdown of WT1 or Adriamycin treatment results in epigenetic silencing of the Nphs2 and Synpo genes.

**Conclusions:** Thus, our results reveal a previously unrecognized repair attempt in podocytes immediately after Adriamycin injury mediated by WT1 and Foxc2 to transcriptionally activate target genes required to maintain the GFB. In the Adriamycin model, this initial attempt is immediately unsuccessful, but transcriptional reprogramming may represent a therapeutic modality to maintain the GFB after podocyte injury.

Funding: NIDDK Support

SA-PO194

**Acute Kidney Slices as a Tool to Dissect Calcium Signals in Podocytes**

*Julia Binz,1 Hadiolah Khallili,2 Bernhard Schermer,1 Thomas Benzing,2 Matthias Hackl,1 *1University Hospital Cologne, Cologne, Germany; 2University Hospital of Cologne, Köln, Germany; 3University of Cologne, Köln, Germany.

**Background:** Calcium signaling in the kidney has been a focus of research for many years, as calcium handling in podocytes has been of great interest since it is implicated to play a role in podocyte injury. As isolated podocytes in cell culture are lacking their physiologic microenvironment and isolated glomeruli are prepared with several treatment steps, acute kidney slices (AKS) represent an ex vivo model where the structural complexity of the glomerulus is preserved and which can be prepared within minutes after sacrificing the animal.

**Methods:** Prior to the preparation of AKS 8-week old c57Bl6 mice expressing GCaMP3 under the PodCrie promoter were treated with Adriamycin (25mg/kg) for 5 days. Untreated mice were used as control group. For AKS preparation mice were sacriﬁced, the kidneys were removed and cut into 500 µm thick slices. During imaging an NMDA agonist was used at 90mM and AKS were treated with an angiotensin-II containing solution to induce calcium signaling in podocytes. As control experiments we used laser-induced calcium signaling and propidium iodide to show that podocytes remain viable and able to produce calcium signals.

**Results:** The podocytes with genetically encoded calcium indicator are viable and able to produce a calcium wave after laser injury as published in vivo. High doses of angiotensin-II elicit calcium signals in podocytes of untreated animals. Furthermore, there is an increase in calcium response after induction of Adriamycin nephropathy.

**Conclusions:** Acute slices of the kidney are a great tool to study podocytes, retaining the complex microarchitecture of the glomerulus, and provide results comparable to in vivo imaging. They allow testing of different dosages and compounds on individual kidney slices as the two kidneys provide enough material for at least 5 slices each. The technical setup needed for preparation is limited and the technique can be quickly taught. A confocal imaging setup is sufficient to image AKS. Therefore, AKS have the potential to become a widely used tool in glomerular research.


SA-PO195

**Podocyte De-Differentiation Repatterns Energy Metabolism and Promotes Cellular Crescent Formation**

*Jiao Miao,1 Qi Sun,1 Junwei Yang,2 *1Center for Kidney Disease, Second Affiliated Hospital of Nanjing Medical University, Nanjing, China; 2Second Affiliated Hospital, Nanjing Medical University, Nanjing, China.

**Background:** The role of podocytes in human crescentic glomerulonephritis (GN) has been underestimated. This may be due to the confounding fact that “dysregulated” proliferation is able to generate, at least in vitro, markers, and undergo de-differentiation. Specific deletion of Tsc1 in podocytes led to spontaneous cellular and ﬁbroblastic crescents at 12 wk of age. These cellular crescents were immunostaining positive for WT-1 and Ki-67, suggesting that podocytes proceed profound phenotype changing in this model. This study is to investigate the mechanism that governs podocyte de-differentiation. Here we demonstrated that a switch of metabolism from oxidative phosphorylation to aerobic glycolysis was the primary feature during podocyte de-differentiation and also might be the initial step to promote proliferating.

**Methods:** Renal biopsies from patients with anti-GBM disease, lupus GN and IgA nephropathy were studied by immunofluorescence for WT-1 for podocyte identiﬁcation and Ki-67 for cell cycle assessment. The de-differentiated podocyte undergoing proliferation was assessed by ﬂow cytometry and ﬂuorescent. Western blot and quantitative real-time PCR were performed to examine the expression level of glycolysis related enzymes. Meanwhile, podocyte-specific Tsc1 knockout mice were generated as a model for crescentic GN.

**Results:** Both gene and protein assay showed that the expression of glycolysis enzymes were upregulated in Tsc1 KO mouse kidneys or in TGFβ1-treated podocytes. Aerobic glycolysis is a metabolic process that generates ATP via glucose metabolism without oxygen, and it is implicated to play a role in podocyte injury. As isolated podocytes in cell culture are lacking their physiologic microenvironment and isolated glomeruli are prepared with several treatment steps, acute kidney slices (AKS) represent an ex vivo model where the structural complexity of the glomerulus is preserved and which can be prepared within minutes after sacrificing the animal.

**Conclusions:** This approach allows for the identiﬁcation of cell-lineage speciﬁc transcripts in whole tissue transcriptome datasets and offers the opportunity to identify novel cell lineage transcripts.

Funding: Government Support - Non-U.S.
**SA-PO196**

**Role of Exocyst Complex in Podocytes**

Ashish K. Solanki,1 Deepak Nihalani,3 Ehtesham Arif,7 Pankaj Srivastava,1 Joshua H. Lipschutz,7 Xiaofeng Zuo,1 Yanhui Lo,4 Wei Xu,5 Medical University of South Carolina, Charleston, SC; 3University of South Carolina, Columbia, SC; 4MUSC, Charleston, SC; 5Medical University of South Carolina, Charleston, SC.

**Background:** Exocytosis is mediated through the exocyst complex, which is critical for protein transport and its disruption causes defects in various cellular processes including cell polarity, migration, cilogenesis and autophagy. Since various glomerular injuries disrupt these processes, we hypothesized that disruption of exocytosis in podocytes will lead to a disease phenotype. In this study, we generated podocyte-specific Exoc5 (a central component of the octameric exocyst complex) knockout mice that showed massive proteinuria and died within 4 weeks of birth.

**Methods:** Exoc5 was genetically deleted in podocytes by crossing Exoc5fl/fl with pod-CreTg/+ mice. Mice were analyzed using biochemical, histological, morphological and immunofluorescence approaches. Exoc5 knocked down stable cultured podocyte cells were created using Exoc5-specific shRNA and stained with acetylated tubulin and cilary phenotype was evaluated by superresolution microscopy.

**Results:** The Exoc5fl/fl;PodCreTg/+ mice were proteinuric and died between 21-27 days after birth. Kidney section analysis showed severe glomerular defects with increased fibrosis and proteinaceous casts. Ultrastructural analysis showed effaced podocytes with loss of slit diaphragm. Immunofluorescence analysis showed significant mislocalization of junctional proteins Neph1 and ZO-1, and decreased Nephrin protein expression. To elucidate the specific role of Beclin 1 in podocytes, we generated Beclin 1-deficient podocytes resulting in severe endothelial damage.

**Conclusions:** We identified a key regulatory protein of the secretory pathway by unravelling a novel function of Beclin 1 in podocytes. Promoting the delivery of secreted factors such as VEGF Beclin 1 is required for glomerular maintenance and might represent a novel pathway being affected in glomerular diseases.

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

---

**SA-PO198**

**Deiodinase 3 Downregulation: A Thyroid Hormone Associated Renoprotective Mechanism**

Nicholas J. Tardi,7 Chuang Chen,7 Ranadheer Dande,7 Jochen Reiser,7 Rush University, Chicago, IL; Rush University Medical Center, Chicago, IL.

**Background:** Deiodinase 3 (D3) is a membrane-bound, catalytic enzyme that regulates cellular metabolism by deactivating tri-iodothyronine (T3), the metabolically active thyroid hormone. As evident by the embryonic lethality of D3 knockout animals, proper regulation of thyroid hormone activity is vital in nearly all cell types. In the kidney, hyperthyroidism increases renal filtration pressure and absorption capacity, while hyperthyroidism thickens the glomerular basement membrane and reduces filtration rate. Despite the prevalence of overlapping complications of thyroid hormone disorders and kidney disease, a unifying mechanism regulating T3 homeostasis in the kidney is absent. Though well studied in endocrine tissues, the role of D3 in local regulation of thyroid hormone in renal tissues has been largely unaddressed. To fill this void, we initially assessed for deiodinase expression in podocytes, as they have a significant role in energy metabolism; having mechanisms that respond to both gluceral enlucated and circulating changes in hormone levels. After discovering D3 was highly expressed in podocytes and downregulated in injury models, we aimed to determine the significance of D3 dysfunction in glomerular kidney disease.

**Methods:** The T3 regulatory capacity of D3 was analyzed via cleavage assay using a radioisotope labeled substrate in cultured podocytes treated with propylthiouracil (PTU). The role of D3 in proteinuric kidney disease was evaluated using podocyte specific D3 KO mice. Glomerular D3 expression was measured in renal biopsies from kidney disease patients by immunofluorescence.

**Results:** D3 expression and activity was downregulated in response to PAN induced podocyte injury in vitro. D3 expression was prominently diminished at the cell membrane, yet remained concentrated in the golgi and perinuclear region where metabolically active T3 resides. Podocyte specific D3 KO mice responded poorly to PTU-induced acute kidney injury, resulting in heavy proteinuria compared to control. D3 expression in glomeruli of kidney disease patients suffering from minimal change disease, diabetic nephropathy, or focal segmental glomerulosclerosis showed unique profiles amongst diseases.

**Conclusions:** Our data shows D3 downregulation in podocytes as a response to injury, and suggests D3 may have a renoprotective role in thyroid hormone associated kidney disease.

**Funding:** NIDDK Support

---

**SA-PO199**

**DDR1 Inhibition Preserves Renal Function in a Mouse Model of Alport Syndrome**

Judith T. Molina David,1 Jin Ju Kim,1 Javier T. Varona Santos,2 Anja Harmet,3 Hans Richter,3 Rodolfo Gasser,3 Christian Faul,5 Marco Prunotto,1 Alessia Forenzi,1 Katz Family Division of Nephrology and Hypertension, University of Miami Miller School of Medicine, Miami, FL; Katz Family Drug Discovery Center, University of Miami Miller School of Medicine, Miami, FL; Hofmann-La Roche, AG, Basel, Switzerland.

**Background:** Alport Syndrome (AS) is a hereditary disease condition caused by mutations in the type IV collagen genes, leading to progressive renal fibrosis, hearing loss and ocular changes. Discoid domain receptor 1 (DDR1) is a receptor tyrosine kinase that is activated by collagen and that promotes fibrosis, whereas genetic deletion of DDR1 in mice protects from renal failure in AS. Our study was aimed at identifying a selective DDR1 inhibitor to prevent kidney disease in Col4a3 knockout (KO) mice.

**Methods:** Approximately 56,000 compounds were screened in vitro binding assay and a fraction of those (circa 1000) were further evaluated in a cell based assay aimed at evaluating DDR1 phosphorylation in disease relevant cell types. Fifteen compounds were finally selected based on their selectivity, potency and pharmacokinetic and pharmacodynamics profile for further in vivo testing and a unique lead compound (cpd) was identified for further in depth in vivo analysis. Four-week-old Col4a3 KO and wildtype (WT) mice were injected intraperitoneally with cpd (80 mg/kg) or vehicle on a daily basis. Experimental groups included: WT+vehicle (n=10), WT+cpd (n=11), KO+vehicle (n=11), and KO+cpd (n=14). At 8-weeks of age, mice were sacrificed and kidney tissue, blood and urine were collected for further analysis. Histological analysis was performed by H&E, PAS, Picrosirius Red and immunofluorescence staining (IF). Serum and urine samples were used to determine BUN, albumin, creatinine. Total and pDDR1 levels were measured in kidney cortex by immunoprecipitation.

**Results:** Fibrosis was assessed by IF for smooth muscle actin (αSMA), collagen type I and laminin. Cpd treatment significantly improved serum BUN, urine albumin/creatinine ratio and fibrosis in KO mice in association with reduced levels of total and phosphorylated DDR1.

**Conclusions:** These results indicate that drugs targeting DDR1 may represent a novel strategy to treat kidney disease in patients with AS.

**Funding:** Commercial Support - Hofmann-LaRoche AG

---

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

Underline represents presenting author.
The Role of DDR1 in Podocyte Lipotoxicity and Progression of Alport Syndrome

Jing Ji Kim,1,2 Judith T. Molina David,3 Javier T. Varona Santos,2,4 Marco Prunotto,5 Sandra M. Merscher,1 Jeffrey H. Miner,1 Alessia Fornoni,1,5 Katz Family Division of Nephrology and Hypertension, University of Miami Miller School of Medicine, Miami, FL; Katz Family Drug Discovery Center, University of Miami Miller School of Medicine, Miami, FL; 6 Hoffman-La Roche Ltd., Basel, Switzerland; 7 Washington University School of Medicine, St. Louis, MO.

Background: The GBM is primarily composed by laminin and Collagen type IV. De novo production of collagen type IV (Col I) has been observed in a mouse models of Alport Syndrome (AS-Coll4a3Ko). Discoidin-domain-receptor 1 (DDR1) is a unique receptor tyrosine kinase that is activated by collagen. Deletion of the DDR1 in Col4a3Ko mice improves survival and renal function. However, how DDR1 activation by abnormally collagen production contributes to podocyte injury and proteinuria is poorly understood.

Methods: Differentiated human podocytes were serum starved, followed by 18hrs treatment with 50ug/mL Col 1 (Corning). Podocyte lipid content was determined by Bodipy 493/503 and Col4a3Ko mice at 8 weeks.

Results: DDR1 phosphorylation was increased in kidney cortex from Col4a3ko mice (p<0.05), whereas the expression of podocyte and synaptopodin was decreased. pDDR1 correlated with blood urine nitrogen (BUN, R² = 0.7, p<0.01). In vitro, podocyte DDR1 inhibition by pharmacological treatment of Col1 at 18 hours increased intracellular lipid accumulation (p<0.05) and FFA uptake (p<0.001) were also observed in Col1 treated podocytes. DDR1 DA transfected HEK293 cells showed increased expression of CD36, a protein involved in FA uptake, and FFA uptake compared to cells transfected with DDR1 WT and DN (p<0.05). Glomeruli isolated from Col4a3ko mice showed increased lipid deposition and expression of CD36.

Conclusions: Our data suggest that col I-inducedDDR1-mediated lipotoxicity may represent a novel mechanism leading to podocyte injury in AS.

Funding: Commercial Support - Hoffmann-La Roche.

SA-PO210 Inducible Podocyte-Specific Deletion of CTCF Leads to Progressive CKD with Severe Bone and Mineral Disease in the Absence of Renal Fibrosis

Martha Hesse,1,2 Jeffrey H. Miner,1,5 Katz Family Division of Nephrology and Hypertension, University of Miami Miller School of Medicine, Miami, FL; 3 Harvard Medical School, Boston, MA; 4 Goldfach Bio, Cambridge, MA; 5 Harvard Medical School, Boston, MA; 6 Harvard University, Boston, MA; 7 Massachusetts General Hospital, Boston, MA; 8 New York Medical College, Valhalla, NY; 9 University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

Background: Progressive chronic kidney disease (CKD) is on the rise worldwide with more than 500 million people affected. However, the sequence of events resulting in onset and progression of CKD remain poorly understood. Likewise, while FGFR2 elevations are associated with increased mortality, its utility as a biomarker of early CKD remains uncertain, and whether it can be manipulated through dietary or pharmacologic interventions is controversial. Animal CKD models exploring these issues are confounded by systemic toxicities or artificial surgical interventions.

Methods: Flexed CTCF mice (CTCFfl/fl) were mated with doxycycline-inducible, podocyte-specific CRE transgenic mice (iCreMA; 2 interstitial fibrosis. This work highlights podocyte-protective strategies rather than the prevention of renal fibrosis as the most promising therapeutic approach for CKD.

Funding: NIDDK Support

SA-PO220 Loss of Function of Rhpn1 Leads to Proteinuria through Downregulation of Wt1 via WtIp

Kan Katayama,1,2 Cardiology and Nephrology, Mie university graduate school of medicine, Tsu, Japan; 3 Medical Biochemistry and Biophysics, Karolinska Institute, Stockholm, Sweden.

Background: Rhophilin-1, Rhpn1 was identified as one of podocyte-enriched proteins and Rhpn1 inactivation in mice showed proteinuria at an early stage. Although the onset of proteinuria was suggested by a mechanism due to the altered actin cytoskeleton structure, the underlying pathogenesis is not fully clarified. Moreover, there is no report in human so far.

Methods: Therefore, we investigated the function of rhpn1 in zebrafish to evaluate whether the phenotypic change was conserved in zebrafish.

Results: Knockdown of rhpn1 in zebrafish caused proteinuria, which was confirmed by the uptake of 500 kDa Fluorescein isothiocyanate-conjugated dextran in proximal tubules. To further analyze the function of Rhpn1, yeast two hybrid screening was performed and Wtms tumor protein 1-interacting protein, Wtp, was identified as an interaction partner of Rhpn1. Rhpn1 knockdown in zebrafish or Rhpn1 knockout in mice resulted in downregulation of mRNA of Wtms tumor protein 1, Wt1. In kidneys from Rhpn1 knockout mouse, nuclear translocation of Wt protein was observed more commonly compared to wild-type mouse kidneys.

Conclusions: Taken together, loss of interaction between Rhpn1 and WtIp might be involved in the development of proteinuria through downregulation of Wt1.

Funding: Daiichi Sankyo Co., Ltd

SA-PO230 Ezrin Plays Important Roles in the Regulation of Foot Process Morphology in the Glomerular Podocytes

Ryo Hatano,3 Ritsumeikan University, Kusatsu, Japan.

Background: Ezrin is highly expressed in the glomerular podocytes, and is reported to form multi-protein complex with a scaffold protein Na+/H+ exchanger regulatory factor 2 (NHERF2), and podocalyxin, a major sialoprotein. Podocalyxin deficient mice died within 24 hrs after birth with anuric renal failure, whereas NHERF2 knockout mice did not exhibit apparent renal phenotype. On the other hand, physiological roles of ezrin in glomerular podocytes still remain unclear.

Methods: To investigate the physiological roles of ezrin in the regulation of glomerular podocyte function, ezrin knockdown mice (Vil2kd) were used in this study. Histological analysis of glomerulus was performed by H&E staining and electron microscopy. Western blotting and immunofluorescent analysis were performed the expression and localization of related proteins in the podocytes. Rho activities were investigated by ELISA-based pull down assay using isolated mouse glomeruli and glomerular podocytes treated with ezrin siRNA.

Results: Vil2kd mice did not exhibit apparent glomerular dysfunction, morphological defects, and disturbance in the localizations of podocalyxin and NHERF2 in podocytes. In Vil2kd glomeruli, Rac1 activity was significantly decreased in Vil2kd glomeruli compared to WT glomeruli although RhoA activity was increased. Then, we examined Rho-activities in E11 cells, in which ezrin expression was downregulated by siRNA. Rac1 activity was significantly decreased in ezrin knockdown E11 cells, whereas significant change in the Rhoa activity was not observed. On the other hand, transfection of constitutively active ezrin (T567D) increased the activity of Rac1. Furthermore, increased ezrin expression and Rac1 activity was observed in the T567D-transfected E11 cells.

Conclusions: Our results suggest that ezrin regulates the foot process formation via the Rac1 activity in the podocytes. Ezrin is known to interact with Rho-GDP dissociation inhibitor (RhoGDI). Since ezrin promotes the activation of Rho via the striping RhoGDI from GDP-bound Rho, activation of ezrin might be involved with Rac1 activation in the glomerular podocytes.

Funding: Poster/Saturday

SA-PO240 The Protective Role of Podocyte Hypertrophy via mTOR Signalling after Mild Podocyte Depletion

Viktor G. Puelles,1 James W. Van der wold,2 Luise A. Cullen-McEwen,1 Luc Furic,1 Kate M. Denton,3 Marcus J. Moeller,4 David J. Nikolic-Paterson,5 John F. Bertram,1 Anatomy and Developmental Biology, Monash University, Melbourne, VIC, Australia; 2Nephrology and Clinical Immunology, University Hospital RWTH Aachen, Aachen, Germany; 3Physiology, Monash University, Melbourne, VIC, Australia; 4Nephrology, Monash Medical Centre, Melbourne, VIC, Australia.

Background: Podocyte depletion is an established key feature of focal segmental glomerulosclerosis (FSGS). However, little is known about the consequences of mild podocyte loss. In addition, activation of parietal epithelial cells (PECs) has been proposed as a major effector in FSGS. This study investigates the consequences of graded podocyte depletion, the hypertropic response of podocytes and associations with PEC activation and thereby glomerulosclerosis.

Methods: We induced selective podocyte depletion in Pod4iDTR mice by injection of diphertheria toxin (DT) at different doses. L-NAMe induced hypertension was used as a second hit challenge after mild podocyte loss. The mammalian target of rapamycin (mTOR) signalling pathway was manipulated using mTOR inhibitors (RAD001) and INK128. Podocyte depletion and hypertrophy were examined by 3D analysis of whole glomeruli in optically-cleared kidney slices.

Results: Pod4iDTR mice injected with a low dose of DT presented mild podocyte depletion, compensatory podocyte hypertrophy and reversible albuminuria without PEC

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

730
activation or glomerulosclerosis, even following a second hit challenge (high blood pressure). These indicate a protective role of podocyte hypertrophy. Injection of a higher dose of DT in PodCre mice led to greater podocyte loss and hypertrophy. However, these mice showed PEC activation, glomerulosclerosis and persistent albuminuria, suggesting there is a limit for the protective role of podocyte hypertrophy. Pharmacological inhibition of PEC during the induction of mild podocyte depletion led to persistent and exacerbated albuminuria, impairment of podocyte hypertrophy, PEC activation and glomerulosclerosis.

Conclusions: Podocyte hypertrophy via mTOR signalling is required for the adaptive hypertrophic response of remaining podocytes after mild podocyte depletion. These results are relevant for the use of mTOR inhibitors in the context of FSGS and CKD.

SA-PO205

HMGA1-Driven Long Non-Coding RNAs Mediate Endothelial-to-Mesenchymal Transition in Kidney Fibrosis

Roeij Bijkerk1, Atefah Lafi2, Wendy Stam1, Angela Koudij1, Ellen Lievers1, Ton J. Rabelink1, Hilal Kazan1, Anton J. Van Zonneveld1, Wendy Laﬁ2, 1Leiden University Medical Center, Leiden, Netherlands; 2CNAG-CRG, Barcelona, Spain; 3Antalya International University, Antalya, Turkey.

Background: Chronic kidney disease associates with the development of interstitial fibrosis characterized by a loss of the microvasculature and myofibroblast formation. Endothelial cells (ECs) are important for maintaining a healthy microvasculature while ECs also provide a potential source for myofibroblasts through endothelial-to-mesenchymal transition (EndoMT). Here, we aimed to identify a role for long non-coding RNAs (IncRNAs), novel central post-transcriptional regulators, in ECs in the development of kidney fibrosis.

Methods: We used endothelial-ERT2;Tomato mice to label and trace endothelial cells. We applied both the ischemia-reperfusion injury (IRI) and unilateral ureteral obstruction (UUO) models followed by FACS sorting of the tomato-positive cells from healthy and diseased kidneys. Subsequently, we isolated RNA from these cells and profiled IncRNAs, as well as gene expression, using comprehensive genome-wide transcript arrays.

Results: Upon kidney injury, we observed substantial co-localization of VE-cadherin-derived tomato positive signal with a SMA staining, indicating that a significant portion (~15-20%) of myofibroblasts originated from ECs. We confirmed that ECs acquired a myofibroblast phenotype by using qPCR on FACS sorted tomato-positive cells showing reduced expression of EC markers CD31 and VE-cadherin while myofibroblast markers α-SMA and col1a1 increased. In UUO and IRI, we found 386 and 416 IncRNAs to be differentially expressed (±2-fold, p<0.05) in the VE-cadherin-derived tomato-positive cells, respectively. Using Ingenuity transcription factor enrichment analysis amongst differentially expressed IncRNAs we found strong enrichment for HMGA1 binding sites, a transcription factor previously described to be essential in EndoMT. Using ChIP-seq, we validated binding of HMGA1 to IncRNAs, including that of MALAT1, one of the differentially expressed and conserved IncRNAs, and subsequently demonstrated in an in vitro model for EndoMT that blocking MALAT1 with gapmers enhanced TGF-β-induced EndoMT.

Conclusions: We demonstrated that HMGA1-induced IncRNAs mediate EndoMT which may provide novel strategies to counteract the development of kidney fibrosis.

SA-PO206

Rap1 and Its Guanine Nucleotide Exchange Factor C3G Are Critical for Drosophila Nephrocyte Function

Christopher P. Dlugos1, Cara Picciotto2, Astrid Wendy Picciotto2, Michael P. Krah1, Rolan Wedlich-Soldner3, Hermann Pavenschädt4, Christian Klambil5, Britta Geering, 1Medizinische Klinik D, University Hospital Münster, Münster, Germany; 2Institute of Internal Medicine, Keio University School of Medicine, Tokyo, Japan; 3Medical Education Center, Keio University School of Medicine, Tokyo, Japan.

Background: We have recently reported the gene-selective epigenetic control in podocytes via KLF4 (Hayashi et al, JCI 2014. KI 2015). However, the precise formation of epigenetic changes involved in diseases states remains unclear. Here we report on KAT5, a histone acetyltransferase which has been reported as a KLF4 interacting protein and an important factor in repairing DNA, to investigate the possible role of DNA damage repair process in formation of epigenetic changes.

Methods: Expression of KAT5 was examined in streptozotocin (STZ)-induced diabetic mice model and the effect of KAT5 gene transfer was evaluated. To analyze the physiological role of KAT5, we generated podocyte-specific KAT5 knockout (KO) mice, and investigated the epigenetic changes and DNA damage status. We performed in vitro studies using cultured human podocytes to examine the mechanism of KAT5-associated epigenetic changes.

Results: KAT5 expression was significantly decreased in isolated podocytes in STZ mice and a marker of DNA double strand breaks γH2AX was increased in glomeruli of STZ mice. Restoration of KAT5 expression in STZ mice using a hydrodynamic-based gene transfer method ameliorated albuminuria, γH2AX and nephrin expression. KAT5 KO mice developed massive proteinuria (6 week-old, WT 3.3±1.6 mg/gCr, K0 33±26 mg/gCr, p<0.05) with segmental glomerulosclerosis and diffuse effacement of podocyte foot process. In KO mice, nephrin expression in isolated podocytes was decreased, and WT podocytes were protected with an overexpression of KAT5. Epigenetic changes and an increase in γH2AX expression were observed in glomeruli of KO mice. In cultured human podocytes, high-glucose treatment (30mM) induced KAT5 reduction and overexpression of KAT5 increased nephrin expression. It was revealed that overexpression of KAT5 induced a decreased methylation and a decreased binding of DNMT1 in the nephrin promoter region by methylation-specific PCR method and ChIP analysis.

Conclusions: DNA damage repair through KAT5 is essential for the maintenance of nephrin expression and has relation to the changes in podocyte epigenome. Increased KAT5 in podocytes ameliorates diabetic nephropathy with promoted DNA damage repair and elevated nephrin expression.

Funding: Government Support - Non-U.S.

SA-PO207

KAT5-Mediated DNA Damage Repair Is Essential for the Maintenance of Podocytes

Akihito Hayashi1, Kaori Hayashi1, Hiroshi Itoh1, Internal Medicine, Keio University School of Medicine, Tokyo, Japan; 2Medical Education Center, Keio University School of Medicine, Tokyo, Japan.

Background: We have recently reported the gene-selective epigenetic control in podocytes via KLF4 (Hayashi et al., JCI 2014. KI 2015). However, the precise formation of epigenetic changes involved in diseases states remains unclear. Here we report on KAT5, a histone acetyltransferase which has been reported as a KLF4 interacting protein and an important factor in repairing DNA, to investigate the possible role of DNA damage repair process in formation of epigenetic changes.

Methods: Expression of KAT5 was examined in streptozotocin (STZ)-induced diabetic mice model and the effect of KAT5 gene transfer was evaluated. To analyze the physiological role of KAT5, we generated podocyte-specific KAT5 knockout (KO) mice, and investigated the epigenetic changes and DNA damage status. We performed in vitro studies using cultured human podocytes to examine the mechanism of KAT5-associated epigenetic changes.

Results: KAT5 expression was significantly decreased in isolated podocytes in STZ mice and a marker of DNA double strand breaks γH2AX was increased in glomeruli of STZ mice. Restoration of KAT5 expression in STZ mice using a hydrodynamic-based gene transfer method ameliorated albuminuria, γH2AX and nephrin expression. KAT5 KO mice developed massive proteinuria (6 week-old, WT 3.3±1.6 mg/gCr, K0 33±26 mg/gCr, p<0.05) with segmental glomerulosclerosis and diffuse effacement of podocyte foot process. In KO mice, nephrin expression in isolated podocytes was decreased, and WT podocytes were protected with an overexpression of KAT5. Epigenetic changes and an increase in γH2AX expression were observed in glomeruli of KO mice. In cultured human podocytes, high-glucose treatment (30mM) induced KAT5 reduction and overexpression of KAT5 increased nephrin expression. It was revealed that overexpression of KAT5 induced a decreased methylation and a decreased binding of DNMT1 in the nephrin promoter region by methylation-specific PCR method and ChIP analysis.

Conclusions: DNA damage repair through KAT5 is essential for the maintenance of nephrin expression and has relation to the changes in podocyte epigenome. Increased KAT5 in podocytes ameliorates diabetic nephropathy with promoted DNA damage repair and elevated nephrin expression.

Funding: Government Support - Non-U.S.

SA-PO208

Isosform Specific Phosphorylation of Dynamin in Regulating the Cortical Actin Cytoskeleton in Podocytes

Nikolina Stoianovic1, Mario Schiffer1, Sanja Sever1, Hannover Medical School, Hannover, Germany; 2Massachusetts General Hospital, Charlestown, MA; 3Massachusetts General Hospital, Charlestown, MA.

Background: Dynamin is an essential actin regulatory protein in podocyte, and loss of its function is closely connected to podocyte injury and proteinuria. Recently, our studies have shown that dynamin directly regulates actin cytoskeleton via its oligomerization state. Importantly, dynamin specific small drug (Bis-T23) that induces its oligomerization ameliorates proteinuria in diverse proteinuric animal models through recovering functional actin structures in injured podocytes. Therefore, it is important to maintain balance between dynamin assembly and disassembly. This dynamin oligomerization can be regulated through interaction with diverse cellular proteins, and it was reported that dynamin1 can differentially alter the affinity for its protein binding partners via phosphorylation by two different serine/threonine kinases, GSK3β and DSG2-containing kinases. Based on such a data, we hypothesize that phosphorylation-dependent dynamin1 oligomerization is an important molecular mechanism that regulates actin dynamics in podocytes.

Methods: Dynamin1 phosphorylation in podocytes was detected by western blot using phospho-dynamin1 specific antibodies in the presence of GSK3β or CDK5 inhibitor. Actin and paxillin in podocytes were stained to observe actin structures and focal adhesions. Cell migration and spreading assays were performed with podocytes expressing phospho-dynamin1 mutants. For zebranin experiments, each phospho-dynamin1 mutant was expressed in dynamin2ζζ zebranin.

Results: 1. Dynamin1 is phosphorylated by GSK3β and CDK5 in podocytes. 2. Expression of phospho-dynamin1 mutants alters cortical actin networks during cell spreading. 3. Expression of phospho-dynamin1 mutants affects cell migration. 4. Expression of phospho-dynamin1 mutants fails to rescue proteinuria in dynamin2ζζ zebranin.

Conclusions: The role of dynamin in actin cytoskeleton in podocytes is essential to maintain the glomerular filtration barrier. Dynamin directly regulates actin structures via its oligomerization state. Our data suggest that dynamin1 phosphorylation is implicated...
in cortical actin dynamics in podocytes, and its balanced phosphorylation by GSK3 and JNK is crucial to podocyte’s function in glomerular filtration.

**Funding:** NIDDK, Support

**SA-PO211**

**Loss of DUSP4 Promotes Insulin Resistance in Podocytes through JNK Activation**

**Benoit Denhez,1 Marina Rousseau,2 Farah Lizotte,3 Mannix Auger-Messier,2 Anne-Marie Cote,1 Pedro M. G Milders2**

**CHUS - Hôpital Fleurimont, Sherbrooke, QC, Canada; 2University of Sherbrooke, Sherbrooke, AB, Canada; 3University of Sherbrooke, Sherbrooke, QC, Canada; 4Université de Sherbrooke, Sherbrooke, QC, Canada.**

**Background:** Diabetic nephropathy is characterized by early damages to podocytes which lead to their dysfunction and loss. Insulin action in podocytes has been shown to be essential for their integrity. Multiple evidences suggested that the activation of JNK can lead to insulin resistance in various cell types. Data from our laboratory showed that the expression of DUSP4, a protein known to inhibit JNK, is reduced in the renal cortex of type 1 diabetic mice and cultured podocytes exposed to high glucose levels. Deletion of DUSP4 in diabetic mice resulted in significant increase of albuminuria, podocyte apoptosis and activation of JNK. The objective is to evaluate the effect of JNK activation induced by the loss of DUSP4 expression on insulin signaling pathway in cultured podocytes exposed to high glucose and diabetic mice.

**Methods:** Non-diabetic (NDM) and diabetic (DM) mice with the deletion of DUSP4 (DKO) were stimulated with insulin to evaluate its downstream signaling pathway on the activation of IRS1 and Akt in the renal cortex. Mouse podocytes were exposed to normal (NG: 5.6 mM) or high (HG: 25 mM) glucose levels for 72 hours with or without the overexpression of DUSP4 adenoviral vector to evaluate the phosphorylation of JNK and the insulin signaling pathway.

**Results:** Insulin-stimulated Akt and ERK phosphorylation in the renal cortex of DM mice was decreased compared to NDM mice, and was further reduced in DM DKO mice. Loss of insulin effects in DM DKO mice was associated with increased phospho-serine 307 of IRS-1, which is known to inhibit IRS1 activity. In cultured podocytes, HG exposure inhibited insulin-induced activation of Akt, which was associated with a reduction in DUSP4 expression and a 2.8 fold increase in phospho-serine 307 of IRS-1.

**Conclusions:** Loss of DUSP4 and both the HG-induced increased phosphorylation of JNK and phospho-serine 307 of IRS-1, and restored insulin-stimulated Akt activation in podocytes.

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

**SA-PO212**

**The Role of the Atypical Cyclin-Dependent Kinase Cdk5 on Development and Function of Podocytes**

**Nicole C. Mangold,1 Henning Hagmann,2 Stuart J. Shankland,1 Markus M. Rihsch,1 Thomas Benzing,3 Paul T. Brinkkoeiter,2 CECAD, Cologne, Germany; 1University of Cologne, Cologne, Germany; 2University of Cologne, Kôn, Germany; 4University of Washington, Seattle, WA.**

**Background:** The atypical cyclin-dependent kinase 5 (Cdk5) controls migration, cell adhesion and synaptic plasticity in neurons. In the kidney Cdk5 expression is highly conserved and plays critical roles in the glomerular filtration barrier. Nephrotic syndrome genes, including TrpC6 and PLCε1, affect podocyte calcium signaling. However, the role of calcium signaling during podocyte development in vivo remains unknown.

**Methods:** Here we aim at understanding the role of calcium signaling during glomerular development using live imaging of zebrafish.

**Results:** Live imaging showed that immature podocytes (48 hours post fertilization) are dynamic and interact with the dorsal aorta to form glomerular capillaries. By 4 days post fertilization (dpf) podocytes stabilize and the filtration barrier is functionally mature. Using the calcium biosensor GCaMP3, we observed spontaneous intracellular calcium transients in podocytes at early stages (2-3 dpf) of development in the zebrafish larva which were silenced by 4 dpf suggesting a role for calcium signaling in podocyte maturation. To determine the source of calcium, larvae were treated with calcium inhibitors and we observed that calcium transients were blocked by cyclopiazonic acid, thapsigargin and 2APB but not by chlorpromazine or nifedipine, indicating calcium release from intracellular stores. pcle1 knockdown resulted in podocyte defects, disorganized capillaries, and loss of podocin expression suggesting a requirement for calcium signaling in podocyte differentiation. Using an unbiased whole glomeruli RNAseq transcriptome approach we identified multiple candidate signaling receptors potentially responsible for developmental podocyte calcium signaling.

**Conclusions:** These studies will help to identify new targets for intervention in glomerular diseases and establish zebrafish as a model for glomerular diseases caused by impaired calcium signaling.

**Funding:** NIDDK Support

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

**Underline represents presenting author.**
cytoskeletal architecture and can reduce cell migration and motility. In podocytes, Cofilin1 dysregulation leads to loss of secondary foot processes and FF effacement. Cofilin1 is also described as a part of a complex with actin and phosphatidyl RNA polymerase (Pol) II, playing a major role in the regulation of gene transcription. In mammalian cells, Cofilin1 is inactivated via phosphorylation and translocated to the nucleus. Because of the role of Cofilin1 in diabetes, sections of Type I diabetic mice induced by STZ, Type II diabetic db/db mice and Type II diabetic patients were evaluated by IF stainings against Cofilin1 and p-Cofilin1. Human and murine podocytes stimulated with glucose or TGF-β were analyzed for Cofilin1, its colocalization with Pol II and the distribution of F-actin. We also analyzed the phosphorylation profile of Cofilin1 at different time points using westernblot. After glucose treatment, migration assays were performed to compare the capability of podocytes to migrate into to the scratched wound with or without addition of p-Cofilin1 blocking peptide.

Results: Phospho-lit Cofilin1 is strongly detected in the nucleus of podocytes in diabetic mice and patients. Stimulation of cultured podocytes with glucose or TGF-β induced the translocation of Cofilin1 into the nucleus and led to a dysregulation of actin filaments, and Cofilin1 phosphorylated on Ser3 is mainly localized to the nucleus. Westernblots indicated an increased phosphorylation of Cofilin1 30 minutes after glucose treatment. Immunofluorescence of p-Cofilin1 with phosphorylated Pol II indicated a redistribution of Pol II from away with p-Cofilin1/actin, which most likely impacts transcriptional elongation. Podocytes remained static after glucose treatment in culture, but their migration ability was restored when p-Cofilin blocking peptide was added.

Conclusions: Localization of p-Cofilin1 to the nucleus is a strong indicator of diabetes induced dysfunction of podocytes; impacting the reorganization of the actin cytoskeleton as well as transcription. The phospho-inhibitor of Cofilin1 is a novel potential candidate to prevent p-Cofilin1 mediated progression of podocyte dysfunction and podocyte damage in diabetes.

SA-PO214
Paricalcitol Prevents PAN-Induced Podocyte Morphological Change via Direct Regulation of Nestin Transcription through the Interaction of VDR/VDRE

Paricalcitol treatment abolished the effect. Downregulation of VDR in cultured podocytes was evaluated. The influence of PAN or paricalcitol on cultured mouse podocytes were also observed. VDR expression was silenced by VDR siRNA or plasmids containing VDR shRNA transfection. Chromatin immunoprecipitation (ChIP) and luciferase reporter assays were performed to study the connection between VDR and nestin gene expression.

Methods: Paricalcitol significantly alleviated PAN-induced proteinuria and podocyte FPE. This protective effect was accompanied by an increased expression of VDR in the glomeruli. Paricalcitol also inhibited PAN-induced glomeruli nestin overexpression. In vivo studies showed that PAN significantly inhibited VDR protein expression and stimulated nestin protein expression which resulted in nestin filament rearrangement. Paricalcitol treatment abolished the effect. Downregulation of VDR in cultured podocytes also resulted in overexpression and rearrangement of nestin. ChIP assays revealed a VDR responsive element (VDRE) in nestin promoter and paricalcitol enhanced the binding of VDR and VDRE. Luciferase reporter assays of the nestin promoter fragment showed paricalcitol effectively repressed nestin reporter gene expression after PAN treatment. However, paricalcitol treatment alone showed no influence on lucerase activity. Mutation of VDRE abolished the effect.

Conclusions: Paricalcitol prevents morphological change of podocytes in PAN nephrosis via direct regulation of nestin transcription through the interaction of VDR/VDRE.

Funding: Government Support - Non-U.S.

SA-PO215
The Melanocortin-1 Receptor Protects Podocytes by Downregulating the Epidermal Growth Factor Receptor

The Melanocortin-1 receptor in podocytes has been suggested as the mediator of the renoprotective effects seen in ACTH treatment of nephrotic syndrome. The protective effect has been proposed to be through stabilization of the actin cytoskeleton in podocytes.

Methods: Using phosphoproteomic mass spectrometry, actin regulatory pathways were identified downstream of the MC1R in podocytes over-expressing the MC1R and treated with the MC1R specific agonist BMS. Confirmation of regulated proteins and pathways was done using western blot. Actin dynamics was studied using phallolidin labeling. To evaluate the protective effect of MC1R-induced ERK phosphorylation and protective effect has been proposed to be through stabilization of the actin cytoskeleton in podocytes.

Results: The role of Cofilin1 in diabetes, sections of Type I diabetic mice induced by STZ, Type II diabetic db/db mice and Type II diabetic patients were evaluated by IF stainings against Cofilin1 and p-Cofilin1. Human and murine podocytes stimulated with glucose or TGF-β were analyzed for Cofilin1, its colocalization with Pol II and the distribution of F-actin. We also analyzed the phosphorylation profile of Cofilin1 at different time points using westernblot. After glucose treatment, migration assays were performed to compare the capability of podocytes to migrate into to the scratched wound with or without addition of p-Cofilin1 blocking peptide.

Conclusions: Phospho-lit Cofilin1 is strongly detected in the nucleus of podocytes in diabetic mice and patients. Stimulation of cultured podocytes with glucose or TGF-β induced the translocation of Cofilin1 into the nucleus and led to a dysregulation of actin filaments, and Cofilin1 phosphorylated on Ser3 is mainly localized to the nucleus. Westernblots indicated an increased phosphorylation of Cofilin1 30 minutes after glucose treatment. Immunofluorescence of p-Cofilin1 with phosphorylated Pol II indicated a redistribution of Pol II from away with p-Cofilin1/actin, which most likely impacts transcriptional elongation. Podocytes remained static after glucose treatment in culture, but their migration ability was restored when p-Cofilin blocking peptide was added.

Conclusions: Localization of p-Cofilin1 to the nucleus is a strong indicator of diabetes induced dysfunction of podocytes; impacting the reorganization of the actin cytoskeleton as well as transcription. The phospho-inhibitor of Cofilin1 is a novel potential candidate to prevent p-Cofilin1 mediated progression of podocyte dysfunction and podocyte damage in diabetes.

SA-PO214
Paricalcitol Prevents PAN-Induced Podocyte Morphological Change via Direct Regulation of Nestin Transcription through the Interaction of VDR/VDRE

Paricalcitol treatment abolished the effect. Downregulation of VDR in cultured podocytes was evaluated. The influence of PAN or paricalcitol on cultured mouse podocytes were also observed. VDR expression was silenced by VDR siRNA or plasmids containing VDR shRNA transfection. Chromatin immunoprecipitation (ChIP) and luciferase reporter assays were performed to study the connection between VDR and nestin gene expression.

Methods: Paricalcitol significantly alleviated PAN-induced proteinuria and podocyte FPE. This protective effect was accompanied by an increased expression of VDR in the glomeruli. Paricalcitol also inhibited PAN-induced glomeruli nestin overexpression. In vivo studies showed that PAN significantly inhibited VDR protein expression and stimulated nestin protein expression which resulted in nestin filament rearrangement. Paricalcitol treatment abolished the effect. Downregulation of VDR in cultured podocytes also resulted in overexpression and rearrangement of nestin. ChIP assays revealed a VDR responsive element (VDRE) in nestin promoter and paricalcitol enhanced the binding of VDR and VDRE. Luciferase reporter assays of the nestin promoter fragment showed paricalcitol effectively repressed nestin reporter gene expression after PAN treatment. However, paricalcitol treatment alone showed no influence on lucerase activity. Mutation of VDRE abolished the effect.

Conclusions: Paricalcitol prevents morphological change of podocytes in PAN nephrosis via direct regulation of nestin transcription through the interaction of VDR/VDRE.

Funding: Government Support - Non-U.S.

SA-PO215
The Melanocortin-1 Receptor Protects Podocytes by Downregulating the Epidermal Growth Factor Receptor

The Melanocortin-1 receptor in podocytes has been suggested as the mediator of the renoprotective effects seen in ACTH treatment of nephrotic syndrome. The protective effect has been proposed to be through stabilization of the actin cytoskeleton in podocytes.

Methods: Using phosphoproteomic mass spectrometry, actin regulatory pathways were identified downstream of the MC1R in podocytes over-expressing the MC1R and treated with the MC1R specific agonist BMS. Confirmation of regulated proteins and pathways was done using western blot. Actin dynamics was studied using phallolidin labeling. To evaluate the protective effect of MC1R-induced ERK phosphorylation and
146a−) and podocyte-specific miR-146a knockout (KO) animals using streptozotocin (STZ).

Results: We further confirmed that podocyte miR-146a expression decreased in the glomeruli of type 2 diabetes (T2D) patients and correlated with increased albuminuria and glomerular damage. Mice lacking miR-146a globally or selectively in podocytes showed substantial improvement of glomerulopathy observed in T2D. miR-146a targets, Notch-1 and ErbB4, were significantly upregulated in the diseased glomeruli and TGFβ signaling was induced. Treatment of podocytes in vitro with TGFβ resulted in increased levels of Notch-1 and ErbB4, increased ErbB4 phosphorylation, and increased mRNA expression of chemokine MCP-1, which suppresses miR-146a via an autocrine loop. Similarly, administration of low-dose LPS to podocyte-specific miR-146a KO mice resulted in increased albuminuria as compared to the WT mice, further suggesting that podocyte-expressed miR-146a protects from glomerular damage.

Conclusions: We suggest a novel role for miR-146a in protecting against glomerular injury via protecting podocytes from injury and cell death. This indicates that miR-146a might have a therapeutic potential in DN.

Funding: NIDDK Support

SA-PO218

Cell Adhesion Function of β-Catenin in Podocytes Is Crucial for Glomerular Filtration Barrier Michelle Duong,1 Beina Teng,2 Hermann G. Haller,2 Mario Schiffner.1 Hanover Medical School, Hannover, Germany; 1Hanover Medical School, Hannover, Germany; 2Medical School Hannover, Hannover, Germany.

Background: β-Catenin has two functions: it mediates cell adhesion and Wnt signaling. Its function depends on its subcellular localization, as membranous β-catenin localizes to adherens junctions with cadherins, whereas cytoplasmic β-catenin transcriptional activity is regulated by a nuclear β-catenin localization. We have shown that β-catenin interacts with PKCε and PKCδ deficiency leads to a nuclear localization of β-catenin. PKCε/− podocytes show a increased cell detachment, apoptosis and reduced differentiation. P-cadherin and IQGAP1 are proteins involved in membranous β-catenin stability. We therefore investigated the relationship of this complex in podocytes.

Methods: We performed time course Western blot of cellular lysates of murine PKCδ−/− podocytes and tested the IQGAP1 and P-cadherin expression. We used adenoviral PKCε and PKCδ constructs to overexpress these proteins in PKCε−/− deficient podocytes. Immunofluorescent staining was performed on murine kidney sections and podocytes to examine the P-cadherin and vinculin expression. Zebrafish larvae were injected with β-catenin1 morpholino and localization mutant β-catenin RNAs to investigate their function in vivo.

Results: During the differentiation of PKCe−/− podocytes, IQGAP1 and P-cadherin expression was reduced compared to WT cells. Overexpression of only PKCe, but also β-catenin, could reverse this effect and lead to a normal IQGAP1 expression. We saw in immunofluorescence and western blot analysis a downregulated vinculin expression in PKCε−/− podocytes, which could be reversed by β-catenin overexpression. β-Catenin1 knockdown in zebrafish led to both with proteinuria and edema. This could be partially rescued with overexpression of a β-catenin mutant expressed in the membrane, while a β-catenin mutant expressed in the nucleus could not reverse proteinuria.

Conclusions: We show that β-catenin as a upstream mediator of cell-adhesion by its interaction with the adherens junction proteins P-cadherin, IQGAP1 and focal adhesion molecules such as vinculin. This complex is disturbed in functionally disabled podocytes, β-catenin−/− podocytes. Our data in vivo and in vitro support the idea that the function of β-catenin plays a more important role in the maintenance of the glomerular filtration barrier in zebrafish. The Wnt signaling function of β-catenin alone seems not to promote kidney health.

Funding: NIDDK Support

SA-PO219

Podocytes from 129S1 Mouse Glomerular Outgrowths Can Be Used for Functional Studies Hong Wang,1 Kathleen A. Lincoln,4 Christina S. Bartlett,1 Jay Kuo,2 Steven S. Pullen.1 Boehringer Ingelheim, Ridgefield, CT; 3Boehringer Ingelheim Pharmaceutical, Inc., Ridgefield, CT; 4Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT.

Background: Podocytes are specialized, terminally differentiated epithelial cells which are essential for integrity of the glomerular filtration barrier. Efforts to develop podocyte-directed therapies have been hampered by lack of in vitro systems for studying podocyte functions. Immortalized podocyte cell lines fail to represent native podocyte behaviors, and current in vivo models with cadherin-deficient mice are not available.

Methods: Glomeruli were isolated from 129S1/Slv mice using Dynabead perfusion and magnetic isolation. We modified our protocol to include a brief collagenase incubation and MACS cell dissociation step to reduce handling time and increase viability. Purified glomeruli were resuspended in culture media and seeded on collagen IV coated plates. Intact glomeruli were removed after 4 days in culture. After 6 days, cells were treated with purumycin aminecarboxylate (PAN) for 24 hours. Podocyte markers were measured using Taqman gene expression, and F-actin was visualized using fluorescent phalloidin.

Results: Expression of podocyte specific markers (neprin, podocin, podocalyxin, synaptopodin, WT1, Glep-1) was observed at 6 days of culture from 129S1 glomerular outgrowths. Nephrin gene expression was lost by 10 days of culture, although expression of other markers remained. PAN treatment increased expression of selected genes, whereas treatment with DMSO had no effect. The results were consistent with podocytosis and podocyte markers and integrin gene expression were significantly reduced. Phallolin staining showed highly organized actin fibers present within the cytoplasm of cultured cells and was reduced by PAN treatment.

Conclusions: Successfully cultured primary mouse podocytes from the 129S1 mouse strain, modified the standard protocol to reduce glomerular isolation time, and identified the useful window of utility. This method will be valuable for rapid generation of genetic mouse models of podocytopathy and development of assays for podocyte functional assessment.

Funding: NIDDK Support

SA-PO220

Yap Dependent Mechanotransduction Determines the Podocyte's Response to Injury Markus M. Rinschen,1 Tobias B. Huber,2 Thomas Benzinger,1 Bernhard Schermern.1 University Hospital Cologne, Cologne, Germany; 2University Medical Center Hamburg, Hamburg, Germany.

Background: Podocytes, terminally differentiated cells of the kidney filtration barrier, are subjected to considerable mechanical strain by physiological filtration pressure, which can even be increased by severe hypertension. When injury causes cytoskeletal reorganization and morphological alterations of these cells, the filtration barrier may become compromised and allow proteins to leak into the urine (proteinuria). The activities of the transcriptional co-activators YAP and TAZ are tightly controlled by the Hippo signaling pathway and are sensitive to mechanical cues.

Methods: We used time-resolved quantitative proteomics in the in vivo and in vitro PAN model of podocyte injury.

Results: We show that podocyte injury stimulates YAP activity and the expression of YAP–target genes in a rat model of glomerular disease prior to the development of proteinuria. In contrast, injury of cultured human and mouse podocyte cell lines reduced YAP and TAZ activity when the cells were grown on stiff substrates. However, culturing these cells on soft matrix or inhibiting stress fiber formation recapitulated the damage-induced YAP upregulation observed in vivo, indicating a mechanotransduction-dependent mechanism of YAP activation in podocytes. YAP overexpression in cultured podocytes enhanced the abundance of extracellular matrix–related proteins. YAP activity was increased in mouse models of diabetic nephropathy, and expression of the YAP target CTGF was observed in renal biopsies from patients with glomerular disease. Whereas overexpression of human YAP in mice induced mild proteinuria, pharmacological inhibition of the interaction between YAP and its partner TREAD in rats ameliorated glomerular disease and reduced damage-induced mechanosignaling in glomeruli.

Conclusions: We conclude that perturbation of the mechanosensitive Hippo signaling pathway is a potential therapeutic target for treating some glomerular diseases.

Funding: Government Support - Non-U.S.

SA-PO221

Loss of OMA1 Activates the mTOR Pathway but Fails to Rescue PHB2 Deficient Podocytes Independent of Stress-Induced OPA1 Processing Paul T. Brinkkoetter,1 Alexander Kuczkozki,2 Kristina Schoenfelder,3 Bernhard Schermern,1 Thomas Benzinger.1 University Hospital Cologne, Cologne, Germany; 2University Hospital of Cologne, Cologne, Germany; 3University of Cologne, Köln, Germany.

Background: The dynamin-like GTPase OPA1 is conceived as a central regulatory hub that controls mitochondrial dynamics, fusion and fission responses, under stress and in states of disease. Stress-induced OPA1 processing by the metallocendopeptidase OMA1 triggers mitochondrial fission as seen in podocyte-specific knock-out mouse lacking prohibitin membrane scaffolds as a model of impaired mitochondrial function.

Methods: As reported previously, loss of prohibitins resulted in increased insulin and mTOR signaling and, subsequently, renal failure and premature death after 4-5 weeks after birth. Here, we studied the interplay between the peptide OMA1 and prohibitins and their effect on mitochondrial function and the activation of the mTOR signaling cascade in glomerular podocytes. In contrast to neunors, genetic depletion of OMA1 failed to rescue renal function in PHB2 deficient podocytes and did not prolong animal survival despite stabilizing mitochondrial morphology. OMA1 single knock-out animals showed increased mTOR signaling activity at baseline without compromising renal function or animal survival. This activating effect on mTOR was additive to the PHB2 knock-out effect as OMA1/PHB2 double knock-out animals showed even stronger levels of mTOR activation.

Conclusions: Taken together, impairment of mitochondrial dynamics results in activation of mTOR, which is not sufficient to cause podocyte disease at baseline. Additional insults, such as increased cellular stress or a destabilized slit-diaphragm as shown for PHB2 are required to induce podocyte disease. These findings not only emphasize the central role of mitochondria to control insulin and mTOR signaling in podocytes but also provide additional evidence for an additional function of prohibitins in podocytes beyond their established role as protein scaffolds at the inner mitochondrial membrane.
SA-PO222

Dlg1 Is a Novel Regulator of Silt Diaphragm Formation in the Drosophila Nephrocyte
John S. Poulton, University of North Carolina at Chapel Hill, Chapel Hill, NC.

Background: Proper glomerular filtration requires the formation and maintenance of slit diaphragms (SDs) between podocyte foot processes. Mutations affecting SD formation/function result in nephrotic syndrome. SD formation is coupled to podocyte maturation, which involves changes in cell polarity. Previous work in mammalian systems has revealed that apical polarity proteins play important roles in SD formation, however the basolateral polarity complex appears dispensable.

Methods: To further explore the role of polarity proteins in SD formation, I took advantage of the Drosophila nephrocyte, which form SDs analogous to vertebrate podocytes. The facile genetics of Drosophila allowed efficient screening of multiple RNAi lines targeting components of the basolateral polarity complex.

Results: Consistent with previous findings in mouse podocytes, I found no obvious role for Dlg1 in the basolateral polarity protein Scrib in SD formation. In addition, knockdown of Lgl, another key component of the basolateral complex also produced no defects in SD formation. Surprisingly, loss of Discs Large1 (Dlg1) led to dramatic mislocalization of core SD components, including the fly homologues of Nephrin, Nep1, and ZO-1. Transmission electron microscopy of Dlg1 knockdown nephrocytes revealed significant reduction in the number of SDs, though some small patches of nephrocyte surface did retain SDs. Intriguingly, numerous ectopic SDs were observed internal to the cell surface, lining the labyrinthine channels—a phenotype not observed in wildtype nephrocytes.

Conclusions: These data identify Dlg1 as a novel and vital regulator of SD formation and function through the JNK pathway independently with Nephrin Phosphorylation. Yoshiyasu Fukusumi, Ying Zhang, Hiroshi Kawachi. Dept. Cell Biology, Kidney Research Center, Niigata University, Niigata, Japan.

SA-PO225

Ephrin-B1 Bound to Nephrin at the Silt Diaphragm Controls Podocyte Function through the JNK Pathway Independently with Nephrin Phosphorylation
Yoshiyasu Fukusumi, Ying Zhang, Hiroshi Kawachi. Dept. Cell Biology, Kidney Research Center, Niigata University, Niigata, Japan.

Background: We have reported ephrin-B1 is a novel component of the slit diaphragm (SD), and interacts with nephrin via their extracellular domains in cis form. We also reported that the podocyte-specific ephrin-B1 conditional knockout (CKO) mice showed proliferation and disarrangement of podocyte components. However, the precise function of the ephrin-B1 and nephrin at the SD is not well elucidated yet.

Methods: The mechanisms of the phosphorylations of ephrin-B1 and nephrin, and their downstreams were analyzed with HEK293 cell system, the rat nephrotic model and the ephrin-B1 CKO mice. The role of the nephrin-binding ephrin-B1 in regulating cell function was analyzed.

Results: Analyses with the HEK cells showed that not only nephrin but also the nephrin-binding ephrin-B1 was phosphorylated by the anti-nephrin antibody stimulation, and that the phosphorylation was Src kinase dependent. By contrast, the nephrin bound to ephrin-B1 was not phosphorylated by the stimulation to ephrin-B1. The ephrin-B1 co-transfected with the truncated nephrin lacking phosphorylation sites was phosphorylated more evidently, indicating the nephrin phosphorylation lowered the phosphorylation of the nephrin-binding ephrin-B1. Although the phosphorylation of nephrin was enhanced by the co-expression with ephrin-B1, the co-expression of the ephrin-B1 lacking tyrosine residues did not enhance, indicating the phosphorylation of ephrin-B1 is necessary for the enhancement of nephrin phosphorylation. Ephrin-B1 phosphorylation was also detected in glomeruli of the nephrotic model caused by anti-nephrin antibody. The phosphorylated ephrin-B1 phosphorylated JNK evidently. By contrast, nephrin signaling did not phosphorylate JNK. JNK phosphorylation was not detected in glomeruli of the ephrin-B1 CKO mice. The wound-healing assay with the HEK cells showed that the phosphorylation of ephrin-B1 promoted the cell motility, while nephrin did not promote it.

Conclusions: The phosphorylations of nephrin and the nephrin-binding ephrin-B1 were causally regulated, and the phosphorylation of the ephrin-B1 transferred the signals to downstream via another route of the nephrin signaling. Ephrin-B1 controls podocyte function through JNK pathway. The ephrin-B1 resisted together with nephrin at the SD plays an essential role in maintaining podocyte function.

Funding: Government Support - Non-U.S.

SA-PO223

Novel Genetic Modeling of Podocyte Diseases and Early Mesodermal Development
Bridgette Drummond, Rebecca A. Winger. University of Notre Dame, Notre Dame, IN.

Background: Specialized renal epithelial cells known as podocytes create an essential filter that when comprised is causative of numerous kidney diseases. Podocyte morphology and genetic regulatory systems are conserved in zebrafish, making them a simplified and accessible model to study podocyte development and disease states.

Methods: To systematically elucidate the network of podocyte development genes, we have developed a haploid ethylmethionite (ENU) screen to identify novel podocyte regulators.

Results: In the emerging panel of these new congenital models of podocyte genesis, we have isolated classes of defects including podocyte abrogation, reduction of podocyte number suggesting alterations in proliferation or survival of the lineage, and delayed differentiation. Of these, one mutant that has been identified has a complete loss or significant reduction of several established podocyte markers. In conjunction with this, the presented mutant is proximally abrogated and has a dramatic decrease in several soluble transporter cells that distinguish both proximal and distal tubule segments. Interestingly, several known renal progenitors that demarcate the intermediate mesoderm also reduced in these mutants.

Conclusions: Elucidation of the genetic lesions in these mutants will provide valuable insights into the molecular components that are involved in podocyte development, and possibly models for congenital defects and other kidney diseases.

Funding: NIDDK Support

SA-PO224

TRPC5 Overexpression and Activation Do Not Per Se Cause Nor Augment Kidney Disease
Xueying Wang, Ranadeerhe Dande, Hao Yu, Mehmet M. Altintas, Jochen Reiser. Rush University Medical Center, Chicago, IL.

Background: The transient receptor potential canonical cation channel, subfamily C, member 5 (TRPC5) is broadly expressed in brain and kidney with the capability to mediate the calcium (Ca²⁺) influx as well as cell migration. It was reported that TRPC5 is vital for Ca²⁺ homeostasis in podocytes due to its location in podocyte foot process cytoplasm. It is believed to regulate podocyte cytoskeletal remodeling through its association with active Rac1 GT-Pase. Genetic knockout or pharmacological inhibition of TRPC5 protects mice from albuminuria. However, the gain of function role of TRPC5 by drug affects the podocytes function and proteinuria level. TRPC5 appears not only a mediator of glomerular kidney disease. Its role in other renal diseases requires further study.

Results: TRPC5 mRNA and protein level were significantly higher in TG and DN compared with WT and control. However, no increase in proteinuria was found among TG, DN and B6. TEM analysis revealed a similar level of foot process effacement among three groups of animals. TRPC5 activator Englerin A injection induced no change in proteinuria. TRPC5 inhibitor ML204 treatment did not rescue kidney filtration barrier injury from LPS challenge.

Conclusions: Overexpression of TRPC5 does not cause kidney injury over time per se or more podocyte damage to LPS challenge. Neither agomizing nor antagonizing TRPC5 by drug affects the podocytes function and proteinuria level. TRPC5 appears not act as a mediator of glomerular kidney disease. Its role in other renal diseases requires further study.

Funding: NIDDK Support

SA-PO226

Nephrin Is Necessary for Podocyte Recovery Following Injury in an Adult Mature Glomerulus

Background: Nephrin (Nphs1) is an adhesion protein and is expressed at the podocyte intercellular junction in the glomerulus. Nphs1 mutations in humans or deletion in animal genetic models results in a developmental failure of foot process formation. Though nephrin is essential for foot process (FP) development, its role following development is not well defined. In order to understand the role of nephrin following development we initially generated a nephrin flox mouse. Using this mouse we were able to delete nephrin in an inducible manner using tamoxifen (Nphs1Flox/Cri). We used biochemical and cell biology techniques to assess nephrin expression in the glomerulus. Proteolysis of the SWN (PS) and nphrotic serum (NTS) were used to study the role of nephrin following injury and in recovery.

Results: Deletion of nephrin using Nphs2Cre-Cre resulted in FP spreading and proteinuria by 10-12 d following birth. Nephrin expression decreased by 85% at 10 days post-induction with tamoxifen. The Nphs1Flox/Cri mice had normal FP ultrastructure and intact filtration barrier upto 4-6 weeks post-induction. Interestingly, nephrin expression was restored at the slit diaphragm upto 16-20 wks post-tamoxifen. Nphs1Flox/Cri mice developed proteinuria 8 wks following induction along with FP structural changes. Nphs1Flox/Cri mice showed failure to reduce albuminuria in vivo 2 wks post induction subjected to PS model of podocyte injury, demonstrated failure of recovery following heparin sulfate. Similarly, Nphs1Flox/Cri mice failed to recover from T1D NPHS2/PS with persistence of proteinuria and FP effacement.

Conclusions: As in development nephrin is necessary for maintenance of a healthy glomerular filter. Interestingly, nephrin expression persists for several months following
deletion. The small fraction of nephrin that remains is relatively stable and is sufficient to maintain the filtration barrier wks. It is likely that some nephrin is either recycled continuously at the membrane or is stably linked to actin. Following injury, recovery requires larger amount of nephrin as evident by failure of recovery following PS and NTS injury. This would suggest that induction or maintenance of nephrin expression would be beneficial to prevent proteinuric kidney diseases.

**Funding:** NIDDK Support

SA-PO227

Novel Methods to Analyze Mechanisms of TRPC6 Activation

Alex B. Deg,1 Fang Li,1 Simon J. Atkinson,1 Mark Kowala,1 Mark Rekhter,1 Eil Lilly and Company, Indianapolis, IN; 1Indiana University - Purdue University Indianapolis, Indianapolis, IN.

**Background:** TRPC6 is a calcium channel activated by diacylglycerol (DAG) and reactive oxygen species (ROS). TRPC6 mutations are associated with proteinuria in human focal segmental glomerulosclerosis. New data suggest that circulating factors in diabetes induce kidney injury via TRPC6-mediated calcium flux. It is unknown how different factors activate TRPC6. The goal of this study was to develop a platform for analysis of DAG and ROS in TRPC6 activation.

**Methods:** Full length human TRPC6 cDNA was cloned into pcDNA5/TO (Thermo Fischer) under CMV promoter and transfected into HEK293 cells. Stable clones were selected based on the TRPC6 expression. Calcium signaling was analyzed using FLIPR membrane potential assay. DAG synthesis was monitored using recombinant circularly permuted probe, Downward DAG (Montana Molecular). Cells were infected with baculovirus carrying the biosensor construct. Fluorescent signal was captured using FLIPR for ROS detection, cells were stained with Cell-ROX dye and analyzed using a confocal microscope.

**Results:** The stable cell line, C11, showed >7000x increase in hTRPC6 gene expression. Calcium signaling was stimulated in a dose-dependent manner by angiotensin II (AngII), 1-oleoyl-2-acetyl-sn-glycerol (OAG), endothelin 1 and hyperforin 9 (Hyp9), specific activator of TRPC6. DAG signal was increased by Hyp9 and endothelin, but not by AngII. However, AngII but neither Hyp9 nor endothelin 1 induced ROS formation.

**Conclusions:** We generated novel tools to investigate mechanisms of TRPC6 activation and demonstrated differential involvement of DAG and ROS in TRPC6-induced calcium flux.

**Funding:** NIDDK Support

SA-PO228

The Role of APOL1 and Cholesterol Dependent Podocyte Injury in Focal Segmental Glomerulosclerosis

Menichi Yu,1,2,3,4,5 Alexis J. Sloan,1,2 Javier T. Varona Santos,1,2,3 Christopher E. Pedigo,1 Armando Mendez,4 Jeffrey B. Kopp,4 Sandra M. Merscher,1,2 Alessia Forroni,1,2 Katz Family Division of Nephrology and Hypertension, University of Miami Miller School of Medicine, Miami, FL; 1Katz Family Drug Discovery Center, University of Miami Miller School of Medicine, Miami, FL; 2Diabetes Research Institute, University of Miami Miller School of Medicine, Miami, FL; 3Kidney Disease Service, Diabetic Nephropathy, Division of Nephrology and Digestive and Kidney Diseases, National Institute of Health, Bethesda, MD.

**Background:** Focal segmental glomerulosclerosis (FSGS) is the most common primary glomerular disorder causing chronic kidney disease (CKD). Susceptibility to FSGS in African Americans is associated with the presence of genetic variants of the Apolipoprotein L1 gene (APOL1) named G1 and G2. APOL1 is an integral component of high-density lipoprotein (HDL) particles suggesting it might be involved in cholesterol efflux from cells. Since parietal epithelial cells (PECs) are still under debate to be a type of progenitor cell for podocytes, we performed comparative gene expression analysis between freshly isolated podocytes, cultured primary PECs and cultured primary podocytes of mice. Furthermore, we performed ChiP-Seq analysis to identify putative interaction partners and target genes of Tcf21.

**Methods:** We identified differentially regulated genes in freshly isolated podocytes in comparison to PECs and podocytes in culture. Tcf21 was identified as one of the most upregulated genes in freshly isolated podocytes (24- and 15-fold, respectively) as compared to PECs and podocytes, respectively, in culture. Interestingly, the expression of Tcf21 in PECs induced multilobulation and budding of the nuclei, and the formation of microneurites (MMB). Furthermore, we found an increased number of tetraploid cells. The multilobulation of nuclei was reversible after the addition of nocodazole and taxol indicating an involvement of microtubules. By qRT-PCR and Western blot analysis we found that Tcf21 regulates the transcription factor YY1. Co-expression of YY1 and Tcf21 rescued the formation of MBB. Moreover, we observed that Tcf21 levels regulate the expression of cyclin D1 and cyclin D2, suggesting a role of Tcf21 in cell cycle control. Additionally, by ChIP-Seq analysis we identified a genome-wide Tcf21-binding site (CAGCGT), which matched the CANNATG sequence that is the common E-box binding motif used by bHLH factors. Interestingly, many of the Tcf21 targets genes are involved in the regulation of the cell cycle, cell division, microtubule-based processes and chromosome segregation. Taken together, Tcf21 is a transcription factor that appears to be importantly involved in the cell cycle regulation and function of podocytes.

**Funding:** Government Support - Non-U.S.
Loss of Glomerular Endothelial Surface Layer and Cell Integrity Is Mediated by Increased Ednra and Crodast with Podocyte Derived Edn1 Kerstin Eberof,4 Robert Wiemer,5 Evren U. Azealoglu,6 Borje Haraldsson,7 Ise S. Daen,1 Health School of Medicine at Mount Sinai, New York, NY; 2Novartis, Gothenburg, Switzerland; University of Gothenburg, Gothenburg, Sweden.

Background: Chronic kidney disease is increasing in prevalence worldwide with evidence that it is caused by glomerular diseases, including diabetic and hypertensive nephropathy and glomerulonephritis. There is emerging evidence that the specialized fenestrated glomerular endothelial cells (ECs) maintain the charge selective barrier to proteinuria via the endothelial surface layer (ESL) or glycocalyx. The ESL is a polycarboxylic gel that lines the luminal surface composed of glycosaminoglycans (GAGs). We have previously demonstrated that activated podocytes can release endothelin-1 (Edn1) causing stress and dysfunction of ECs via increased Edn receptor A (Ednra) and consequently, podocyte loss in mice. We hypothesize that podocyte-EC crosstalk results in loss of early glomerular endothelial integrity.

Methods: Ultrastructural assessment of glomerular ECs by scanning EM at different time points of Dox induced TGF-β type I receptor signaling specifically in podocytes (PodTbr1 mice). We measured ESL thickness by intralipid infusion EM and IsocalcinB4 (IB4). Atomic force microscopy (AFM) measured the nanomechanical properties of the ESL in murine glomerular ECs (mGEC), we measured IB4, heparan sulfate (HS) by FACS, Heparanase (Hype) and Hyalurondase (Hyal) expression by RT-PCR.

Results: Compared to ECs of control mice showing extensive fenestration, we detected a striking loss of fenestrate and significant cellular blebbing after 4d of Dox in the absence of foot process effacement and significant microalbuminuria. After 4d of Dox, there was a robust reduction of ESL thickness, decreased further over time, and the ESL loss was prevented by Ednra inhibitor BQ-23. We examined whether loss of ESL is mediated by podocyte released Edn1. mGEC were treated with Edn1 or co-incubated with supernatant from control or Sulf-1/β-deficient for Sulf-1 and -2 were analyzed. Urinary albumin was measured by ELISA. AFM measurements showed a significant reduction in ESL by Edn1 and DoxSN, concomitant with decreased IB4 and HS, and prevented by BQ123. Upregulation of Hps and Hype expression denoted increased GAG degradation and remodeling by ECs in response to podocyte-secreted ESL.

Conclusions: We show evidence of early crosstalk between podocytes and glomerular ECs that results in loss of EC integrity preceding podocyte foot process effacement in glomerular disease. Funding: NIDDK Support, Private Foundation Support

SA-P0232

CLIC5A Protects Renal Glomeruli from Diabetes-Induced Damage Xing Wang,1 Laij Li, Barbara J. Ballermann. University of Alberta, Edmonton, AB, Canada.

Background: Podocyte injury, including foot process (FP) effacement, is a critical early step in the development of diabetic nephropathy. Activated ezrin, podocalyxin and type I receptor signaling specifically in podocytes lead to glomerular damage and albuminuria.

Methods: Podocyte injury, including foot process (FP) effacement, is a critical early step in the development of diabetic nephropathy. Activated ezrin, podocalyxin and type I receptor signaling specifically in podocytes lead to glomerular damage and albuminuria.

Results: In podocytes, CLIC5A activates Rac1 and Cdc42 and stimulates FP effacement. The findings in mice that CLIC5A is necessary for the association of PIs4P5K with GTP-Rac1/Cdc42, and that ezrin activation is profoundly reduced in diabetic mice.

Conclusions: Podocytes, CLIC5A activates Rac1 and Cdc42 and stimulates FP effacement. The findings in mice that CLIC5A is necessary for the association of PIs4P5K with GTP-Rac1/Cdc42, and that ezrin activation is profoundly reduced in diabetic mice. Funding: Private Foundation Support

SA-P0233

A Syndrome of IgA-Related Polycthemia Camille Cohen,1,2,3 S Dévéline Coulon,4 Kanit Bhusiki,5 Michaël Dussiot,6 Antoine Neuraz,7 Martin Flamant,7 Francois Vrotnovik,12 Aurelie Hummel,16 Bertrand Knebelmann,17 Laurent Mesnard,1 Eric Rondoue,2 Marc Benhamou,2 Christophe M. Legendre,1 Olivier Hermine,7 Khalil El Karoui,1 Anna K. MacGillivray,8 Anaiah A. Schroder,1 Laura Stagg,1 Mario Schiffer,1 Janina Müller-Deile,2 Heiko J Schenk,1 Joen-Keun Park,1 Hermann G. Haller,1 Hannover Medical School, Hannover, Germany; 2MHM, Hannover, Germany; 3Mount Desert Island Biological Lab, Salisbury Harbor, ME; 4Mount Desert Island Biological Laboratory, Salisbury Cove, ME.

Background: IgA nephropathy (IgAN) is associated with elevated levels of polymeric IgA (pIgA1) and circulating IgA1 complexes. We previously reported that pIgA1 controls erythropoiesis through activation of transferrin receptor (Coulon et al, Nat Med 2011), but data in patients are still lacking to involve pIgA1 in normal or pathologic erythropoiesis.

Methods: Sera from patients with IgAN and unexplained polycthemia (IgAN-Pcy, persistent hematocrit (Ht) >54%) were collected after written consent. Human placenta-derived ECs were cultured in low IgA1-Pcy conditions in the absence of IgA1 or in presence of IgA1, pIgA1 or IgA1/Pcy. Cdc42 and Rac1 activity were induced with streptozotocin (50 mg/kg, IP X 5 days) in wild-type (WT) or CLIC5A deficient (KO) mice. Controls were given buffer IP. Histology was evaluated on Masson-Trichrome stained sections (n= 3-6 mice/group). Results: Increased Edn1 and DoxSN, concomitant with decreased IB4 and HS, and prevented by BQ123. Upregulation of Hps and Hype expression denoted increased GAG degradation and remodeling by ECs in response to podocyte-secreted ESL.

Conclusions: We show evidence of early crosstalk between podocytes and glomerular ECs that results in loss of EC integrity preceding podocyte foot process effacement in glomerular disease. Funding: NIDDK Support, Private Foundation Support

SA-P0234

The Loss of Heparin Sulphate Editing Enzyme Sulf1 Reduces VEGF Signaling and Enhances Endothelial Glomerular Injury and Proteinuria Xiaohong Liu,1,2 Mengyi Zhang,1,2 Alexandre J. Legendre,3,4 Laura-Ann Hummel,1,5 Beverly-Stagg,5 Mario Schiffer,1 Janina Müller-Deile,2 Heiko J Schenk,1 Joen-Keun Park,1 Hermann G. Haller,1 Hannover Medical School, Hannover, Germany; 2MHM, Hannover, Germany; 3Mount Desert Island Biological Lab, Salisbury Harbor, ME; 4Mount Desert Island Biological Laboratory, Salisbury Cove, ME.

Background: the endothelial cell surface is covered by the heparin sulphate proteoglycans (HSPG). Alterations in the level of 6-O-sulfation of the HS chains modulate the binding and release of signaling molecules and affect vascular function. The regulation of the glycosalyx is not well understood. Heparan sulphate 6-O-endosulfatase (sulf1 and -2) regulate the binding properties of the glycoalyx. We tested the hypothesis that 6-O-sulfation is important for glomerular stability and that changes in 6-O-sulfation lead to glomerular damage and albuminuria.

Methods: To assess sulf-1 and -2 function in vivo we used a transgenic zebrafish model (Tg(fg-alt:-gfp:DBP)) and measured edema formation and loss of fluorescent protein from the circulation after knock-down of sulf-1 and -2. We further tested whether loss of sulf1 enhanced glomerular injury in zebrafish using PAN injury. In addition, mice deficient for Sulf-1 and -2 were analyzed. Urinary albumin was measured by ELISA. Immunohistochemistry was performed on cryostat or paraffin sections.

Results: Loss of Sulf-1 and -2A/B lead to a dose-dependent increase in edema formation and albuminuria in zebrafish. Vascular permeability was enhanced after sulf1-2 knockdown. Reduction of sulfatases enhanced the PAN-induced albuminuria significantly. Vascular patterning was slightly affected by Sulf-2, indicating a role in vascular development of the isoform. In Sulf-2 deficient mice albuminuria occurred after week 4. The glomerular mesangium showed increased proliferation. Glomerular VEGF as well as p38 and JAK2/STAT3/ERK signaling was increased.

Conclusions: The level of 6-O-sulfation of HS chains of the glycoalyx is an important determinant of glomerular health and pathophysiology. Our results suggest that Sulf-1 and -2 regulate the signaling properties of VEGF and other growth factors in the glomerulus. Funding: Support- Government Non-U.S.
Tripartite Motif-Containing 55 (TRIM55) participates in the Immune Response in Experimental Anti-Thy1 Glomerulonephritis

Lei Chen, Hongli Jiang. 1 Dialysis Center of First Affiliated Hospital of Medicine School, Xi’an Jiaotong University, Xi’an, Shaanxi, China; 2 Dialysis Department of Nephrology Hospital, First Affiliated Hospital of Medicine School, Xi’an Jiaotong University, Xi’an, China.

Background: Mesangial proliferative glomerulonephritis (MpgGN) is considered as an immune-related disease. Its pathogenesis is involved with activation of mesangial cells and the subsequent immune inflammatory response. However, the mechanism underlying the regulation of immune response remains largely elusive. Tripartite motif family was reported to be closely related to immune regulation. In this study, we performed a series of experiments in vivo and vitro to investigate the role of tripartite motif-containing 55 (TRIM55), a member of tripartite motif family, in the progression of MpgGN.

Methods: 36 male SD rats were randomly divided into 6 groups, 5 of which were received tail vein injection of anti Thy-1 antibody (2.5 mg/kg body weight), and the remaining group was received PBS injection as negative control (NC). Specimens of the NC group were collected at 0d after the injection, while those of other groups were collected at 1d, 2d, 3d, 4d, and 5d, respectively. Immunohistochemical staining of CD68 was performed to evaluate the level of macrophages infiltration. qPCR analysis of glomerulus was performed to examine the expression of TRIM55. Primary RMCs with overexpression of TRIM55 were obtained through plasmid transfection. In addition, si-RNA tranfection was used to knock down the expression of TRIM55 in primary RMCs. qPCR analysis was conducted to detect the level of cytokines, such as TNF-α, CCL2, CCL5, CXCL1, CXCL10, and IL-6.

Results: PAS staining results indicated mesangial dissolution occurred since 1d, followed by inflammatory cell infiltration. CD68 immunohistochemical staining results showed that macrophages infiltration peaked at 1d and then decreased gradually. The expression of TRIM55 mRNA also peaked at 1d and decreased gradually, which was consistent with the trend of macrophages infiltration. In primary RMCs, knockdown of DBP led to down-regulation of the expression of cytokines (TNF-α, CCL2, CCL5, CXCL1, CXCL10 and IL-6). On the other hand, the expression of those cytokines (TNF-α, CCL2, CCL5, CXCL1, CXCL10 and IL-6) significantly increased in TRIM55-overexpressed primary RMCs.

Conclusions: The above results indicate that TRIM55 participates in the immune response in anti-Thy1 nephritis by regulating the production of cytokines. We duce TRIM55 may be a promising therapeutic intervention to ameliorate leukocyte infiltration in MpgGN.

Nephronectin Is a Component of Novel Glomerular Adhesions That Regulate Mesangial Adhesion and Behavior

Chikale Hiremath, Denise K. Marciano. University of Texas Southwestern Medical Center, Dallas, TX.

Background: Defects in the glomerular basement membrane (GBM) cause heritable glomerular disease and are associated with the majority of acquired glomerular diseases, although their role in pathogenesis of the latter is unclear. The GBM contacts all cells of the glomerular tuft, namely podocytes, endothelia, and mesangial cells, whose function is coordinated to form an integrated filtration unit. Much of the GBM is deposited between mesangial cells and endothelia, where it is well known to form a critical part of the permeability barrier. However, the GBM also interacts directly with mesangial cells. Currently, little is known of specific GBM-mesangial interactions and their role in glomerular development, maintenance, and disease.

Methods: We utilize several mouse models in this study including conditional deletion of Nptn, the gene encoding nephronectin, using the Sirt2cre line and PodcintCre line.

Results: We find nephronectin, a GBM component and known ligand of α6β1 integrin, is produced by podocytes and deposited into the GBM, where it is required for formation of a novel GBM-mesangial cell adhesion structure. These specialized adhesions occur at sites of mesangial cell protrusion that are highly enriched in α6β1 integrin and appear to anchor capillary loops. Absence of nephronectin disrupts these adhesion structures, leading to mislocalization of α6β1 integrin, pronounced increase in mesangial cell number, and mesangial sclerosis.

Conclusions: These results demonstrate a novel role for nephronectin-α6β1 integrin in a newly described adhesion complex.

Funding: NIDDK Support, Other NIH Support - March of Dimes

Impact of Tryptophan Metabolism Alteration by Kyurenone 3-Monoxygenase Inhibition on Renal Cells and Its Role in Diabetic Renal Disease

Patricia M. Schaefer,1,2,3 Heiko J. Schenk,1 Janina Müller-Deile,1 Hermann G. Haller,1 Mario Schiffer,1 1Hannover Medical School, Hannover, Germany; 2Mount Desert Island Biological Laboratory, Salisbury Cove, ME.

Background: The kyurenine pathway (KP) is the major route for tryptophan catabolism, and changes in KP metabolites correlate with renal complications in a diverse range of pathologies. Previous work from our group identified the enzyme kyurenine 3-monoxygenase (KMO) as a factor underlying the onset of proteinuria in diabetes by
Contributing to morphological changes in podocyte foot processes. However, in spite of the correlational evidence for kynurenine involvement in the worsening of renal function, the pathological and functional significance of the increase in KP metabolites on renal cells remains unknown.

**Methods:** To assess if the enzymes of the KP are altered in diabetic kidney disease we performed IF staining of mouse kidney sections after Streptozotocin (STZ) injections, as a model for type I diabetes. Alongside this, cultured murine and human podocytes were analyzed upon inhibition of KMO to define the impact of KP dysregulation. Cell shape, size and substrate adherence were monitored. Finally, since KMO is an integral part of the mitochondrial membrane and the KP plays a role in the production of NAD⁺, we assessed mitochondrial function of podocytes after KMO inhibition by measuring bioenergetics parameters in a microplate-based live-cell metabolic assay.

**Results:** In line with our previous results, STZ-injected mice show reduced KMO expression in the renal cortex. Similarly, the expression of Arylformamidase, that catalyzes the production of kynurenine, is altered in diabetes. This change is more prominent in the glomeruli, where a reduction in the nuclear localization of AFMID was observed. Furthermore, KMO inhibition in cultured podocytes resulted in a substantial reduction in average cell size, and changes in Parcillin staining show alterations in the focal adhesions, which correlate with an increase in cellular detachment. Moreover, the changes in spare respiratory capacity observed after KMO inhibition are consistent with mitochondrial dysfunction which could affect the cells' ability to respond to variations in energy demand.

**Conclusions:** Taken together, these results highlight the prominent role of the KP in the maintenance of podocyte function as its dysregulation has an impact on cell morphology, substrate adherence and metabolic profile.

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

**SA-PO240**

**Macrophage Activation Syndrome (MAS) and Systemic Lupus Erythematosus (SLE): Early Diagnosis Improves Outcomes – Case Series from a Tertiary Centre**


**Imperial College Lupus Centre, Hammersmith Hospital, London, United Kingdom.**

**Background:** MAS is a life-threatening complication of SLE, characterised by fevers, hyperferritinaemia, pancytopenia, high triglycerides, abnormal liver, neurological & renal function. We report our case series & growing experience which led to improved recognition & outcomes.

**Methods:** From clinical records & identifying all those patients in our lupus nephritis biopsy database (1997-2016, 475 patients, 806 biopsies) aged >18yrs with serum ferritin >2000ng/ml not explained by other causes, we report clinical & laboratory features & outcomes of 17 patients with 18 episodes of MAS.

**Results:** Of the 17 patients, 82% were female, median age 45 yrs (29-62). At time of acute MAS, 59% had new-onset SLE & 41% were flaring. Clinical & biochemical features summarised in table 1 (image). Aggressive therapy with a combination of IV cyclophosphamide, plasma exchange, IV & oral steroids, IVIg & anti CD20 mAb was used. Where tolerated, tacrolimus given for 2 wks at presentation. Compared to dismal outcomes in the literature (as low as 34%), majority of patients responded to therapy (83%) though 3 (17.6%) died: 1 refractory to therapy & 2 in whom immunosuppression limited by infections.

**Conclusions:** This case series likely underestimates incidence: a) only a minority of patients with features of MAS have renal biopsies; b) until recently, few patients with severe SLE had ferritin measured acutely. MAS develops in context of a highly active SLE & should be screened for using serum ferritin, LDH, blood film, amylase & triglycerides to ensure early diagnosis. Our relatively low mortality & very high response rates reflect rapid diagnosis allowing early aggressive therapy aimed at quenching the inflammatory storm & treating the underlying SLE.

**SA-PO241**

**Urinary AlphaM Subunit of Integrin Mac-1 Associates With Glomerular Inflammation in Lupus Nephritis**

Akinitsu Kitagawa, Naotake Tsuibo, Yutaka Kaminuma, Takayuki Katsuno, Shoichi Maruyama.

**Nagoya University Graduate School of Medicine, Nagoya-shi, Aichi, Japan.**

**Background:** One of the pathogenesis of glomerulonephritis is glomerular accumulation of leukocytes. Integrin Mac-1 is composed of a unique α (α; CD11b) complexed to a common β2 subunit (CD18) on neutrophils and monocytes/macrophages. Mac-1 has been demonstrated to support various immunological functions on glomerular endothelium including leukocyte recruitment and immune-complex clearance. Interestingly, leukocytes have been shown to release Mac-1 from the surface upon cell activation under inflammatory conditions. In the current study, we evaluated the association of urine levels of CD11b (U-CD11b) with histological disease activity in experimental animals with glomerulonephritis and patients with various glomerular diseases, in particular lupus nephritis (LN).

**Methods:** Antibody-mediated glomerulonephritis was induced by rabbit anti-mouse nephrotoxic serum in male C57BL/6j mice (NTS-GN). Urine and kidney samples from NTS-GN mice and from 272 patients with glomerular diseases including LN between 2008 and 2014 in Nagoya University were subjected to the study. Urinary concentrations of CD11b, hemoglobin scavenger receptor CD163 (U-CD163), and MCP-1 (U-MCP-1) were measured by ELISA. Glomerular CD11b⁺ cells for neutrophils and monocytes/macrophages were also immunohistologically analyzed. In 118 LN patients, histological disease activity was evaluated semiquantitatively using the biopsy activity index (BAI).

**Results:** U-CD11b was evident on day 14 and elevated until day 21 in NTS-GN mice. In human patients, U-CD11b levels were significantly increased in ANCA-associated vasculitis and LN group, particularly in the ISN/RPS class IV. In LN, the number of
glomerular CD11b+ cells was correlated with U-CD11b concentration (r=0.547) and BAI (r=0.457). We conclude that corticosteroid treatment significantly reduced U-CD11b excretion associated with the disease amelioration both in experimental animals with NTS-GN and human LN patients. In the ROC curve generated to predict ISN/RPS class specificity of U-CD11b was greater than that of U-CD13 and U-MCP-1.

**Conclusions:** These data collectively suggest that U-CD11b can be a useful biomarker for prediction of histological disease activity in LN.

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

SA-PO242

**Improvement of Prognosis of Lupus Nephritis in Recent Years: A Single Center Retrospective Study**

Yunja Suwa,1 Hideaku Ikeuchi,1 Masao Nakasatomi,2 Toru Sakairi,1 Yoriaki Kaneko,1 Akito Maeshima,1 Yoshishisa Nojima,1 Keiji Hiromura.1

Department of Nephrology and Rheumatology, Gunma University Graduate School of Medicine, Maebashi, Japan; 2Department of Rheumatology and Nephropathy, Japan Red Cross Maebashi Hospital, Maebashi, Japan.

**Background:** The treatment of SLE has been changing year by year, but it is not clear how the change actually relates to the improvement of the prognosis.

**Methods:** The treatment of lupus nephritis (LN) has been changing. In the present study, we examined the change of prognosis of LN in our facility.

**Results:** Median age was 34 years (IQR 28-47), median observation period was 105 months (IQR 47-189). ISN/RPS Class was as follows: III(a) x 35, III(c) x 35, IV(a) x 82 pts; pure V, 23 pts. The prognosis was significantly better in patients after 2000 in both renal events + patient death or renal events alone (P=0.0196 and P<0.001, respectively, Figure). In addition, frequency of proteinuric remission was significantly better in patients after 2000 at both of 6 months and 12 months after treatment (43.1% vs 68.8%, P<0.001; 60.7% vs. 78.7%, P= 0.031; respectively). There was no significant difference in levels of Scr and complements, and frequency of anti-DNA antibodies at baseline. Regarding the treatments, frequencies of steroid pulse therapy and dose of prednisolone were not different between the 2 groups. However, frequencies of immunosuppressants for the first induction therapy were different between before and after 2000: p.o. cyclophosphamide, 45.0% vs 3.3%, P=0.01; tacrolimus, 0.0% vs 11.2%, P=0.014; mycophenolate mofetil + tacrolimus, 0.0% vs 23.5%, P=0.01.

**Conclusions:** In our facility, the prognosis of active LN has been improved in recent years. The changes of immunosuppressants might contribute to better proteinuric remission rate at 6 and 12 months after induction therapy and lead to better long-term prognosis of LN.

SA-PO243

**Acute Tubular Necrosis in Lupus Nephritis**

Shikha Wadhwani, Joshua Leisring, Anjali A. Satskar, Samir V. Parikh, Brad H. Rovin. Ohio State University Wexner Medical Center, Columbus, OH.

**Background:** Glomerular pathology drives management of lupus nephritis (LN) although acute tubular necrosis (ATN) is frequently seen on biopsy. The prevalence and significance of ATN in LN is unknown. To address these questions, we queried our native cohort to evaluate the frequency of ATN and its clinical characteristics in LN.

**Methods:** We reviewed ISN/RPS class, clinical, laboratorial, and histologic data on patients with LN. The relationship of ATN to patient demographics, pathology findings, and clinical outcomes were examined using Fischer’s exact or Mann-Whitney tests, as appropriate.

**Results:** ATN was found in 78 (25%) LN patients. Patients with ATN had significantly higher serum Cr (2.18 ± 29 vs 1.55 ± 1.37 mg/dL; P<0.001) and proteinuria (4.66 ± 4.3 vs 3.22 ± 3.05 g/g; P=0.032) at time of biopsy than those without ATN. The presence of ATN was not affected by race or gender. Patients with active crescents (P= 0.006), glomerular capillary necrosis (P=0.035), or interstitial inflammation (P=0.001) were significantly more likely to have ATN than patients without these lesions. The degree of interstitial fibrosis and tubular atrophy was not increased in patients with ATN. Of the patients with at least 3 years of follow-up (mean 7.3 ± 2.2 years in ATN group, 8.4 ± 2.3 years in no ATN group), serum Cr at follow-up was not significantly different in those with ATN (r=20) and those without (r=62).

**Conclusions:** ATN commonly accompanies severe glomerular injury in LN, and is associated with impaired kidney function and high levels of proteinuria. However patients with ATN do not seem to have more long-term renal damage than patients without ATN.

**Funding:** Clinical Revenue Support

SA-PO244

**Male Pediatric Lupus Nephritis Patients Experience Greater Mortality but Less Progression to ESKD**

Halei Benefiel,1 Meghan A. Jobson,2 Anna L. Baldwin,1 Eve Wu,1 William F. Fendergait,3 Keisha L. Gibson.1

The University of North Carolina, Chapel Hill, NC; 2University of North Carolina Kidney Center, Chapel Hill, NC; 3University of North Carolina School of Medicine, Chapel Hill, NC; 4University of North Carolina at Chapel Hill, Chapel Hill, NC.

**Background:** Epidemiological data on pediatric lupus nephritis are lacking. Here we present characteristics and outcomes of a racially diverse cohort of pediatric lupus nephritis patients.

**Methods:** We evaluated disease history and outcomes of patients age <19 years with tissue read through the UNC Nephropathology department as biopsy-proven lupus nephritis. Primary outcomes were end-stage kidney disease (ESKD) and death. Secondary outcomes included kidney transplant and adverse events per years of follow-up. Univariate logistic regression was used to calculate odds ratios and 95% confidence intervals with race (black or white) and sex coded as dichotomous categorical variables.

**Results:** Of 87 patients identified, 52 (60%) were female, 54 (62%) were black, 21 (24%) were white, and 12 (14%) were other. The mean follow-up duration was 11.6 years (SD 8.0). At diagnosis, 80% of patients presented with renal involvement, 59% with cutaneous symptoms, and 43% with hematological manifestations. The median age at biopsy was 14.6 years (IQR: 12.4, 17.2). 17 patients (20%) died with a median age at death of 20.8 years (18.9, 24.7). 18 patients (21%) progressed to ESKD with a median time to ESKD from first biopsy of 5.1 years (1.9, 7.4). Four patients (5%) underwent kidney transplant. Black patients experienced a median of 1.1 (0.4, 3.4) adverse events per years of follow-up versus 0.7 (0.4, 1.2) in white patients; male patients experienced 0.6 (0.4, 1.7) events versus 1.6 (0.5, 4.0) in female patients. Black patients had 1.7 times the odds of death (95% CI: 0.4, 6.8) and 3.0 times the odds of ESKD (0.6, 14.7) compared to white patients. Male patients had 1.4 times the odds of death (0.5, 4.1) but 0.2 times the odds of ESKD (0.06, 0.9) as compared to female patients.

**Conclusions:** Our findings suggest that black pediatric patients with lupus nephritis have higher morbidity and mortality than white patients and that male patients have higher mortality but less renal morbidity than female patients. Longer follow-up and continued cohort enrollment will be important to broaden our knowledge of pediatric lupus nephritis.

SA-PO245

**Evaluation of the slope of Change in eGFR as a Treatment Response Variable in Lupus Nephritis**

Ingrid R. Bispo, Evandro Klumb, Jose H. Saussanna. Rio de Janeiro State University, Rio De Janeiro, Brazil.

**Background:** In spite of treatment advances, up to 60% of lupus nephritis (LN) patients may eventually develop CKD. The current manifestations of LN include an active urinary sediment, proteinuria, and a loss of GFR. They are also the main tools determine treatment response, usually in a static fashion. We are not aware of any study that examined the predictive value of the slope of changes in renal function over time.

**Methods:** Of 660 patients with SLE that attended our institution, between August of 2014 and June of 2016, we found and analyzed 227 patients with established LN. Estimated GFR by the CKD-EPI equation was evaluated longitudinally by linear regression and slopes calculated as ΔGFR in mL/min/month. Patients were grouped in tertiles of GFR. Each tertile was analyzed by social-demographic, clinical, laboratorial and histopathologic features. Results were compared to treatment response variables as established in the literature. CKD and time to ESRD were analyzed as secondary outcomes.

**Results:** Women comprised 87% of the patients and mean age was 30 years. Proliferative GN predominated (77%) and mean of proteinuria at presentation was 3.6g/24h. The lowest tertile (worst response) was independently associated with race (Afro-Brazilians, P<0.05), lower levels of education (P<0.002) and with proliferative nephritides (P=0.03). Patients in this tertile also had more flares (P=0.003) but less active urinary sediment (P=0.03). On the other hand, the upper tertile (better response) was associated with higher education (P<0.001), lower number of flares (P<0.001), higher creatinine in the acute phase (P<0.001). Subjects in low tertile and those that did not achieve complete response were more like to present CKD and ESRD.

**Conclusions:** The combination of traditional response variables along with slopes of change in GFR may provide an added discriminatory predictive value for evaluation of the treatment response in lupus nephritis.

SA-PO246

**Impact of Extraglomerular Involvement on Clinical Presentation and Outcomes in Patients with Lupus Nephritis**

Krishan Lal L. Gupta, Hari A. Prasad, Manish Rathi, Aman Sharma, Ritambhara Nada. Post Graduate Institute of Medical Education & Research, Chandigarh, India.

**Background:** In patients with lupus nephritis, treatment and prognosis is characterized by its class which is based on glomerular pathology. Extra glomerular involvement, seen frequently was not considered in classification of lupus nephritis. Aim of this study was to analyze the incidence of tubulointerstitial and vascular involvement in lupus nephritis and their correlation with clinical presentation and outcomes.

**Funding:** Clinical Revenue Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Methods: This was a prospective retrospective cohort study including patients with biopsy-proven lupus nephritis. A total of 241 patients were included in the study period between January 2010 and June 2016.

Results: The mean age of study population was 29 years. Among 241 patients in the study group, male: female ratio was 1.7. Although the clinical parameters at presentation were similar between the two groups, male patients had poor outcomes when compared with females (response rates 58.6% vs 79.7%, P = 0.04; resistant disease 34.5% vs 15.7%, P = 0.01). Interstitial involvement including interstitial inflammation, interstitial fibrosis and tubular atrophy was seen in 60.1% and vascular involvement was seen in 32.3% of biopsies (Table 1). Patients with interstitial involvement had worse clinical parameters at presentation and poor outcomes at the end of 6 months of therapy (response rates 65.5% vs 82.7%, P < 0.01; resistant disease - 21.3% vs 10.7%, P = 0.03). Similarly in those with vascular involvement also had worse clinical parameters at presentation and poor outcomes (complete remission 38.2% vs 61.9%, P = 0.01; resistant disease - 26.3% vs 14.3%, P = 0.02). This trend of poor outcomes was especially seen in those with vascular TMA (response rates - 60% vs 79.1%, P = 0.04)(Table 1).

Conclusions: The involvement of extraglomerular compartment in lupus nephritis is common and they play an important role in determining the outcomes along with glomerular lesions.

Distribution of Extra glomerular lesions on renal biopsy

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Male (%)</th>
<th>Female (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial inflammation</td>
<td>45/410</td>
<td>17/75</td>
</tr>
<tr>
<td>Acute tubular necrosis</td>
<td>4/25</td>
<td>1/10</td>
</tr>
<tr>
<td>Vascular inflammation</td>
<td>13/115</td>
<td>1/5</td>
</tr>
<tr>
<td>Vascular injury</td>
<td>17/115</td>
<td>1/5</td>
</tr>
<tr>
<td>Tubular atrophy</td>
<td>2/25</td>
<td>0/10</td>
</tr>
<tr>
<td>Vascular TMA</td>
<td>0/115</td>
<td>0/5</td>
</tr>
<tr>
<td>Arterioles</td>
<td>1/25</td>
<td>1/10</td>
</tr>
</tbody>
</table>

SA-PO248

Clinical Parameters after Induction Treatment Are Better Predictors of 36-Month Renal Survival Than the Baseline Biopsy Histopathological Scores in Lupus Nephritis

Sonia Rodríguez,1 Luis E. Morales-Buenrostro,1 Norma O. Uribe-uribe,2 Juan M. Mejia-Vilte,3 Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico, Mexico; Instituto Nacional de Ciencias Medicas y Nutricion, Salvador Zubiran 4; Mexico City, Mexico; Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico.

Background: Baseline clinical parameters and histopathological scores have been associated with lupus nephritis (LN) outcomes. Recently, it was suggested that adding intimal hyperplasia findings to the NIH chronicity score (CS) may enhance its predictive value. We evaluated the capacity of before and after-treatment clinical and histopathological parameters to predict 36-month renal survival.

Methods: We included a cohort of 255 patients with class III, IV or V LN and a minimum 36-month follow-up. We registered clinical and histopathological parameters and determined their predictive value for 36-month renal survival by means of logistic regression and ROC curves. A new chronicity score (CS+vasc) was created by adding 0 or 1 point to the NIH chronicity score based on vascular intimal thickening findings.

Results: The cohort comprised 89% female patients, median age 28 years (IQR 23-37). Median baseline eGFR and proteinuria were 81ml/min (IQR 43-117) and 3.2g/g (IQR 1.9-5.3) respectively. Forty patients (15.7%) developed end-stage renal disease by 36 months. The ROC curves area under the curve were 0.732 for baseline eGFR, 0.602 for baseline proteinuria, 0.620 for the NIH activity score, 0.739 for the chronicity score, 0.760 for CS+vasc, 0.857 for 12-month eGFR, 0.835 for 12-month proteinuria (figure). A 12-month proteinuria <0.8 had 71% sensitivity and 88% specificity for 36-month survival (LR 5.70). The activity score was associated with lower renal survival exclusively at a cutoff of over 10 points.

Conclusions: Post-treatment 12-month proteinuria is an individual good renal survival predictor. At baseline, the best predictor is the histopathological NIH CS, which improved little with the addition of points for intimal thickening evaluation.
SA-PO250

The Long Term Outcome and Histological Transformation of ISN/RPS Class II Lupus Nephritis: A Retrospective Cohort Study

Background: Class II lupus nephritis (LN) due to the lack of scientific evidence. The role of immunosuppression, however, is less clear. The primary objective of this study is to assess the response of immunosuppressive therapy, the long-term prognosis and the histological transformation to other ISN/RPS classes among those who underwent a repeated biopsy.

Methods: A retrospective study was carried out that included patients who had received a diagnosis of LN class II on their first renal biopsy, between the years 1996 till 2016. The rate of complete remission, defined as Proteinuria less than 0.3 g per day, with normal creatinine 6 month after biopsy were also evaluated. We also compared the histological transformation among those who underwent a repeated biopsy during the follow-up.

Results: The study included 32 female patients with SLE and class II LN with the mean age of 31.2 years. The most frequent presentation (72%) was asymptomatic hematuria and/or subnephrotic range Proteinuria. The median serum creatinine and proteinuria at presentation were 78 umol/l and 0.8 gm per day, respectively. Acute kidney injury was noted in 7 patients (22%) and 3 patients (9.4%) had a nephrotic range proteinuria. The management was steroid alone in 25 patients (78%), Mycophenolate Mofetil in 6 patients (18.8%) and cyclophosphamide in 1 patient. Among the 25 patients treated with prednisolone alone (0.5-1 mg/kg), complete remission was seen in 22 patients (92%). After a median follow up of 8 years, two patients doubled their serum creatinine. The repeated biopsy was done in 17 patients (53%) and the detail of transformation to other classes is shown in table 1. The repeated biopsy showed transformation to other classes in 11 patients (65%).

Conclusions: Daily steroid monotherapy may be an appropriate first-line treatment for class II LN. Larger, prospective, trials are needed to validate this strategy and identify those patients who are less likely to obtain remission.

Funding: Government Support - Non-U.S.

SA-PO251

Early Renin-Angiotensin System Blockade Improved the Short-Term and Long-Term Renal Outcomes of Lupus Patients with Antiphospholipid-Associated Nephropathy

Background: Antiphospholipid-associated nephropathy (aPLN) represents a constellation of renal vasculopathies associated with antiphospholipid antibodies. Coexisting aPLN is associated with more severe renal involvement and worsened renal outcome in patients with lupus nephritis. Our aim with this research was to investigate the renal protective effects of early renin-angiotensin-aldosterone system (RAAS) blockade in lupus patients with aPLN.

Methods: Medical data of 57 lupus patients with biopsy proven aPLN were included. Early RAAS blockade was defined as administration of renin-angiotensin system inhibitors (RASI) within 3 months after kidney biopsy and continued for at least 12 months.

Results: Patients were comparable in demographic data, laboratory findings, and renal histology by the time of kidney biopsy, except that the RASI group had higher proteinuria level (5.2 [2.8-8.8] vs 1.9 [0.6-2.8] g/d, p=0.005) and higher prevalence of hypertension (75 vs 29%, p=0.001). The two groups were comparable in estimated glomerular filtration rate (eGFR), mean arterial pressure (MAP), and proteinuria level at 12 months after kidney biopsy. The improvement ratio of eGFR at 12 months was significantly higher in the RASI group (26 [5.5, 86] vs -2 [20, 50%], p=0.028), and the rate of change in eGFR after 12 months were comparable between groups. During a mean 80-month follow-up, 4 (23%) patients in the non-RASI group and 3 (8%) patients in the RASI group developed kidney disease progression. Early RAAS blockade significantly decreased the risk of kidney disease progression (HR 0.11 [0.02-0.59]; p=0.009). Proteinuria and hypertension controls were comparable between groups.

Conclusions: Early RAAS blockade improved the short-term and long-term renal outcomes in lupus patients with aPLN. The renal protective effect of RASI was independent of its antihypertensive and antiproteinuric effects.

SA-PO252

Successful Multitarget Therapy in Refractory Lupus Nephritis: A Retrospective Cohort

Background: Multitarget therapy (MT) with mycophenolate mofetil (MMF), calcineurin inhibitor and steroids has been studied for induction treatment of lupus nephritis (LN). Nevertheless, its use in refractory LN is still being evaluated.

Methods: Retrospective cohort study of adult patients with refractory LN (EULAR/EARA recommendations) treated with MT. Clinical characteristics, serological data and long-term follow-up were analyzed. Complete response (CR) and partial response (PR) were defined by KDIGO Clinical Practice Guideline for Glomerulonephritis.

Results: Data from 8 patients with refractory LN are shown in Table 1. The mean age was 34.6 ± 6 years and 87.5% were female. Mean sCr was 0.8 ± 0.2 mg/dl and median proteinuria was 3.7 (3.1 – 4.1) g/24h. All patients were treated with MMF (1 – 2g/day) plus cyclosporine A 2.5 – 4.0 mg/kg/day (7 patients) or tacrolimus 0.06 mg/kg/day (1 patient) plus steroids. After a follow-up of 18 (7.5 – 29.8) months, 7 patients had CR or PR, mean sCr was 1.0 ± 0.3 mg/dl and median proteinuria was 1.4 (0.8 – 2.0) g/24h. There were no major adverse events (severe infections or drug nephrotoxicity).

Conclusions: MT successfully induced CR or PR in most patients with refractory LN with no major adverse events.

Table 1. Patients characteristics and long-term follow-up of Multitarget Therapy in refractory lupus nephritis

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (y)</th>
<th>Gender</th>
<th>ISN/RPS Classification</th>
<th>Before Multitarget Therapy</th>
<th>Multitarget Therapy</th>
<th>Last visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>F</td>
<td>II-V + + + V</td>
<td>V</td>
<td>MMF/CYC</td>
<td>CR</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>M</td>
<td>II-V + + + V</td>
<td>CYA-MMF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>41</td>
<td>F</td>
<td>IV-A + V + V</td>
<td>CYA-MMF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>F</td>
<td>II-V +  + V</td>
<td>CYM-MF</td>
<td></td>
<td>PR</td>
</tr>
<tr>
<td>5</td>
<td>39</td>
<td>F</td>
<td>V-A + V + V</td>
<td>CYM-MF/CYC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>34</td>
<td>F</td>
<td>IV-A + V + V</td>
<td>CYM-MF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>35</td>
<td>F</td>
<td>III-V + + V</td>
<td>CYA-MMF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>42</td>
<td>F</td>
<td>IV-A + V + V</td>
<td>CYA-MMF</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cumulative incidence of kidney disease progression in lupus patients with aPLN, a kidney disease progression defined as 30% decline of eGFR or ESKD. 2B, kidney disease progression defined as 15% decline of eGFR or ESKD.

SA-PO253

Predictors of Renal Outcomes in Sclerotic Class ANCA GN

Background: The ANCA GN classification has been shown to have prognostic value in ANCA associated glomerulonephritis (GN) with sclerosing class portending poor renal outcomes. Relevant published data on factors predicting outcomes in sclerotic ANCA GN is limited and these patients are not well covered in published guidelines.

Methods: Patients were recruited from 1998-2016 from 4 centers worldwide (N= 45) for this retrospective cohort study. All patients had biopsy proven sclerotic ANGN with > 50% of sampled glomeruli showing global sclerosis. We describe the clinical characteristics of this cohort and evaluate predictors of one year GFR and ESRD.
Descriptive data are described as mean (SD). Logistic and linear regression models were used as appropriate.

Results: Of the 45 patients, 91% were Caucasian and 58% male with a mean age of 60 years. 80% had new diagnosis, 71% had renal limited disease and 84% were MPO ANCA positive. Kidney biopsies contained a mean (SD) 25 (18) glomeruli, mean (SD) % sclerosis was 69(12) with 96% showing moderate to severe interstitial fibrosis (IF). 43 patients received immunosuppressive therapy: 69% pulse solumedrol, 71% cyclophosphamide, 24% rituximab and 18% received plasmapheresis. Disease remission was achieved in all. The mean (SD) eGFR at entry was 15 (18) and at 1 year was 17(13) ml/min/1.73m. Entry GFR, rituximab use and IF but not % normal glomeruli were predictive of 1 year GFR (Table 1). Over a mean (SD) follow up of 60 (58) months, 25 patients reached ESRD and baseline GFR predicted risk of ESRD (p=0.04).

Conclusions: Entry GFR, use of RTX and lesser degree of IF predicted better GFR 1 year in sclerotic ANCA GN. Further studies are needed to validate these findings.

Predictors of GFR at 12 Months

- **Age:** p<0.05
- **Gender (Female):** p=0.07
- **ANCA type (PR3):** p=0.3
- **GFR at Entry:** p=0.12
- **Use of RTX versus CYC:** p=0.25
- **Glomerular Sclerosis ≥ 50%:** p=0.05
- **Percentage of normal glomeruli ≥ 50%:** p=0.05
- **Degree of Interstitial Fibrosis:** p≤0.005

Random effects meta-analysis of long-term, low dose GC as compared to GC discontinuation on relapse per patient year.

SA-PO256

Outcome Predictors in Childhood-Onset Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis: Clinicopathological Analysis in a Nationwide Japanese Survey

Daishi Hirano,1 Kazumoto Iijima,2 Shuichi Ito.1 1Department of Pediatrics, Graduate School of Medicine, Yokohama City University, Yokohama, Japan; 2Dep't of Pediatrics, Kobe Univ. Graduate School of Medicine, Kobe, Japan. 1The Jikei university school of medicine, Tokyo, Japan.

**Background:** Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) occurs mainly in adults (estimated annual incidence = ∼20 per million, peak age at onset 60 years). Little is known about the disease in children. Here, we examined clinicopathological predictors of patient and renal outcomes in childhood-onset AAV.

**Methods:** This was a retrospective nationwide multicenter survey of patients with AAV diagnosed before age 16. Eligibility criteria were: (1) fulfilled the Chapel Hill Consensus Conference criteria for microscopic polyangiitis (MPA) or granulomatosis with polyangiitis (GPA), and (2) kidney biopsy showing histology consistent with AAV.

**Results:** The cohort consisted of 46 children; 35 (76%) were female, 38 (83%) had GPA, 12 (26%) had MPA, 91% had GPA, 83% were MPO-ANCA-positive, 13% were PR3-ANCA-positive. Median age at onset was 10.7 years, and median time to diagnosis was 2.0 months. Initial symptoms included fever and fatigue (43%), renal (74%), pulmonary (30%), ocular (20%), and mucocutaneous involvement (22%). Clinical features differed between MPA and GPA. Remission was achieved after induction therapy in 27 (55%) cases. After a median follow-up of 3.6 years, 14 (30%) patients had chronic kidney disease stages 2–3. Seven (15%) patients progressed to end-stage renal disease (ESRD). Renal outcome was better in GPA than MPA. In univariate analysis, although sex, age at onset, and diagnosis delay were not associated with risk of progression to ESRD, type of AAV, nphreotic-range proteinuria, and histological chronicity indices predicted renal outcome.

**Conclusions:** There were significant differences between two types of AAV in terms of clinical features and outcomes. Nephrotic-range proteinuria was an independent included. Quality of evidence was assessed using modified Newcastle-Ottawa criteria. Meta-analysis was completed using a random-effects model of DerSimonian and Laird.

**Results:** 24 studies met criteria with 2272 patients. 13 (54%) discontinued GC in < 1 year. The pooled relapse rate was 14.3 per 100 patient years (95% CI 4.5,24.0). Relapse was more frequent when discontinuation was compared to long-term, low-dose GC (20.7 per 100 patient years, 95% CI 6.3,34.5 vs. 8.0 per 100 patient years, 95% CI 5.7,21.7 Figure 1). Multivariable linear meta-regression confirmed that long-term, low-dose GC was associated with lower relapse rates (β = -0.16, 95% CI -0.26,0.07, P = 0.001) and follow up time was associated with increased relapse rates (β = 0.003, 95% CI 0.001,0.006, P = 0.002). Multivariable linear meta-regression did not demonstrate any association of GC dosing with infections.

**Conclusions:** Long-term, low-dose GC was associated with decreased relapse rates in patients with AAV. Characterization and reporting of adverse events limited analysis. RCT are needed to determine optimal GC administration.

**Funding:** Private Foundation Support
**SA-PO257**

**Design of the Maintenance of ANCA Vasculitis Remission by Intermittent Rituximab Dosing Based on B Cell Reconstitution versus a Serologic ANCA Flare (MAINTANCAVAS) Trial**

**Frank B. Cortazar,1 William F. Pendergraft,2 Colleen B. Dunbar,2 Karen A. Laliberte,2 John Niles,2 1University of North Carolina Kidney Center, Chapel Hill, NC; 2Nephrology, Massachusetts General Hospital, Boston, MA.**

**Background:** B cell depletion with rituximab (RTX) is an effective strategy for maintenance of remission in ANCA vasculitis. Unfortunately, cessation of therapy is associated with a high rate of relapse, while indefinite continuation of fixed-dose treatment is associated with significant complications. No clinical trial data exists to guide the optimal use of RTX after two years of maintenance therapy. To address this unmet need, we designed the MAINTANCAVAS Trial.

**Methods:** The MAINTANCAVAS Trial is an open-label, randomized, and two-arm controlled trial to evaluate the efficacy of two RTX dosing strategies to prevent disease relapse: 1) RTX dosing upon B cell reconstitution (B cell arm), and 2) RTX dosing upon a significant rise in ANCA titer (ANCA arm). Eligible patients have a history of ANCA vasculitis and have completed at least 24 months of fixed-interval (i.e., every 4-6 months) RTX maintenance therapy in remission (BV AS-WG=0 and prednisone ≤ 7.5 mg/day). Upon randomization, patients discontinue fixed-interval RTX and are followed with clinical assessment and laboratory monitoring every three months. Patients assigned to the B cell arm are re-dosed with RTX 1 gm x 1 when the CD20 count rises above 10/mm3, while patients in the ANCA arm are re-dosed with RTX 1 gm x 2 (separated by 2 weeks) when the ANCA titer rises by pre-specified level. The primary outcome is disease relapse at 36 months. Secondary outcomes include significant adverse events, vasculitis damage, patient preference for RTX utilization. At an alpha level of 0.05 and power of 0.80, 180 patients are required to detect a 15% difference in relapse between the strategies.

**Results:** Enrollment commenced 6/7/2016. To date, a total of 43 patients have been enrolled. No relapses have occurred. Six patients in the B cell arm (n=22) have been re-dosed with RTX at the following times: 6 months (n=2), 9 months (n=3), and 1 year (n=1). No patients in the ANCA arm have been re-dosed. There have been no serious adverse events.

**Conclusions:** The optimal long-term RTX dosing strategy for maintenance of remission in ANCA vasculitis remains unknown. The MAINTANCAVAS trial should provide useful information to address this important question.

**SA-PO258**

**Associated Clinical Characteristics in Anti-Neutrophil Cytoplasmic Antibody Negative, Pauci-Immune Crescentic Glomerulonephritis: Results of a Case Series at a Tertiary Care Center**

**Amacchi,1 Briner,1 Milos N. Buda,1,2 Charleston, SC; 2Medical University of South Carolina, Charleston, SC; 3Medical University of South Carolina, Charleston, SC.**

**Background:** Pauci-immune crescentic glomerulonephritis (PCGN) is the most common cause of rapidly progressive glomerulonephritis in adults and elderly patients. Approximately 30-50% of patients with PCGN have anti-neutrophil cytoplasmic antibody (ANCA) negative vasculitis. The literature on the etiology of idiopathic ANCA negative PCGN has never been clearly characterized besides a few case reports. We therefore conducted a case series of patients in our tertiary care center diagnosed with pauci-immune crescentic glomerulonephritis in the last 33 years to see if there was any specific associated factors.

**Methods:** We looked at all the patients in our hospital that had a diagnosis of pauci-immune crescentic glomerulonephritis from November 1994- June 2017. Those with additional diagnosis such as glomerular basement membrane disease or other autoimmune disorders were excluded. We identified 59 patients however, some had incomplete records and they were further excluded. The final number was 14 patients, of which 10 were ANCA- positive and 4 were ANCA-negative. Their medical records were evaluated for any associated medical conditions.

**Results:** Out of the 4 patients who were ANCA-negative, all of them had an infection that triggered their illness and that was clearly present at the time of renal failure diagnosis (100%); whereas, only 2 out of the 10 who were ANCA-positive had an associated infection with their illness (20%). In this small series of patients, the two categories of patients had a similar severity of illness as estimated by their Sequential Organ Failure (SOFA) score at the time of onset (3.6 and 3.5 respectively).

**Conclusions:** 100% of our patients with a diagnosis of ANCA-negative PCGN had associated infections preceding their illness, whereas this was true of only 20% of the ANCA-positive ones. The infections involved included BK virus, Parvovirus, Staph aureus meningitis and streptococcal pneumonia. Our results suggest that there is a positive link between otherwise idiopathic ANCA-negative crescentic pauci-immune glomerulonephritis and a preceding episode of infection.

**SA-PO259**

**Relapse Free Survival after Steroid Withdrawal in ANCA Vasculitis**

**Eirini LIoudaki,3 Marie B. Condon,4 Lubna Rashid,4 Fiona E. Harris,3 David Makanjuola,4 Bhirju Raj Sood,2 EPSOM and St Helier NHS Trust, Surrey, United Kingdom; 3West South Thames Renal Unit, Carshalton, United Kingdom; 4St Helier Hospital, London, United Kingdom; St Helier Hospital, Surrey, United Kingdom; ST HELIER HOSPITAL, London, United Kingdom.**

**Background:** Current immunosuppressive regimens have made a marked difference to patient and organ survival; toxicity associated with long term treatment is recognised. Withdrawal of treatment is associated with disease relapse. It is unclear if there are cohorts of patients in whom immunosuppression can be withdrawn and if so when. We report, from our centre on the long term outcomes on 93 patients(p) in whom steroid maintenance treatment was withdrawn after a stable remission was achieved.

**Methods:** 93 pts identified from a long term cohort of 219 pts presenting over a 13 year period. Data collected from medical records. Follow up ranged from 6 - 168 mths (median 66mths). Remission was achieved with standard induction (Plasma Exchange, Cyclophosphamide (cy clo) (oral or intravenous), mycophenolate mofetil (MMF) or Rituximab; all in combination with corticosteroids) and maintained with Azathioprine or MMF in combination with corticosteroid. In patients in whom a stable remission was achieved, withdrawal of corticosteroid would begin at 18 to 24 mths. We have looked at steroid withdrawal and subsequent disease activity.

**Results:** 38 female; 87 white ethnicity; median age at diagnosis of 69 yrs (range 18-89). Median creatinine (creat) at presentation was 309mmol/L; 22 pts with a serum creat >500. Induction: 86 pts cyclo (6 oral, 80 IV); 1 Rituximab, 1 Azathioprine, 5 MMF. 30 pts received plasma exchange. Median time to cessation of prednisolone from induction was 25mths (4-93). 72 pts (77%) remain relapse free at a median of 39 months since steroid withdrawal (3-126). Antibody class or induction treatment did not predict relapse free status; neither did presentation renal function (median creat 309 in non relapse pts / creat 230 in relapse). Follow up of patients who had relapsed was longer than for those who were disease free; 110 (53-163) versus 66 (14-165) mths, however 62 patients have remained disease free for over 18mths off steroid. (median 24 (range 4-93)).

**Conclusions:** In this cohort we have so far not identified a clear predictor of steroid withdrawal without relapse; however 77% of our patients remain relapse free off steroid with significant follow up period. We would suggest that withdrawal of steroid should be the aim when patients have achieved a stable remission, and that this can be achieved safely with close monitoring.

**SA-PO260**

**Combination Therapy with Rituximab and Cyclophosphamide for Remission Induction in ANCA Vasculitis**

**Frank B. Cortazar,4 Saif A. Mulhins,1 William F. Pendergraft,2 Zachary S. Wallace,3 Colleen B. Dunbar,2 Karen A. Laliberte,2 John Niles,1 Massachusetts General Hospital, Boston, MA; 2University of North Carolina Kidney Center, Chapel Hill, NC; 3Nephrology, Massachusetts General Hospital, Boston, MA.**

**Background:** Remission induction in ANCA vasculitis may be complicated by slow response to treatment and toxicity from glucocorticoids. More effective and less toxic regimens are needed.

**Methods:** Patients were included if they had ANCA vasculitis and were treated with a standardized remission induction regimen (SIR) (Rituximab 1000 mg Q 2 weeks x 2 doses, oral cyclophosphamide 2.5 mg/kg x 1 week and 1.5 mg/Kg x 7 weeks (adjusted for eGFR), and a rapid prednisone taper that lowers the dose to ≤15mg by 1 month. Complete remission (CR) was defined as a BV AS-WG of 0 and a prednisone dose ≤ 7.5 mg/d.

**Results:** We identified 129 patients treated with the SIR, 31% of whom also received PLEX for RPGN or pulmonary hemorrhage (PH). Seventy percent of patients had MPO-ANCA and 30% had PR3-ANCA. Median time to CR was 4 months (IQR, 3.9 to 4.4), and by 5 months 84% of patients were in CR. Prednisone was tapered to discontinuation as tolerated, such that the median prednisone dose at 8 months was 0 mg/day (IQR, 0 to 2.5). In patients with RPGN (n=75), PR3-ANCA was associated with a greater increase in eGFR at 6 months compared with MPO-ANCA (16.1 [IQR 0.0 to 22.5] versus 5.6 [IQR, -0.4 to 15.6] ml/min/1.73m2; p=0.028). During the first year following CR, 1 major relapse occurred over 122 patient-years. Serious infections occurred more frequently in patients receiving PLEX and were associated with increasing age and PH. Four deaths occurred, 3 of which were associated with serious infections.

**Conclusions:** Combination therapy with rituximab and cyclophosphamide was efficacious, allowing for rapid tapering of high-dose glucocorticoids and was well tolerated.

**Funding:** NIDDK Support, Clinical Revenue Support
SA-PO261

Plasmapheresis, Rituximab, and Low-Dose Cyclophosphamide for Remission Induction Therapy in Severe ANCA-Associated Vasculitis


Background: Rituximab (RTX) is an established treatment for remission-induction in ANCA-associated vasculitis (AAV), though data regarding its use in immediately organ- or life-threatening disease are limited. We have studied the use of RTX as adjunctive therapy to plasmapheresis (PEX), cyclophosphamide (CYC) and oral steroids in patients presenting with diffuse alveolar haemorrhage (DAH) or severe renal failure (presenting requirement for dialysis or serum creatinine >500μmol/L).

Methods: This is a cohort study of patients treated for severe AAV between 2011-15 with a combination of PEX, low dose pulsed i.v. CYC (6x500-750mg) and RTX (2x1g after completion of PEX) and tapered oral corticosteroids (initial dose 1mg/kg, maximum 60mg od) without intravenous steroids. Maintenance therapy was commenced at 3 months with azathioprine (MMF if intolerant) and patients received prophylactic treatment for PCP, peptic ulcer disease and osteoporosis. Data are reported as median & IQR.

Results: Thirty patients have been treated with this regimen, with median follow-up 2.1 yrs. Median age was 62 yrs (IQR 55-75); 50% were PR3-ANCA+ve, 50% MPO-ANCA+ve. Presenting BVAS was 21 (16-25), creatinine 452 μmol/L (338-590), and 43% required dialysis. DAH was present in 43%. Patients received 7 (7-10) plasma exchanges, and cumulative RTX and CYC doses were 2g (all patients) and 3g (2.5-3.5), respectively. At 6 months, 90% of patients were in remission (BVAS=0). All patients achieved B cell depletion (<1 cell/µL) and 83% became ANCA negative at median 5.1 months. The median time to B cell repopulation (>10 cell/µL) was 35 months. Sustained B cell depletion was associated with low rates of relapse during long-term follow up: at 1, 3 and 5 years, 96%, 84% and 75%, of patients, respectively, were in sustained remission. The serious infection rate was 0.4/yr and 6 patients developed hypogGl. Renal survival was 72%, 64%, 64% at 1, 3 and 5 years. Overall patient survival was 93%, 79% 79% at the same respective time points.

Conclusions: This combination regimen was an effective remission-induction strategy in severe AAV. Long-term relapse rates and renal and patient survival were favourable in a cohort of patients presenting with life-threatening disease manifestations. Combination regimens warrant further investigation in severe AAV.

SA-PO262

ATwo-CentreCohortExperienceofAnti-GBMDisease

Marilina Antonelou,1 Benjamin A. Oliveira,2 Astrid Baumann,1 Mark Blunden,1 Mark Harber.2 1Royal Free Hospital, London, United Kingdom; 2UCL centre for Nephrology, London, United Kingdom; 3Royal London Hospital, London, United Kingdom.

Background: The important determinant for the response of therapy and long term prognosis in anti-glomerular basement membrane (GBM) disease is early diagnosis. The aim of this study is to identify possible delays in the recognition and treatment of the disease and determine renal outcomes.

Methods: Retrospective review of cases of all patients identified as anti-GBM positive presenting in two tertiary referral centres and associated district hospitals between 1978 and 2016. Case notes, pathology archives and laboratory results were reviewed to collect demographic and clinical data at presentation and last follow-up.

Results: Forty nine patients presented across both sites with anti-GBM disease (28 at the Royal Free and 21 at the Royal London Hospital), 27 (34.2%) of which initially presented to a district hospital prior to transfer. Twenty five (51%) were male. Their median age was 58 (10-82) years and GBM titre 134(31-779) U/ml. Thirty (61%) had a renal biopsy. Seven (14%) had pulmonary haemorrhage at presentation. Figure 1 shows different time interval points where delays can occur from presentation to treatment. The median follow up was 4 (0.3-37.9) years. 70% became dialysis dependent within a month of presentation. At last follow-up (n=41), 12(29.3%) had received a renal replacement therapy (RRT) dependent, 12(29.3%) had received a renal transplant and three (7.3%) were RRT independent. Fourteen (34.1%) patients died.

Conclusions: Patients with (GBM) disease are at increased risk of morbidity and mortality. Local review of clinical practice is crucial to avoid delays in establishing a diagnosis and initiating treatment.

SA-PO263

Describing the Natural History of C3 Glomerulopathy

Chloe E. Campert,1,2 Richard J. Smith,2,3 Carla M. Nester,2,3 University of Iowa Carver College of Medicine, Iowa City, IA; 2Molecular Otolaryngology and Renal Research Laboratories, University of Iowa, Iowa City, IA; 3Rare Renal Disease Clinic, Department of Pediatrics and Internal Medicine, University of Iowa, Iowa City, IA.

Background: C3 glomerulopathy (C3G) is a rare, aggressive form of complement-mediated glomerular disease that carries the highest risk for irreversible renal failure of the known glomerular diseases. This dismal outlook results not only from a poor understanding of the natural history of disease (i.e. both what marks disease activity and what constitutes treatable disease), but also from the lack of disease-directed therapeutics. We have recently expanded the clinical data capture for our research subjects, and now include all patients with C3G seen in the University of Iowa’s Rare Renal Disease Clinic. The following is the initial clinical cohort.

Methods: Data are derived from the clinic records of a contemporary cohort of 36 patients with a biopsy-proven diagnosis of C3G who have at least 1 year of clinical follow-up. Data are reported (without censoring for broader pathology characteristics) from time of presentation and at last follow-up.

Results: 29 C3GN and 7 DDD patients met criteria for evaluation. There was no difference in C3 at presentation or follow-up between the two disease types. No statistically significant difference was noted in eGFR at presentation. At last follow-up, 38% and 57% of C3GN and DDD patients respectively were at CKD Stage 3 or greater. DDD patients were more likely to progress to transplant.

Conclusions: C3GN and DDD are clinically similar, aggressive diseases with high risk for progression to late stage CKD. Routine clinical parameters and biomarkers of disease do not distinguish the two groups. Expansion of the cohort size and longitudinal re-evaluation is ongoing. Analyses of pathology and expanded biomarkers are ongoing. We expect this data will be critical for devising effective treatments for this group of patients.

Funding: NIDDK Support
Table 1. Clinical and biological data according to histological type

<table>
<thead>
<tr>
<th>HC (n=29)</th>
<th>KD (n=7)</th>
<th>p value (v=0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Cr (mg/dL)</td>
<td>1.5</td>
<td>1.6</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m2)</td>
<td>54.3</td>
<td>32.9</td>
</tr>
<tr>
<td>Serum C3 (mg/dL)</td>
<td>90.3</td>
<td>66.7</td>
</tr>
</tbody>
</table>

SA-PO264
Overlap of C3 Glomerulonephritis and Thrombotic Microangiopathy
Aishwarya Ravindran, Fernando C. Fervenza, Sanjeet Sethi. Mayo Clinic, Rochester, MN.

Background: Dysregulation of the alternate pathway (AP) of complement underlies the pathogenesis of both C3 glomerulonephritis (C3GN) and thrombotic microangiopathies (aHUS/TMA). In this study, we describe both the disease entities occurring in a series of 5 patients.

Methods: We identified 114 patients seen at the Mayo Clinic from 2007-2016 with a diagnosis of C3 glomerulopathy (C3GN or DDD) in native kidney biopsies. Patients with tissue diagnosis of thrombotic microangiopathy along with C3GN were included in this study. We reviewed the clinical and laboratory data at the time of diagnosis of C3GN or DDD. We also reviewed their data at the time of diagnosis of aHUS/TMA.

Results: The median age at diagnosis was 58 years (range: 28-69), all were male. The median serum creatinine and proteinuria at presentation were 2.2 mg/dL (range: 1.7-3.2) and 2089 mg/24 hours (range: 250-5220). Monoclonal protein was present in 1 of the 3 patients tested. None of the patients had a history of infection or autoimmune disease. Light microscopy showed a membranoproliferative GN in 3 patients and a mesangioproliferative GN in 2 patients. Immunofluorescence showed bright C3 staining in the mesangium and or capillary walls. On electron microscopy, capillary loops showed marked subendothelial expansion by fluffy material (and absence of deposits in these loops). However, capillary wall deposits were present in other loops in 4 (80%) of 5 patients. Mesangial deposits were present in all the biopsies. Ultrastructural features of DDD were not present; thus all biopsies were consistent with C3GN and aHUS/TMA. Dysregulation of the AP of complement proteins due to over activation of the alternative pathway of complement.

Conclusions: We describe the clinicopathological features and renal outcomes of patients with features of both C3GN and aHUS/TMA. Dysregulation of the AP of complement can result in either C3GN, aHUS/TMA, or overlapping C3GN/aHUS.

SA-PO265
Triggering Factors and Associated Conditions in C3 Glomerulopathy
Aishwarya Ravindran, Fernando C. Fervenza, Sanjeet Sethi. Mayo Clinic, Rochester, MN.

Background: C3 glomerulopathy (C3G), comprising C3 glomerulonephritis (C3GN) and dense deposit disease (DDD), is characterized by glomerular accumulation of complement proteins due to over activation of the alternative pathway of complement. Most of the reports on C3G were based on individual cases or small series of C3GN/DDD patients. There are no large scale studies describing the triggers/acquired conditions associated with C3G.

Methods: We identified 114 patients seen at the Mayo Clinic from 2007-2016 with a diagnosis of C3G, of which 102 (89.5%) had C3GN and 12 (10.5%) had DDD. We reviewed the clinical and laboratory data at the time of diagnosis of C3GN or DDD. Patients with tissue diagnosis of thrombotic microangiopathy along with C3GN were included in this study. We reviewed the clinical and laboratory data at the time of diagnosis of aHUS/TMA.

Results: Our study revealed 3 main triggers/acquired conditions associated with C3G: monoclonal Ig, infections and autoimmune diseases (figure 1). 1) Ninety five (83.3%) of the 114 patients were evaluated for a monoclonal Ig. Overall, 36 (32.7%) had a monoclonal Ig; furthermore, 65.1% patient’s 50 years had a monoclonal Ig. Twenty-six patients were classified as MGUS/MGRS, 5 as multiple myeloma, 2 as smoldering myeloma, 1 as CLL, 2 with cryoglobulins of which one was associated with lymphoma of the stomach. 2) Thirty-three (28.9%) patients had a history of infection at the time of diagnosis, with upper respiratory tract infection as the most common infection associated with C3G. Post-infectious GN was ruled out as these patients continued to have persistent hematuria long after resolution of the infection. 3) Twenty-seven (23.7%) patients had history of autoimmune diseases. The most common findings of autoimmunity was a positive ANA in 12 (10.2%), positive dsDNA in 6 (5.2%) and positive antiphospholipid antibody in 3 (4.1%) patients.

Conclusions: Triggering factors and acquired conditions are commonly present and can be the principal drivers of C3G. Each case should be evaluated for these conditions as these disorders can be important therapeutic targets in the management of C3G.
Routine Urinalysis Does Not Correlate with Kidney Pathology in IgA Nephropathy after Steroid Therapy

Hyaejin Yun,1 Byoung-soo Cho,2 Sung min Jung,2 Wang kwang Hong,4 Daeyoung Kim,3 Sung-gyu Ha,1 Haengil Ko.1
1MIRAE ING Kidney Center, Seoul, Republic of Korea; 2MIRAE ING Kidney Center, Seoul, Republic of Korea; 3MIRAE ING kidney center, Seoul, Republic of Korea; 4Byuea plastic surgery, Seoul, Republic of Korea; 5-biotech, Seoul, Republic of Korea.

Background: Routine urinalysis, especially hematuria and proteinuria, has long been used as the most important laboratory tools in the diagnosis of glomerulonephritis and also as the most frequently used screening tool for kidney problems at follow-up or health checking program. Recently other newly developed markers for kidney injury, such as cystatin-c, KIM-1, L-FABP, NGAL etc., were developed but not routinely used because of lack of accumulated convincing data as yet.

Methods: We performed follow up kidney biopsy who showed normal urinalysis and serum cystatin-c for more than 3 months after steroid therapy to check the kidney status in 23 patients with IgA nephropathy. All 23 patients took long-term steroid therapy more than 6 months. Mean age was 28.1 years old. Mean follow up biopsy interval was 13.3 months. Table 1 showed performed at the OPD level without admission. We used ACE-Cut disposable biopsy needle under the ultrasound guide.

Results: All 25 cases showed abnormal urinalysis such as persistent hematuria, persistent proteinuria or associated with hematuria and proteinuria at initial kidney biopsy, and showed persistent normal urinalysis findings include hematuria and proteinuria more than 3 months at the time of follow up renal biopsy. Twenty cases showed persistent original diseases although slight to moderate degree pathological improvement. However only 5 cases progressed renal pathologies at the time of follow up biopsy. Among five patients, four already progressed. 3 cases showed improvement of urinalysis findings and urine protein to creatinine ratio.

Conclusions: Although further studies are needed, anyone who showed segmental or global sclerosis, when associated with moderate to severe tubular atrophy and interstitial fibrosis at initial kidney biopsy, follow up kidney biopsy is mandatory even showed persistent normal urinalysis and lab findings before finishing steroid therapy.

The Cure Glomerulonephropathy (CureGN) IgA Nephropathy and IgA Vasculitis Pediatric Cohort David T. Slezak1, Raed Bou Matar2, Yi Cai3, Aftab S. Chishti4, Vivette D.D’Agati5, Cynthia J. D’Alessandro-Silva3, Rasched A. Gbadegesin6, Debbie S. Gipson7, Margaret Helmhut4, Sandra Iragorri2, Myda Khalid5, Helen Liapis8, Francesca Lugani9, Sherene Mason2, Carla M. Mester2, Damien G. Noone2, Michelle N. Rheault, Rajasree Sreedharan, Tarak Srivastava, Agnieszka Swiatecka-Urban, Kjetil Tonnessen10, All kidney biopsy performed by Ismail D.A. Weaver,1 Hong Yin,1 Krzysztof Kirepl2, Children’s Health Care of Atlanta, Atlanta, GA; 3Columbia University, New York, NY; 4The Hospital for Sick Children, Toronto, ON, Canada; 5Arbor Research Collaborative for Health, Ann Arbor, MI; 6Arkan Laboratories, Munich, Germany; 7Children’s Hospital of Pittsburgh of UPMC, Pittsburgh, PA; 8Children’s Mercy Hospital, Kansas City, MO; 9Columbia University College of Physicians and Surgeons, New York, NY; 10Connecticut Children’s Medical Center, Hartford, CT; 11Duke University Medical Center, Durham, NC; 12G.Gaslinski Children’s Hospital, Genova, Italy; 13Helen De Vos Children’s Hospital, Grand Rapids, MI; 14Indiana University, Indianapolis, IN; 15Levine Children’s Hospital at Carolinas Medical Center, Charlotte, NC; 16Medical College of Wisconsin, Wauwatosa, WI; 17Medical University of South Carolina, Charleston, SC; 18Cleveland, OH; 19University of Iowa, Iowa City, IA; 20University of Kentucky, Lexington, KY; 21University of Minnesota, Minneapolis, MN; Group/Team: On behalf of the CureGN IgA writing group.

Background: Cure Glomerulonephropathy (CureGN) is a multi-center(66 sites), NIDDK-funded longitudinal observational cohort study of 2400 prevalent (biopsy within 5 years) patients with minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, and IgA nephropathy (IgAN), including IgA vasculitis (IgAV), previously referred to as Henoch-Schönlein Purpura). The IgAN/IgAV cohort has recently filled and we present the enrollment data for pediatric IgAN and IgAV.

Methods: Data for all pediatric patients (-18 years) with biopsy confirmed IgAN or IgAV were reviewed. This analysis compares those with IgAN and IgAV. Data (lab) treatment up to the time of enrollment are shown using descriptive statistics and univariate tests with results as median(IQR) or N(%).

Results: 590 patients are enrolled in the IgAN/IgAV cohort including 235 pediatric patients (43.6%) IgAN and 92 (19%) IgAV. A comparison of IgAN and IgAV is presented in Table 1. Those with IgAN differed significantly in age at diagnosis, disease duration, proteinuria at biopsy, and serum albumin at biopsy. Those with IgAV were significantly more likely than those with IgAN to receive immunosuppression and combination therapy (Table 1).

Conclusions: This study reveals significant differences in the demographics, disease presentation and treatments in children with IgAN and IgAV. Participants will now be followed longitudinally. CureGN will further define disease characteristics such as disease progression, pathophysiology, and response to therapy.

SA-PO268

Clinical Glomerular Disorders: Vasculitis, C3G, IgAN

Poster/Saturday

Occurrence of IgA Nephropathy with Lupus Nephritis Ana Malvar1, Valeria G. Alberton4, Bruno J. Lococo, Renzo Tais,1 Matias Ferrari,1 Pamela Delgado,1 Angelica Sarabia,1 Brad H. Rovin,2 Fernandez Hospital, Buenos Aires, Argentina; 3Ohio State University Wexner Medical Center, Columbus, OH; 4HOSPITAL FERNANDEZ, Buenos Aires, Argentina; ‘hospital Fernandez, Buenos Aires, Argentina; ‘DIAVERUN, Buenos Aires, Argentina.

Background: IgA nephropathy (IgAN) without lupus nephritis (LN) has been seen in a small number of patients with SLE who developed proteinuria. The coincident occurrence of IgAN and LN has been previously reported. We describe 5 patients with LN who had prominent mesangial IgA deposits that persisted after induction therapy for LN resulted in resolution of the other immune complexes.

Methods: A cohort of 131 proliferative LN patients had a kidney biopsy for diagnosis (Bi x1) and again after induction with steroids plus MMF or cyclophosphamide (Bi2). Mean follow up was 42 ±7 months.

Results: Five patients (4 females; average age 38) were found to have dominant IgA deposits before and after induction therapy for LN. LN class, immunofluorescence pattern, serum creatinine (Scr), and 24-hour proteinuria (prot) are described in the table. At Bi2 20% of IgA-dominant patients achieved a complete renal remission (prot < 0.5 g/d; normal Scr mg/dl) compared to 41% of the whole cohort. CKD developed in 60% of the IgA-dominant patients and 20% of the whole cohort after 4 years of follow up.

Conclusions: We identified a small subset of patients with proliferative LN who simultaneously appeared to have IgAN. This subset of patients did not appear to do as well with induction therapy or during long-term follow-up of a contemporaneous cohort of proliferative LN patients.

SA-PO270

Chronic HBV Infection Was Associated with Failure to Complete Remission of IgA Nephropathy Hasting Wu,1 Zhen Wu,2 Yubing Wen,3 Jianfang Cai,4 Hang Li,2 Xiaomei Li,2 Xuewang Li.2 Beijing Frendship Hospital, Capital Medical University, Beijing, China; 3Peking Union Medical College Hospital, Chinese Academy of Medicine Sciences & Peking Union Medical College, Beijing, China.

Background: Chronic HBV infection is associated with Glomerulopathies including IgA nephropathy. We conducted a retrospective study to investigate the association between chronic HBV infection and remission of IgA nephropathy.

Methods: In this retrospective cohort, 715 patients with biopsy-proved IgA nephropathy were included, of whom 95 were diagnosed as chronic hepatitis B virus (HBV) infection defined as persistent positivity of hepatitis B virus surface antigen. Data on age, sex, body mass index, presence of hypertension and diabetes mellitus, laboratory tests prior to treatment, and therapeutic regimens were retrospectively retrieved from medical records. Complete remission (CR) was defined as a 24-hour urinary protein <0.3 g/d with a stable estimated glomerular filtration rate (eGFR). Multiple logistic regression analysis was used to estimate the association of HBV infection with CR and a 30% decline in eGFR.

Results: Patients with chronic HBV infection were younger (27.31±3.64 vs 35.64±11.51, P<0.005) and more likely to present heavier proteinuria (3.02±3.44, 2.0±2.18 g P<0.001) and avoid using immunosuppressive agents (10.52%, 58.57%, P<0.001) compared with those free of chronic HBV infection. However, the two groups did not differ in baseline eGFR, presence of hypertension and diabetes, administration of RAAS inhibitors and glucocorticoids. In one-year follow-up, HBV infection was associated with failure to CR in proteinuria (OR [95% CI], 2.10 [1.173-3.758], P=0.013),
but not with a 30% decline in eGFR(OR [95% CI], OR 1.192 [0.438-3.249], p=0.731), independently of gender, age, diabetes, hypertension, baseline eGFR, 24-hour urinary protein, use of glucocorticoids, immunosuppressive agents and RAAS inhibitors.

Conclusions: Chronic HBV infection may be associated with failure to complete remission of IgA nephropathy.

SA-PO271

The Derivation and Validation of an International Multi-Ethnic Risk Prediction Model in IgA Nephropathy Sean Barbour, Rosanna Coppo, Yusuke Suzuki, Zhi-Hong Liu, Gabriela Espin-Hernandez, Heather N. Reich, Daniel C. Catran, BC Renal Agency, Vancouver, BC, Canada; Torino, Italy; 1Universidad de Tokyo, Tokyo, Japan; 2Nanjing University, Nanjing, China; 3University of Toronto, Toronto, ON, Canada; 4University of BC, Vancouver, BC, Canada. Group/Team: International IgAN Collaboration.

Background: Predicting renal outcome in IgA nephropathy (IgAN) is challenging. A prediction model is needed to improve risk stratification that is properly validated in multiple ethnic groups worldwide and can be used in clinical practice. To overcome these obstacles, we used large datasets from international collaborators to generate an accurate prediction model in IgAN.

Methods: The derivation dataset was from European, Japanese and Chinese adult cohorts; the validation dataset was from separate North/South American, European, Chinese and Japanese cohorts. Time from biopsy to the composite outcome (50% decline in eGFR or ESRD) was analyzed using Cox survival models.

Results: The validation dataset (N=2784) is 42% Caucasian, 21% Japanese and 37% Chinese; 18% (N=495) experienced the composite outcome over a median 4.8 years of follow-up. Two models were considered: a reduced model containing eGFR, blood pressure, proteinuria at biopsy, and MEST score; and a full model that also contained age, sex, race, use of RAS blockade/immunosuppression, and crescents. Compared to the reduced model, the full model had improved prediction with better AIC (5679 vs 5648), R² (19 vs 21%), ΔC-statistic (0.01, 95%CI 0.008-0.03), continuous NRI (0.17, 95%CI 0.110-0.27) and IDI (0.03, 95%CI 0.011-0.05), with similar calibration curves. We will next externally validate the full model in the validation dataset (N=1461), and convert the model into web and mobile app calculators for implementation in clinical practice.

Conclusions: Using the largest and most diverse datasets to date in IgAN, we will generate the first risk prediction tool that is externally validated in multiple ethnic groups worldwide and can be easily implemented in clinical practice using web/app-based calculators. We expect the prediction model will become the international standard for risk stratification in IgAN, and will facilitate both clinical trial recruitment of high-risk patients and testing the added prediction benefit of novel biomarkers.

SA-PO272

Short-Term Anti-Proteinuric Effect of Tacrolimus Is Not Related to Preservation of Glomerular Filtration Rate during 5 Year-Follow Up Period in IgA Nephropathy Mi-yeon Yu, Yong Chul Kim, Ho Jun Chinn. 1Seoul national university hospital, Seoul, Republic of Korea; 2Seoul National University Bundang Hospital, Seong num, Republic of Korea.

Background: It has been known that tacrolimus reduced proteinuria in IgA nephropathy for a short period of time. We investigate persistent effects of proteinuria reduction and improvement of kidney function after discontinuation of the tacrolimus administration.

Methods: Patients with biopsy-proven IgA nephropathy were randomly selected for two treatment groups and control groups for each group; 1) patients treated with tacrolimus (Tac group) and 2) a placebo group (placebo group) by stratification with using a random angiotensin system blocker. The Tac group was treated up to 16 weeks and then stopped administration of tacrolimus at the final visit (trial phase). We tracked patients at 12-, 24-, 52-, and 240-week (observational phase). The primary outcome was the percentage change of time-averaged proteinuria (TA-proteinuria; g/g cr) and estimated glomerular filtration rate (eGFR) between the trial and observational phases. The TA-proteinuria was defined as the average of urine protein to creatinine ratio (UPCR) measured every three month during the two phases.

Results: Significant reduction of UPCR was observed in the Tac group compared to its control group at 4-week and 8-week visits during the trial phase (p=0.023 and p=0.003, respectively). The difference between Tac and its control group was not evident at the other periods, estimated by repeated measured ANOVA. The percent change of TA-proteinuria in the Tac group was more than the control group (116 ± 96% vs. 63 ± 239 %, p=0.004). Therefore the TA-proteinuria during the observational phase was not significantly different between the Tac and control groups (1.50 ± 0.733 g/g cr vs 1.455 ± 2.017 g/g cr, p=0.775). The levels of eGFR throughout the observational phase were not significantly different between the two groups. Furthermore, the mean rate of eGFR change during the whole phase was -6.6 ml/min/1.73 m²/year in the control group and -5.4 ml/min/1.73 m²/year in the Tac group (p=0.988).

Conclusions: The anti-proteinuric effect of tacrolimus was promptly reversed 3 months after discontinuation of drug. The use of tacrolimus for a short period of time in patients with IgA nephropathy temporarily reduces proteinuria, but ultimately, there is no long-term efficacy such as reduction of proteinuria and improvement of renal function.

SA-PO273

The Effects of Renin Angiotensin Aldosterone System Inhibitors (RASI) for IgA Nephropathy (IgAN) Patients with Oxford T1/2 Lesions Takahiro Kamiyama, Takahito Moriyama, Marie Nakano, Kazunori Karasawa, Kosaku Nitta. 1Department medicine, Kidney Center, Tokyo Women’s Medical University, Tokyo, Japan; 2Tokyo Women’s Medical University, Tokyo, Japan; 3Tokyo Women’s Medical University Hospital, Tokyo, Japan.

Background: IgAN has been recognized as a not a benign disease and 40% of patients developed to end-stage renal disease (ESRD) within 20 years. Severe histological findings have been reported as risk factors of IgAN. Global sclerosis was one of the risk factors, and in Oxford classification, it was recognized as same as tubulointerstitial (T) lesions according to their correlation. Therefore, in IgAN patients with T lesions, the glomerular hyperfiltration and histopathological were seemed to be occurred, and, RASI might be effective to decrease them and preventing progression to ESRD. However, these beneficial effects of RASI on patients with T lesions haven’t been previously reported.

Methods: In this retrospective cohort study, from 697 biopsy proven IgAN patients in our centre from between 1990 to 2010, we divided 88 patients with T1/2 lesions into two groups: RASI group (n=47, treated with RASI) and control group treated with antplatelets agents (APA group, n=40). We analyzed the clinical and histological background, the serial change of blood pressure and the amount of urinary protein (U-Pro, progression to ESRD, risk factors for progression to ESRD).

Results: After adjusting clinical findings with significant difference at baseline, 22 cases from each group were selected, and clinical and histological characteristics were similar between both groups. The mean eGFR 58.5 ± 51.1 ml/min/1.73m², and median 12 months of follow-up, 1.395 g/day in APA group, respectively. The serial change of blood pressure during two years after treatment was significantly decreased in RASI group (p=0.0029), but not in APA group. The serial change of U-pro was tended to decrease in RASI group, though it was not significant (1.14 ± 0.47 g/cre), but it was similar in APA group (0.95 ± 0.85 g/cre). The renal survival rate in Kaplan Meyer Analysis was 96%±20% years in RASI group and 20%±20% years in APA group (p=0.0119). In multivariate Cox regression analysis, RASI was an independent factor to prevent from progression to ESRD (HR 3.91, 95% CI 1.53-22.8).

Conclusions: RASI has shown significant beneficial effect on histologically advanced IgAN patients with Oxford T1/2 lesions, who were suspected to have glomerular hypertension and hyperfiltration according to severe global sclerosis.

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

Poster/Saturday

Clinical Glomerular Disorders: Vasculitis, C3G, IgAN
SA-PO276

Renal CD141+ Dendritic Cell Infiltration in IgA Nephropathy: Titi Chen,1 Qi Cao,1 Padmasree Rao,2,3 Guoping Zheng,4 Yiping Wang,2 David C. Harris,3,7 Centre for Transplant and Renal Research, Westmead Millennium Institute, University of Sydney, Sydney, NSW, Australia; 2Centre for Transplantation and Renal Research, Westmead Millennium Institute, The University of Sydney, Westmead, NSW, Australia; 3Sydney Medical School - University of Sydney, Terrey Hills, NSW, Australia; 4The University of Sydney, Sydney, NSW, Australia; 5Westmead Millennium Institute for Medical Research, Parramatta, NSW, Australia; 6School of Medicine, University of Sydney, Westmead, NSW, Australia; 7Centre for Transplant and Renal Research, The Westmead Institute for Medical Research, Westmead, NSW, Australia.

Background: Previous studies have shown that the severity of interstitial inflammatory infiltrates, which include myeloid dendritic cells (DCs), correlates with progression of IgA nephropathy. CD141+ DCs have recently been identified as a unique myeloid DC subset that plays a significant role in the induction and perpetuation of immune responses. DCs from IgA nephropathy patients showed increased infiltration in the kidney biopsy of patients with severe disease. Herein we compared the density of CD141+ DCs in glomeruli and interstitium in patients with IgA nephropathy. The CD141+ DC density was significantly associated with worse serum creatinine and proteinuria.

Methods: Thirty adult patients with a sole diagnosis of IgA nephropathy were included in this study. Patients were excluded if they had received glucocorticoids or immunosuppressant therapy before renal biopsy. The histological classification was scored according to the Oxford classification. CD141+ DCs were identified through immunofluorescence staining and visualised using confocal microscopy.

Results: The density of CD141+ DCs was greater in glomeruli and interstitium in patients with severe disease. CD141+ DC density was significantly associated with worse serum creatinine (r=0.81, P=0.015) and proteinuria (r=0.75, P=0.049). Higher CD141+ DC density was also associated with increased severity of tubular atrophy/interstitial fibrosis (P=0.025), but not with mesangial hypercellularity, endocapillary hypercellularity, segmental glomerulosclerosis, or number of crescents.

Conclusions: Our data highlight the close correlation between the density of CD141+ DCs and clinical characteristics, outcomes and prognosis in IgA nephropathy patients. Further studies will be conducted in human samples and murine models to investigate whether CD141+ DCs mediate kidney injury, and the possible mechanisms involved.

SA-PO278

Improvement of Clinical Outcome in Kidney Diseases via the On-line Thai SA-PO278

Poster/Saturday

Clinical Glomerular Disorders: Vasculitis, C3G, IgAN

Background: Before our present study, available data mainly came from developing countries including Thailand, where the prevalence of IgA nephropathy is 14.4%. However, we do not have detailed information about the clinical characteristics, outcomes and prognosis in Thai glomerular disease patients. We aim to investigate the relationship between CD141+ DC infiltration and clinical characteristics, outcomes and prognosis in Thai glomerular disease patients.

Methods: Among 1,556 patients, the most common renal pathology finding in IgA nephropathy (IgAN) is the most common primary glomerular disease (41.4%). Most of the patients had high initial blood pressure at time of biopsy (sCr ≥ 1.2 mg/dL, 77.5%). Clinically, both systolic and diastolic blood pressure at time of biopsy had the significantly high in patients who had serum creatinine ≥ 3 mg/dL compared to < 3 mg/dL (167±1/88±14 vs. 13±6±18±12 mmHg, p = 0.001 and p = 0.048). Histologically, an analysis of The Oxford Classification of IgAN, interstitial fibrosis/tubular atrophy (T) = 50% had significantly high in patients who had serum creatinine ≥ 3 mg/dL.

Conclusions: The prevalence of IgAN in our study was 13.5%. Two independent factors of severe manifestation at the time of biopsy were high blood pressure and high score of tubulointerstitial involvement. Further follow-up of clinical outcomes is being investigated.

Funding: Private Foundation Support

SA-PO277

The Beneficial Effect of Tonsillectomy Combined with Steroid Pulse Therapy on IgA Nephropathy Patients with Impaired Renal Function Saeko Kuman,1 Takahito Moriyama,2 Takahiro Kamiyama,4 Satoru Oi,3 Kosaku Nakano,1 Rieko Shindo,1 Satoshi Nakano,1,4,5 1Department of Urology, 2Kosoku General Medical Center, 3Tokyo Women’s Medical University, Tokyo, Japan; 4Tokyo Women’s Medical University, Tokyo, Japan; 5Tokyo Women’s Medical University Hospital, Tokyo, Japan.

Background: Tonsillectomy combined with steroid pulse therapy (TSP) has been reported to have beneficial effects on IgA nephropathy (IgAN), and has become a major treatment in Japan. However, it is still controversial whether TSP is effective for IgAN with impaired renal function or not, though the impaired renal function at the time of renal biopsy is still recognized as one of the severe risk factor of IgAN. Therefore, we analyzed the efficacy of TSP in IgAN with impaired renal function.

Methods: In this retrospective analysis, IgAN patients who were diagnosed from January 2006 to May 2015 in our institution, age≥16, >0.5g/day proteinuria and estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73m² were divided into two groups: the patients treated with TSP (TSP group; n=25) and the patients treated with oral prednisolone (oPSL group; n=41). We compared the clinical and histological findings at baseline, renal survival rate until 25% decline of eGFR from base line and progression to end stage renal disease (ESRD), and clinical remission (CR) rate defined as < 0.3 g/day proteinuria and < 5 urinary red blood cells per high-powered field (HPF) between both groups.

Results: There was no significant difference in clinical and histological findings between both groups (mean eGFR: 44.6 vs. 44.3 mL/min/1.73m²; p=0.875, median proteinuria: 1.78 vs. 1.37 g/g creatinine; p=0.247, distribution of the amount of proteinuria: 1, 2, 11, 3 vs. 3, 13, 5, 4 (<5, 5-20, 21-50, >51/HPF; p=0.097). The renal survival rate, until 25% reduction from baseline eGFR, and until progression to ESRD was significantly higher in TSP than oPSP group (79.7% vs. 40.4%/5 years; p=0.009, 147 vs. 219/5 years, p<0.001, respectively). The remission rate of hematuria was significantly higher in TSP than oPSP group (92.9% vs. 47.1%/4 years; p=0.0001, respectively), though the remission rate of proteinuria was similar between both groups. TSP was the only independent factor to decrease hematuria and trend to the multivariate Cox regression analysis (OR: 3.10, 95% CI: 1.40-6.77, p=0.006).

Conclusions: TSP was effective for remission of hematuria and long term renal prognosis in IgAN patients with impaired renal function.

SA-PO278

Maintenance of Remission Following Completion of OMS721 Treatment in Patients with IgA Nephropathy (IgAN) Geoffrey A. Block,1 Steve Whitaker,2 Denver Nephrology, Denver, CO; 3Onemus Corporation, SEATTLE, WA.

Background: The leitken pathway of complement has been implicated in the pathogenesis of several glomerulopathies including IgAN. OMS721 is a fully human monoclonal antibody that inhibits mannann-associated lectin-binding serine protease-2 (MASP-2), the effector enzyme of the lectin pathway. In a clinical trial, all OMS721-treated patients with IgAN achieved partial remission. These patients were followed after the trial. The duration of remission after OMS721 treatment was assessed.

Methods: The 4 IgAN patients are from an ongoing OMS721 Phase 2 clinical trial. All completed the trial. For inclusion, patients demonstrated 1 biopsy-diagnosed IgAN, 2) uACR > 0.6 g/g, 3) eGFR ≥ 30 mL/min/1.73 m², 4) controlled BP on stable ACEI/ARB treatment, and 5) a stable steroid dose ≥ 10 mg prednisone. All patients received OMS721 IV once weekly for 12 weeks. After OMS721 treatment, patients were followed for 6 more weeks with uACR and eGFR. After trial completion, patients were followed for 6 months. During this time, patients were followed for uACR and eGFR. During the trial, the mean uACR decreased by 74% (p = 0.026). Three patients maintained partial remission during available follow-up (54%, 79%, and 88% uACR decreases at 12, 12, and 5 months, respectively). One patient had 90% of baseline uACR at 7 months. Three patients also demonstrated improved eGFR by 7, 13, and 7 mL/min/1.73 m² during the follow-up. The fourth patient’s eGFR was stable. All patients discontinued steroids. OMS721 was well tolerated. All adverse events were mild with headache and sinus congestion considered possibly related by the investigator.

Conclusions: Proteinuria significantly decreased in patients with IgAN during the 12-week treatment with OMS721. This reduction in proteinuria was maintained for up to

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

Underline represents presenting author.

749
SA-PO279
Natural History of IgA Nephropathy and Henoch-Schönlein Purpura Nephritis
Benjamin L. Spector, Jason Misurac. University of Iowa, Iowa City, IA.

Background: Though histopathologically identical, Henoch-Schönlein purpura nephritis (HSPN) and IgA nephropathy (IgAN) are thought to follow markedly different courses. Despite their relatively high prevalence, limited data exist describing their natural histories.

Methods: This retrospective analysis examines all biopsy-confirmed cases of HSPN (n=22) and IgAN (n=19) at our institution from January 1989 to May 2016 through 1-year of follow-up. Inclusion criteria were before age 18 years, minimum 1-year of follow-up, and absence of pre-existing renal disease. We compared demographics, clinical biomarkers, and treatments.

Results: Both cohorts show male predominance. In HSPN, age at diagnosis was younger and renal biopsies showed higher rates of glomerular crescents and endocapillary proliferation. The IgAN cohort presented more often with gross hematuria (31.8% vs 63.2%, p= 0.06), hypertension (HTN), and lower estimated glomerular filtration rate (eGFR). Urine protein/creatinine ratio (UPC) and overall hematuria rates were equivalent between groups. At 1-year follow-up, there were no differences in clinical features of immunosuppressant use.

Conclusions: In HSPN, patients had younger presentation and higher prevalence of crescents and endocapillary proliferation on biopsy. IgAN was more likely to present with HTN, gross hematuria, and lower eGFR. There were no significant differences in clinical biomarkers at 1-year follow-up.

Demographics and clinical features

<table>
<thead>
<tr>
<th></th>
<th>HSPN</th>
<th>IgAN</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (years)</td>
<td>8.4</td>
<td>12.4</td>
<td>0.09</td>
</tr>
<tr>
<td>eGFR at diagnosis (mL/min/1.73m²)</td>
<td>60</td>
<td>62</td>
<td>0.01</td>
</tr>
<tr>
<td>eGFR at 1-year (mL/min/1.73m²)</td>
<td>95</td>
<td>100</td>
<td>0.61</td>
</tr>
<tr>
<td>UPC at diagnosis</td>
<td>3.8</td>
<td>1.1</td>
<td>0.54</td>
</tr>
<tr>
<td>UPC at 1 year</td>
<td>0.2</td>
<td>0.2</td>
<td>0.77</td>
</tr>
</tbody>
</table>

SA-PO280
Is MEST Score a Risk Predictor in Pediatric Henoch-Schönlein Purpura Nephritis? Ashton Chen,1 Dan P. Goldstein,2 Marcia Voigt,2 Andrew M. South,3 Jonathan J. Hogan.1 1Wake Forest Baptist Health, Winston Salem, NC; 2Wake Forest School of Medicine, Winston Salem, NC; 3Wake Forest University School of Medicine, Winston Salem, NC.

Background: Oxford Classification of IgA nephropathy (IgAN) includes the histologic components: mesangial (M) and endocapillary (E) hypercellularity, segmental sclerosis (S) and interstitial fibrosis or tubular atrophy (T). These have been utilized as the natural histories.

Methods: This retrospective analysis examines all biopsy-confirmed cases of HSPN (n=22) and IgAN (n=19) at our institution from January 1989 to May 2016 through 1-year of follow-up. Inclusion criteria were before age 18 years, minimum 1-year of follow-up, and absence of pre-existing renal disease. We compared demographics, clinical biomarkers, and treatments.

Results: Both cohorts show male predominance. In HSPN, age at diagnosis was younger and renal biopsies showed higher rates of glomerular crescents and endocapillary proliferation. The IgAN cohort presented more often with gross hematuria (31.8% vs 63.2%, p= 0.06), hypertension (HTN), and lower estimated glomerular filtration rate (eGFR). Urine protein/creatinine ratio (UPC) and overall hematuria rates were equivalent between groups. At 1-year follow-up, there were no differences in clinical features of immunosuppressant use.

Conclusions: In HSPN, patients had younger presentation and higher prevalence of crescents and endocapillary proliferation on biopsy. IgAN was more likely to present with HTN, gross hematuria, and lower eGFR. There were no significant differences in clinical biomarkers at 1-year follow-up.

Demographics and clinical features

<table>
<thead>
<tr>
<th></th>
<th>HSPN</th>
<th>IgAN</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (years)</td>
<td>8.4</td>
<td>12.4</td>
<td>0.09</td>
</tr>
<tr>
<td>eGFR at diagnosis (mL/min/1.73m²)</td>
<td>60</td>
<td>62</td>
<td>0.01</td>
</tr>
<tr>
<td>eGFR at 1-year (mL/min/1.73m²)</td>
<td>95</td>
<td>100</td>
<td>0.61</td>
</tr>
<tr>
<td>UPC at diagnosis</td>
<td>3.8</td>
<td>1.1</td>
<td>0.54</td>
</tr>
<tr>
<td>UPC at 1 year</td>
<td>0.2</td>
<td>0.2</td>
<td>0.77</td>
</tr>
</tbody>
</table>

SA-PO281
Long-Term Outcome of Pneumococcal Haemolytic Uraemic Syndrome: A Case Report
Laura M. Dember,1 Jonathan J. Hogan,1 Abrami Cancer Center, University of Pennsylvania, Philadelphia, PA; 2Pathology, University of Pennsylvania, Philadelphia, PA; 3Nephrology, University of Pennsylvania, Philadelphia, PA.

Background: Though histopathologically identical, Henoch-Schönlein purpura nephritis (HSPN) and IgA nephropathy (IgAN) are thought to follow markedly different courses. Despite their relatively high prevalence, limited data exist describing their natural histories.

Methods: This retrospective analysis examines all biopsy-confirmed cases of HSPN (n=22) and IgAN (n=19) at our institution from January 1989 to May 2016 through 1-year of follow-up. Inclusion criteria were before age 18 years, minimum 1-year of follow-up, and absence of pre-existing renal disease. We compared demographics, clinical biomarkers, and treatments.

Results: Both cohorts show male predominance. In HSPN, age at diagnosis was younger and renal biopsies showed higher rates of glomerular crescents and endocapillary proliferation. The IgAN cohort presented more often with gross hematuria (31.8% vs 63.2%, p= 0.06), hypertension (HTN), and lower estimated glomerular filtration rate (eGFR). Urine protein/creatinine ratio (UPC) and overall hematuria rates were equivalent between groups. At 1-year follow-up, there were no differences in clinical features of immunosuppressant use.

Conclusions: In HSPN, patients had younger presentation and higher prevalence of crescents and endocapillary proliferation on biopsy. IgAN was more likely to present with HTN, gross hematuria, and lower eGFR. There were no significant differences in clinical biomarkers at 1-year follow-up.

Demographics and clinical features

<table>
<thead>
<tr>
<th></th>
<th>HSPN</th>
<th>IgAN</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (years)</td>
<td>8.4</td>
<td>12.4</td>
<td>0.09</td>
</tr>
<tr>
<td>eGFR at diagnosis (mL/min/1.73m²)</td>
<td>60</td>
<td>62</td>
<td>0.01</td>
</tr>
<tr>
<td>eGFR at 1-year (mL/min/1.73m²)</td>
<td>95</td>
<td>100</td>
<td>0.61</td>
</tr>
<tr>
<td>UPC at diagnosis</td>
<td>3.8</td>
<td>1.1</td>
<td>0.54</td>
</tr>
<tr>
<td>UPC at 1 year</td>
<td>0.2</td>
<td>0.2</td>
<td>0.77</td>
</tr>
</tbody>
</table>

SA-PO282
Renal Outcomes in Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits
Ramina I. Gumber,1 Jordan B. Cohen,2 Matthew Palmer,1 Laura M. Dember,1 Brendan M. Weiss,1 Jonathan J. Hogan.1 1Abrami Cancer Center, University of Pennsylvania, Philadelphia, PA; 2Pathology, University of Pennsylvania, Philadelphia, PA; 3Nephrology, University of Pennsylvania, Philadelphia, PA.

Background: The natural history and response to therapy of proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is poorly characterized.

Methods: We retrospectively analyzed renal responses of 20 patients with PGNMID evaluated at our center from 2011 through 2016. Patients were stratified by treatment approach: targeted to detected clonal cell type or non-targeted. Renal response was defined as: 1. complete response (CR) if proteinuria decreased to <0.5 gms (per 24h urine collection or urine protein:creatinine ratio<0.5) with return to baseline of serum creatinine (SCr) 2. partial response (PR) if there was ≥50% decrease in proteinuria (and at least ≤50% with a stable SCr). Additional information pertaining to recurrence.

Results: Over 60% of P-HUS patients under follow up have chronic kidney disease. Ongoing analysis involving more UK centres is underway including those discharged from care. Reference: 1. Waters et al, J Pediatr. 2007 Aug;151(2):140-4
SA-PO283

Diversity of Biopsy-Proven Kidney Diseases in Thai Diabetic Patients: Analysis of Thai Glomerular Disease Collaborative Network (TGGCN) 

Veerapar Ninkiemkajorn,1 Ratana Chawansanuntaropoj,2 Ngeontra Tantranoti,2 Porpenn Sangthiwam,1 Warangkana Pichaiwong,2 1Medicine, RAVJITHI HOSPITAL, Bangkok, Thailand; 2Medicine, Prince of Songkla University, Songkla, Thailand; 1Medicine, Buddhism, Narai hospital. 

Background: Diabetic nephropathy (DN) is the leading cause of chronic kidney disease worldwide including Thailand. However, there is also increasing recognized diagnosis of non-diabetic renal diseases (NDRD) in diabetic patients, which may influence in the different treatment and outcomes. This study reported the spectrum and clinical characteristics of NDRD and DN superimposed DN in Thai diabetic population.

Methods: Clinical data of the diabetic patients with aged > 18 years undergone kidney biopsy were collected via the national web-based Thai glomerular diseases registry from TGGCN during 2014-2017. These data including the demographic data and laboratory data together with kidney biopsy pathological findings.

Results: The 276 from 1,556 patients were recruited in this study; 123 cases were male (44.6%). The mean age was 51.8±8.7 years, and the median serum creatinine was 1.99 mg/dL (0.42-13.2). The 114 cases (41.3%) were diagnosed NDRD, while 23 cases (8.3%) were diagnosed DN superimposed DN. The rest of the patients were diagnosed isolated diabetic nephropathy; DN (50.4%). FSGS was either the most prevalent glomerulopathy in both NDRD (23.7%) and NDRD superimposed DN (34.8%).

The second and third kidney biopsy findings in NDRD were lupus nephritis (21.9%), IgA nephropathy (13.2%), respectively. In DN superimposed DN, membranous nephropathy (26.1%) and post-infectious glomerulonephritis (21.7%) were the second and third pathological findings. NEPHRIS was the clinical presentation of NDRD and NDRD superimposed DN approximately 15.8% and 13%, whereas it was not found in DN. Nephrotic syndrome was more common in DN and NDRD superimposed DN than in NDRD (80.6%, 73.9%, and 37.7%, respectively, p<0.05). Moreover, the quantity of proteinuria was found to be higher in DN and NDRD superimposed DN than in NDRD (6.4, 6.5, and 3.7 g/day, respectively, p<0.05).

Conclusions: This report disclosed the diversity and prevalence of NDRD that was diagnosed in more than one-third of Thai diabetic patients. Presence of nephritis was the more suggestive diagnosis of NDRD or NDRD superimposed DN. However, kidney biopsy is still the important means for the definite diagnosis of glomerular disease in diabetic patients.

Funding: Private Foundation Support

SA-PO284

Distribution of Glomerular Diseases in Taiwan: Preliminary Report of National Renal Biopsy Registry – Report on behalf of Taiwan Society of Nephrology 

Hsien-Fu Chu,1 Kuo-cheng Lu,2 Hung-Chun Chen,3 Kuo-hsiung Shu,4 Taichung Veteran General Hospital, Taichung, Taiwan; 1Division of Nephrology, Department of Medicine, Cardinal Tien Hospital, School of Medicine, Fu Jen Catholic University, New Taipei City, Taiwan; 2Kaohsiung Medical Univ, Taichung, Taiwan; 3Lin Shin Hospital, Taichung, Taiwan. 

Background: Despite the development of biomarkers and noninvasive imaging tools, biopsy remains the only method for correctly diagnosing patients with unexplained hematuria or proteinuria or failure. Renal biopsy has been performed for several decades in Taiwan; however, a national data registry is still lacking until 2013.

Methods: The Renal Biopsy Registry Committee was established within the Taiwan Society of Nephrology in January 2013. A biopsy registry format, including basic demographic data, baseline clinical features, laboratory data, and clinical and pathological diagnosis was developed. Approval from the local institutional review board was obtained in each participating medical center.

Results: From January 2014 to September 2016, 1445 renal biopsies were identified from 17 medical centers. 53.8% cases were reported in men. The mean age at biopsy was 48±16.6 years. The median serum creatinine was 1.6 (IQR 0.9–3.3) mg/dL. The median daily urine protein was 2.7 (IQR 0.7–6.8) g/day, whereas 57.3% patients had hematuria. Primary glomerulonephritis (GN), secondary GN, tubulointerstitial diseases, and post-renopaty proteinuria accounted for 40.7%, 33.6%, 10.3%, and 15.3%, respectively. Among primary GN, IgA nephropathy (26.0%), focal segmental glomerulosclerosis (FSGS) (21.6%), and membranous nephropathy (MGN) (20.6%) were most frequently diagnosed. Diabetic nephropathy (22.4%) and lupus nephritis (21.8%) were the most common secondary GN. Patients with minimal change disease (MCD) and MGN had heavier proteinuria than those with FSGS and IgA nephropathy. The most common cause of nephrotic syndrome in primary glomerular disease was MGN (28.8%), followed by MCD (28.2%). IgA nephropathy was the leading cause of chronic nephritic syndrome, acute post-infectious syndrome, and persistent hematuria. The incidence was 0.55, 0.47, 0.45, and 0.41 in 100,000/year for IgA nephropathy, FSGS, MGN, and MCD, respectively. The incidence of primary GN was 2.19 in 100,000/year.

Conclusions: This is the first report of the National Renal Biopsy Registry in Taiwan. IgA nephropathy is the most common primary GN, while MGN is the most common cause of nephrotic syndrome. Primary GN distribution in Taiwan is slightly different from that in other Asian countries.
SA-PO287

Very Low Levels of Microscopic Hematuria in Potential Living Kidney Donors Is Associated with Pathology That Precludes Donation

Vincenta Kumar,1 Manish K. Saha, Bruce A. Julian,2 Jayme E. Locke,2 Robert S. Gaston.1 1UNC Kidney Center, Chapel Hill, NC; 2University of Alabama at Birmingham, Birmingham, AL.

Background: A threshold of ≥3 rbc/hpf (red blood cells/high power field) or higher prompts additional testing when evaluating potential living kidney donors at most centers in the United States. In our experience, a lower degree of hematuria has yielded pathology that precluded kidney donation and here in we present the results of a single center experience.

Methods: We prospectively identified isolated asymptomatic microscopic hematuria in 19 out of 1124 potential living kidney donors. Microscopic hematuria was defined as presence of ≥1 rbc/hpf and persistent by presence on ≥2 separate urinalysis. Isolated was defined as presence of microscopic hematuria and with preserved GFR, absence of proteinuria, microalbuminuria or hypertension and no identifiable anatomical cause on native kidney imaging. Donors expressing continued interest had an evaluation with a cystoscopy. If unrevealing, they underwent a native kidney biopsy analyzed by a single pathologist using light, immunofluorescence and electron microscopy.

Results: There were no biopsy related complications. Degree of hematuria was modest ranging from 0-2 up to 3-10 rbc/hpf. Higher degree of hematuria was not isolated. 3/19 had IgNephropathy and were not approved for kidney donation. All of these donors were related to their recipients. 1/19 had arteriolar sclerosis. Thin basement membrane disease (GBM) diagnosed after ruling out Alport’s was the common finding in 11/19 patients and 4/19 had possible first trimester GBM based on regression of proteins. These 15/19 were given a choice to donate after extensive counseling. One and two year follow up data have no worsening of hematuria or any of the renal parameters since donation.

Conclusions: Persistent asymptomatic microscopic hematuria of very minor degree in potential living kidney donors with a biologically related recipient can be associated with pathologic findings that preclude kidney donation. A higher threshold of ≥3 rbc/hpf on urine analysis as currently used can lead to a missed diagnosis and alter long term prognosis. At our center we have lowered our definition to ≥1 rbc/hpf after the results of this analysis.

SA-PO288

IgA Nephropathy with Positive Anti-Neutrophil Cytoplasm Antibody – A Case Series

Amy Kang,2 H. Terence Cook,3 Charles D. Pusey.3 1Imperial College London, London, United Kingdom; 2Imperial College Renal and Transplant Centre, London, United Kingdom; 3Imperial College of London, London, United Kingdom.

Background: IgA nephropathy (IgAN) with positive anti-neutrophil cytoplasm antibody (ANCA) is rare and may have different clinical characteristics from isolated IgAN.

Methods: We describe seven biopsy-proven IgAN patients (3% of our cohort) with positive ANCA (age 25–66 years, 5 male and 2 female, median Cr 57mmol/L, eGFR 51mL/min/1.73m²). Two initially ANCA negative patients developed worsening renal function and ANCA seroconverted. One recovered renal function with immunosuppression; the other was not immunosuppressed and progressed to dialysis. Five patients were ANCA positive from presentation. Two patients, with features of systemic vasculitis, received immunosuppression; one recovered renal function and the other progressed to dialysis. Two out of three patients with renal-limited disease had stable renal function on mycophenolate mofetil, and one was lost to follow-up. On biopsy, three out of the seven patients had segmental necrosis and crescents on a background of IgAN. Of the remaining four patients, one had features of endocapillary proliferation and the other three did not.

IgAN can be associated with both PR3 and MPO – ANCA, but MPO-ANCA was more frequent in our cases (5 out of 7).

Results:

SA-PO289

Anti-Ro Antibodies: A Novel Scleroderma Renal Crisis Biomarker

Sarah M. Gordon, Stephen W. Olson. Nephrology, Walter Reed National Military Medical Center, Bethesda, MD.

Background: Autoimmunity is thought to play a significant role in the pathogenesis of scleroderma renal crisis (SRC). Anti-RNA polymerase III (RNAPOL3-Ab) is associated with SRC but only present in 20–30% of cases. Therefore, additional autoimmune risk factors for SRC are likely. Anti-Ro antibodies (Ro-Ab) are known to be associated with systemic sclerosis (SSc), but have not been studied at or before SRC diagnosis.

Methods: We queried the military electronic medical record for ICD9 code 701.1 (SSc) between 2005 and 2016. By individual chart review we identified 54 SRC cases and 407 SSc without SRC disease controls. Background data was collected to include presence of Ro-Ab. Department of Defense Serum Repository (DoDSR) provided up to 3 longitudinal prediagnostic serum samples for 16 SRC cases and 30 age, sex, race, and age of serum matched SSc without SRC disease controls. Ro-Ab levels were measured at the NIH using an established technique. We first compared presence of Ro-Ab among the 54 SRC cases to the 407 SSc without SRC controls at SSc diagnosis. We then compared longitudinal pre-diagnostic Ro-Ab levels in 16 SRC cases to that of 30 SSc matched disease controls. The non-white group was predominantly Black or ‘Other’.

Results: More SRC cases had Ro-Ab at diagnosis than SSc without SRC disease controls (27% vs.13%, p=0.03). Ro-Ab were only associated with SRC in the non-White subgroup (38% vs.17%, p=0.04) versus the White subgroup (15% vs. 10%, p=0.69). More non-White SRC cases had persistent significantly elevated prediagnostic Ro-Ab than non-White SSc patients without SRC controls (40% vs.6%, p=0.01). In each SRC case, the Ro-Ab was greater than 30 times normal in the earliest available index sample up to 26.1 years before clinical presentation. No White cases had an elevated prediagnostic Ro-Ab level. Prediagnostic Ro-Ab and RNAPOL3-Ab were not present in the same cases.

Conclusions: We report for the first time that Ro-Ab are elevated both at and before SRC diagnosis, making it a potential predictive biomarker in non-Whites. Elevated serial prediagnostic Ro-Ab levels found decades before clinical SRC suggest a ‘multi-hit’ mechanism of disease that requires a second insult to manifest clinical disease. Our results also suggest that the subclinical pathophysiology of SRC may vary by race, similar to known clinical and serologic heterogeneity in SSc.

Funding: Other NIH Support - Labs were run at the NIH.

SA-PO290

Activated Farnesoid X Receptor by GW4064 Protects against Renal Fibrosis through Regulation of Hippo Pathway

Bryan D. Tseng,1 Eun Hui Bac,1 Seong Kwon Ma,2 Soo Wan Kim.1 1Chonnam National University Hospital, Gwangju, Republic of Korea; 2Chonnam National University Medical School, Gwangju, Republic of Korea.

Background: Renal fibrosis is the common pathway of chronic kidney disease progression. transforming growth factor-β (TGF-β) induced SMA2/3 is a critical event in progressive chronic kidney disease. However, the role of non-SMAD signaling in fibrotic process and its underlying molecular mechanisms remain unexplored.

The nuclear receptor farnesoid X receptor (FXR), a ligand-activated transcriptional factor, may play a pivotal role in renal fibrosis.

Methods: We tested whether activated-FXR by GW4064 protects against renal fibrosis through non-SMAD signaling. To explore anti-fibrotic effects of FXR, we investigated the effects of GW4064 in TGF-β induced renal fibrosis in human proximal tubular epithelial (HK-2) cells. We also examined the phosphorylation level of epidermal growth factor receptor (EGFR), Src kinase and Hippo pathway to identify the anti-fibrotic signals. To explore the anti-fibrotic effects of FXR agonist in the kidney of unilateralel ureteral obstruction (UUO) mouse model, we treated with vehicle or GW4064 (30mg/kg) for 5 days, and checked the fibrosis markers.

Results: TGF-β-induced Ssc kinase and EGFR phosphorylations were decreased by the FXR agonist GW4064 which was not altered by the treatment of chenodochyslastic acid (CDCA), FXR agonist. TGF-β-induced fibronectin, connective tissue growth factor and α-smooth muscle actin expressions were markedly decreased by GW4064 treatment. Phosphorylations of yes-associated protein (YAP), Ms1 and Lats were increased by GW4064 treatment, which facilitates blocked YAP nuclear accumulation and protects against renal fibrosis. The in vivo experiments showed that FXR agonist GW4064 protected against renal fibrosis in UUO mice.

Conclusions: These results suggested that activated nuclear receptor FXR by GW4064 protected against renal fibrosis through non-SMAD signaling. To explore the anti-fibrotic effects of FXR agonist in the kidney of unilateralel ureteral obstruction (UUO) mouse model, we treated with vehicle or GW4064 (30mg/kg) for 5 days, and checked the fibrosis markers.

Funding: Government Support - Non-U.S.
**SA-PO291**

**Inability to Increase Fatty Acid Oxidation Following Renal Injury Worsens Renal Fibrosis**

Mardiana Leo,1,2 Peter F. Mouni,1 Marina Katerelos,1 Kurt Gleich,1 David A. Power,1,2 Austin Health, Melbourne, VIC, Australia; 2Diabetes Complications in the streptozotocin-induced diabetic ApoE knockout mice model. Mice were stressed. We aimed to determine whether reduced fatty acid oxidation contributes to renal fibrosis.

**Methods:**
- The folate nephropathy (FAN) and unilateral ureteric obstruction (UUO) models were induced in male ACC1/2KI mice and wild type (WT) controls. Mice were sacrificed at 14 and 7 days, respectively. Samples were studied by histomorphometry, Western blot and qRT-PCR.
- There was no difference in the appearance or function of ACC1/2KI kidneys at 8-10 weeks of age compared with WT. Reduced expression of genes controlling fatty acid oxidation was confirmed in the FAN model. In both FAN and UUO models there was increased accumulation of lipid by Oil Red O staining in ACC1/2KI mice (p<0.05 and p<0.01, respectively). Sirius red staining demonstrated increased fibrosis in ACC1/2KI mice in both models (p<0.05 and p<0.001). This was associated with increased expression of α-smooth muscle actin by Western blot (p<0.05) and qRT-PCR (p<0.01).

**Results:**
- In the FAN model, ACC1/2KI mice also had increased mRNA transcripts for Collagen I (P=0.05) by qRT-PCR compared with WT.

**Conclusions:**
- These data indicate that a reduced ability to regulate fatty acid oxidation in response to renal injury contributes to the development of renal fibrosis, and is not simply a consequence of injury. Regulation of fatty acid oxidation may be a potential therapeutic target in renal fibrosis.

**Figure 1. Quantification of PicroSirius Red stained kidney sections analysis showing increased Collagen in KI UUO compared to WT UUO (***P<0.001).**

**SA-PO292**

**Lipoxins Attenuate Diabetic Complications in the ApoE-/− Mouse**

Eoin P. Brennan,2 Muthukumar Mohan,1 Monica De gaetano,2 Chris Tikellis,1 Mariam Marai,1 Mark Ziemann,3 Orina Belton, Assam El-Osta,1 Karin Jandelet-Dahm,1 Mark E. Cooper,1 Phillip Kantharidis,1 Katherine Godson,1 Department of Diabetes, and Central Clinical School, Monash University, Melbourne, VIC, Australia; 2Diabetes Complications Research Centre, UCD Conway Institute & School of Medicine UCD, University College Dublin, Dublin, Ireland; 3School of Biomolecular and Biomedical Science, University College Dublin, Belfield, Dublin, Ireland.

**Background:**
- Targeting both inflammation and fibrosis in diabetes-related complications has proven elusive. Endogenous lipid mediators including Lipoxins (LXs) actively promote the resolution of inflammatory responses. We investigated the potential of Lipoxin A4 (LXA4), an endogenously produced mediator that promotes the resolution of inflammation, and a synthetic lipoxin 15(15R)-Benzox-LXA4 as experimental therapeutics in the streptozotocin-induced diabetic ApoE−/− mouse, a model of diabetic complications.

**Methods:**
- Diabetes was induced with low-dose streptozotocin (55mg/kg). Following 10 weeks of diabetes progression, mice were administered either vehicle (0.1% ethanol), LXA4 (5μg/kg), or Benzo-LXA4, analogue (1.7μg/kg) for 6 additional weeks.

**Results:**
- Lxs attenuated kidney disease, with evidence of reduced albuminuria (Diabetes+Vehicle: 25.1±2.1 μg/24h vs Diabetic+LXA4: 17.3±2.4 μg/24h), glomerular expansion, and collagen deposition. RNA-Seq transcriptome profiling identified the diabetic renal gene signature (725 genes) and subsets regulated by Lxs. Pathway analysis identified established (TGFB-1, PDGF, TNF-α, and NF-kB) and novel (EGR-1) networks regulated by Lxs. Lxs also reduced aortic atherosclerotic plaque development and pro-inflammatory signaling pathways in vascular tissue. LXs attenuated vascular smooth muscle cell proliferation and migration, and inhibited monocyte-monocytedendelial cell adhesion. Treatment of human carotid plaques ex vivo with LXA4, secreted attenuation of pro-inflammatory cytokines including IFN-γ, IL-1β and TNF-α, thereby highlighting the potential clinical relevance of LX-based therapeutics. Finally, we have previously identified the let-7 miRNA family as important mediators of renal fibrosis, and here we demonstrate that restoration of let-7 levels in aortic vascular tissues could provide a new target for an anti-inflammatory approach in diabetic vascular disease.

**Conclusions:**
- In conclusion, these data support a novel pro-resolution therapeutic approach for treating and preventing comorbidly multiple vascular complications of diabetes.

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

**SA-PO293**

**TGF-β1 Promotes Fibrotic Gene Expression through Induction of Histone Variant H3.3 and Histone Chaperone HIRA**

Toshiohiro Shindo, Shigeo Doi, Kensuke Sasaki, Ayumu Nakashima, Takao Masaki, Hiroshima university, Hiroshima city, Japan.

**Background:**
- Recent studies show that histone variants and their chaperones serve as epigenetic marks that regulate transcriptional activity. In this study, we investigated transforming growth factor (TGF)-β1-induced histone variant H3.3 and its histone chaperone, HIRA, on fibrotic genes in vivo and in vitro.

**Methods:**
- Male C57BL/6J mice underwent unilateral ureteral obstruction (UUO) and were sacrificed on day 7. In UUO mice, expression of H3.3, HIRA, and α-smooth muscle actin (αSMA) were evaluated by western blotting (WB) and immunohistochemistry (IHC) with or without administration of a TGF-β1-neutralizing antibody. For in vitro experiments, rat renal tubular cells (NRK52E) and rat kidney fibroblasts (NRK49F) were used. TGF-β1-induced expression of H3.3, HIRA and αSMA was assessed by WB with pretreatment of Smad3 or HIRA siRNAs. Furthermore, chromatin immunoprecipitation (ChIP) assays were carried out using primers for fibrotic genes, which were designed to include a NRK52E cell element, in TGF-β1-stimulated NRK52E cells.

**Results:**
- Expression of H3.3 and HIRA was increased in UUO mice, and the TGF-β1-neutralizing antibody suppressed their expression. Smad3 siRNA treatment inhibited expression of H3.3 and HIRA in TGF-β1-stimulated NRK52E cells. HIRA siRNA treatment attenuated expression of H3.3 and αSMA in TGF-β1-stimulated NRK52E cells.

**Conclusions:**
- TGF-β1-induced expression of H3.3 and HIRA play an important role in expression of fibrotic genes.

**SA-PO294**

**Galectin-1 Is a New Renal Fibrosis Gene Upregulated in Type 1 and Type II Diabetes**

Samy L. Habib, UTHSCSA, San Antonio, TX.

**Background:**
- Chronic exposure of tubular renal cells to elevated blood glucose contributes to tubulointerstitial changes seen in diabetic nephropathy. Tubular cells are primary targets of hyperglycemia, and chronic exposure to elevated blood glucose levels contributes to the tubulointerstitial changes seen in overt diabetic nephropathy.

**Methods:**
- Kidney tissues from wild type and diabetic mice from both type 1 DM (Akita) and type 2 (db/db) groups at age of 4, 6, 8 months old were used. RNA sequence and analysis of Gal-mRNA were performed in RNA extracted from kidney tissues.
- Proximal tubular epithelial renal cells treated with high glucose and/or HG+Insulin for different time points were used to measure promoter activity and protein expression of Gal-1. Gal-1 was cloned and transcription factor AP4 was immunoprecipitated to bind to Gal-1 promoter to upregulate its function. The mutated binding sites of AP4 to Gal-1 promoter showed decrease in protein and function activity of Gal-1.

**Results:**
- The present study, we identified a new fibrosis gene called Galectin-1 (Gal-1) that highly expressed in tubular cells in kidney of type 1 and type II mouse models of diabetes. Gal-1 protein and RNA expression showed significant increased in kidney cortex of Akita and db/db mice compared to wild type mice. Mice proximal tubular exposed to high glucose (HG) and HG+Insulin showed significant increase in phosphorylation of Akt that associated with significant increase in expression of Gal-1. We identified that AP4 binds to Gal-1 promoter to upregulates its function. The mutated binding sites of AP4 to Gal-1 promoter showed decrease in protein and function expression of Gal-1. Inhibition of Gal-1 by OTX-008 showed significant decrease in phosphorylation of Akt and expression of AP4 and Gal-1 protein/promoter activity. In addition, downregulation of AP4 by siRNA resulted in significant decrease in protein expression and promoter activity of Gal-1.

**Conclusions:**
- In summary, our data showing that Gal-1 is highly expressed in kidney of type 1 and II diabetic mouse and Ap4 is a major transcription factor that activates Gal-1 under hyperglycemia through activation of Akt. Inhibition of Gal-1 by OTX-008 blocks activation of Akt and prevent accumulation of Gal-1 suggest a novel role of Gal-1 inhibitor as possible therapeutic target to treat renal fibrosis in diabetes.

**Funding:** Veterans Affairs Support
SA-PO295

Knockdown of Peroxiredoxin V (Prdx V) Exacerbates Unilateral Ureteral Obstruction-Induced Renal Fibrosis

Hoon In Cho,

2 Taec-Hoon Lee,

1 Jung Sun Park,

2 Donghyun Kim,

2 Eun Hui Bae,

2 Seong Kwon Ma,

2 Soo Wan Kim.

1 School of Dentistry, Chonnam National University, Gwangju, Republic of Korea; 2 Chonnam National University Medical School, Gwangju, Republic of Korea.

Background: Renal fibrosis is closely associated with chronic inflammation. Peroxiredoxin V (Prdx V), an atypical 2-Cys member of the Prdx family, functions as an anti-inflammatory effector as well as a thiol-dependent peroxidase in its catalytic cysteine-dependent manner. Recently, we demonstrated that overexpression of Prdx V attenuates TGF-β-induced fibrosis in NRK-49F cells. However, the relevance of Prdx V to renal pathobiology has not been fully characterized and the underlying mechanism remains poorly understood.

Methods: To investigate the role of Prdx V in renal fibrosis, we used a transgenic mouse model with PrdxV siRNA expression controlled by U6 promoter (C57BL/6J-Tg(U6-PrdxVsi)IIIhKrb; Prdx V-/- mice). For in vivo experiments, both Prdx V+/- and Prdx V-/- mice were divided to two groups (Control vs UUO group, each n = 8). The UUO groups were subjected to unilateral ureteral obstruction (UUO) by ligation of the left ureter for seven days. The control groups were performed to the same treatment for seven days, with the exception of the ligature.

Results: Consistent with our previous data, the protein expression of Prdx V was less in UUO group kidney than the control group kidney. Compared with UUO-induced Prdx V-/- mouse kidney, UUO-induced Prdx V+/- mouse kidney had more stained by TGF-β and α-SMA which is gradually increased by fibrosis progression. Knockdown of Prdx V, an atypical 2-Cys member of the Prdx family, results in significant increase in fibrotic marker expression, such as TGF-β, α-SMA, and vimentin, and also, augmented the reduction of E-cadherin, an epithelial marker as well as the increase in oxidative stress, such as nitrotyrosine and lipid peroxidation. Furthermore, we observed the activation of canonical and non-canonical TGF-β signal pathway, resulting in renal fibrosis progression. In canonical TGF-β signal, the increase of Smad4 that plays a critical role in nucleocytoplasmic shuttling of TGF-β, the increase of Smad4 that plays a critical role in nucleocytoplasmic shuttling of TGF-β, α-SMA which is gradually increased by fibrosis progression. Knockdown of Prdx V, an atypical 2-Cys member of the Prdx family, results in significant increase in fibrotic marker expression, such as TGF-β, α-SMA, and vimentin, and also, augmented the reduction of E-cadherin, an epithelial marker as well as the increase in oxidative stress, such as nitrotyrosine and lipid peroxidation. Furthermore, we observed the activation of canonical and non-canonical TGF-β signal pathway, resulting in renal fibrosis progression. In canonical TGF-β signaling, the increase of Smad4 that plays a critical role in nucleocytoplasmic shuttling of Smad2/3 is remarkable in UUO-induced Prdx Vsi signals, phosphorylation of Stat3 is accentuated in UUO-induced Prdx Vsi mouse kidney. In non-canonical TGF-β signals, phosphorylation of Stat3 is accentuated in UUO-induced Prdx Vsi mouse kidney consistent with our earlier in vitro data.

Conclusions: Prdx V is an anti-fibrotic effector that sustains renal physiology. Negative regulation mechanism of TGF-β signaling by Prdx V could be a therapeutic target to protect renal fibrosis.

SA-PO296

The Kidneys and the Lungs in the Rat Show Different Vascular and Fibrotic Changes in an Acute Model of Fat Embolism in the Presence or Absence of the Renin Inhibitor Aliskiren

Isham Elsherbiny,

1 Farnaz Khalafi,

2 Vasili Liv N. Vaidyanathan,

3 Alan Poisner,

2 David Arti,

Ahaan Siddiqui,

1 Agostino Molteni.

1 University of Missouri at Kansas City, Kansas City, MO; 2 Univ of Kansas Medical Center, Overland Park, KS; 3 University of Missouri-Kansas City, Kansas City, MO; 4 University of Missouri-Kansas City, Kansas City, MO.

Background: In a rat model of fat embolism (FE) induced by injection of triolein (T), a severe inflammatory reaction leads to vasculitis and pulmonary fibrosis that is mitigated by interfering with the renin angiotensin system (RAS): a renin inhibitor aliskiren (ALI). We extended the study to the kidneys by evaluating the renal arterial response to T treatment in this FE model and the effect of ALI.

Methods: 22 Sprague Dawley rats received T (0.2 ml IV, n=18) or saline (n=4). The T-treated rats were divided into three groups of 6 rats each and injected IP one hour later with saline, ALI 50 mg/kg or ALI 100 mg/kg. Four controls received saline. Rats were killed 48 hours later, the organs fixed and stained with H&E, trichrome and smooth muscle actin (SMA). The vascular evaluation included lumen patency (LP) and media adventitia ratio (MAR), a marker of edema. Photos at 400 X and 100 X were taken on each slide by two pathologists unaware of the slide identity. Alpha SMA and trichrome-stained slides were digitally analyzed by image J software (NIH) to quantify the amount of myofibroblasts and collagen present in each slide.

Results: Rats injected with T + saline showed the expected severe pulmonary vascular inflammation markedly reduced by both ALI doses but no significant inflammatory response was observed in the kidneys. T + ALI 50 showed a significant (p<0.01) increase in pulmonary lumen patency vs the T + saline group which revealed only a trend in reduction vs the controls. No differences in lumen patency were seen for renal arteries. The pulmonary MAR measurements were similar in the four groups whereas there was a significant effect in the kidneys (p=0.0007) with a slightly larger ratio for the T + saline and T + ALI groups. Image J determination revealed other organ differences with ALI: reduced proteoglycans in the kidney causes both tubule and glomerular Abnormalities.

Conclusions: In conclusion, serelaxin reverses DOCA-Salt induced cardiac and renal dysfunction by modulating inflammation, lipid metabolism, and fibrosis.

Funding: NIDDK Support, Commercial Support - Novartis

SA-PO297

Reduced Proteoglycans in the Kidney Causes Both Tubule and Glomerular Abnormalities

1 Nabin Poudel,

2 Maria C Munteanu,

3 Robert Silasii-Mansat,

4 Florea Lupu,

3 Myron Hindsale.

1 Physiological Sciences, Oklahoma State University, Stillwater, OK; 2 Program of Cardiovascular Biology Research, Oklahoma Medical Research Foundation, Oklahoma City, OK; 3 Department of Cell Biology, University of Oklahoma, Oklahoma City, OK.

Background: Most cells produce some form of proteoglycan(s). The initial assembly of glycosaminoglycans (GAG) on the core protein of proteoglycans (PG) requires the transfer of a xylose to a designated serine. The enzyme responsible for this is xylosyltransferase and it exists in two isoforms as xylosyltransferase 1 (XyIT1) and 2 (XyIT2). The latter is ubiquitously expressed in many organs suggesting a significant biochemical role of XyIT2 dependent proteoglycans in these organs. In our XyIT2 knockout mice (XyIT2-/- mice), substantial XyIT2 activity remains in the kidney due to the remaining XyIT1 activity. However, considerable renal abnormalities still occur including glomerular basement membrane changes, fibrosis, and tubule dilution. Our previous findings in XyIT2-/- mice established that proteoglycans are important in cyst development in the liver. Considering our findings in the XyIT2-/- mice and that reduced proteoglycans occurs in many different diseases affecting the kidney (e.g. polycystic kidney disease, PKD), we hypothesize that GAG levels have a modifying role in kidney function. Notably, PKD patients can develop proteoglycans, indicating a much poorer long-term prognosis.

Methods: Blood Urea Nitrogen (BUN) was measured from XyIT2-/- mice. Western blotting was performed on urine of XyIT2-/- mice to detect proteumirna. Transmission Electron Microscopy (TEM) was used to evaluate the structural changes in glomerular basement membrane and kidney tubule. In addition, TEM was performed on kidneys from mice injected with polyethylene glycol (PEG) to measure anionic sites in the GBM.

Results: XyIT2-/- mice have increased BUN, proteumirna, and, in aged mice, renal failure. Investigations also show that additional changes occur ultrastructurally in the glomerular basement membrane including decreases in anionic charge. Furthermore, tubule structure is also impacted indicating tubule dysfunction.

Conclusions: The findings in the XyIT2 deficient kidneys indicates that XyIT2-dependent glycosaminoglycans (GAG) assembly onto core proteins is important in nephron homeostasis. Our analyses suggest that one source of the proteumirna could be reduced renal proteoglycans.

Funding: NIDDK Support, Other NIH Support - P20GM103648, DK078989, Private Foundation Support

SA-PO298

Serelaxin Imcribes Cardiac and Renal Function in a DOCA-Salt Model of Cardiorenal Syndrome in Rats

1 Dong Wang,

2 Yuhuan Luo,

3 Komurariah Myakala,

3 Xiaoxin Wang,

3 David J Orlicky,

4 Evgeniya Dobriniskikh,

5 Moshe Levi.

1 University of Colorado, Aurora, CO; 2 University of Colorado Anschutz Medical Campus, Aurora, CO; 3 University of Colorado Denver, Aurora, CO; 4 University of Colorado, Denver, Aurora, CO; 5 medicine, U c denver, Aurora, CO.

Background: Serelaxin, a recombinant form of the naturally occurring peptide hormone relaxin-2, is a pleiotropic vasodilating hormone that has been studied in patients with acute heart failure. In this study, the effects of serelaxin on cardiac and renal function, fibrosis, inflammation and lipid accumulation were studied in DOCA-salt treated rats.

Methods: Uninephrectomized rats were assigned to two groups: controls provided with normal drinking water and DOCA provided with DOCA pellets and sodium chloride drinking water. After 4 weeks, the DOCA-salt rats were randomly selected and implanted with osmotic micropumps delivering vehicle or serelaxin for another 4 weeks.

Results: Treatment with serelaxin prevented cardiac and renal dysfunction in DOCA-salt treated rats. Serelaxin prevented cardiac and renal fibrosis, as determined by Picrosirius Red staining and Second Harmonic Generation (SHG) Microscopy. Treatment of DOCA-salt rats with serelaxin decreased renal inflammation, including the expression of TGF-β, NFkB, MCP-1, interleukin-1, interleukin-6, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and CD68 macrophages. Serelaxin also decreased lipid accumulation in kidney in part by decreasing SREBP-1c, SREBP-2, a key regulator of lipid metabolism.

Conclusions: In conclusion, serelaxin reverses DOCA-Salt induced cardiac and renal dysfunction by modulating inflammation, lipid metabolism, and fibrosis.

Funding: NIDDK Support, Commercial Support - Novartis
The RNA Binding Protein Staufen2 Is Required to Maintain Integrity of the Golgi Apparatus and Podocyte Cell-Matrix Adhesion

Jessica J. Harris, Valerie A. Schumacher, Boston Children's Hospital, Boston, MA; "Children's Hospital Boston, Boston, MA.

Background: Proper adhesion of podocytes to the glomerular basement membrane is necessary to withstand high transcapillary filtration pressure and to prevent glomerulosclerosis. Our preliminary data shows that the RNA binding protein Staufen2, known to mediate mRNA transport and local translation in neurons, is required for podocyte-matrix adhesion. In addition, we demonstrate that mice deficient in Staufen1 and 2 are more susceptible to glomerular disease, suggesting a role for local translation in the maintenance of the glomerular filtration barrier. The present study aims at determining the molecular mechanisms by which Staufen2 regulates cell-matrix adhesion.

Methods: A cell biological and biochemical approach was used to study the role of Staufen2 in the maintenance of cell-matrix adhesion.

Results: The most critical cell-matrix adhesion receptor in podocytes is podocin, which bridges laminin 521 in the GBM to the intracellular actin cytoskeleton. We show that glycosylation of integrin β1 is altered in Staufen2 knockdown immortalized podocytes and that there is decreased phosphorylation of the b1 integrin effector Src tyrosine kinase and focal adhesion kinase (FAK). Specifically, complex-type N-glycans added to b1 integrin in the Golgi apparatus by glucosaminyltransferases Gnt-III and V were decreased in Staufen2 knockdown cells. Both corresponding mRNAs were found to be bound and stabilized by Staufen2, suggesting a role for Staufen2 in regulating complex-type glycosylation. In addition, the Golgi apparatus was severely fragmented in Staufen2 knockdown podocytes, especially following mechanical stretch. This coincided with an increase in F-actin, known to cause Golgi fragmentation.

Conclusions: Staufen2 mediated morphological and functional integrity of the Golgi apparatus may represent a novel mechanism by which podocyte-matrix adhesion with an increase in F-actin, known to cause Golgi fragmentation.

Funding: NIDDK Support

SA-PO299

The Role of Plekha7 in Renal Fibrosis

Michael M. Yeboah, 1 Marla A. Chesnik, 2 Medicine, Medical College of Wisconsin, Milwaukee, WI; 2 Medicine, Medical College of Wisconsin, Milwaukee, WI.

Background: Chronic kidney disease (CKD) affects about 12% of all adults in the United States and is associated with significant morbidity, including but not limited to progression to end-stage kidney failure, and increased cardiovascular death. The associated healthcare costs are enormous and continues to increase. Progression to interstitial fibrosis (TIF) is the hallmark of CKD irrespective of the underlying kidney disease. TIF results from excessive deposition and accumulation of extracellular matrix in the renal interstitium by myofibroblasts which may originate from tubular epithelial cells through a process called epithelial-mesenchymal transition (EMT). The plekstrin homology domain containing family A member 7 (Plekha7) is a novel protein that is localized at the adherens junction of epithelial cells in association with E-cadherin which is involved with intercellular contacts. Plekha7 is also linked to signaling molecules (including β-catenin) and the cellular cytoskeleton. A SNP in Plekha7 has been associated with hypertension in multiple genome-wide association studies, and mutation of Plekha7 is involved with intercellular contacts. Plekha7 is also linked to signaling molecules.

Methods: In vivo, plekha7 mutant and wild type rats underwent unilateral ureteral obstruction (UUO), an established model of kidney fibrosis. The animals were euthanized after 2 weeks and the kidneys were retrieved for analysis of fibrosis markers. In vitro, plekha7 was stably knocked down or overexpressed in HK-2 cells via lentiviral transduction.

Results: Plekha7 mutation resulted in increased TGF-beta expression, macrophage recruitment, and fibrosis in rat kidneys after UUO. In HK-2 cells, plekha7 knockdown reduced E-cadherin and increased alpha-smooth muscle actin and collagen 1A1 expression, while plekha7 overexpression in the cells was associated with increased E-cadherin and reduced fibronectin and collagen 1A1 expression.

Conclusions: Mutation of Plekha7 results in increased renal fibrosis in rats. Knockdown of plekha7 protected HK-2 cells, while plekha7 overexpression restores the epithelial phenotype and reduces TGF-β-induced EMT.

Funding: Clinical Revenue Support

SA-PO301

Characterization of a Synthetic Adeno-Associated Virus (AAV-2/Anco80) That Targets Kidney Stroma and Validation through Gli2 Deletion in Fibrosis

Yoichi Ikeda, 4 Ru Xiao, 1 Luk Vandenberge, 1 Zhao Sun, 2 Benjamin D. Humphreys, 7 Schepps Eye Research Institute, Harvard Medical School, Boston, MA; 2 Washington University School of Medicine, Clayton, MO; 1 Washington University in St Louis, Saint Louis, MO; 7 Washington University, School of Medicine, St. Louis, MO.

Background: AAV is a non-integrating virus currently in human clinical trials for gene therapy. There are no reports of AAV with tropism to kidney, limiting our ability to deliver genetic material to that organ. We characterized the kidney tropism for a panel of AAV serotypes to set the stage for future use in human clinical trials.

Methods: Pseudotyped AAV with various capsid proteins and promoters were prepared and tested to validate the efficacy of transduction in mouse kidney. Initial studies utilized GFP reporters and later studies used AAV viruses that express Cre recombinase. To establish whether an AAV-based approach could efficiently delete floxed genes in kidney pericytes, we injected AAV-2/Anco80-CASI-Cre (3x10^11 G/C mouse) into Gli2(f/f);R26(tdTomato) mice or control. After three weeks, we performed UUO surgery, then administered renoviral INPCK during IP CKD. Kidney fibroblasts from patients were exposed to AAV-GFP and analyzed with fluorescent microscopy.

Results: Of all serotypes of AAV analyzed, AAV-2/Anco80-CASI most efficiently transduced kidney cell types. When AAV-2/Anco80-CASI-Cre was injected into R26(tdTomato) reporter mice, 58.9±3.5% (mean±SEM) of all pericytes became TdTomato positive. Other reporter positive cells were mesangial cells and juxtaglomerular cells. AAV-Cre injected Gli2(f/f);R26(tdTomato) mice had reduced fibrosis including 30 – 60% reduction in αSMA, fibronectin, collagen 1A1, collagen3A1 mRNA and protein levels after UUO compared to control, which is consistent to immunefluorescent stainings of αSMA and collagene. There were 40 fewer myofibroblasts in the Gli2loxox compared to control kidneys after UUO. There was no toxicity to extrarenal organs with this dose, though higher doses (10×12 G/C mouse) of AAV-2/Anco80-CASI did cause hepatitis. AAV-2/Anco80-CASI-GFP drove GFP specifically in stromal cells of human IPSC kidney organoids (30 of total Meis1 positive cells) and primary human kidney fibroblasts.

Conclusions: We demonstrate that AAV-Cre targets kidney pericytes and efficiently deleted Gli2 leading to an antifibrotic effect. AAV strategies will be useful both in preclinical models but also in human clinical trials.

Funding: NIDDK Support

SA-PO302

Adult Renal Stem/Progenitor Cells Can Revert LPS-Induced Endothelial-to-Mesenchymal Transition of Endothelial Cells

Fabio Sallustio, Alessandra Stasi, Claudia Curci, Rossana Franzini, Chiara Divella, Paola Laghi, Giuseppe De Palma, Angela Picerno, Monica Rutigliano, G. Lucarelli, Michele Battaglia, Giuseppe Castellano, Loreto Gesualdo. DETO, University of Bari, Bars, Italy.

Background: Acute Kidney Injury (AKI) is the major complication encountered in sepsis. Lipopolysaccharides (LPS) are frequently involved in the pathogenesis of AKI, triggering a myofibroblast phenotype characterized by endothelial cell (EC) dysfunction. EC acquire a myofibroblast phenotype, by endothelial-to-mesenchymal transition (EndMT), contributing to the renal fibrosis. Resident adult renal stem/progenitor cells (ARPCs) enhance tubular regenerative mechanism during AKI, but little is known about their effects on endothelial compartment. The aim of this study is to investigate the effects of ARPCs on endothelial dysfunction.

Methods: Endothelial cells were stimulated in vitro with LPS for 48h and co-cultured with ARPCs for 24h. MTT cell viability assay was used to analyze the EC proliferation rate following LPS stimulation and in co-culture with ARPCs. FACs analysis was used to study the expression of myofibroblast markers. Gene expression profiles of ARPCs and EC were generated using Agilent Microarrays.

Results: We observed a significant increase of EC proliferation after stimulation with LPS. ARPCs in co-culture with EC normalized their proliferation rate and decreased the cell growth rate, even in presence of LPS. Moreover, LPS induced a significant decrease of EC markers, CD31 and VE-cadherin and a significant increase of EC dysfunction markers, Collagen I and Vimentin. ARPCs in co-culture with EC abrogated the LPS-induced EndMT by restoring the high expression of CD31 (95% vs 66%) and VE-cadherin (96% vs 31%) and limiting Collagen I (18% vs 75%) and Vimentin (35 % vs 50.86%) expression. Microarray analysis showed that LPS induced the upregulation of 305 genes and the down regulation of 694 genes in ARPCs (Q value <0.05 and Fold change >2). Gene Set Enrichment Analysis (GSEA) pathway analysis of the upregulated list of 27 genes specifically involved in prevention and recovery from infections caused by external agents.

Conclusions: Our data demonstrate that ARPCs could preserve EC phenotype by regulating LPS-induced EndMT. Interestingly, LPS induces the expression of a specific gene set in ARPCs able to prevent EC dysfunction.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO303

Alpha-Actinin-4 Is Required for Shp2 Activation in Podocytes

Hsing-Hui Lee. Department of Life Sciences and Institute of Genome Sciences, National Yang-Ming University, Taipei, Taiwan.

Background: Integrins mediate cell-matrix interaction and form focal adhesion (FA) to connect with cytoskeleton in adherent cells. Previously, we found that Shp2 promotes ROCKII activation that facilitates FA maturation and stress fibers orientation to optimize cellular tension in response to the increase of matrix rigidity.

Methods: Results: In this study, we identified that α-actinin-4 interacts with Shp2 at FAs in mouse embryonic fibroblasts by an in vitro pull-down assay with recombinant Shp2-N-terminus. This interaction between endogenous Shp2 and α-actinin-4 at FAs was confirmed by co-immunoprecipitation and proximity ligation assay. Since α-actinin-4 plays an important role in podocytes adhesion, we then used a mouse temperature-inducible inducible podocyte line and found that differentiated podocytes exhibited distinct FAs and stress fibers with the role of Shp2 blocking of α-actinin-4. Knockdown of α-actinin-4, which encodes α-actinin-4, by CRISPR/Cas9 reduced Shp2 activation significantly in podocytes. Furthermore, inhibition of Shp2 reduced ROCKII activation, FA stress fibers, and BSA-filtration ability of podocytes.

Conclusions: Taken together, our results suggest the essential role of α-actinin-4 in Shp2 activation that is crucial for the cell adhesion and filtration function in podocytes.

Funding: Government Support - Non-U.S.

SA-PO304

Expression of APOL1 Risk Alleles (G1 and G2) Compromises Spreading of Podocytes by Down Regulation of β3 Integrin

Ali Hussain,1 Rukhsana Aslam,1 Vinod Kumar,1 Ashwani Malhotra,2 Karl Skorecki,3 Pravin C. Singhal.1 Feinstein Institute for medical research, Glenoaks, NY; 2Feinstein Institute of Medical Research, New York, NY; 3North Shore LIJ Health System, Great Neck, NY; 4Rambam Health Care Campus, Haifa, Israel.

Background: Genetic epidemiology indicated that Africans Americans are at four-fold higher risk for in development of focal segmental glomerulosclerosis when compared to European Americans. This disparity amongst African American has been attributed to carrying APOL1 risk alleles (G1 and G2). Expression of APOL1 G1 and G2 by podocytes has been reported to promote cell death both in vitro and in vitro studies. However, role of APOL1 G0 (wild-type) in podocytes is far from clear. Podocytes are normally detached and excreted in the urine in a normal physiological state. However, adjacent podocytes are able to maintain the integrity of the glomerular filtration barrier by spreading over the naked basement membrane caused by detachment of podocytes. We hypothesized: Taken together, our results suggest the essential role of α-actinin-4 in spreading when compared to podocytes compromising integrity of glomerular filtration barrier.

Methods: Cultured immortalized human podocytes proliferate at 33°C and differentiate at 37°C. Podocytes stably expressing vector, APOL1G0, APOL1G1, and APOL1G2 grown on coverslips (collagen coated) were incubated in media for 12 and 24 hours (37°C = n-4). Subsequently, podocytes were labeled with α-actinin antibody and examined under a confocal microscope. Average size of podocytes determined at 8 random fields using J Image program. Proteins extracted from the cells treated under similar conditions, were probed for β3 integrin and α-actinin expression and reproposed for actin.

Results: Podocytes expressing APOL1 G1 and G2 displayed decreased (P<0.01) spreading when compared to podocytes expressing vector (V) or APOL1G0 (Mean podocyte size at 12 hours: V, 74 ± 18.6; APOL1G0, 87.8 ± 15.3; APOL1G1, 42.5 ± 12.2; APOL1G2, 35.2 ± 9.7 μm) and at 24 hours: V, 118.1 ± 15.7; APOL1G0, 130.6 ± 17.5; APOL1G1, 65.1 ± 18.0; APOL1G2, 79.7 ± 16.4 μm) both at 12 and 24 h. Podocytes expressing APOL1G0 displayed increased (P<0.05) spreading when compared to vector. Western blot analysis showed 2-5 fold decreased expression of β3 integrin and α-actinin in podocytes expressing APOL1G1 and G2 when compared to podocytes expressing vector and APOL1G0.

Conclusions: Expression of APOL1 risk alleles (G1 and G2) compromised podocyte spreading by down regulation of β3 integrin α-actinin expressions.

Funding: NIDDK Support

SA-PO305

Inhibiting Post-Translational Core Fucosylation Protects against Albumin-Induced Proximal Tubular Epithelial Cell Injury

Yong Deng. The First Affiliated Hospital of Dalian Medical University, Dalian, China.

Background: Albuminuria is an independent risk factor for renal interstitial fibrosis (RIF). Albumin-over-filtered albumin may cause injury to proximal tubular epithelial cells (PTECs) in endocytic and non-endocytic pathways via megalin and TGFβRII respectively. As megalin and TGFβRII are both modified by post-translational core fucosylation which plays a critical role in RIF, we identified whether or not core fucosylation is a potential target for reducing albumin-induced injury to PTECs.

Methods: We constructed a human PTEC-derived cell line of HK-2 cells and a bovine serum albumin (BSA) injury model in vitro. RNAi was used to inhibit expression of megalin, TGFβRII and FUT8. Western blotting, immunostaining, enzyme-linked immunosorbant assay, lectin blotting and fluorescence-activated cell sorting were used to determine BSA-induced endocytic and non-endocytic damage in HK-2 cells. FUT8 is a core fucosylation-related gene, the expression of FUT8 was significantly increased after incubation with BSA in HK-2 cells.

Results: FUT8isRNA significantly reduced core fucosylation of megalin and TGFβRII. Meanwhile, it could also inhibit activation of the TGFβ/TGFβRII/Smad3/2 signaling pathway. Furthermore, FUT8isRNA could reduce monocye chemotactic protein-1, reactive oxygen species and apoptosis; and significantly decrease fibronectin and collagen I levels in BSA-overloaded HK-2 cells. Notably, inhibiting core fucosylation is more effective than either inhibiting megalin or inhibiting TGFβRII in the prevention of albumin-induced injury to PTECs.

Conclusions: Inhibition of core fucosylation could effectively alleviate albumin-induced endocytic and non-endocytic injury to PTECs, our study provides a potential therapeutic target in albuminuria-induced injury.

Funding: Government Support - Non-U.S.

SA-PO306

Binding of Anti-dsDNA Antibodies to Major Vault Protein of Proximal Renal Tubular Epithelial Cells Resulted in Increased Fibronectin Expression and MCP-1 Secretion

Susan Yang, Shirlit S. Ho, Abel Chun, Kin Yi Au, Kwok Fan Cheung, Mel Chau, Daniel Tak Mao Chau. Department of Medicine, The University of Hong Kong, Hong Kong SAR, Hong Kong.

Background: Anti-dsDNA antibodies deposit in the kidney parenchyma in lupus nephritis. In addition to complement activation by immune complexes and activation of downstream pro-inflammatory mechanisms, whether these antibodies could directly induce organ damage remains controversial. We investigated the binding of human anti-dsDNA antibodies to proximal renal tubular epithelial cells (PTEC) and the downstream impact on cell functions.

Methods: Human polyclonal anti-dsDNA antibodies were isolated from the sera of lupus nephritis patients using affinity chromatography and those with high binding affinity were selected for further studies. PTEC membrane, cytosolic and nuclear proteins were isolated and immunoprecipitated with anti-dsDNA antibodies to identify cross-reactive antigens using liquid chromatography-mass spectrometry (LC-MS).

Results: Anti-dsDNA antibodies bound to a 100 kDa protein, identified as major vault protein (MVP), which was present in the cytosolic and nuclear fractions, but not in the plasma membrane fraction. Incubation of PTEC with anti-dsDNA antibodies increased MVP expression, as determined by Western blot analysis, in a time-dependent manner (P<0.01, for 24h), and accompanied by increased fibronectin expression (P<0.01) and MCP-1 secretion (P<0.05) compared to cells incubated with IgG from healthy controls. Immunohistochemical studies showed predominantly perinuclear localization of MVP and weak intracellular expression of fibronectin under basal conditions. MVP overexpression in PTEC, by transfection with MVP plasmid, resulted in clustering of MVP in the cytoplasm, which was accompanied by fibronectin accumulation in the extracellular matrix and increased MCP-1 secretion (P<0.01). MVP gene silencing using RNAi resulted in 40% reduction in fibronectin expression and 53% reduction in MCP-1 secretion. Kidney biopsies from lupus nephritis patients showed markedly increased MVP expression, predominantly on proximal tubular epithelial cells.

Conclusions: Our data showed that anti-dsDNA antibody binding to MVP in PTEC was associated with downstream inflammatory and fibrogenic processes.

Funding: Government Support - Non-U.S.

SA-PO307

Module IV-Defected Mutant CCN2 Knock-In Transgenic Mice Grow and Develop Normally, but Fibrotic Properties Are Attenuated in a Number of Kidney Diseases

Tsunomo Inoue, Ono Atsushi, Hirokazu Okada. Saitama Medical University, Iruma-gun, Saitama, Japan.

Background: CCN2 has been considered as important therapeutic target for CKD. It also plays a part in wound healing and metabolism in hard tissues, thus inhibition of the supplementation of CCN2 is practical as a treatment. Therefore, we are focusing on the modules that are responsible for fibrosis in the kidney.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: In the UUO model, interstitial fibrosis was progressed at 24 hours, and 7 days in a time-dependent manner. The fibrotic area detected by Masson trichrome staining was significantly increased in CCN2+/- mice. Expression of mutant CCN2 was elevated in CCN2Ex5-/- mice in comparison to CCN2Ex5+/+ mice. On the other hand, the expression of type I collagen (0.86 ± 0.28 vs. 0.52 ± 0.18), TGF-β1 (0.35 ± 0.07 vs. 0.23 ± 0.06), PAI-1 (0.13 ± 0.05 vs. 0.06 ± 0.04) were significantly decreased in CCN2Ex5-/- mice compared to the wild type. In the IR model, although there was no significant difference in fibrosis or cytokine expression in the acute phase (3 days), both the progression of fibrosis and expression of related cytokines were significantly suppressed in CCN2Ex5-/- mice in the chronic phase (2 weeks). The same results were obtained with the 56% model. Western blot analysis using UUO 24-hour whole kidney samples revealed that there were no significant differences in signal alterations in previously-reported cascades, including MAPK (ERK, p38, JNK) and Wnt/β-catenin pathway, between CCN2Ex5+/+ and CCN2Ex5-/- mice.

Conclusions: As non-specific inflammatory CCN2 probably acts in a dominant-negative manner, the progression of interstitial fibrosis was suppressed in our transgenic mice. Also, this study indicates that module IV specifically contributes to the progression of CKD regardless of the type of primary disease process.

Funding: Government Support - Non-U.S.

SA-PO308

Sexual Dimorphism in the AKI to CKD Transition in the Rat

Methods: Thirty-nine female (F) and 39 male (M) rats were included. The rats were divided into two groups: sham operated and rats underwent 45 min bilateral renal ischemia (F+IR, and M+IR). All groups were studied and sacrificed at: 24 h, 1, 2, 4, and 4-months after IR. Also, 41 oophorectomized rats were included and divided into sham or IR groups (Op and Op+IR). At the end of each experimental period, physiological, histopathological, and molecular studies were performed.

Results: We found a sexual dimorphic response in the AKI to CKD transition. After 24 h, IR induced a similar functional and structural extent of renal injury in females and males, but female rats exhibited less oxidative stress and increased renal GSH content. After 4 months and despite similar renal injuries, the M+IR group developed CKD characterized by progressive proteinuria, renal dysfunction, tubulo-interstitial fibrosis and glomerular hypertrophy. Most of these alterations were observed since the 3rd month after IR and were associated with increased oxidative stress and a significant reduction in HIF-1α, VEGF and endothelin receptor B mRNA levels since the 1st month. Interestingly, F+IR group did not develop CKD. Moreover, this group exhibited a significant increase in eNOS, TGFβ and Hif1α mRNA levels, since the 1st month after IR. Supporting this sexual dimorphism, Op+IR rats developed CKD similar to that observed in M+IR group.

Conclusions: We found a sexual dimorphic response in the AKI to CKD transition. Early male death of mice with higher TGβ, HIF1α and eNOS mRNA levels were among the renoprotective mechanisms that the F+IR group demonstrated.

Funding: Government Support - Non-U.S.

SA-PO309

Kidney-Resident Macrophages (KRM) Upregulate Pro-Angiogenic Response in Chronic Ischemic Kidney Injury

Background: Kidney-resident macrophages (KRM) are non-inflammatory monocytes that are present in the healthy kidney, and can also be identified in human kidneys. KRM show a more robust response to ischemic injury than non-KRM. We found that module IV-defective CCN2 probably acts in a dominant-negative manner, the progression of interstitial fibrosis was suppressed in our transgenic mice. This study indicates that module IV-specifically contributes to the progression of CKD regardless of the type of primary disease process.

Funding: Government Support - Non-U.S.

SA-PO310

Hypoxia-Induced Proteins as Novel Biomarkers of Early Stage Kidney Disease

Methods: Using CX3CR1CreRosa26tdTomato mice we fate-mapped the KRM and non-KRM. We found that module IV-defective CCN2 probably acts in a dominant-negative manner, the progression of interstitial fibrosis was suppressed in our transgenic mice. Also, this study indicates that module IV specifically contributes to the progression of CKD regardless of the type of primary disease process.

Funding: Government Support - Non-U.S.

SA-PO311

Hypoxia-Inducible Factors-1α (HIF-1α) as Novel Therapeutic Targets for Chronic Kidney Disease

Background: Under hypoxic conditions, several aspects of lipid metabolism including lipoprotein metabolism, cholesterol biosynthesis, and fatty acid metabolism are upregulated in the renal cortex. Therefore, we hypothesize that HIF-1α pathway may provide a switch through which lipoprotein metabolism, cholesterol and fatty acid biosynthesis, and gene expression in the renal cortex are regulated under hypoxia.

Funding: Government Support - Non-U.S.
Methods: Western blot and qPCR analysis were performed to examine the levels of lipid catabolism enzymes, glycolytic enzymes and HIF-1α in folic acid (FA) induced renal fibrotic mice. Then, FA mice were administered with control or dinitrophenol (DNP), which causes kidney hypoxia and activates HIF-1α, to determine whether HIF-1α affects metabolic switch. Further mechanism was searched in tubular epithelial cells in vitro.

Results: We identified significant lipid accumulation and higher expression of glycolytic enzymes accompanied with up-regulated HIF-1α in renal tissues of FA mice. DNP treatment decreased fatty acid oxidation and increased glycolysis, which served to maintain sustained ATP and promote fibroblast proliferation and ECM production in mice kidney. In tubular epithelial cells, TGF-β-accumulated higher amount of lipids through a combination of metabolic alterations including fatty acid uptake, decreased fatty acid oxidation, and activated glycolysis enzymes, while increased the markers of collagen fibrils. Transfection with siRNA to HIF-1α reversed the effect in vitro.

Conclusions: It can be concluded that HIF-1α plays a major role in the metabolic reprogramming of renal fibrosis. Targeting the HIF pathway may provide novel therapeutic approach of kidney fibrosis.

Funding: Government Support - Non-U.S.

SA-PO312

Autophagy in FOXD1 Stroma-Derived Cells Plays a Critical Role in Renal Tubulointerstitial Fibrosis Yong Kwan Kim,1,4 Sun-ah Nam,2 Chul Woo Yang,1 Jin Kim,2 1Seoul St. Mary’s Hospital, Seoul, Republic of Korea; 2Chulalongkorn University, Bangkok, Thailand; 3The Catholic University of Korea, Seoul, Republic of Korea; 4Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Background: Autophagy is a cellular process of degradation of damaged cytoplasmic components and regulates cell survival. It remains unclear whether the induction of autophagy has positive impact or negative impact in renal TIF. Here, we hypothesized that autophagy in FOXD1 lineage stromal cell may have a protective role in development of renal TIF, which may be a new therapeutic target for renal TIF.

Methods: To examine the distribution of cells where autophagy was induced, we used GFP-LC3 transgenic mice. We also generated conditional knockout mice in which Atg7 is genetically ablated specifically in FOXD1-lineage cells (Atg7f/f;FOXD1-Cre+). Our data showed that autophagy in FOXD1 stroma-derived cells play a protective role in development of renal TIF, which may be a new therapeutic target for renal TIF.

Results: Punctate distribution of GFP-LC3 was highly expressed in not only renal tubular epithelial cells but also interstitial cells, which were colocalized with PDGFR-β positive cells. Tubulointerstitial fibrosis was enhanced in Atg7f/f;FOXD1-Cre+ after UUO through Smad dependent TGF-β signaling compared with wild type mice. In Atg7f/f;FOXD1-Cre+, the accumulation of interstitial myofibroblasts was increased and the differentiation of pericyte into myofibroblasts was enhanced compared with WT mice after UUO. The peritubular capillary rarefaction and the apoptosis of interstitial cells were accelerated in Atg7f/f;FOXD1-Cre+ after UUO.

Conclusions: Our data showed that autophagy in FOXD1 stroma-derived cells play a protective role in development of renal TIF, which may be a new therapeutic target for renal TIF.

SA-PO313

Autophagy Is Induced via HIF-1α to Facilitate Renal Interstitial Fibrosis during Unilateral Ureteral Obstruction in Mice and Hypoxia in Tubular Cells Jing Liu,1,2 Man J. Livingston,3 Qingqing Wei,2 Zheng Dong,2,1 1Department of Nephrology, The Second Xiangya Hospital, Central South University, Changsha, China; 2Augusta University Medical College of Georgia, Augusta, GA.

Background: Autophagy, a fundamental cellular catabolic process, has recently been implicated in renal fibrosis. However, it is unclear how autophagy is activated under this condition. Hypoxia-inducible factors (HIF) are master regulators of hypoxia responsive genes and may contribute to renal fibrosis. Whether HIF is involved in autophagy activation during renal fibrosis is largely unknown.

Methods: In vivo, renal fibrosis was induced by unilateral ureteral obstruction in mice. In vitro, renal proximal tubular cells were exposed to hypoxia to induce fibrotic changes. YC-1 was used to inhibit HIF pharmacologically. Kidney proximal tubule-specific HIF-1 knockout (PT-HIF-1 KO) mice were also examined.

Results: After YC-1 administration, kidney proximal tubular cells showed significantly lower autophagy during YC-1 treatment. In addition, knockdown HIF-1 in these cells attenuated autophagy activation and fibronectin accumulation during hypoxia exposure.

Conclusions: The results suggest that in renal fibrosis, HIF-1 may activate autophagy in renal tubular cells to facilitate the development of renal interstitial fibrosis.

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

SA-PO314

Screening Fibroblasts for Novel Therapeutic Targets in CKD Ian Logan,1 Neil S. Sheerin,1 Victoria G. Shuttleworth,2 Newcastle University, Newcastle upon Tyne, United Kingdom; 2Newcastle University, UK, Newcastle Upon Tyne, United Kingdom; 1newcastle hospitals, Newcastle.U.K.

Background: The most significant problem in nephrology is the progression of Chronic Kidney Disease (CKD) to End Stage Renal Disease (ESRD), which requires either dialysis or transplantation to sustain life. Despite our knowledge that ESRD is caused by accumulation of fibrotic scar tissue leading to organ failure, no treatments are...
Mechanisms Associated with Kidney Fibrosis - II

Mechanisms Associated with Kidney Fibrosis - II

Potsdam, Germany

1Charité-Universitätsmedizin, Berlin, Germany; 2University of Potsdam, Germany; 3Delic, Thomas; 4Blaut, Moritz; 5Hocher, Ahmed; 6Hasan, Andrei; 7Eltrich, Thomas; 8Völker, Volker; 9Selpin, Ewald; 10Terzi, Delia; 11Moritz, Moritz; 12Blottner, Michael; 13Brenner, Bernhard; 14Vangheluwe, Xavier; 15Krammer, Martin

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

Background: Acute kidney injury (AKI) is a risk factor for the development of chronic kidney disease (CKD). After ischemia-reperfusion injury (IRI), a major aetiology of AKI, resolution of renal inflammation allows tubular regeneration, whereas ongoing inflammatory injury mediated by infiltrating leukocytes leads to nephron loss and renal fibrosis, typical hallmarks of CKD. The atypical chemokine receptor 2 (ACKR2) is a chemokine decoy receptor, which scavenges inflammatory CC-chemokines and reduces local leukocyte accumulation and inflammation. Here, we hypothesized that ACKR2 limits leukocyte infiltration, inflammation and fibrotic tissue remodelling after renal IRI, thus preventing progression to CKD after AKI. We tested this hypothesis by subjecting wild-type (WT) and Ackr2-deficient mice to IRI induced by transient renal pedicle clamping. In addition, in vitro experiments were performed with tubulointerstitial tissue isolated from wild-type and Ackr2-/- mice.

Results: Compared to WT control Ackr2 deficiency lead to significantly increased CCL2 levels in TNF-stimulated tubulointerstitial tissue in vitro. In vivo, Ackr2 deficiency did not affect renal dysfunction and tubular injury in early IRI one day after bilateral or 5 days after unilateral pedicle clamping, although accumulation of mononuclear phagocytes increased in postischemic Ackr2-/- kidneys. Regarding long-term outcomes, postischemic Ackr2-/- kidneys displayed significantly more tubular injury 5 weeks after unilateral IRI, which was associated with persistent increases in mononuclear phagocytes and T cell infiltrates compared to WT. Moreover, Ackr2 deficiency resulted in more severe inflammation in postischemic kidneys, with increased expression of proinflammatory chemokines and M1 macrophage markers, and enhanced accumulation of Ly6C<sup>hi</sup> inflammatory macrophages. This was associated with aggravated renal fibrosis in Ackr2-/- kidneys 5 weeks after IRI, as revealed by increased expression of matrix molecules, renal accumulation of αSMA<sup>+</sup> myofibroblasts and enhanced renal fibrosis of bone marrow-derived fibrocytes.

Conclusions: These data suggest that the chemokine decoy receptor ACKR2 plays an important role in limiting persistent inflammation, tubular loss, and renal fibrosis after ischemic AKI, and represents a potential novel target for disease progression to CKD.

Funding: Government Support - Non-U.S.

SA-PO317
Loss of the Protein Cystathionine ß-Synthase during Kidney Injury Promotes Renal Tubulointerstitial Fibrosis Qingjiong Yuan, Xiangya Hospital, Central South University, Changsha, China.

Background: Renal tubulointerstitial fibrosis (TIF) is the common pathway of progressive chronic kidney disease. Inflammation has been widely accepted as the major driving force of TIF. Cystathionine ß-synthase (CBS) is the first and rate-limiting enzyme in the transsulfuration pathway. The purpose of this study was to investigate the potential role and mechanism of CBS in renal inflammation and TIF.

Methods: Renal function, tubulointerstitium damage index score, extracellular matrix (ECM) deposition, and the expressions of CD3, CD68, IL-1β, TNF-α were measured in sham operation and UUO rats. Proteomics and gene array analysis were performed to screen differentially expressed molecules in the development of renal inflammation and TIF in UUO rats. The expression of CBS was detected in patients with obstructive nephropathy and UUO rats. We confirmed the expression of CBS using western blot and real-time PCR in HK-2 cells. Overexpression plasmid and siRNA were transfected specifically to study the possible function of CBS in HK-2 cells.

Results: Abundant expression of CBS, localized in renal tubular epithelial cells, was revealed in human and rat renal tissue, which correlated negatively with the progression of fibrotic disease. Expression of CBS was dramatically decreased in the obstructed kidney from UUO rats as compared with the sham group. In addition, knocking down CBS exacerbated ECM deposition, whereas CBS overexpression attenuated TGF-β1-induced ECM deposition in vitro. Inflammatory and chemotactic factors were also increased in CBS knockdown HK-2 cells stimulated by IL-1β.

Conclusions: These findings establish CBS as a novel inhibitor in renal fibrosis and as a new therapeutic target in patients with chronic kidney disease.

Funding: Government Support - Non-U.S.

SA-PO316

Background: The atypical chemokine receptor 2 (ACKR2) is a chemokine decoy receptor, which scavenges inflammatory CC-chemokines and reduces local leukocyte accumulation and inflammation. Here, we hypothesized that ACKR2 limits leukocyte infiltration, inflammation and fibrotic tissue remodelling after renal IRI, thus preventing progression to CKD after AKI. We tested this hypothesis by subjecting wild-type (WT) and Ackr2-deficient mice to IRI induced by transient renal pedicle clamping. In addition, in vitro experiments were performed with tubulointerstitial tissue isolated from wild-type and Ackr2-/- mice.

Results: Compared to WT control Ackr2 deficiency lead to significantly increased CCL2 levels in TNF-stimulated tubulointerstitial tissue in vitro. In vivo, Ackr2 deficiency did not affect renal dysfunction and tubular injury in early IRI one day after bilateral or 5 days after unilateral pedicle clamping, although accumulation of mononuclear phagocytes increased in postischemic Ackr2-/- kidneys. Regarding long-term outcomes, postischemic Ackr2-/- kidneys displayed significantly more tubular injury 5 weeks after unilateral IRI, which was associated with persistent increases in mononuclear phagocytes and T cell infiltrates compared to WT. Moreover, Ackr2 deficiency resulted in more severe inflammation in postischemic kidneys, with increased expression of proinflammatory chemokines and M1 macrophage markers, and enhanced accumulation of Ly6C<sup>hi</sup> inflammatory macrophages. This was associated with aggravated renal fibrosis in Ackr2-/- kidneys 5 weeks after IRI, as revealed by increased expression of matrix molecules, renal accumulation of αSMA<sup>+</sup> myofibroblasts and enhanced renal fibrosis of bone marrow-derived fibrocytes.

Conclusions: These data suggest that the chemokine decoy receptor ACKR2 plays an important role in limiting persistent inflammation, tubular loss, and renal fibrosis after ischemic AKI, and represents a potential novel target for disease progression to CKD.

Funding: Government Support - Non-U.S.
SA-PO318
Paraquat-Induced CKD in Animal Models: Relevance to CKD of Unknown Origin (CKDu)
Fan Lei,1 Qingtian Li,1 Yi Tang,1,2 Leping Huang,1 Luan D. Truong,2 David Shelkh-Hamad,1 Baylor College of Medicine, Houston, TX; 3The Methodist Hospital, Houston, TX; 4Baylor College of Medicine, Houston, TX; 5West China Hospital of Sichuan University, Chengdu, China.

Background: CKDu is typically encountered in farm workers from different regions of the world, and kidney biopsies from representative patients display tubulointerstitial injury and inflammation. Survey of patients with chronic kidney disease of unknown etiology (CKDu) encountered at a safety net hospital in Houston, identified the herbicide Gramoxone (parquat-based) as a possible etiologic factor for CKDu in migrant workers originally engaged in agricultural/farm work before their immigration to the US. These subjects described repeated and chronic (years) skin exposure to Gramoxone, as protective gear is not ordinarily used during preparation and spray work. We tested the hypothesis that repetitive exposure of mice to parquat will lead to chronic kidney disease; as such, repetitive exposure to the herbicide Gramoxone might produce CKD in humans.

Methods: Mice were given 10 i.p. injections of 20 mg/kg parquat, given weekly, and allowed free access to food and water. This dose was based on titration experiments where a single dose produces no functional or histological changes in the kidney. At the end of week 10, 24h urine was collected and blood samples were obtained for measurement of creatinine clearance. Mice were euthanized and kidneys were subjected to PAS and Trichrome stains and immunostain for T cells (CD3) and macrophages (F4/80); parallel examination of lung, liver and spleen was carried out to determine the effects on other organs.

Results: Parquat-treated mice displayed doubling of serum creatinine, 50% reduction in creatinine clearance, three-fold increase in T-cells and macrophage infiltration, and increased trichrome staining. There were no changes in the morphology or macrophage infiltration in the liver and lung; however, the spleen showed increased macrophage infiltration.

Conclusions: Repetitive exposure of mice to parquat given i.p. to simulate exposure of farm workers to parquat (Gramoxone), produced CKD characterized by tubulointerstitial injury and inflammation, reminiscent of the pathological picture observed in human CKDu subjects. Our data suggest that chronic exposure to the herbicide Gramoxone by farm workers in different regions of the world should be considered as a possible etiologic factor for CKD.

Funding: Veterans Affairs Support, Private Foundation Support

SA-PO319
Development of a Refrained Subtotal Nephrectomy Mouse Model to Study Progressive Renal Disease
James O’Sullivan, Sarah L. Finnie, Laura Denby, University of Edinburgh, Edinburgh, United Kingdom.

Background: Chronic Kidney Disease (CKD) is characterised as the decline of renal function over time. Metabolomics data has elucidated new metabolites, including citrulline, to be associated with human CKD indicating alterations in metabolic pathways being involved in CKD [Rhee EP et al, 2013]. Furthermore, defective fatty acid oxidation has been found to be involved in tubulointerstitial fibrosis [Kang HM et al, 2015]. The rat subtotal nephrectomy (STNx) model is a commonly used model of progressive renal disease and replicates many aspects of human CKD. However, a consistent mouse model of STNx which mimics most of the typical features of CKD would be advantageous to elude the pathophysiology.

Methods: Inbred 129/S2/SvHsd mice were randomised to sham or one-step subtotal nephrectomy (STNx) surgery and sacrificed after 6 (n=8/group) or 10 weeks (n=8/group). The one-step STNx involves flank incision nephrectomy followed by flank incision removal of upper and lower poles of the remaining kidney. At sacrifice, tissue was taken for RNA, protein and histological analyses. At baseline, 6 weeks and 9 weeks animals had urine collected and echocardiography performed. Blood pressure (BP) was measured by tail cuff plethysmography (baseline and 9 weeks). Parallel examination of lung, liver and spleen was carried out to determine the effects on other organs.

Results: In these experiments, we found that acute up-regulation of Fatty acid oxidation pathways, while the longer term treatment showed a suppression of activated inflammatory pathways, and suppression of drivers of fibrosis (TGFβ) and of transcriptional regulators known to be involved in progressive forms of DN (STAT1). Short-term late treatment with FT011 showed a reduced inhibitory effect on inflammatory pathways. Comparison with the transcriptome from human DN showed several overlapping key features and pathways of the human disease to be recapitulated in the animal model used, with a significant z-score of 6.4.

Conclusions: Analysis of transcriptional changes mediated by treatment with FT011 has shown an early up-regulation of fatty acid oxidation pathways, while the longer term treatment showed a suppression of activated inflammatory pathways, and suppression of drivers of fibrosis (TGFβ) and of transcriptional regulators known to be involved in progressive forms of DN (STAT1). Short-term late treatment with FT011 showed a reduced inhibitory effect on inflammatory pathways. Comparison with the transcriptome from human DN showed several overlapping key features and pathways of the human disease to be recapitulated in the animal model used, with a significant z-score of 6.4.

Funding: Government Support - Non-U.S.

SA-PO322
Modulation of Upregulated Transcriptional Signaling Pathways in Rodent Diabetic Nephropathy after Treatment with a Novel Anti-Fibrotic Agent FT011: Correlates with Human Diabetic Kidney Disease
Robyn G. Langham,1 Sebastian Martin,1 Felix H. Eichinger,2 Viji Nair,3 Matthias Kretzler,2 Darren J. Kelly,3 Ludwig Maximilian University Munich, Munich, Germany; 4University of Michigan, Ann Arbor, MI; 5Monash University, Melbourne, VIC, Australia.

Background: Transcriptional analysis of diabetic nephropathy (DN) biopsy tissue has provided valuable insights into the regulatory networks that may drive progressive disease. In this study, we undertook a transcriptomic analysis associated with demonstrated improved histological and clinical effects of a new anti-fibrotic, FT011, in a rodent model of DN. We also aimed to compare the animal findings with that already understood to be involved in human DN, a means of predicting utility of FT011 in humans.

Methods: Control and diabetic Ren(2) rats were treated with either FT-011(200mg/ kg/day) or vehicle for 16 weeks(Early), or for the last 2 days of the study(Late). Total RNA was isolated from renal cortex, reverse transcribed, linearly amplified, and hybridized on Affymetrix microarrays. The Ingenuity® Pathway Analysis Software Suite was used for gene analysis.

Results: Gene expression data in diabetic rats showed early findings in keeping with Type 1 diabetes, early suppression of lymphocyte genes, and an increase in known diabetes-related genes. Short term FT011-treatment of rats with established DN showed acute up-regulation of Fatty acid oxidation pathways, while the longer term treatment showed a suppression of activated inflammatory pathways, and suppression of drivers of fibrosis (TGFβ) and of transcriptional regulators known to be involved in progressive forms of DN (STAT1). Short-term late treatment with FT011 showed a reduced inhibitory effect on inflammatory pathways. Comparison with the transcriptome from human DN showed several overlapping key features and pathways of the human disease to be recapitulated in the animal model used, with a significant z-score of 6.4.

Conclusions: Analysis of transcriptional changes mediated by treatment with FT011 has shown an early up-regulation of fatty acid oxidation, and a later, more sustained anti-inflammatory and anti-fibrotic action. Similarity of the changes seen in the animal model to the human transcriptional data set highlights the close alignment of this model to the human disease. As well, the ability of FT011 to modulate key signaling pathways identified as important in the pathogenesis of human DN further supports its potential utility as a new therapy for DN.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Melatonin Ameliorates Intrarenal Renin-Angiotensin System in a 5/6 Nephrectomy Rat Model
Savaya Ishigaki, Naro Ohashi, Takashi Matsuyama, Shinsuke Isobe, Naoko Tsuji, Tomoyuki Fujikura, Takayuki Tsuji, Akihiko Kato, Hideo Yasuda. Hamamatsu University School of Medicine, Hamamatsu, Japan.

**Background:** Activation of the intrarenal renin-angiotensin system (RAS) plays a critical role in the pathophysiology of chronic kidney disease (CKD) and hypertension. Recent evidence suggests that the intrarenal RAS is important in the development of interstitial fibrosis and there has been great interest in developing strategies that target the RAS in the treatment of CKD. Melatonin is recognized as a powerful antioxidant, and we recently reported that impaired nighttime melatonin secretion correlates negatively with urinary angiotensin excretion, the surrogate marker of intrarenal RAS activity in patients with CKD. However, whether melatonin supplementation ameliorates the augmentation of intrarenal RAS in CKD has remained unknown. We aimed to clarify whether exogenous melatonin ameliorates intrarenal RAS activation via the reduction of ROS production.

**Methods:** 5/6 nephrectomized (Nx) rats were used as a chronic progressive CKD model and compared with sham-operated control rats. The Nx rats were divided into untreated Nx rats and melatonin-treated Nx rats. The levels of intrarenal RAS, ROS components, and renal injury were evaluated after 4 weeks of treatment.

**Results:** Compared with the control rats, the untreated Nx rats exhibited significant increases in intrarenal RAS (angiotensinogen, angiotensin II type 1 receptors, and angiotensin II), accompanied by elevated blood pressure, higher oxidative stress (8-hydroxy-2’-deoxyguanosine), lower antioxidant (superoxide dismutase) activity, and increased markers of interstitial fibrosis (α-smooth muscle actin and type I collagen) in the renal remnants. Treatment with melatonin significantly reversed intrarenal RAS and ROS activation (angiotensin II positive area (%)); Nx: 5.54 ± 0.44 vs. Nx+MEL: 2.99 ± 0.33, p<0.01 and superoxide dismutase (U/g tissue); Nx: 27.4 ± 5.0 vs. Nx+MEL: 42.4 ± 3.2, p<0.01), decreased renal tubular iron deposition in proximal tubules (PT). We hypothesize that ET-1 regulates renal iron trafficking in iron overload-associated sickle nephropathy.

**Sa-PO325**

**Targeting Src Attenuates Peritoneal Fibrosis and Inhibits Epithelial to Mesenchymal Transition of Peritoneal Mesothelial Cells**

Jun Wang,1 Luiqiu Xu,2 Na Liu,1 Shougang Zhuang,1 Rhode Island Hospital, American Medical School of Boston University, Department of Nephrology, Shanghai East Hospital, Tongji University, Shanghai, China. Department of Nephrology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China.

**Methods:** Src mediates tissue fibrosis in several organs, but its role in peritoneal fibrosis remains unknown.

**Results:** We evaluated the therapeutic effect of a highly selective Src inhibitor KX2-391, on development of chlordroxhexide chloride (CG)-induced peritoneal fibrosis in a rat model. Results: Daily intraperitoneal CG injections induced peritoneal fibrosis, indicated by submesothelial collagen fibril accumulation and microfibrilactrov stimulation, accompanied by time-dependent Src phosphorylation at tyrosine 416. KX2-391 attenuated CG-induced peritoneal fibrosis, decreased Src phosphorylation of Src and multiple signaling molecules associated with tissue fibrosis, including epidermal growth factor receptor, Akt, Signal transducer and activator of transcription 3 and nuclear factor-κB in the injured peritoneum. KX2-391 inhibited proinflammatory cytokine production and macrophage infiltration of injured peritoneum. Src inhibition by KX2-391 was correlated human peritoneal mesothelial cells led to decreased expression of α-smooth muscle actin, fibronectin and collagen I, markers of epithelial to mesenchymal transition.

**Conclusions:** Src may be a critical mediator of epithelial to mesenchymal transition, fibronectin and collagen I expression and peritoneal fibrosis. Src could be a potential therapeutic target for treating peritoneal fibrosis.

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

**SA-PO326**

**Renal Iron Trafficking – Potential Role for Endothelin**

Malgorzata Kasztan, Kelly A. Hyndman, David M. Pollock. University of Alabama at Birmingham, Birmingham, AL.

**Background:** Elevated endothelin-1 (ET-1) levels reported in sickle cell disease correlate with microalbuminuria, linking ET-1 with renal iron deposition and early sickle nephropathy. In humanized sickle cell mice (HbSS), long-term ET receptor antagonism prevented maladaptive repair and fibrosis after acute kidney injury (AKI). To induce CKD, Folic Acid (FA) 250 mg/kg (i.p.) was administered to WT mice. To induce HAMP knockout (Hamp KO) kidneys, 0.5% Adenine + 0.5% carbonyl iron diet. Mice were euthanized after 8 weeks of experimental diet. Data were analyzed with ANOVA followed by Tukey post-hoc test.

**Results:** Adenine-induced CKD, as expected, was characterized by elevated serum hepcidin, low serum iron, and low hemoglobin. iron normalized serum iron and improved anemia in mice with CKD, while further elevating serum hepcidin. Iron therapy led to elevated non-iron content in the kidneys of mice with and without CKD. mRNA expression of iron exporter ferroportin was induced by high iron diet in control mice but not in mice with CKD, while kidney ferroportin protein expression was reduced in CKD, irrespective of iron therapy. Iron therapy did not reduce expression of AT1R in HAMP KO kidneys, that was not seen in WT kidneys. We hypothesized that hepcidin dependent changes in systemic iron homeostasis may contribute to progressive loss of kidney function in patients with chronic kidney disease (CKD) through its effects on hepatic and splenic macrophages. Hepcidin reconstitution exacerbated renal fibrosis in Hamp het kidneys. Arginase-1 showed a downward trend in HAMP KO kidneys. Compared to WT kidneys, there was a significant reduction in both NOS-3 and NOS-2 and increased expression of M. Hamm,1 Edwin M. Akohunrin,2 Edwin A. Patino,3 Divya Bhattia,2 Vidhi Dalal,3 Sureshbabu Angara,3 Stefano Rivella,3 Mary E. Choi,3 Children’s Hospital of Philadelphia, Philadelphia, PA;4 Weill Cornell Medicine, New York City, NY; Weill Cornell Medical College, NEW YORK, NY;5 NYP,4 Cornell, Cornell, NY.

**Background:** Autophagy has been implicated in the pathophysiology of chronic renal injury and fibrosis. Iron therapy is common in patients with chronic kidney disease (CKD) and non-hematologic effects of iron therapy in CKD are of great interest. Iron-induced oxidative stress can damage cellular proteins and organelles, which then need to be recycled by autophagy. However, the effect of iron on renal autophagy has not been elucidated.

**Methods:** Autophagy proteins Beclin 1 and LC3b were evaluated by western blot in the whole kidney lysates of juvenile C57Bl/6 male mice fed the following four diets from age 3 to 11 weeks: (1) physiologic diet, (2) 0.2% adenine diet (CKD), (3) 0.5% carbonic acid diet (iron therapy), (4) 0.2% adenine + 0.5% carbonic acid diet. Mice were euthanized after 8 weeks of experimental diet. Data were analyzed with ANOVA followed by Tukey post-hoc test.

**Results:** Adenine-induced CKD, as expected, was characterized by elevated serum hepcidin, low serum iron, and low hemoglobin. Iron therapy normalized serum iron and improved anemia in mice with CKD, while further elevating serum hepcidin. Iron therapy led to elevated non-iron content in the kidneys of mice with and without CKD. mRNA expression of iron exporter ferroportin was induced by high iron diet in control mice but not in mice with CKD, while kidney ferroportin protein expression was reduced in CKD, irrespective of iron therapy. Iron therapy did not reduce expression of AT1R in HAMP KO kidneys, that was not seen in WT kidneys. In contrast, expression of NCOA4, a marker of ferritinophagy, was reduced in mice with CKD, without significant influence of systemic iron status.

**Conclusions:** To our knowledge, this is the first study that demonstrated induction of renal autophagy by iron therapy in CKD. This effect was not specific to ferricophagy, as ferritin cargo receptor NCOA4, which mediates its autophagy, was not induced by iron therapy in this model. In our ongoing experiments, we are evaluating mechanistic relationship between iron-mediated autophagy and renal fibrosis in CKD.

**Funding:** NIDDK Support, Other NIH Support - NCAATS UL1TR000457

**SA-PO327**

**Role of Heparin and Iron Homeostasis in the Progression of AKI to CKD**

Raffi M. Grizzi,1 Yogeesh M. Solia,2 Valentine N. Saleh Mohammud,3 Sunitsingh Swami,1 AO Brotzu Cagliari,2 Stefano Scindia,2 Valentina Loi,1 Antonino Mandziak,1 Angelo Pagani,1 Antonio Cotturanelli,1 U. M. Scindi,3 Lucio Angara,2 Stefano Mandziak,1 Angara,1, Naro Ohashi, Cagliari, Italy; 1University of Virginia, Charlottesville, VA; 2University of Virginia, Charlottesville, VA.

**Background:** Maladaptive repair and fibrosis after acute kidney injury (AKI) contributes to progressive loss of kidney function. Systemic iron depletion strategies using iron chelators or diet-induced iron deficiency are known to reduce renal fibrosis. Splenic red pulp macrophages are one of the primary storage sites for iron. Heparin (Hamp), the master regulator of iron homeostasis, plays an important role in anemia of chronic kidney disease (CKD) through its effects on hepatic and splenic macrophages. We hypothesized that hepcidin dependent changes in systemic iron homeostasis may contribute to progressive loss of kidney function. Systemic iron depletion strategies using iron chelators or diet-induced iron deficiency are known to reduce renal fibrosis. Splenic red pulp macrophages are one of the primary storage sites for iron. Heparin (Hamp), the master regulator of iron homeostasis, plays an important role in anemia of chronic kidney disease (CKD) through its effects on hepatic and splenic macrophages. We hypothesized that hepcidin dependent changes in systemic iron homeostasis may contribute to progressive loss of kidney function.

**Methods:** To induce CKD, Folic Acid (FA) 250 mg/kg (i.p.) was administered to WT, Hamp KO and HAMP Het mice (all on C57BL/6 background). BUN was measured on day 2. In some experiments HAMP Het mice were reconstituted with exogenous hepcidin (50 μg. i.p.) after the onset of AKI. Renal function and fibrosis related parameters were examined 19 days later.

**Results:** Compared to WT mice, AKI and mortality were reduced in HAMP Het and Hamp KO mice. This initial worse AKI translated to more severe fibrosis on day 19 in WT, as indicated by collagen i and α smooth muscle actin content. Both these parameters were significantly lower in Hamp deficient mice. There was a large infiltration of F4/80+ macrophages in the fibrotic kidneys of the WT and Hamp KO mice, that was not seen in HAMP Het mice. Compared to WT kidneys, there was a significant reduction in both NOS-2 and Arginase-1 gene expression in HAMP Het kidneys. Arginase-1 showed a downward trend in Hamp KO kidneys also. HAMP Het reconstitution exacerbated renal fibrosis in HAMP Het mice.

**Conclusions:** Our studies reveal a novel protective role of hepcidin deficiency in progression of AKI to CKD. This protection was associated with reduction in splenic iron content and renal macrophage infiltration.

**Funding:** NIDDK Support
Copper and Copper Transporter 1 Promote Renal Interstitial Fibrosis by Regulating Intracellular and Extracellular Transport of Copper Ions

Niuyangyang, Chen Yu. Shanghai Tongji Hospital, SHANGHAI, China.

Background: Copper is an essential trace element required for many biological processes. Some studies have demonstrated that copper accumulating was related to liver fibrosis, but the underlying mechanism is not very clear. Copper is the essential unit of lysyl oxidase (LOX), which are the key enzymes of crosslinking of extracellular matrix. Copper transporter 1 (CTR1) is the most important factor responding to copper transport.

Methods: Sprague-Dawley rats were divided into the sham group, unilateral ureteral obstruction (UUO) operated group and UUO treated with copper chelating agents tert-butylhydroxytetrade (TH). Rat kidney fibrolastic cells (NRK-49F) were used in vitro. The concentration of copper, the LOXs activity and the degree of cross-linking of extracellular collagen were detected in vivo and vitro.

Results: (1) The copper concentration in serum, urine and kidney of rats increased significantly at 7 days after UUO surgery; After treatment of TGF-β1, the intracellular copper concentration was increased significantly in cells; (2) The expression of CTR1 was upregulated in the kidneys of UUO rats, The level of CTR1 was increased significantly by TGF-β1 in vitro; (3) Blockage of Smad2/3 suppresses TGF-β1-induced expression of CTR1; (4) Downregulation of CTR1 significantly inhibited the intracellular copper concentration; (5) The activity of LOXs was increased significantly after TGF-β1 treatment; (6) Downregulation of CTR1 significantly inhibited the activity of LOXs and the cross-linking of extracellular collagen induced by TGF-β1 in vitro; (7) The concentration of copper, the degree of collagen cross-linking and the deposition of collagen were decreased in the kidney tissue of UUO rats after treatment with TM. The concentration of intracellular copper, the activity of LOXs and the degree of collagen cross-linking were attenuated with treatment of TM in vitro.

Conclusions: We confirmed that the intracellular copper accumulating was closely related to renal fibrosis. The underlying mechanism was related with the increasing expression of CTR1 and activity of LOXs. Treatment with TM ameliorated the renal fibrosis. This study presented a novel treatment target.

Funding: Vietnam Affairs Support, Government Support - Non-U.S.

SA-PO329

Background: We showed previously that NF-kB signaling inhibition attenuates renal injury and inflammation in the 5/6 renal ablation (Nx) model (AJPRenal, 2007). We subsequently showed that the NLRP3 inflammasome, another innate immunity pathway, contributes to renal injury and inflammation in the kidneys of mice with unilateral ureteral obstruction (UUO). We investigated whether NLRP3 inhibition by ALLO exerts renoprotection in Nx.

Methods: It was previously shown that the xanthine oxidase (XO) inhibitor allopurinol (ALLO) inhibits NLRP3 activation. We investigated whether ALLO reduced the renal injury and inflammation in the 5/6 renal ablation (Nx) model (SciRep, 2017). There is evidence that the xanthine oxidase inhibitor allopurinol (ALLO) inhibits NLRP3 activation. We investigated whether NLRP3 inhibition by ALLO exerts renoprotection in Nx.

Results: (1) The copper concentration in serum, urine and kidney of rats increased significantly at 7 days after UUO surgery; After treatment of TGF-β1, the intracellular copper concentration was increased significantly in cells; (2) The expression of CTR1 was upregulated in the kidneys of UUO rats, The level of CTR1 was increased significantly by TGF-β1 in vitro; (3) Blockage of Smad2/3 suppresses TGF-β1-induced expression of CTR1; (4) Downregulation of CTR1 significantly inhibited the intracellular copper concentration; (5) The activity of LOXs was increased significantly after TGF-β1 treatment; (6) Downregulation of CTR1 significantly inhibited the activity of LOXs and the cross-linking of extracellular collagen induced by TGF-β1 in vitro; (7) The concentration of copper, the degree of collagen cross-linking and the deposition of collagen were decreased in the kidney tissue of UUO rats after treatment with TM. The concentration of intracellular copper, the activity of LOXs and the degree of collagen cross-linking were attenuated with treatment of TM in vitro.

Conclusions: We confirmed that the intracellular copper accumulating was closely related to renal fibrosis. The underlying mechanism was related with the increasing expression of CTR1 and activity of LOXs. Treatment with TM ameliorated the renal fibrosis. This study presented a novel treatment target.

Funding: Veterans Affairs Support, Government Support - Non-U.S.

SA-PO330
Protective Effect of DNA Methyltransferase Inhibitor against Progressive Renal Tubulointerstitial Inflammation and Fibrosis

Yong-Soo Niu,1 Soojeong Kim,2 Seok Joon Shin,1 Cheol Whee Park,1 Chul Woo Yang,1 Yong-Soo Kim,1 Sungjin Chu.1 1Department of Internal Medicine, The Catholic University of Korea College of Medicine, Seoul, Republic of Korea; 2Department of Biochemistry, The Catholic University of Korea College of Medicine, Seoul, Republic of Korea; 3Division of Nephrology and Hypertension, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN.

Background: Renal fibrosis is the final common pathway of virtually all progressive kidney diseases and correlates with the aggravation of renal function. However, the contribution of DNA methylation to the process of renal fibrosis is not clarified. The current study examined the impact of DNA methyltransferase inhibitor on the progression of inflammation and fibrosis in kidneys of mice with unilateral ureteral obstruction (UUO).

Methods: Zebularine (225 mg/kg/day), a DNA methyltransferase inhibitor, or vehicle was administered to male C57BL/6 mice intra-peritoneally for 3 or 7 days after UUO operation.

Results: Administration of zebularine significantly attenuated renal tubulointerstitial fibrosis and inflammation as assessed by trichrome, α-smooth muscle actin, collagen IV, transforming growth factor-β1 staining both at 3 and 7 days after UUO. Zebularine downregulated mRNA expression levels of matrix metalloproteinase (MMP) 2, MMP9 and fibronectin, and it also suppressed nuclear factor-κB derived cytokines such as tumor necrosis factor-α, interleukin (IL) – β and IL-6 in obstructed kidneys. Furthermore, zebularine treatment upregulated the nuclear expression of nuclear factor erythroid-2 derived like 2 factors 2 (Nrf2) and its subsequent antioxidant enzymes such as heme oxygenase-1, catalase, superfoside dismutase 1 and NAD(P) H: quinone oxidoreductase-1 in UUO kidneys.

Conclusions: Our findings suggest that inhibition of DNA methylation could restore the disrupted balance in pro-inflammatory pathway and antioxidant defence mechanism and alleviate renal fibrosis.

Funding: Ac-SDKP is a natural peptide with anti-fibrotic and anti-inflammatory properties in vascular, myocardial and kidney diseases. Ac-SDKP is present in urine and increases under angiotensin converting enzyme inhibitors (ACEi). Ac-SDKP is released from Thymosin B4 (Tβ4) by two step enzymatic reactions by meprin-α and the prolyl 4-hydroxylase enzymes (POP) and degraded by angiotensin converting enzyme (ACE). Tβ4, Meprin-α and POP enzymes has been reported in kidney. We hypothesized that Ac-SDKP is produced in the kidney.

Methods: We evaluated the presence of Tβ4, Meprin-α and POP mRNA by analyzing the transcriptome in each segment of the nephron using the public access NHI database ESBL. We confirmed kidney expression of Meprin-α and POP by immunofluorescence and enzyme activity measurements. The Stop Flow Pressure technique was used to evaluate the Ac-SDKP formation in different segments of the nephron, in normal condition and under POP inhibition (POPi) and ACEi. All experiments were performed in Sprague-Dawley rats.

Results: Tβ4 mRNA was present in all the nephron segments, however Meprin-α mRNA was only expressed in proximal tubule (s3 region) and POP mRNA was present in proximal tubule, loop of Henle (inner medulla) and distal nephron (distal, connecting and collecting tubules). We confirmed the expression of Meprin-α by immunofluorescence in proximal tubules and the POP was found in the distal convoluted tubule in cortex and in higher amounts in the medullary region. POP mRNA activity was also high in kidney medulla (comparable to 613.6x±352.1 vs. Medulla 1162.2±408.5 pmol/min/mg prot; P<0.01). The stop flow technique showed the high Ac-SDKP/Inulin ratio in the distal tubule: 10.5±0.8 vs. 4.2±0.1 in the proximal segments (p<0.01). POPi infusion into the kidney decreased Ac-SDKP/Inulin in comparison to the vehicle group in distal (10.5±0.8 vs. 5.6±0.8, p=0.01) and proximal nephron segments (4.2±0.1 vs. 2.1±0.2, p<0.01). ACEi increased the Ac-SDKP/Inulin ratio in all nephron segments mainly in the distal part. Chronic infusion of POP inhibitor increased kidney medullary interstitial fibrosis and that was prevented by Ac-SDKP (Fibrotic area in %: Vehicle 1.84±0.8, POPi 3.3±1*, POPi+Ac-SDKP 1.37±0.58; p<0.001 POPi vs. Vehicle and POPi+Ac-SDKP).

Conclusions: We conclude that Ac-SDKP is released by the nephron and has an important antifibrotic effect in the kidney.

Funding: Other NIH Support - NHLBI

SA-PO332
Renal Release of Ac-SDKP Is Part Of An Antifibrotic Peptidergic System in the Kidney

Cesar 1 Oscar 2 Sena, Vivian 1 Zatz, M. 1.1 Inje University, 1Inje University, GoYang, Republic of Korea; 2Inje University College of medicine, Busan, Republic of Korea.

Background: Epithelial mesenchymal transition (EMT) represents conversion of epithelial cells into mesenchymal phenotype. It is an important mechanism in tissue...
fibrosis including kidney, Epstein-Barr virus (EBV), which is well known cause of acute febrile diseases and lymphoproliferative diseases, is reported to induce tissue fibrosis such as lung, skin, and liver. However, it is not reported its association with renal fibrosis. We tested whether EBV could induce EMT in renal epithelial cells.

Methods: HK2 cells were incubated with EBV. HK2 cells changed their shape from cobble stone into spindle shape. After incubation of mesenchymal changes of HK2 cells, we evaluated E-cadherin, N-cadherin, vimentin, TGF-β for mesenchymal markers, MCP-1, IL8, TNF-α, IL18 for inflammatory changes, and Slug, Snail, TGF-beta and some of EMT markers were tested using real-time PCR for mRNA and western blotting for protein expression. Results: The expressions of E-cadherin, N-cadherin, and vimentin, TGF-β for mesenchymal markers were increased after EBV infection. And expressions of Slug, Snail, and pSTAT3 were also increased. And inflammatory markers such as MCP-1, IL8, TNF-α, IL18 were increased. To confirm these changes were due to EBV transfection or secretory proteins from EBV, the HK2 cells were stimulated with latent membrane protein 1 (LMP-1), which is representative EBV-related protein. LMP-1 downregulated the expression of E-cadherin, and upregulated those of vimentin and VSIG4. These findings suggested that EMT was induced by LMP-1 alone. To test VSIG4 involvement in LMP1-induced EMT, VSIG4 siRNA were treated in LMP1-stimulated HK2. The expression of E-cadherin and vimentin were reversed. The expression of E-cadherin was increased and that of vimentin was decreased.

Conclusions: In conclusion, EMT was induced by EBV-associated protein, LMP1, not by EBV itself. The LMP-1-induced EMT was related with VSIG4 changes. This result provided the possibility of EBV-related EMT in renal fibrosis.

SA-PO333
Novel Role of IL-20 Subfamily in the Pathogenesis of CKD

Domenkous Pak,1,2 Rita Lippai,1 Apor Veres-Székely,1 Réka Ronokay,1 István M. Takács,1 Erna Zsíkszász,1,2 Beáta Szebeni,1 Andrea Fekete,1 Attila J. Szabo,1 Adám Soczy,1 Gábor Szabó,1,2 Society University of Pediatrics, Budapest, Hungary; 2MTA-SE, Pediatrics and Nephrology Research Group, Budapest, Hungary; 3MTA-SE, Lendület Diabetes Research Group, Budapest, Hungary.

Background: Regardless of the etiology kidney fibrosis is a common outcome of progressive kidney diseases. Our recent study showed that levels of interleukin (IL)-20 subfamily members, including IL-19 and IL-24 significantly increased in newborn rat kidneys underwent unilateral ureteral obstruction (UUO). However, their precise role in the pathomechanism of fibrosis has not been studied.

Methods: To study the role of IL-20 cytokine subfamily we applied a mouse model of UUO induced kidney fibrosis on wild type and IL-20 receptor beta gene knockout (IL-20R KO) mice. Masson’s trichrome and Picro-Sirius Red staining, real-time RT-PCR and western blot method were used to investigate the expression of fibrosis associated genes in mRNA and protein level between the two strains. We also investigated the intracellular effect of IL-24 treatment on transforming growth factor beta (TGF-β) and platelet derived growth factor B (PDGFB) expression of human proximal tubular epithelial (HK-2) cells at real-time RT-PCR and flow cytometry.

Results: We found elevated level of IL-19, IL-24 and IL-20R in the fibrotic kidneys. Lack of IL-20R β in KO mice was associated with decreased level of the pro-fibrotic marker alpha smooth muscle actin, TGF-β and PDGFB-B expression and also with reduced amount of extracellular matrix deposition in the obstructed kidneys. Treatment of renal epithelial cells with IL-24 increased their TGF-β and PDGFB-B production.

Conclusions: Increased expression of IL-19, IL-24 and IL-20R in the fibrotic kidney suggest their role in the pathomechanism of obstructive nephropathy. IL-24 may mediate tissue remodeling induced toward an excessive deposition of extracellular matrix components via increased production of pro-fibrotic factors. Our data suggests that inhibition of IL-24 may have significant anti-fibrotic effect.

SA-PO334

Jiong Zhang,1 Xiong Tang,1 Ming-chao Zhang,1 Longjiang Zhang,2 Zhi-Hong Liu.1 National Clinical Research Center of Kidney Diseases, Jilin Hospital, Nanjing University School of Medicine, Nanjing China; 2Department of Pediatrics, Nanjing University School of Medicine, Nanjing China.

Background: The key contributors to the progression of nearly all forms of CKD are reduced microvascular blood flow, tubular injury and fibrosis. Despite their importance, clinicians currently have no means of noninvasively assessing these factors, except historically relied on percutaneous renal biopsy. Recent advances in imaging technology have raised the exciting possibility of MRI. The aim of this study was to evaluate the feasibility of magnetic resonance imaging (MRI) for the functional assessment of renal morphology and diffusion, tubular injury, also fibrosis burden in CKD.

Methods: Seventy CKD patients were studied. The feasibility of three fMRI sequences, which were diffusion-weighted-imaging (DWI), aquaporins (AQP), and magnetic resonance elastography (MRE) were investigated. Extracellular microrobuculation disorder, tubular injury and scarring burden. Capillary assessment was investigated by peritubular capillaries number, which was showed by CD34 staining. Tubular injury was measured by AQP1 staining. Cortex fibrosis was measured by kidney sections stained with Masson’s trichrome, which were scanned with an Aperio ScanScope system and analyzed using imageScope.

Results: Functional MRI sequence DWI-AQ showed negative correlation with glomerulosclerosis and cortex fibrosis burden, R=0.128 and 0.167 respectively, P<0.01. Apparent DWI-AC cortex values were significantly increased in CKD stage 3 and 4, which is far higher than CKD stage 1 (P=0.02). There were no significant relationships with PTCs number per x400 image. AQP1 staining, which stands for AQP in tubular cells, was significantly decreased in later stages (P<0.01). Although, the fMRI-AQ value did not show statistical correlation with renal AQP staining changings in cortex (P=0.796), AQP1-SLAP showed positive correlation with cortex fibrosis burden (P=0.032, P=0.028). Apparently, MRE60Hz had negative correlation with glomerulosclerosis and cortex scarring burden in these patients (R=0.115 and 0.026 respectively, P<0.040 and 0.052). Interestingly, it was showed that MRE values were significantly lower in serious renal fibrosis subgroup than mild group or normal.

Conclusions: In this pioneer study, DWI, AQ and MRE sequence from functional MRI appear to serve as noninvasive evaluation method for evaluating renal microcirculation, tubular injury and fibrosis.

SA-PO335
A Broad-Spectrum Protein-Tyrosine-Kinase Inhibitor Prevents Upregulation of Inflammation/Fibrosis-Related Genes Induced by IgA-Containing Immune Complexes in a Passive Mouse Model of IgA Nephropathy

Hungary, 1,2 Erna Rita SA-PO333

Results: In this pioneer study, DWI, AQ and MRE sequence from functional MRI appear to serve as noninvasive evaluation method for evaluating renal microcirculation, tubular injury and fibrosis.

SA-PO336
Previous Resistance Training Impact in CKD Leading to Improvements in Proteinuria, Creatinine Clearance, and Mortality Rate Reduction in Rats

Alexandre Saul,1 Rafael Luiz,1 Natália Reinecke,1 Wesley Silva,1 Samuel T. Filho,1 Rodolfo R. Rampaso,3 Nestor Schor,1 None, São Paulo, Brazil; 2UNIFESP, São Paulo, Brazil; 3Universidade Federal de São Paulo/ Escola Paulista de Medicina, São Paulo, Brazil; 4Universidade Federal de São Paulo, São Paulo [SP], Brazil.

Background: The resistance training is applied to improve and increase muscle mass, however, how resistance exercise improves renal function is not fully understood. The aim of this study was to evaluate the EXE effects on renal function and mortality rate in rats with CKD.

Methods: Adult Wistar rats were divided in four groups (n=8): Previous Exercise + Nx 5/6 + post surgery Exercise (ENE), Previous Exercise + Nx 5/6 + post surgery Sedentary (ENS), Sedentary + Nx 5/6 + post surgery Exercise (SNE) and Sedentary + Nx 5/6 + post surgery Sedentary (SNS). We evaluated mean arterial pressure (MAP), treatment of the kidney injury model (KIM), bodyweight, serum creatinine, blood urea nitrogen (BUN), maximal load test (MLT), and mortality rate. ENE was performed as follows: 6 to 12 clumbs/day, 5 days a week, during 8 weeks, 40 to 60% of maximal load test.

Results: Exercise in ENE group prevented the increase in proteinuria rate (45.7±3.6 mg/dl vs 103.6±5.02 vs SNS, Creatinine Clearance[1,2±0.1±min p<0.05] vs all and mean BUN[33,3±2,7±mg/dl. p<0.05] was lower compared with the SNS and ENS groups. A

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

Underline represents presenting author.

Funding: NIDDK Support
gain of strength was observed in ENE vs all (556 ± 35 g p<0.05). A lower mortality rate was present in HFD + Exercise vs all (7%, p<0.05). MAP was lower in NER vs NSR group (p<0.05). Physical Capacity (MLT, VO2peak and Mtest) was reduced in NER vs NSR group (p<0.05). Physical capacity increased in NER vs NSR group (p<0.05). MAP was lower in NER vs NSR group (p<0.05). Physical Capacity (MLT, VO2peak and Mtest) was increased in NER vs NSR group (p<0.05). A lower mortality rate was observed in NS (30%).

**Conclusions:**
Results suggested that the 4 weeks of RT improve the impact of CrCl (43%) and improve in glomerulosclerosis (44%). These parameters indicate that exercise could have a protective effect, especially under this experimental protocol. Thus, this study suggests that the exercise plays a preventive role in mortality and could be an additional strategy to be employed in CKD.

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

**Table 1:**

<table>
<thead>
<tr>
<th>Group</th>
<th>Weight (g)</th>
<th>R</th>
<th>NER</th>
<th>NSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>NER</td>
<td>56.3148</td>
<td>61.01</td>
<td>61.01</td>
<td></td>
</tr>
<tr>
<td>NSR</td>
<td>55.64</td>
<td>61.01</td>
<td>61.01</td>
<td></td>
</tr>
<tr>
<td>NER</td>
<td>56.3148</td>
<td>61.01</td>
<td>61.01</td>
<td></td>
</tr>
<tr>
<td>NSR</td>
<td>55.64</td>
<td>61.01</td>
<td>61.01</td>
<td></td>
</tr>
</tbody>
</table>

**SA-PO337**

**Four Weeks of Resistance Training (RT) Improves Physical Capacity, Creatinine Clearance, and Glomerulosclerosis and Decreases Mortality Rate in Rats with CKD**

Rafael Luis Perez, Alexandre Saud, Wael Shaheen, Edson A. Pessoa, Nester Schor, UNIFESP, SÃO PAULO, Brazil.

**Background:** The aim of this study was to evaluate if 4 weeks of RT improves physical capacity, creatinine clearance, and glomerulosclerosis and mortality in rats with CKD by nephrectomy 5/6 (Nx 5/6).

**Methods:** Adult Wistar rats were divided in four groups (n=8): Sedentary (S) Exercise (E), Nx 5/6 + Sedentary (NSR), Nx 5/6 + Exercise (NER). We evaluated creatinine clearance (CrCl), proteinuria (uProt), blood urea nitrogen (BUN), glomerulosclerosis, mean arterial pressure (MAP) as well mortality rate. EXE periods were as follows: 6 to 12 gym/day, 5 days a week, 40 to 60% of maximal load test (MLT). The physical capacity was performed with maximal load test (MLT), exercise capacity test (VO2max), and maximal exercise test (MTest).

**Results:** The CrCl improved in NER (43%) vs NS group, (p<0.05). Proteinuria was different in NSR and NER vs S and R. Glomerulosclerosis was different in NSR vs NER (p<0.05). CrCl was lower in NER vs NS group (p<0.05). MAP was lower in NER vs NSR group (p<0.05). Physical Capacity (MLT, VO2max, and Mtest) was increased in NER vs NSR group. A higher mortality rate was observed in NS (30%).

**Conclusions:** Results suggested that the 4 weeks of RT improve the impact of 5/6Nx by increase in physical capacity (MLT, VO2max, and Mtest), reduce the impact on CrCl (43%) and improve in glomerulosclerosis (44%). These parameters indicate that exercise could have a protective effect, especially under this experimental protocol. Thus, this study suggests that the exercise plays a preventive role in mortality and could be an additional strategy to be employed in CKD.

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

**SA-PO341**

**RIPK3 Blockade Ameliorates Renal Fibrosis in Diabetic Model of eNOS Knockout Mice**

Ye Shi, Yongli Zhao, Chunling Huang, Ximing Chen, Carol A. Pollock, The Second Hospital of Dalian Medical University, Dalian, China; *kolding Institute, the University of Sydney, Sydney, NSW, Australia.

**Background:** Current therapies for renal fibrosis are largely ineffective. Therefore, identification of novel therapeutic targets is essential. RIPK3 is identified as a crucial regulator of necrosis, apoptosis and inflammation, which have been well recognised to be involved in renal fibrogenesis. To date, the role of RIPK3 in renal fibrosis has not been revealed.

**Methods:** Endothelial nitric oxide synthase (eNOS) knockout mice were used in the study. STZ (55 mg/kg/day) was administered to induce diabetic model by Ip. for 5 weeks. Dabrafenib (RIPK3 inhibitor) or vehicle were used as treatment on diabetic mice. After 24 weeks treatment, mice were sacrificed and kidney function was measured by 24 hour of urinary albumin excretion and urinary albumin creatinine ratio (UACR) by ELISAs. Kidney histological change and ECM deposition was assessed by PAS, Masson’s trichrome, picrosirius red staining and immunohistochemistry. TGF-β expression level was detected by quantitative RT-PCR analysis.

**Results:** RIPK3 inhibition reduced 24 hours urinary albumin excretion and UACR compared to the increased level of vehicle diabetic group. Histological detections demonstrated the vehicle diabetic group had more renal fibrosis and ECM deposition compared to Dabrafenib treated mice. Immunohistochemistry showed consistent results on type III and type IV collagen expression on above groups. Moreover, quantitative RT-PCR exhibited Dabrafenib treated mice had lower expression level of TGF-β.

**Conclusions:** These results suggest that RIPK3 blockade may be a potential novel target in renal fibrosis.

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

**SA-PO342**

**BET Bromodomains Regulate Tubular EMT Program during Renal Fibrogenesis**

Biener Tampe, Desiree Tampe, Gerhard A. Mueller, Michael Zeisberg, University Medical Center Goettingen, Goettingen, Germany.

**Background:** Kidney fibrosis is associated with loss of functional parenchyma, directly linked to compromised kidney function. Intratubular program of TECs has been shown to contribute to impaired tubular function and correlates with disease progression. In this context, TWIST is considered as a master regulator of EMT. Transcriptional activation is associated with local N-acetylation of lysine side chains towards amino-terminal tails of histone proteins. Members of the bromodomain and dextramembrane (BET) family of bromodomains-containing epigenetic readers associate with acetylated chromatin structures promoting chromatin remodeling, recruitment of proteins involved in transcriptional initiation and activation. It has recently been shown that BRD4 interacts with di-acetylated TWIST to facilitate its recruitment to target gene promoters, initiating EMT program. Because genetically inhibition of TWIST-mediated EMT program in TECs has been shown to facilitate protection of functional parenchyma, we hypothesized that pharmacological BET inhibition equally blocks TEC-EMT program.

**Methods:** In an in vitro system of TEC-EMT, BET inhibition was performed using specific siRNAs and small compounds i-BET151, RX-208, PFI-1 and (+)-JQ1. Using mice challenged with UUO, the impact of (+)-JQ1 administration was evaluated by immunohistochemistry and qRT-PCR with regard of renal fibrosis and solute/solvent transporters of functional parenchyma.

**Results:** Here, we provide evidence that TWIST-mediated EMT in TECs requires BRD4. BET inhibition by targeting BET bromodomains with (+)-JQ1 blocks BRD4/TWIST-mediated transcriptional EMT program, restores altered solute and solvent transporter expression, ultimately associated with attenuation of experimental kidney fibrogenesis. This mechanism is not limited to rodents, we provide evidence that EMT program is also driven by BRD4/TWIST in human cells. Based on existing transcriptional profiling datasets among CKD patients, induction of BRD4/TWIST is associated with intrarenal EMT program (reflected by TWIST1, SNAIL, SNAI2) and kidney fibrosis (reflected by COL1A2 and ACTA2), suggesting that pre-requisites for therapeutic intervention by targeting BRD4/TWIST (e.g. through administration of (+)-JQ1) are also present in humans in principle.

**Conclusions:** In summary, inhibition of BET bromodomains in the context of EMT represents a potential anti-fibrotic therapy.
Mechanisms Associated with Kidney Fibrosis - II

SA-P0343

Wnt/β-Catenin-Promoted Macrophage Proliferation, Migration, and Alternative Activation Contribute to Kidney Fibrosis Ye Feng, Chunsun Dai. Nanjing medical university, Nanjing, China.

Background: The Wnt/β-catenin pathway initiates a signaling cascade that is crucial in both normal development and throughout life. However, the role and mechanisms for Wnt/β-catenin in regulating macrophage activation and its contribution to kidney fibrosis remain to be determined.

Methods: A mouse model with tamoxifen-inducible deletion of β-catenin in macrophages was created.

Results: Here we found that in addition to promoting macrophage proliferation and migration, the truncated Wnt/β-catenin could exacerbate IL4 or TGFB1-induced macrophage M2 polarization via activating STAT3 molecule. This observation was further confirmed in a mouse model with inducible deletion of β-catenin in macrophages. In that model, kidney fibrosis, macrophage accumulation, proliferation and M2 polarization were all diminished in the fibrotic kidneys compared to their control littermates.

Conclusions: This study demonstrated that Wnt/β-catenin signaling activation promotes kidney fibrosis may be ascribed to stimulating macrophage proliferation, migration, and M2 polarization.

Funding: Government Support - Non-U.S.

SA-P0344

Therapeutic Activity of the Novel Kinase Inhibitor ANG3070 in Models of Renal Scarring Accompanied by Co-Morbidities Prakash Narayanan, Bin Duan, Ping Zhou, Latha Paka, Michael A. Yamini, Izhak D. Goldberg. 1Angion Biomedica Corp, Uniondale, NY; 2Angion Biomedica Corp, Uniondale, NY.

Background: Chronic kidney disease (CKD), characterized by extracellular matrix deposition in the renal interstitium, is driven, in part by aberrant receptor tyrosine kinase signaling. We investigated the effects of a novel small molecule receptor tyrosine kinase inhibitor, ANG3070, in clinically relevant models of CKD accompanied by co-morbidities.

Methods: Approximately 18 month old male Fischer 344 rats were subjected to 5/6 nephrectomy (or sham surgery) to model CKD in middle-aged patients. Following onset of renal disease, animals were randomized to vehicle or ANG3070 (various doses, PO, BID). In order to model CKD in the setting of metabolic syndrome, ~8 week old, obese, male, ZSF1 rats were subjected to 5/6 nephrectomy, and following onset of renal disease, randomized to vehicle or ANG3070 (various doses, PO, BID). In both models, after 8 weeks of drug treatment, a comprehensive panel of renal functional and histological endpoints was evaluated to assess the effects of ANG3070.

Results: Intervention with ANG3070 in aged rats with CKD, reduced albuminuria and attenuated several indices of renal scarring including kidney hydroxyproline content, α-smooth muscle actin expression and collagen (picrosirius red staining). Intervention with ANG3070 in the rat model of metabolic syndrome and CKD was associated with reduced kidney hydroxyproline content, α-smooth muscle actin expression and collagen (Masson’s trichrome and picrosirius red staining).

Conclusions: In conclusion, relevant models of renal scarring, intervention with the novel receptor tyrosine kinase inhibitor ANG3070 is beneficial.

Funding: Other U.S. Government Support

SA-P0345

Inhibition of NF-κB Signaling in Neural Crest-Derived Fibroblasts Attenuates Renal Fibrosis Tadashi Yoshida, Maho Yamashita, Matsuhiro Hayashi. 1Apheresis and Dialysis Center, Keio University School of Medicine, Tokyo, Japan; 2Apheresis and Dialysis Center, Keio University School of Medicine, Tokyo, Japan; 3Apheresis and Dialysis Center, Keio University School of Medicine, Tokyo, Japan.

Background: It has been recently reported that renal fibroblasts are derived from neural crest and phenotypic conversion of fibroblasts into myofibroblasts contributes to renal fibrosis in chronic kidney disease. The aim of the present study was to determine whether the NF-κB signaling in neural crest-derived fibroblasts was involved in renal fibroblast phenotype and fibrotic renal damage.

Methods: Transgenic (P0-Cre/IXBAN) mice, in which truncated IXB was expressed and the NF-κB signaling was inhibited selectively in neural crest-derived cells, were generated. Renal fibrosis and infiltration of inflammatory cells were examined in P0-Cre/IXBAN and control mice following UUO.

Results: In response to UUO, renal fibrosis was developed in P0-Cre/IXBAN and control mice, as determined by Masson trichrome staining and SM α-actin staining. However, of importance, renal fibrosis was significantly attenuated in P0-Cre/IXBAN mice, to be compared to control mice 14 days after UUO. By contrast, renal infiltration of inflammatory cells, including neutrophils, F4/80-positive macrophages, and CD3-positive lymphocytes, was not different between P0-Cre/IXBAN and control mice.

Conclusions: Results suggest that the NF-κB signaling in fibroblasts originated from neural crest plays an important role in renal fibrosis in chronic kidney disease.

Funding: Private Foundation Support

SA-P0346

Potential Impact of Adenine (P0) Receptors on Urinary Albumin/ Creatinine Ratio in CKD Yue Zhang, Christa E. Müller, Tao Liu, Anna U. Brands, Bellamkonda K. Kishore. 1Univ. of Utah & VA Medical Center, Salt Lake City UT; 2Univ. of Utah & VA Medical Center, Salt Lake City, UT; 3Univ. of Utah and VA Medical Center, Salt Lake City UT; 4University of Wuppertal, Bonn, Germany; 5Univ. of Utah & VA Medical Center, Salt Lake City, UT.

Background: P0 is a G protein-coupled receptor (R), which binds adenine with high affinity, but not adenosine, AMP/ADP/ATP. Blood levels of adenine are markedly elevated in chronic kidney disease (CKD), and positively correlate with the duration or severity of CKD. We observed that P0-R is expressed in all regions of the mouse kidney, and hypothesized that blocking this in CKD will have significant effects.

Methods: 5/6 nephrectomized (NX) CD-1 mice were divided into two groups. One group was infused with PSB-08162, a selective antagonist of P0-R, through osmotic minipumps to attain steady state plasma concentration ~30 μM. Controls were sham-operated. After 4 weeks of infusion, urine and blood samples were collected, and the mice were euthanized.

Results: The results of analysis (mean ± the se) of terminal urine and serum samples are shown in the Table. Despite no significant differences in serum creatinine (CR) between Nx and Nx+PSB groups, the latter showed marked increase in urinary albumin/CR ratio (UACR), apparently due to low urinary CR excretion. In parallel the serum levels of 3-hydroxybutyrate, a ketone body, were significantly elevated.

Conclusions: Our results suggest that blocking the P0-R in CKD may elevate UACR by reducing urinary excretion of CR, probably by decreasing its secretion by the kidney. The elevated adenine acid may also contribute to reduction in CR secretion in the kidney. Conversely, the elevated adenine levels in CKD may increase CR secretion in the kidney, and thus may decrease UACR values.

Funding: Veterans Affairs Support, Private Foundation Support

SA-P0347

Omega 3 Fatty Acid Attenuates Kidney Fibrosis in Ureteral Obstructed Mice via Enhancement of Autophagy Flux Dae Eun Choi, Yoon-Kyung Chang, Hyunsu Choi, Chang hun Song, Jiwon M. Lee, Kiyang Na, Kang Wook Lee, Hong jin Bae, Youngrok Ham. 1Nephrology, School of Medicine, Chungnam National University, Daejeon, Republic of Korea; 2Nephrology, School of Medicine, The Catholic University of Korea, Daejeon, Republic of Korea; 3Clinical Institute of Medicine, Daejeon St. Mary’s Hospital, Daejeon, Republic of Korea; 4Pediatrics, School of Medicine, Chungnam National University, Daejeon, Republic of Korea.

Background: It has been known that unilateral ureteral obstruction (UUO) induces autophagic activation in obstructed kidney. Inhibition of autophagy aggravates renal injury in UUO mice. Recently, it is reported that Omega 3 fatty acid regulate the autophagy. we evaluated whether omega-3 fatty acid may attenuate renal fibrosis in UUO mice, and evaluated associating mechanism.

Methods: 10-week-old male C57Bl/6 mice were divided into 4 groups; sham, Omega 3, sham, vehicle (normal saline, same volume to Omega 3 + UUO, Omega 3 + UUO). Omega 3 and vehicle were administered orally using an NG tube (Omega 3 100mg/kg/day) from pre-operation day to 7 days after operation. Mice were sacrificed at 7 days after surgery and kidney tissue were collected. Real time RT-PCR, western blot and immunohistochemistry for molecular study and H&E stain and PAS stain for histologic examination were performed.

Results: Omega 3 treated UUO mice showed improvement of renal cell survival, renal function, and pathologic damage compared to vehicle treated UUO mice. Also omega-3 treatment reduced the renal expression of MCP-1, collagen IV, and TGF-β in UUO kidney. UUO mice kidney showed that higher amounts of LC3, Beclin1-1, Atg7 and p62 compared to sham mice. Omega 3 treated UUO kidney showed higher amounts of LC3, Beclin1-1 and Atg7 and lower amounts of p62 compared to vehicle treated UUO kidney. Moreover, renal cathepsin D and ATP6e were also increased in Omega 3 treated UUO mice compared to vehicle treated UUO mice.

Conclusions: Omega 3 fatty acid ameliorate renal fibrosis in UUO kidney via enhancement of autophagy flux.

Funding: Government Support - Non-U.S.
The Effect of Hirudin on PAR-1, TGF-β1, α-SMA of Renal Intertitial Tissue in Rats with Unilateral Ureteral Obstruction

Dai Lu,° Yang Kang,° Pei Ming,° Ren Tong,° Shouchi Hu,° Lijuan Wei,° Bo Yang,° Lin Yan,° Hongtao Yang,° Tianjin University of Chinese Traditional Medicine, Tianjin, China; 2Division of Nephrology, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin, China.

Background: In the process of renal interstitial fibrosis, hirudin may reduce the expression of proteins and α-SMA of PAR-1 in the renal interstitium. We explored the intervention effect of hirudin by establishing a unilateral ureteral obstruction model.

Methods: The 90 healthy Sprague-Dawley (SD) male rats, with the average weight of 180g, were randomly divided into Sham-operation group(SOR, n=18), unilateral ureteral obstruction model group(UUO, n=18), UUO with high dose Hirudin treatment group(UUO+H, n=18), UUO with low dose Hirudin treatment group(UUO+L, n=18), UUO with Lotesin treatment group(UUO+LOT, n=18). On 3rd, 7th, 14th days after the operation, 6 rats from each group were randomly sacrificed, the obstructive side of kidneys were stored for RT-PCR and Western Blot tests to detected the expression of proteins and genes of PAR-1, TGF-β1, α-SMA with drug intervention.

Results: 1 Western blot test: Compared with UO group, the expression of PAR-1, TGF-β1 and α-SMA at each time points in each intervention groups were reduced (P<0.05). 2 RT-PCR test: Compared with UO group, the expression of PAR-1 and α-SMA at each time points in each intervention groups were reduced (P<0.05). Compared with UO group, the expression of TGF-β1 at different time points in UO+H group, on the 14th day in UO+L and UO+LOT groups were decreased (P<0.05).

Conclusions: High dose of hirudin can significantly reduce the protein expression of PAR-1, TGF-β1 and α-SMA in renal interstitial of UUO rat model. Both high dose and low dose of hirudin can reduce the mRNA expression of PAR-1, TGF-β1, α-SMA in different degrees. Compared with UO+L group, UO+H group has a better effect on the down-regulation of the protein and mRNA expression of PAR-1, TGF-β1, α-SMA, the difference between two groups may be related to the mechanism of the best drug effective dose.

Funding: Government Support - Non-U.S.

The chart of Western Blot result:

Impact of Intrarenal and Circulating APOL1 Expression Levels on Phenotypes in Nephrotic Syndrome

K Yasutake,° Anders H. Berg,° Khuloud Shukura,° Martin R. Pollak,° Matt G. Sampson,° Beth Israel Deaconess Medical Center, Boston, MA; 2Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA; 3Boston, MA; 4University of Michigan, Ann Arbor, MI. Group/Team: NEPTUNE.

Background: Although high-risk (HR) APOL1 genotypes are associated with FSGS development & worse outcomes in patients with nephrotic syndrome (NS), less is known about the relationship between APOL1 expression & clinical parameters. While in population & CKD cohorts, circulating APOL1 levels are not CKD-associated, this relationship has not been studied in NS. Intrarenal APOL1 expression level is not associated with HR genotype in NS patients. But higher APOL1 expression, even the wildtype form, is associated with cytotoxicity & FSGS in model systems. Does increased APOL1 expression contribute to poor outcomes in NS across races? To assess this, we characterized associations of intrarenal & circulating APOL1 expression levels with clinical & histological phenotypes in black & non-black patients in the Nephrotic Syndrome Study Network (NEPTUNE).

Methods: NEPTUNE is a prospective study of NS patients of all ages receiving a clinically indicated biopsy. We identified APOL1 genotypes patients with baseline & longitudinal clinical data and intrarenal mRNA expression profiling of microdissected global (GLOM, n=160) & intrarenal (Ti, n=70). 95 circulating APOL1 protein levels measured with ELISA. Non-blacks made up 29% of patients with intrarenal & 68% with circulating expression. As a function of baseline GLOM, Ti, or circulating APOL1 expression, we modeled baseline eGFR, interstitial fibrosis (IF) on biopsy, complements (C3, C4), & a composite endpoint. We also did analyses stratified by race & risk genotype.

Results: In multivariable analyses of black patients, higher T1 expression of APOL1 was significantly associated with lower eGFR (9.9 ml/min per doubling of APOL1 expression; p=0.002) and increased IF (p=0.01), independent of APOL1 risk genotype. These associations were not observed with T1 APOL1 expression in non-black or GLOM in black & non-black patients. There were no significant association of circulating APOL1 levels with clinical or histologic parameters, across races & risk genotypes.

Conclusions: In black patients with NS, elevated T1 APOL1 expression, independent of risk genotype, was associated with lower eGFR & more fibrosis. It may be worth investigating whether decreasing intrarenal APOL1 level is beneficial in any black NS patient. Further inquiry in larger cohorts of non-blacks with NS is also warranted.

Funding: NIDDK Support

Distribution of APOL1 Renal Risk Variants in General Population from Central Africa (Democratic Republic of Congo) (DRC)

Pepe M. Ekolu,° Michel N. Aketch,° Elena N. Lepira,° Pediatrics, University of Kinshasa, Kinshasa, Congo (the Democratic Republic of the); 2Nephrology Internal Medicine, University of Kinshasa, Kinshasa, Congo (the Democratic Republic of the); 3Pediatric Nephrology, KU Leuven, Leuven, Belgium.

Background: The susceptibility in chronic kidney disease among sub-Saharan African descent has been attributed to apolipoprotein-L1 (APOL1) genetic variants G1 and G2. However, in Africa, data related to the geographical distribution of APOL1 risk variants are limited, and there is no reliable data from Democratic Republic of Congo (DRC). We aimed to describe the frequencies of APOL1 risk variants in a large population from Central Africa and to assess the association with the early kidney damage in children.

Methods: A total of 465 participants from four large districts in Kinshasa were enrolled. APOL1 high-risk alleles were absent in 50% of CKD patients, 41% of controls and 52% of relatives. Two APOL1 risk alleles were present in 10% of CKD patients, 8.6% of controls and 12% of relatives. In CKD patients, there was no difference in blood pressure, eGFR, proteinuria based on any allele combination. The prevalence of JCV in CKD patients was 21% compared to 6% for BKV, with coinfection present in four participants. JCV was present in only 7% CKD patients compared to 39% of controls and 21% of relatives; P<0.0001, Fisher’s exact test. None of the CKD patients had evidence of BKV. There was no difference in mean log viral load JCV between CKD patients and controls (P = 0.2644), between CKD patients and their relatives (P = 0.3074) or between controls and relatives (P = 0.7073).

Conclusions: Apolipoprotein-L1 risk variants are infrequent in black South Africans with hypertensive CKD. There was a higher prevalence of JCV infection in black South Africans with normal renal function. JCV virus seems to protect against development of kidney disease.
SA-PO352
Houston Encounters of CKD of Uncertain Origin (CKDu): Lack of Major Etiologic Factor, except for Exposure to Herbicide Ilse M. Espina,1 Edlyn G. Bustamante,2 Maria E. Maldonado,1 Roniqua N. Ceasar,1 Jose R. Dominguez,2 David Sheik-Hamad,1 1Baylor College of Medicine, Houston, TX; 2Harris Health, Houston, TX.

Background: CKD Du (aka MesoAmerican Nephropathy) is encountered globally. Proposed etiologies for CKDu include dehydration, toxic exposure and infection. To identify possible etiology for CKDu among patients encountered at a safety net hospital in Houston, we carried out chart review of CKD5 patients matching the inclusion criteria for the study.

Methods: Thirty patients were identified based on history consistent with CKD – young, migrant worker, otherwise healthy who presented in renal failure. Patients were included in the study if 1) laboratory studies are consistent with CKD5 (BUN, serum creatinine, Ca/Po4, IPTH and anemia), 2) kidney ultrasound showing small kidneys, 3) urine studies without significant proteinuria or urine sediment, and 4) negative studies for viral hepatitis, syphils, HIV, ANA, ANCA, SPEP, UEPE. Exclusion criteria: history of diabetes, known primary or secondary renal disease.

Results: 10 patients were available for interview. 9/10 male, 1/10 female; 6/10 from Mexico, 3/10 from El Salvador, 1/10 from Honduras. Only one had knowledge of kidney disease upon presentation, 3 had family history of CKD, 4/10 had occasional intake of Tylenol. Mean age at presentation 32.8 years (median: 33, range 25-43). Mean stay in the US before CKD5 diagnosis 9.2 years (median: 8, range 1-15). Before immigrating to the US, 7/10 lived in a village/farm, 3/10 lived a city. 8/10 lived in hot climate zones (6/10 in Mexico, 2/10 in the US). 4/10 worked in agriculture (8-15 years). While in the US, 6/10 worked in construction, 3/10 in landscaping, 0/10 in the US, 7/10 lived in a village/farm, 3/10 lived a city. 8/10 lived in hot climate zones (6/10 in Mexico, 2/10 in the US). While in Mexico/US, 9/10 had exposure to animal stock; 3 had chronic intermittent exposure to Gramaxone (paraquat-based herbicide), while 1/10 had exposure to bug killer and fertilizers. 4/10 drank well water, the rest consumed bottled water, and only 2/10 consumed sweetened drinks; uric acid levels were normal (available on 3/10).

Conclusions: Patients with CKDu encountered are migrant workers, male, young, originally from a farming village, living in hot mountainous regions. Hydration solutions consisted of water. We found no clear identifiable risk factors for CKDu except for chronic exposure to Gramaxone/paraquat in farm workers.

Funding: Private Foundation Support

SA-PO353
CKD in Mexican Children: The Case of Poncitlan, Jalisco
Guillermo Garcia-Garcia,1 Ricardo Rubio,1 Melina D. Amador,2 Margarita Ibarra-Hernández,3 Librado De La Torre-Campos, Alexia C. Romero,4 Guillermo Navarro blackaller,5 Francisco golondo Rodriguez garcia.6 Hospital Civil De Guadalajara, University of Guadalajara, Guadalajara, Mexico.

Background: An elevated prevalence of CKD of unspecified cause (CKDu) has been documented in various developing countries. It has been reported by the media a high prevalence of CKDu among children in towns located by Chapala Lake, particularly within the municipality of Poncinitlan, Jalisco. Environmental facets have been blamed as the probable cause of the pandemic.

Methods: Since 2006, we pioneered screening people at risk for the presence of CKDu using mobile units that travel to rural and urban communities of Jalisco. Trained personnel collected demographic and clinical data, and obtained blood and urine for serum chemistry and dipstick urinalysis. Those individuals who were aware they had kidney disease were not assessed; all others were eligible to participate. GFR was estimated with the Schwartz equation. CKD was defined as an eGFR < 60 ml/min/1.73m², HTN, malnutrition, and obesity were defined by gender, age, and height specific normative values.

Results: Between 2007-2016, 659 children were screened in the mobile units, 144 of them in the municipality of Poncinitlan. Results were compared with those of all Jalisco municipalities (Table 1)

Conclusions: The prevalence of proteinuria and malnutrition was higher in Poncinitlan as compared to other Jalisco municipalities. Undergoing studies will provide information on the possible causes of this high prevalence. Screening programs should be linked to community- and individual-level interventions to reduce the risk of chronic kidney disease in adulthood.

Funding: Private Foundation Support

SA-PO354
Prevalence and Risk Factors of CKD among Workers in the Brick Making Industry of La Paz Centro, Nicaragua
Lynne E. Gallo,1 Comal Basra,2 Mauricio E. Sanchez-Delgado,3 Tania M. Gamez,3 Caryn M. Senneti,1 Rebecca L. Laws,2 Juan J. Amador,1 Damaris A. Lopez pilarte,1 Yorghos Tripodiad,3 Michael Mcleean,3 Joseph Kupferman,1 Daniel J. Gedman,1 Gabriel A. Gonzalez,2 Melinda K. Scammell,1 Ana G. Garcia,1 Daniel R. Brooks,2 Aurora Aragon,1 Boston University, Boston, MA; 2Boston University School of Public Health, Boston, AL; 3MINSN, Chinandega, Nicaragua, 4None, Brookline, MA; 5Research Center on Health, Work and Environment at National Autonomous University of Nicaragua, Leon, Lein, Nicaragua; 6UNAN-Lein, Lein, Nicaragua.

Background: Western Nicaragua is a hotspot for Chronic Kidney Disease (CKD) of non-traditional etiology, also called Mesoamerican Nephropathy. This disease has killed tens of thousands of economically active individuals; primarily agricultural workers at sea level. The aim of this study is to establish the prevalence of CKD among workers in the artisanal brick and tile industry, and explore associations between risk factors of interest and changes in kidney function over time.

Methods: In 2016, 257 workers in small brick and tile making industries in the La Paz Centro region of Nicaragua were recruited for a prospective cohort study. Of those, 224 (93.5%) participated in follow-up four months later. At both baseline and follow-up, serum creatinine was measured using the Jaffe methods at the biochemical laboratory at the Medical Faculty of UNAN-Lein and used to estimate glomerular filtration rate (eGFR) using the CKD-EPI formula. CKD was defined as two measurements of eGFR<60 ml/min/1.73m² at least 3 months apart.

Results: 14.8% of participants had eGFR<60 at baseline. Virtually all were confirmed at follow-up for a 3% decline of CKD of 14.3%. 97% of cases were male, 25% were less than 35 years of age, and 28% had stage 5 CKD (eGFR<15). The mean difference in eGFR between measured baseline and follow-up was -4.1 (standard deviation=20.4), suggesting a decrease in mean kidney function in this brickmaking population over the study period. Linear mixed effects models indicate predictors include a job task that entails loading or operating the oven, age, sex, education, smoking status, water intake and having an immediate family member with CKD.

Conclusions: CKD prevalence among the workers in La Paz Centro was similar to prevalence reported in cross sectional studies conducted in the sugarcane growing region of Nicaragua, and slightly lower than prevalence among lowland agricultural workers in El Salvador.

Funding: Community Support - Funding was provided by Los Azacarenos Del Istan Centroamericano (AICA), and was managed by the CDC Foundation. Donors had no prior review of these results nor influence on content of abstract.

SA-PO355
Association between Obesity and Prevalence of CKD in Patients with Type 2 Diabetes Mellitus and/or Arterial Hypertension
Laura Cortes-Sanabria,1 Rafael A. Ayala cortes,2 Clementina E. Calderon Garcia,1 Enrique Rojas-Campos,3 Alfonso M. Cueto-Manzano,4 Instituto MEXICANO DEL SEGURO SOCIAL, GUADALAJARA, Mexico; 4Instituto Mexicano del Seguro Social, Guadalajara, Jalisco, Mexico; 3Mexican Social Security Institute, Guadalajara, Mexico; 5None, Zapapan, Jalisco, Mexico; 6Unidad de Investigación Médica en Enfermedades Renales, Guadalajara, Jalisco, Mexico.

Background: Obesity, directly or through several comorbidities such as diabetes mellitus, high blood pressure, metabolic syndrome or cardiovascular disease, increases the risk for development and progression of CKD. It is noteworthy, however, the lack of information in this regard in settings with high prevalence of risk factors for CKD, such as Latin America, and particularly Mexico. Aim: To determine the association between obesity and CKD in patients recently diagnosed with only type 2 diabetes mellitus (DM2), arterial hypertension (AHT) without DM2, and DM2+AHT.

Methods: Cross-sectional study. Patients with transient causes of albuminuria were excluded. All patients had a medical history and clinical examination, glomerular filtration rate was estimated (eGFR) by the CKD-EPI formula and albuminuria/creatininuria was determined by nephometry. Obesity was classified according with WHO criteria and CKD according with KDIGO guidelines.

Results: 2123 patients (DM2 = n 767; DM2+AHT = n 877, and AHT = n 570) were studied. Mean age was 60±12 yrs, 62% women, DM2 vintage 9 (4-13) yrs and AHT vintage 7 (3-14) yrs. Prevalence of obesity was lower in DM2 (35%) compared to DM2+AHT (45%) and AHT (46%) (p<0.0001). Comparing patients with obesity vs normal weight, prevalence of CKD were lower in DM2 (31% vs 42%, respectively, p = 0.01), but it was higher in DM2+AHT (38% vs 20%, p<0.04) and AHT (40% vs 16%, p = 0.01). Results of multivariate analysis are shown in the Table

Conclusions: Frequency of obesity was significantly higher in patients with DM2+AHT. The risk to present CKD is higher in DM2+AHT than in isolated DM2 or AHT. It is necessary to advise for modification of negative lifestyle habits, especially in patients with diabetes and hypertension in order to prevent development and progression of kidney damage.
Logistic regression model of variables predicting CKD

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.97</td>
<td>0.958-1.000</td>
<td>0.027</td>
<td>0.95</td>
<td>0.950-0.958</td>
<td>0.038</td>
<td>0.94</td>
<td>0.932-0.947</td>
<td>0.031</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.19</td>
<td>1.12-1.27</td>
<td>0.031</td>
<td>1.17</td>
<td>1.29-2.43</td>
<td>0.006</td>
<td>1.17</td>
<td>1.09-2.47</td>
<td>0.06</td>
</tr>
<tr>
<td>DM duration</td>
<td>0.87</td>
<td>0.85-0.90</td>
<td>0.0001</td>
<td>0.86</td>
<td>0.84-0.88</td>
<td>0.0001</td>
<td>0.86</td>
<td>0.84-0.88</td>
<td>0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.95</td>
<td>0.94-0.97</td>
<td>0.008</td>
<td>0.95</td>
<td>0.94-0.97</td>
<td>0.008</td>
<td>0.95</td>
<td>0.94-0.97</td>
<td>0.008</td>
</tr>
<tr>
<td>Overweight/obesity</td>
<td>1.34</td>
<td>1.29-1.63</td>
<td>0.038</td>
<td>1.35</td>
<td>1.30-1.48</td>
<td>0.035</td>
<td>1.35</td>
<td>1.30-1.48</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Conclusions: It may be better to create VA earlier to postpone initiation of dialysis especially in patients with poor baseline conditions such as faster eGFR declined rate, lower serum albumin level and, if patients with DM, higher HbA1c level.

SA-PO358
Renal Biopsy Results from Patients with Multiple Myeloma: Data from a Comprehensive National Cancer Institute: A 10 Year MD Anderson Experience
Laila S. Lakhani,1,2 uten Selamat,1, Ali Ziaollah,3 William F. Glass,3 Amanda Tchakarov,1,2 Abada Budヤyck,3,4 MD Anderson Cancer Center, Houston, TX; 3,4 University of Texas MD Anderson Cancer Center, Houston, TX; 2,4 University of Texas, Houston, TX; 3,4 University of Texas Medical School at Houston, TX; 2,4 University of Texas – Houston Medical School, Houston, TX.

Background: Around 50% of patients with Multiple Myeloma (MM) have renal involvement at presentation. Renal lesions in MM is both heterogeneous and multifactorial. We set out to study the spectrum of these deposits and electron micrographic lesions, to determine their extent and correlation with biochemical paraproteinemia, clinically significant proteinuria and the other systemic findings in this population.

Methods: Data is extracted from the retrospective chart review of all patients at MD Anderson Cancer Center who received a renal biopsy between Jan 2008 – 2017.

Results: Out of 193 patients who underwent renal biopsy during this period, 39 had the diagnosis of Multiple Myeloma at the time of biopsy, with 14/39 (36%) on active chemotherapy and 11/39 s/p stem cell transplant. An equal gender distribution was evident (20 males, 20 males) with an average age of 62.5 years. The co-existing medical conditions included HTN (69%), DM (36%), and rarely other malignancies (8%). The most common indication for renal biopsy was AKI–85%, followed by proteinuria in 67% patients - (2% had nephrotic range proteinuria). 2/39 were inadequate biopsy samples. For the remaining 37 biopsies (75%) had glomerulopathy and tubulopathy from cast deposition, 4/37 (11%) had AL Amyloidosis and 1 patient had granulomatous TIN (AFB/fungal stains negative). Interestingly 19/37 (51%) had no evidence of myeloma kidney, the most common findings in these patients were focal glomerulosclerosis, hypertensive arterial and arteriolar glomerulosclerosis and diabetic nodular glomerulosclerosis.

Conclusions: The severity of renal involvement confers worse prognosis in patients with Multiple Myeloma. The biopsy findings helps us to predict outcomes and tailor our clinical approach and treatment regimens to minimize morbidity and mortality in patients with Multiple Myeloma.

Funding: Clinical Revenue Support

SA-PO359
TGF Beta Pathway Enriched as Candidate Plasma Severity Biomarkers in CKD
Jennifer E. Van eyk,1 Lesley Inker,1 Jose Corsh,1 Paul L. Kimmel,2 Adrienne Tim,3 Cedars Sinai Medical Center, Los Angeles, CA; 2National Institute of Diabetes and Digestive Kidney Diseases (NIDDK), Bethesda, MD; 3Tufts Medical Center, Boston, MA; 4Welch Center for Prevention, Epidemiology & Clinical Research, Baltimore, MD. Group/Team: Biocon 1.

Background: Our hypothesis is that in-depth proteomics discovery could identify plasma biomarkers that will be useful for risk assessment for development of chronic kidney disease (CKD) and to monitor progression (severity) of CKD.

Methods: A four group design in which 64 plasma samples collected at two time points (T0 and T1) for 16 cases and 16 controls were analyzed. Cases were individuals with GFR slope >5 ml/min/year and a total decline of at least 30 ml/min/year follow-up of at least 3 years while the controls had <1 ml/min/year for at least 3 years matched by age, sex, race, diabetes, hypertension, GFR at T0, ACR. Each sample was depleted of the top 14 abundant plasma proteins, fractionated using reversed phase HPLC, digested, analyzed by mass spectrometry and batched searched. Proteins were ranked based on p values for prognosis (protein differences between cases and controls at T=0) and severity (cases between T0 & T1 / controls between T0 & T1) and determined pathways between these various candidate severity markers.

Results: Across all plasma samples, 1151 nonredundant proteins were identified with a protein and peptide probability of <0.1% (with >625,000 peptide linkages). There were 43 candidate severity markers that were found to be statistically significant (p<0.01 and p<0.05, respectively). Within this top group of severity markers were APO II, APO III, Haptoglobin and APOLI which were ranked 4th (p=0.0058), 6th (p=0.011), 13th (p=0.018) and 19th (p=0.021), respectively for prognosis. There were 2 and 66 candidate severity markers with p=0.01 and p=0.05, respectively. Of these CRP, Cystatin C and beta trace protein were ranked 6th (p=0.004), 7th (p=0.006) and 18th (p=0.04), respectively, as severity markers. Interestingly, the TGF beta pathway proteins were enriched in the candidate severity proteins (p=0.05) based on over 15 protein linkages. Although TGF 

Conclusions: This study indicates that de novo proteomic analysis of plasma can confirm changes of known biomarkers and identify potential new biomarkers. That different plasma proteins are aligned with prognosis versus severity. Proteins in the TGF beta pathway are particularly enriched as candidate severity biomarkers.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
SA-PO360
The Role of Renal Vascular Endothelial-Mesenchymal Transition in Systemic Lupus Erythematosus Associated Thrombotic Microangiopathy
Weixin Hu, Ying Zhou, Ying-hua Chen, Ming-choa Zhang, Shao-shan Liang, Fan Yang, Zheng-zhao Liu, Zhi-Hong Liu. National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, Nanjing China, Nanjing, China.

Background: To investigate the phenotypic changes of renal vascular endothelial cells and its relationship to the vascular injury and renal interstitial fibrosis in patients with SLAE associated thrombotic microangiopathy (SLE-TMA).

Methods: Biopsies from 30 SLAE patients who showed lupus nephritis and renal TMA were included in this study. TMA was divided into acute and chronic TMA according to the histology. The expression of vascular endothelial CD31, vessel endothelial cadherin (VE-cadherin), α-smooth muscle actin (α-SMA) and transforming growth factor-β (TGF-β) were stained with immunofluorescence and immunohistochemical assays, the intensity of endothelial marker expression recorded as the mean density (integral optical density/area of vascular endothelial layer) and the extent of renal interstitial fibrosis were quantitatively analyzed with Image-Pro-Plus 6.0 and ImageScope (Aperio) respectively.

Results: Confocal immunofluorescence microscopy demonstrated no α-SMA expression in endothelial cells in normal renal vessels while markedly higher endothelial α-SMA expression in renal vessels showing TMA. Compared with the normal group, the intensity of endothelial CD31 and VE-cadherin expression was significantly lower (P<0.05), and α-SMA expression was much higher (P<0.001) in acute TMA group. The endothelial CD31, VE-cadherin and TGF-β expression were significantly lower, while the α-SMA expression significantly higher in chronic TMA group than that in acute TMA group and normal group (P<0.001). The intensity of endothelial α-SMA expression was positively correlated with the extent of renal interstitial fibrosis (r=0.439, P<0.05), while the endothelial CD31 expression was negatively correlated with renal interstitial fibrosis (r=-0.458, P<0.05). Furthermore, endothelial-α-SMA expression was also an independent risk factor for the poor treatment response in patients with SLE-TMA.

Conclusions: In SLE-TMA, the lower expression of normal endothelial cell markers and higher α-SMA expression indicated a pathogenic process of vascular endothelial to mesenchymal transition, which was related with renal interstitial fibrosis and poor treatment response.

SA-PO361
Cystinosis Is Associated with Abnormal Bone Microarchitecture and Sarcopenia in Children and Adults
Candice Sheldon,1 Paul C. Grimm,2 Jessica R. Whalen,1 Kyla Kent,2 Jin Long,1 Maira Simas,1 Mary B. Leonard.1

1Stanford, Palo Alto, CA; 2Stanford School of Medicine, Palo Alto, CA; 3Stanford University, Palo Alto, CA; 4Stanford University Medical Center, Stanford, CA.

Background: Cystinosis is associated with multiple risk factors for abnormal bone metabolism, including phosphaturia wasting, metabolic acidosis, malnutrition, chronic kidney disease, hypothyroidism, myopathy, delayed puberty and male hypogonadism. Prior bone studies are limited to case reports and a case series. Muscle mass has not been quantified.

Methods: Regional and whole body DXA scans were obtained in 37 cystinosis patients, age 6-49 yr. High-resolution quantitative CT (QCT) tibia scans were obtained in cystinosis patients and 61 matched controls. DXA results were converted to sex, race and age-specific Z-scores using robust population-based reference data in children and adults. Linear regression was used to assess group differences in QCT results, adjusted for age, sex and tibia length.

Results: Total Hip (mean ± SD: -0.96 ± 1.22), femoral neck (-1.23 ± 1.14), and 1/3rd radius (-1.02 ± 1.48) bone mineral density (BMD) Z-scores were reduced compared with reference data (all P<0.001) and were comparable in children and adults. Appendicular lean mass Z-scores were reduced in children (-0.93 ± 1.27, p<0.01) and adults (-1.80 ± 1.32, p<0.001), and were positively associated with DXA BMD Z-scores at all sites (R 0.46±0.50, p<0.01). Median (interquartile range) eGFR was 58 (32-76) mL/min/1.73m2. DXA Z-scores were not associated with eGFR. Tibia diaphysis cortical thickness and BMD (p=0.02), metaphysis trabecular bone volume fraction, thickness and number (p=0.01) and final elementary estimate of failure load in the diaphysis and distal tibia (p=0.0001) were lower in cystinosis vs. controls in multivariable analyses. Appendicular mass was highly associated with failure load (p=0.001) independent of age, sex and tibia length. Adjustment for lean mass eliminated group differences in cortical thickness and failure load in the diaphysis (p=0.20) and attenuated differences in failure load in the distal tibia (p=0.06). In contrast, trabecular deficits persisted.

Conclusions: Cystinosis is associated with severe musculoskeletal deficits in children and adults. Bone deficits were correlated with sarcopenia suggesting a role of decreased biomechanical loading. Studies are needed to identify interventions to improve bone strength and muscle mass in cystinosis.

Funding: Private Foundation Support

SA-PO362
Plasma 25-Hydroxyvitamin D Levels and Renal Function Decline in African Americans Joseph Lunyera,1 Clementina A. Davenport,1 Clarissa J. Diamantidis,1 Nrupen A. Bhavsar,1 Mario Sims,2 Myles S. Wolf,1 Jane F. Pendergast,1 L. Ebony Boulware,1 Julia J. Scialla.1 1Duke University School of Medicine, Durham, NC; 2University of Mississippi Medical Center, Jackson, MS.

Background: 25-hydroxyvitamin D [25(OH)D] deficiency is highly prevalent among African Americans and may contribute to their disproportionate risk of adverse chronic kidney disease (CKD) outcomes. We examined the association between plasma 25(OH)D levels and adverse CKD outcomes in the Jackson Heart Study (JHS).

Methods: We adjusted plasma 25(OH)D3 levels measured at baseline for monthly variation in sunlight exposure by using the residuals from the regression of 25(OH)D3 on the month of blood draw plus the overall mean. We examined the associations between baseline adjusted 25(OH)D3 and (a) annual estimated glomerular filtration rate (eGFR) decline and (b) incident CKD during follow-up using generalized linear models adjusted for demographics, behavioral factors, and comorbidity. Incident CKD was defined as either eGFR <60 mL/min/1.73m2 and a 25% decline in eGFR between baseline and follow-up, or albumin-to-creatinine ratio ≥30 mg/g at follow up among those without CKD at baseline.

Results: Among 5164 participants with non-missing 25(OH)D3 (97% of JHS cohort), the median [IQR] adjusted 25(OH)D3 was 12.0 [8.71-16.56] ng/mL, and mean ± SD eGFR was 94.11 ± 29.89 mL/min/1.73m2 at baseline. Over a median of 8 years, the mean ±SD annual eGFR decline was 1.27 ± 1.96 mL/min/1.73m2 per year, and 249 participants (12% of those whose CKD status could be determined) developed incident CKD. After adjusting for demographics, behavioral factors and comorbidity, each 10 ng/mL lower adjusted 25(OH)D3 was associated with 0.19 (95% CI 0.05-0.33) mL/min/1.73m2 per year faster eGFR decline. However, the association did not persist after additional adjustment for baseline eGFR (p=0.146). 25(OH)D3 was not associated with incident CKD [OR [95% CI] per 10 ng/mL lower 25(OH)D3, 1.12 [0.85,1.47].

Conclusions: Plasma 25(OH)D3 was not associated with risk of kidney function decline in African Americans after adjusting for baseline eGFR or other covariates. Despite low levels at baseline, our data do not support a role of supplementation in preventing or slowing CKD in African Americans.

Funding: NIDDK Support

SA-PO363
Soluble Urokinase Plasminogen Activation Receptor (suPAR) in the German Chronic Kidney Disease (GCKD) Study Claudia Sommerer,1 Nicole G. Metzendorf,1 Matthias Schmid,1 Kai-Uwe Eckardt,1 Jochen Reiser,1 Martin G. Zeier.1 1Kidney Center Heidelberg, Heidelberg, Germany; 2Rush University Medical Center, Chicago, IL; 3University Hospital of Heidelberg, Heidelberg, Germany; 4University of Erlangen-Nuremberg, Erlangen, Germany; 5Institute of Biometry, University of Bonn, Bonn, Germany; 6Group/Team: On behalf of GCKD investigators.

Background: Soluble urokinase plasminogen activation receptor (suPAR) is an emerging biomarker for prediction and progression of kidney disease and cardiovascular events. The value of suPAR as a biomarker was evaluated in the large prospective observational German Chronic Kidney Disease (GCKD) study.

Methods: Chronic kidney disease (CKD) patients aged 18-76 years with an estimated glomerular filtration rate (eGFR) of >30 <90 mL/min/1.73m2 or eGFR<60 enrolled in the GCKD study. suPAR was measured in baseline samples of participants and categorized in quintiles for investigation of the underlying disease, age and renal function.

Results: A total of 4994 CKD patients were studied (60.09 % males, mean age 60.08 ±11.98 years). Mean eGFR was 49.47 ± 18.29 mL/min/1.73 m2 and median (IQR) albumin/creatinine ratio was 50.85 (25% quantile: 9.61, 75% quantile 387.17) mg/g. Mean suPAR level was 2184±1952 pg/mL with a range from 221 to 45433 (mean: 1771, 25% quantile: 1446.9, 75% quantile 2254.1). Prevalence of patients with cardiovascular diseases, diabetic nephropathy, systemic diseases and smoking showed an upwards trend from suPAR quintile 1 to quintile 5. Median suPAR concentration increased with worsening renal function (CKD stage 1 to CKD stage 4, p=0.0001) and age (p<0.0001). Within CKD categories, suPAR rose with increase of albuminuria.

Conclusions: suPAR was evaluated in one of the worldwide largest CKD cohorts. In this study cohort, suPAR was associated with underlying cardiovascular disease, diabetic nephropathy as well as systemic disease involving the kidney. suPAR depended on demographic, proteinuria and age. The predictive value of suPAR on development of renal function and cardiovascular disease will be evaluated in this prospective study.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
The Relationship between Intrarenal Dopamine and Intrarenal Renin-Angiotensin System in CKD Patients Is Dependent on Renal Function

Takashi Matsuyama, Naro Ohashi, Sayaka Ishigaki, Shinsuke Isobe, Naoko Tsuji, Tomoyuki Fujikura, Takayuki Tsuji, Akihiko Kato, Hideo Yasuda.

Background: The mechanisms to activate intrarenal renin-angiotensin system (RAS) depend on the conditions of kidney diseases. In the angiotensin II (AngII) infusion models, the circulating AngII is filtered into renal tubular lumens and activates intrarenal RAS. Intrarenal dopamine system activation was shown to reduce angiotensinogen (AGT) expression in the proximal tubules and suppress intrarenal RAS activity. In the chronic kidney disease (CKD) models where filtered plasma AGT into the tubular lumens due to glomerular injury activates intrarenal RAS, the relationship between intrarenal dopamine system and intrarenal RAS in CKD models has not been clarified. Therefore, we performed this study to determine the mutual relationship in CKD patients.

Methods: We recruited 46 CKD patients (age: 51.1 ± 20.0 years old, 16 males, causes of CKD: chronic glomerulonephritis; 34, diabetic nephropathy; 2, nephrosclerosis; 4, others; 6) without undergoing dialysis or taking RAS blockers. The urinary dopamine (U-DOPA) excretion as an indicator of intrarenal dopamine activity and the urinary AGT (U-AGT) excretion as a surrogate marker of intrarenal RAS activity were measured, and the relationships were investigated.

Results: U-DOPA excretion levels in patients with CKD stage 5 were significantly lower compared to those with other CKD stages, and U-DOPA excretion levels tended to decrease as the CKD stages progressed. Conversely, U-AGT excretion levels in patients with CKD stage 5 were significantly higher than those in patients with CKD stages 1 to 3, and tended to increase as the CKD stages progressed. U-DOPA excretion levels were significantly and negatively correlated with U-AGT excretion levels (r = -0.42, p < 0.01) and positively and positively correlated with estimated glomerular filtration rate (eGFR) (r = 0.64, p = 0.01). Multiple regression analysis revealed that U-DOPA excretion levels were associated with U-AGT excretion levels after adjustment of age, sex, and body mass index (β = -0.034, p = 0.025). However, the correlation disappeared when eGFR was additionally adjusted (β = -0.057, p = 0.70).

Conclusions: The negative correlation between intrarenal dopamine system and intrarenal RAS system in CKD patients is affected by renal function.

Impact of Bariatric Surgery on Prognosis of CKD

Allon N. Friedman, Abdus S. Wahed, Junyao Wang, Anita Courcoules, Gregory Dakin, Paul L. Kimmel, James E. Mitchell, Jonathan Q. Purnell, Carel W. Le roux, Richard C. Thribly, Bruce M. Wolfe, Indiana University School of Medicine, Indianapolis, IN; NRI, CHASKA, MN; National Institute of Diabetes and Digestive Kidney Diseases (NIDDK), Bethesda, MD; Oregon Health & Science University, Portland, OR; Oregon Health and Science University, Portland, OR; University College Dublin, University College Dublin, Ireland; University of Pittsburgh, Pittsburgh, PA; University of Pittsburgh Medical Center, Pittsburgh, PA; Virginia Mason, Seattle, WA; Weill Cornell Medical College, New York, NY.

Background: Obesity is linked to the development and progression of chronic kidney disease (CKD) but whether weight reduction through bariatric surgery protects against CKD is poorly understood. Our goal was to assess if bariatric surgery influences the prognostic risk for CKD.

Methods: We studied the patient cohort from Longitudinal Assessment of Bariatric Surgery 2 (LABS-2), which included 2458 adults who underwent bariatric surgery from March 2006 to April 2009 at 10 US hospitals in 6 geographically diverse clinical centers. Participants underwent roux-en-Y gastric bypass (n = 1350), laparoscopic adjustable band (n = 523), sleeve gastrectomy (n = 52), banded gastric bypass (n = 22), or biliopancreatic diversion with duodenal switch (n = 17). The primary outcome was prognostic risk for CKD as measured by the Kidney Disease Improving Global Outcomes (KDIGO) consortium criteria.

Results: Patients were 79% female and 87% white with a median age of 46 years. Using the KDIGO criteria 41% and 22% of the group classified at moderate prognostic risk for CKD before surgery (n = 254; 11.9% of total cohort) had improvement in their risk category at 1 year and 7 years, respectively. In patients with high prognostic risk at baseline (n = 73; 3.4% of total cohort) 56% and 29% improved their risk category at 1 and 7 years, respectively. In patients with very high prognostic risk at baseline (n = 29; 1.4% of total cohort) 35% and 7% improved their risk category at 1 and 7 years, respectively. The proportion of patients whose prognostic risk category for CKD worsened was minimal (<3%) and only 5 patients developed end stage renal disease during the follow-up period. When year 1 was used as baseline in order to minimize the effect of weight loss on serum creatinine (and thereby influencing CKD prognostic risk), the magnitude of the benefits was reduced though results were qualitatively similar.

Conclusions: Treatment with bariatric surgery was associated with a reduction in the prognostic risk for CKD in a large proportion of patients for up to 7 years, especially in those with high risk at baseline. These findings support the consideration and further study of bariatric surgery as a treatment for CKD in obese patients.

Funding: NIDDK Support
Kidney Produces Fibroblast Growth Factor 23 in Rat CKD Model
Hidekazu Sugiyura,1 Nobuo Nagano,1 Kosaku Nitta,2 Ken Tsuchiya.1
1Hidaka-ku, Takasaki-shi, Japan; 2Tokyo Women’s Medical University, Shinjuku-ku, Japan; 1Department of Nephrology, Division of Medicine, Saiseikai Kurashi Hospital, Saitama, Japan.

**Background:** Fibroblast growth factor 23 (FGF23) is a hormone secreted from the bone, and involved in phosphorus metabolism. FGF23 mainly binds to the fibroblast growth factor receptor, which is accompanied by αKlotho expressed in the kidney or parathyroid, and regulates the expression of phosphatase co-transporter, production of 1,25-dihydroxyvitamin D3 (1,25(OH)2D3), and secretion of parathyroid hormone (PTH). In chronic kidney disease (CKD), blood FGF23 level rises, which is believed to be associated with cardiac hypertrophy and mortality.

**Methods:** In this study, we chose unilateral nephrectomy rat fed with high-phosphorus diet, 5/6 nephrectomy rat and doxorubicin renal failure rat as CKD model animals, and analyzed expression of renal FGF23 in each CKD model animal by real-time PCR and Western blot analysis.

**Results:** All model rats showed renal dysfunction and increased level of blood phosphorus. In both unilateral nephrectomy rat with high-phosphorus diet and 5/6 nephrectomy rat, blood FGF23 and PTH level were increased. However, level of 1,25(OH)2D3 was increased in unilateral nephrectomy rat fed with high-phosphorus diet and decreased in 5/6 nephrectomy rat. In all three model animals, mRNA expression of αKlotho, Na-dependent phosphate co-transporter type IIa and type IIc were decreased in kidneys. FGF23 mRNA was also measured in kidney. While FGF23 mRNA expression in kidney was barely detectable in control groups, it was detectable in CKD model groups. The difference between two groups was statistically significant. In unilateral nephrectomy rat fed with high-phosphorus diet and 5/6nephrectomy rat, Western blot showed the level of renal FGF23 protein was increased.

**Conclusions:** This result suggests that FGF23 is expressed in kidney of the CKD model rat. FGF23 produced in kidney is suggested to affect the phosphorus metabolism in the kidney. We demonstrated in this study that FGF23 is produced in the kidney in CKD model rats.

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

---

SA-PO369
Phosphorus Is an Exacerbation Factor in the Progression of CKD Model by the Accumulation of Small Kidney Injury in Klotho Deficit Mice
Ken Tsuchiya,1 Hidekazu Sugiyura,2 Norio Hanafusa,3 Kosaku Nitta.4
1Department of Blood Purification, Tokyo Women’s Medical University, Shinjuku-ku, Japan; 2Department of Nephrology, Saiseikai Kurashi Hospital, Kuki, Japan; 3Department of Medicine IV, Tokyo Women’s Medical University, Shinjuku-ku, Japan.

**Background:** It has been established that klotho protein is a key molecule in the axis of Ca/P metabolism in CKD-MBD, on the other hand, klotho is speculated to be implicated in the mechanism of preceding the CKD, in which klotho suppression is likely to be a result and a cause of CKD. Previously, we reported that repeated minor kidney injury results in more reduction of klotho and cause of CKD in klotho deficit mice. In this study with this model, we investigated several factors which may be involved in making worse or accelerating the progression of CKD.

**Methods:** Short time clamping of renal artery for 20 minutes was performed and repeated once a week for 3 weeks in the klotho gene heterozygous mice (klotho+/−). Renal function, the score of tissue damage and altered expression factors were monitored with immunohistochemistry and RT-PCR for mRNA expression. Then, klotho expression was modified by erythropoietin treatment or diet therapy assuming clinical matter. Practically, 200 µg/kg BW of recombinant erythropoietin (ESA) was injected subcutaneously 3 times per week. Since phosphorus is an old and new aggravating factor for CKD which has been drawing attention, stepwise dose of phosphorus was fed in diet in whole experimental period for dietary modification.

**Results:** Repeated ischemia reduced the renal function and worsen tissue score in klotho+/− mice than in wild type mice. These changes were attenuated by ESA treatment. Klotho mRNA slightly recovered and the expression of fibrotic factors were reduced. Phosphorus is an aggravating factor that stands out than the other factors. Klotho deficit mice treated with repeated minor kidney injury were more sensitive to high phosphorus (2%) loading than control, resulting in more severely reducing the expression of klotho and accelerating renal damage (ATN scores 2-4 folds vs. control).

**Conclusions:** Repeated ischemia possibly initiate or accelerate CKD in reduced klotho expression. Phosphorus loading damaged the kidney much more in these klotho−/− mice, which may suggest that phosphorus restriction (reflecting low protein diet) is likely to be meaningful for the attenuation of the progression of CKD, indicating the importance of re-estimating of the significance of low protein diet (namely, low phosphorus) in clinical practice.

---

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

**Underline represents presenting author.**
Vitamin D Deficiency Impairs the Renal Expression of M2 Macrophages in Rats Submitted to 5/6 Nephrectomy

**Background:** 5/6 nephrectomy (Nx) is a classical experimental model of chronic kidney disease (CKD). Many studies have shown a pivotal role of macrophages (M0) in the progression of CKD. Broadly, two main groups of M0 are designated: M1 (proinflammatory M0) and M2 (tissue repair M0). Moreover, recent investigations have been linking Vitamin D Deficiency (VDD) to inflammatory process and predisposition to fibrosis formation.

**Methods:** For 90 days, male Wistar rats were fed a standard [Sham and Nx groups] or a vitamin D-free (VDD and VDD+Nx) diet. On day 30, Nx and VDD+Nx rats were submitted to Nx surgery. On day 90, we measured serum levels of 25(OH)D and PTH by ELISA, inulin clearance (Cin), mean arterial pressure (MAP), immunoblotted for TGF-β and performed IHC for M2 (Mannose Receptor). Also, we estimated the interstitial enlargement by fraction interstitial area (FIA).

**Results:** As described in Table 1, VDD were associated with MAP elevation and decreased Cin in VDD+Nx group. Moreover, we observed higher expression of M1 macrophages and TGF-β as well as larger FIA in the renal cortex of those animals. Interestingly, we found a lower expression of M2 macrophages in VDD+Nx rats, indicating an important role of Vitamin D in the tissue repair and maintenance of inflammatory process.

**Conclusions:** Our study suggests that VDD is involved in tissue repair and fibrosis formation after Nx, reinforcing the role of VDD as an aggravating factor for CKD progression. (Financial Support: FAPESP 2015/55313-1)

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

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Sham</th>
<th>VDD</th>
<th>Nx</th>
<th>VDD+Nx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cin (mL/min/100g BW)</td>
<td>1.65±0.01</td>
<td>1.58±0.01</td>
<td>1.48±0.01</td>
<td>1.44±0.01</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>15.6±5.7</td>
<td>16.8±6.9</td>
<td>17.4±7.5</td>
<td>17.5±7.2</td>
</tr>
<tr>
<td>BW (g)</td>
<td>48.0±1.0</td>
<td>49.1±1.0</td>
<td>49.4±1.0</td>
<td>49.3±1.0</td>
</tr>
<tr>
<td>TGF-β (pg/mL)</td>
<td>311.2±24.2</td>
<td>310.5±24.3</td>
<td>310.0±24.4</td>
<td>310.0±24.0</td>
</tr>
<tr>
<td>M1 (positive area)</td>
<td>0.20±0.02</td>
<td>0.20±0.02</td>
<td>0.20±0.02</td>
<td>0.20±0.02</td>
</tr>
<tr>
<td>M2 (positive area)</td>
<td>0.18±0.02</td>
<td>0.18±0.02</td>
<td>0.18±0.02</td>
<td>0.18±0.02</td>
</tr>
<tr>
<td>MGP (mRNA)</td>
<td>1.00±0.96</td>
<td>0.98±0.96</td>
<td>0.98±0.96</td>
<td>0.98±0.96</td>
</tr>
<tr>
<td>Fox-p3 (mRNA)</td>
<td>7.5±7.26</td>
<td>7.5±7.26</td>
<td>7.5±7.26</td>
<td>7.5±7.26</td>
</tr>
</tbody>
</table>

Data are expressed as means±SEM. BW: Body weight. a p<0.001 vs Sham; b p<0.01 vs Sham; c p<0.05 vs Sham; d p<0.001 vs VDD; e p<0.01 vs VDD; f p<0.05 vs VDD; g p<0.01 vs Nx; h p<0.01 vs Nx; i p<0.05 vs Nx.

**SA-PO373**

**Tubular Matrix Gla Protein Expression Increases Progressively with CKD**

**Background:** Renal MGP expression was significantly increased in 5/6Nx rats: 2.16-fold (2 days, p=0.002), 3.27-fold (2 weeks, p=0.0002), and 3.31-fold (4 weeks, p=0.0002). There was a trend for patients with advanced CKD (n=8) to have greater tubulointerstitial (TI) cMGP staining vs controls (NS). In NEPTUNE samples, there was an inverse relationship between eGFR and the TI MGP transcript. The TI MGP transcript correlated (TI) cMGP staining vs controls (NS). In NEPTUNE samples, there was an inverse relationship between eGFR and the TI MGP transcript. The TI MGP transcript correlated with CKD progression and was associated with interstitial fibrosis, tubular atrophy, and tubular injury (p<0.01).

**Methods:** We performed 5/6 nephrectomy (Nx) in rats, sacrificed them at 2 days, 2 weeks, and 4 weeks, and measured gene expression by microarray. Altered expression of many proteins involved in vascular calcification. We focused on MGP, is a potent in vivo inhibitor of arterial calcification. Little is known about de novo matrix Gla Protein (MGP), a vitamin K–dependent protein, with CKD progression and was associated with interstitial fibrosis, tubular atrophy, and tubular injury. (p<0.01).

**Results:** As described in Table 1, MGP expression was significantly increased in 5/6Nx rats: 2.16-fold (2 days, p=0.002), 3.27-fold (2 weeks, p=0.0002), and 3.31-fold (4 weeks, p=0.0002). There was a trend for patients with advanced CKD (n=8) to have greater tubulointerstitial (TI) cMGP staining vs controls (NS). In NEPTUNE samples, there was an inverse relationship between eGFR and the TI MGP transcript. The TI MGP transcript correlated with CKD progression and was associated with interstitial fibrosis, tubular atrophy, and tubular injury (p<0.01).

**Conclusions:** Our study suggests that MGP is involved in tissue repair and fibrosis formation after Nx, reinforcing the role of VDD as an aggravating factor for CKD progression. (Financial Support: FAPESP 2015/55313-1)

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

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Sham</th>
<th>VDD</th>
<th>Nx</th>
<th>VDD+Nx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cin (mL/min/100g BW)</td>
<td>1.65±0.01</td>
<td>1.58±0.01</td>
<td>1.48±0.01</td>
<td>1.44±0.01</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>15.6±5.7</td>
<td>16.8±6.9</td>
<td>17.4±7.5</td>
<td>17.5±7.2</td>
</tr>
<tr>
<td>BW (g)</td>
<td>48.0±1.0</td>
<td>49.1±1.0</td>
<td>49.4±1.0</td>
<td>49.3±1.0</td>
</tr>
<tr>
<td>TGF-β (pg/mL)</td>
<td>311.2±24.2</td>
<td>310.5±24.3</td>
<td>310.0±24.4</td>
<td>310.0±24.0</td>
</tr>
<tr>
<td>M1 (positive area)</td>
<td>0.20±0.02</td>
<td>0.20±0.02</td>
<td>0.20±0.02</td>
<td>0.20±0.02</td>
</tr>
<tr>
<td>M2 (positive area)</td>
<td>0.18±0.02</td>
<td>0.18±0.02</td>
<td>0.18±0.02</td>
<td>0.18±0.02</td>
</tr>
<tr>
<td>MGP (mRNA)</td>
<td>1.00±0.96</td>
<td>0.98±0.96</td>
<td>0.98±0.96</td>
<td>0.98±0.96</td>
</tr>
<tr>
<td>Fox-p3 (mRNA)</td>
<td>7.5±7.26</td>
<td>7.5±7.26</td>
<td>7.5±7.26</td>
<td>7.5±7.26</td>
</tr>
</tbody>
</table>

Data are expressed as means±SEM. BW: Body weight. a p<0.001 vs Sham; b p<0.01 vs Sham; c p<0.05 vs Sham; d p<0.001 vs VDD; e p<0.01 vs VDD; f p<0.05 vs VDD; g p<0.01 vs Nx; h p<0.01 vs Nx; i p<0.05 vs Nx.
unclear. We previously reported that the transfer of a small region in Chr. 1 of Brown-Norway (BN) rats which contains 15 genes, including gamma-Add3 (Add3), into the FHH background could restore the impaired renal microvascular function in FHH rats. Our further work identified a K572Q mutation in Add3 in FHH rats as a potential candidate variant in the pathogenesis of renal disease.

Results: RBF increased by 21.5 ± 3.0% in SD, Add3 KO rats (n=7) when mean arterial pressure was increased from 60 to 150 mmHg. In contrast, RBF only increased by 3.5 ± 0.9% in wildtype (wt) SD rats (n=13). The diameter of the renal ar-af decreased by 13 ± 0.8% in SD rats when perfusion pressure was increased from 60 to 120 mmHg, but it increased by 5.0 ± 0.6% in the SD.Add3 KO rats. The myogenic response of the renal prearteriole (af-art) was markedly impaired, and increased pressure was pressure was increased from 60 to 120 mmHg. The myogenic response was restored, and the diameter of Af-art decreased by 12 ± 0.7% and 7 ± 1.0% in FHH. 1h congenic rats (n=27) and Add3 transgenic FHH rats that express wt-Add3. RBF increased by 35.1 ± 0.0% when MAP was increased from 100 to 150 mmHg in FHH rats (n=15) versus only 7.5 ± 1.7% and 6.0 ± 1.3% in FHH1h or a F1 cross of FHH and FHL1h rats (n=9) and in Add3 transgenic FHH rats that express the wt-Add3 gene. The myogenic response of Af-art and autoregulation of RBF were also impaired in MNS rats (n=6) that carry the same K572Q mutation in Add3 as FHH rats. These phenotypes were complemented in an F1 cross of FHH and MNS rats (n=7), but the myogenic response and autoregulation of RBF were restored in an F1 cross of FHH and FHL1h rats with one copy of wt-Add3.

Conclusions: These results suggest that the recessive K572Q mutation of Add3 in FHH and MNS rats plays a causal role in renal microvascular dysfunction that may contribute to their susceptibility to develop diabetic nephropathy. The present study examined the role of the K572Q mutation of Add3 in the pathogenesis of renal disease in the FHH background could restore the impaired renal microvascular function in FHH rats. Our further work identified a K572Q mutation in Add3 in FHH rats as a potential candidate variant in the pathogenesis of renal disease.

SA-PO375

MMD2 Subcellular Trafficking Is Involved in the A KD to CKD Progression Induced by Repeated Cicaplatin Exposure

Hua Su, Huazhong Science and Technology University, Wuhan, China.

Background: Repeated cisplatin (CP) administration frequently leads to the development from acute kidney disease (AKD) to chronic kidney disease (CKD). During above pathogenic process the tubular epithelial cell (T EC) damage is the cardinal event. MMD2 is an E3 ligase and participates in multiple pathophysiological processes. Previously our studies revealed that MMD2 not only involves in AKD but also accounts for CKD by promoting fibroblast activation. However, the role of MMD2 in repeated CP exposure induced AKD to CKD transition is unclear.

Methods: AKD to CKD mouse model was established by intraperitoneal injection of CP (8mg/Kg) once a week. The mice were grouped into 1CP, 2CP, 3CP and 4CP according to the time of CP administration. 7 days after the final injection the mice were sacrificed and kidney cortex was collected. Immunostaining and sucrose gradient ultracentrifugation were utilized to label or isolate subcellular organelles. Immunoprecipitation was employed to examine the interaction between MMD2 with p53 or NHERF1, as well as the ubiquitination of p53 and NHERF1.

Results: We successfully established the CP-induced AKD to CKD mouse model which was proved by the increased NAG and KIM-1 expression in 2 CP group with later upregulated α-SMA, Collagen 3 and serum creatinine in 3CP and 4CP groups. Our data shown in physiological state MMD2 predominantly distributes in nuclei and binds with p53, however after first time of CP administration MMD2 moves from nuclei to cytoplasm along with the increased expression of p53 and upregulated p53 expression. Furthermore, after 4-7 days of CP injection, we found MMD2 further transports into cell membrane and interacts with NHERF1, a negative regulator of PDGF-BB/PDGF-β axis, which leads to the enhanced ubiquitination of NHERF1. Consequently, the abundance of NHERF1 minimized with the activation of PDGF-BB/PDGF-βsignaling, a well-known cytokine pathway involved in AKD to CKD mice model due to intraperitoneal injection of CP (8mg/Kg) once a week. The mice were grouped into 1CP, 2CP, 3CP and 4CP according to the time of CP administration. 7 days after the final injection the mice were sacrificed and kidney cortex was collected. Immunostaining and sucrose gradient ultracentrifugation were utilized to label or isolate subcellular organelles. Immunoprecipitation was employed to examine the interaction between MMD2 with p53 or NHERF1, as well as the ubiquitination of p53 and NHERF1.

Conclusions: Repeated CP administration initiates the MMD2 trafficking form nuclei to cytoplasm, and eventually move to the cell membrane where MMD2 binds with and ubiquitinates NHERF1. Consequently, NHERF1 is degraded and PDGF-BB/PDGF-β signaling is activated.

Funding: Government Support - Non-U.S.

SA-PO376

Adaptive and Pathologic Mechanisms in Diabetic Kidney Disease: A Modeling Analysis

Harish Shankar Mahato, 1Christine Ahlström, 2Rasmus Jansson-Loefmark, 3Gabriel Helmlinger, 1Melissa Hallow, 1AstraZeneca Pharmaceuticals, Waltham, MA; 2AstraZeneca R&D, Mölndal, Sweden; 3University of Georgia, Athens, GA.

Background: Translation from preclinical animal models to human diabetic kidney disease is challenging due to species differences in disease processes and timeframes. Quantitative systems models are helpful in understanding disease mechanisms and interspecies differences. We aimed to apply a physiological model of human renal function to mice, to incorporate adaptive and pathologic mechanisms of diabetes and nephrotoxic observed in the db/db uninephrectomized (UNX) mouse model, and to explore therapeutic strategies to improve renal and cardiac outcomes.

Methods: Some renal structural/functional characteristics are preserved across species (e.g. pressures, single nephron flow rates), while others differ markedly (e.g. nephron number, tubular lengths). We reparameterized a systems model of human renal hemodynamics to represent mice, and ensured appropriate phenotypic behavior (e.g. glomerular filtration rate [GFR], blood pressure). To model the adaptive and pathologic renal effects in kidney disease, we assumed that elevated glomerular capillary pressure causes 1) glomerular capillary hypertrophy, up to a limit, 2) podocyte damage and increased albuminuria, 3) glomerulosclerosis, and 4) in single nephron GFR to keep total GFR stable after UNX. In both cases, glomerular hypertrophy normalized glomerular pressure, so that proteinuria was minimal, as observed experimentally. However, in cases with diabetes a glomerular pressure beyond the adaptive capacity and caused overt progressive proteinuria. The model also reproduced the proteinuria reduction observed in with enalapril, eplerenone and dapagliflozin.

Conclusions: The systems model provides insight into adaptive and pathologic renal processes in db/db UNX mice. By simulating responses to therapies for which preclinical and clinical data is available, it may aid benchmarking for clinical translation.

Funding: Commercial Support - AstraZeneca

SA-PO377

Experimental Heat Stress Nephropathy Is Improved by Allopurinol

Carlos A. Roncal-jimenez, 1Tamar Milagres, 2Miguel A. Lanaspa, 3Ana Andres-hernando, 4Masanari Kuwabara, 5Yuka Sato, 6Thomas Jensen, 7Gabriela E. Garcia, 8L. Gabriela Sanchez-Lozada, 9Ramón García-Trabino, 10Emmanuel Jarquin, 11Jason R. Glaser, 12Brendan D. Johnson, 13Helen A. McNicholl, 14Finnur S. Ólafsson; 1La Isla Foundation, INC., ADA, MI; 2NonInst. Ncd Cardiol. Ignacio Chavez, Mexico City, DF, Mexico, 3University of Colorado Denver, Aurora, CO.

Background: Mesoamerican nephropathy (MN) is a disease of unknown cause observed primarily in sugarcane workers with recurrent dehydration that affect to the kidney chronically (CKD). Some evidence suggests hyperuricemia may be involved; to test that hypothesis we evaluated the role of uric acid (UA) in an animal model of heat stress and subsequent dehydration.

Methods: Mice exposed to heat 39.5 °C x 30 min, 8x daily for 5 weeks, with water provided at night with allopurinol 32mg/Kg/d in drinking water, Group 4 (Heat +AP) or without allopurinol Group 3 (Heat), as well as control groups that were normal mice drinking water or water with allopurinol Groups 1 (Control) and 2 (AP), respectively n=7 per group.

Results: Conclusions: Allopurinol lowered serum uric acid in animals with heat stress and this was associated with less fibrosis, less proximal tubular injury (preserved ACE staining) and improved renal function. Interestingly, lowering serum uric acid was also associated with an increase in serum vasopressin and lower serum osmolality in Heat animals; with higher cGMP, lower urine osmolality in normal mice. p value* shows the value by Bonferroni's post hoc analysis between Heat and Heat+AP.

Funding: Other U.S. Government Support

SA-PO378

Domain-Specific Antibodies Reveal the Membrane Topology of ApoL1

Nidhi Gupta, 1Xinhua Wang, 2Ann De Maziere, 2George Posthuma, 2Paul Moran, 3Michael T. Lipari, 3Daniel Kirchhoff, 3Judith Klumphner, 3Randall J. Brezski, 1Andrew S. Peterson, 1Suzie J. Scales, 1Genentech, Inc., South San Francisco, CA; 2UMC Utrecht, Utrecht, Netherlands.

Background: ApoL1 (Apolipoprotein L 1) is a component of the trypanolytic factor that is secreted by HDL3b particles. ApoL1 protects against Trypanosoma brucei brucei infection. Two common African variants in ApoL1 (G1 and G2) additionally protect against Trypanosoma brucei rhodesiense, but also confer a greater risk of chronic kidney disease in homozygotes. ApoL1 contains three domains named for their roles in trypanolysis—a pore forming domain that forms ion channels leading to lysis; a membrane addressing domain responsible for HDL binding and lysosomal membrane insertion; and an SRA-interacting domain that binds to the serum resistance factor of Trypanosoma brucei rhodesiense. However, little is known about ApoL1 topology i.e. domains are exposed on HDL particles and kidney podocytes, the susceptible cell type in chronic kidney disease.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO379

Modulation of Podocyte (PD) Homeostasis by Mesenchymal Stromal Bone Marrow Cells (MS-BMC) in the Podocyte Two and Single Kidney Injury Models
Rukhsana Aslam,1 Ali Hussain,2 Seyyedeh Shadafarin Marashi Shoshtari,3 Abheesha Mishra,3 Vinod Kumar,4 Ashwani Malhotra,4 Pravin C. Singhal,4 1Feinstein Institute for medical research, Glenoaks, NY; 2Feinstein Institute of Medical Research, New York, NY; 3Feinstein Institute of Medical Research, Northwell Health, Manhasset, NY; 4North Shore LIJ Health System, Great Neck, NY. The Feinstein Institute for Medical Research, Manhasset, NY; 5Division of Nephrology and Inflammation, Feinstein Institute for Medical Research, New York, NY; 6Immunoology and Inflammation, Feinstein Inst.Med research and NSSLI, Manhasset, NY.

Background: Adriamycin has been demonstrated to induce focal segmental glomerulosclerosis (FSGS). Mesenchymal stromal bone marrow cells (MS-BMCs) have been demonstrated to protect cytoprotection by the modulation of cytokine production in several nephrotic models. Recently, parietal epithelial cells (PECs) have been considered as progenitor cells to manage podocyte homeostasis; however, PECs may also act as profibrotic cells in adverse milieu. In the present study, we evaluated the effect of MS-BMCs on modulation of the role of parietal epithelial cells in managing the podocyte homeostasis in Adriamycin-induced podocyte injury in two and single kidney injury models.

Methods: MS-BMCs were harvested from bone marrows of mice and their profile was characterized. Mice in groups of six were administered either buffer (group A), intracapsular instillation of MS-BMCs in left kidney (group B), or intraperitoneal MS-BMCs (2×10^6 cells per mouse) 24 hours prior to Adriamycin (150 mg/kg) subcutaneously administration. Additionally six mice administered normal saline were used as controls. All mice were euthanized after 4 weeks; urine and blood samples were collected for BUN and albumin: creatinine ratio. Kidneys were harvested for histology, immuno-staining for p57 and co-labeling for CD44 and phospho-ERK. Immunoblots were prepared and probed for podocin and WT1 and re-probed for actin.

Results: Group B and C mice displayed a decrease (P<0.05) in albumin: creatinine ratio vs. Group A mice. Immunoblotting studies revealed decreased (P<0.01) podocin, WT1, and p57 expressions in renal tissues of group C when compared to renal tissues of group A. On the other hand, renal tissues of the left kidneys from Group B displayed increased (P<0.01) protein expression of podocin, WT1, and p57 when compared to contralateral kidneys. Kidneys from the group C and right kidneys from the group B displayed increased (P<0.05) number of profibrotic cells (colabeled for phos-ERK and CD44) in C and increased (P<0.05) number of p57+ve cells.

Conclusions: These findings indicate that MS-BMCs provide protection from injurious effect of adriamycin by decreasing the number of pro-fibrotic PECs and increasing the number of progenitor cells.

Funding: NIDDK Support

SA-PO380

The Impact of Canagliflozin on the Gut Microbiota of Non-Diabetic CKD Rats and Its Effect on Cardiovascular System
Sumit Matsumi,1 Ayako Glang,1 Yuhon Ihn,1 Jumpei Ootani,1 Miwako Matsuzaki,1 Tomoko Ito,1 Shu Wakino,1 Hiroshi Itoh,1 KEIO UNIVERSITY, Tokyo, Japan; 2Keio University, Tokyo-to, Japan; 3Keio University School of Medicine, Tokyo, Japan; 4Keio University school of medicine, Tokyo, Japan; 5KEIO University, Tokyo, Japan.

Background: The gut is responsible for the production of some uremic toxins by the microbiota which induces the tissue damages in chronic kidney disease (CKD). Gut microbiota population was reported to be altered in CKD. Novel anti-diabetic reagent sodium glucose cotransporter 2 (SGLT2) inhibitor, canagliflozin (Cana) harbors three domain inhibitory potential to gut-type SGLT1, which is hypothesized to affect the dysbiosis in CKD. We investigated the impact of Cana on the microbiota and on cardiovascular and renal tissues in non-diabetic CKD rats.

Methods: 6-week-old male spontaneously-hypertensive rats (SHRs) were randomly assigned to three experimental groups; sham operated SHR (Sham), 5/6 nephrectomized SHR (Nx), and 5/6 nephrectomized SHR treated with Cana (0.024% mixed in standard chow) (Nx+C). After 12 weeks, microbiota population was examined by T-RFLP and following 3 months, and molecular changes of kidney, cardiovascular systems and intestine were also investigated.

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

SA-PO382

Investigating Endoplasmic Reticulum Stress in the Development of Lupus Nephritis
Mashhile L. Bonnemaison, Erika I. Boesen. University of Nebraska Medical Center, Omaha, NE.

Background: Lupus nephritis is a common complication of the autoimmune disease systemic lupus erythematosus (SLE) and is associated with glomerular and tubular injury. Although recent uptake has shown to induce endoplasmic reticulum (ER) stress in proximal tubule cells in vitro, it is unknown whether ER stress occurs in and contributes to the development of renal injury in SLE.

Methods: To investigate this, the current study used a well-established model of lupus nephritis, the NZBVWF1 mouse (female only). Mice were randomized to receive either vehicle (normal drinking water) or the ER stress blocker 4-phenylbutyric acid (4-PBA, 20 mM) in drinking water starting from 12 weeks of age until 34 weeks of age to determine if pretreatment with 4-PBA prevents or improves renal function in NZBVWF1 mice. At 12 and 34 weeks, mice underwent a standard renal biopsy for histological examination. Urinary albumin was also measured in urine collected at the time of biopsy. The following studies were performed: (1) protein carbonyl levels were measured using the Amplex Red Assay Kit (Invitrogen) to evaluate protein modification by advanced oxidation protein products, (2) Western blotting was used to detect expressions of the ER stress markers CHOP and IRE1, and (3) a TUNEL assay was performed to detect apoptosis.

Results: The data from these analyses were collected in a blinded fashion. When compared to vehicle-treated mice, the 4-PBA group displayed a significant reduction in protein carbonyl levels (P<0.05), a significant reduction in CHOP expression (P<0.05), and a significant reduction in IRE1 expression (P<0.05) at 12 weeks of age. Furthermore, the 4-PBA group displayed a significant reduction in protein carbonyl levels (P<0.01), a significant reduction in CHOP expression (P<0.05), and a significant reduction in IRE1 expression (P<0.05) at 34 weeks of age. In addition, the 4-PBA group showed a significant reduction in the percent of TUNEL-positive cells (P<0.05) at both 12 and 34 weeks of age. These findings indicate that pretreatment with 4-PBA significantly reduces renal injury in NZBVWF1 mice.

Funding: NIDDK Support

SA-PO381

DESI-MSI Based Spatial Metabolomics Reveals Alterations in Metabolome and Increased Pseudouridine in Renal Proximal Tubules of Mice with Diabetic Kidney Disease
Guanshi Zhang,1 Jialing Zhang,2 Rachel J. Dehoog,3 Manjula Darshi,5 Benjamin F. Van espen,3 Subramanian Pennathur,4 Vighnesh Walavalkar,1 Theodore Alexandrov,5 Livia S. Eberlin,4 Kumar Sharma.1,4 Center for Renal Translational Medicine, Division of Nephrology-Hypertension, Institute of Metabolomic Medicine, University of California San Diego, La Jolla, CA; 2Department of Chemistry, The University of Texas at Austin, Austin, TX; 3Division of Nephrology-Hypertension, Veterans Affairs San Diego Healthcare System, La Jolla, CA; 4Division of Nephropathy Department of Internal Medicine, University of Michigan, Ann Arbor, MI; 5Department of Pathology, University of California San Diego, La Jolla, CA; 6Structural and Computational Biology Unit, European Molecular Biology Laboratory, Heidelberg, Germany; 7Skaegg School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, La Jolla, CA.

Background: Diabetic kidney disease (DKD) is the most prevalent complication in diabetic patients, which contributes to high morbidity and mortality. Urine and plasma metabolite studies have reported that both blood and urinary metabolites to provide valuable insights for DKD. Spatial distributions of metabolites in kidney tissues would link circulating metabolites to actual kidney compartments but the techniques are challenging. We employed an ambient desorption electrospray ionization – mass spectrometry imaging (DESI-MSI) approach to characterize the metabolome in a mouse model of DKD coupled to a novel bioinformatics platform (METASPACE).

Methods: DESI-MSI was performed for spatial targeted metabolomics analysis in kidneys of mouse models (F1 C57BL/6-J/Ins2Akita2/2 male mice at 17 weeks of age) of type 1 diabetes (T1D, n = 5) and healthy controls (n = 6). Metabolite annotations from MSI were conducted using METASPACE and further validated by collision induced dissociation or higher-energy collisional dissociation tandem MS analysis. MetaboAnalyzer 3.0 was employed for statistical analyses.

Results: Multivariate analyses (i.e., PCA and PLS-DA (a 2000 permutation test: P <0.001) showed clearly separated clusters for the two groups of mice on the basis of 878 measured m/z’s in kidney cortical tissues. Specifically, mice with T1D had increased relative abundances of pseudouridine (m/z 279.039), fatty acids (FA) (e.g., FA (18,2), m/z 279.131), and glycerophospholipids (GPI) (e.g., PG (36,1), m/z 775.548) in cortical proximal tubules when compared with healthy controls.

Conclusions: Results from the current study further support a role for pseudouridine in DKD and the data suggests that pseudouridine accumulation might originate from proximal tubule cells. Lipidomic annotations from MS data conducted using METASPACE and further validated by collision induced dissociation or higher-energy collisional dissociation tandem MS analysis. MetaboAnalyzer 3.0 was employed for statistical analyses.

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

Underline represents presenting author.
nitrogen was significantly elevated in mice that developed albuminuria before 34 weeks of age, and different between vehicle and 4-PBA groups. Plasma creatinine levels were unchanged over time in both groups. CHOP mRNA expression in the renal cortex was compared between untreated 20 week old mice (prior to SLE development) and vehicle-treated albuminuric and non-albuminuric 34 week old mice. Surprisingly, CHOP mRNA levels of the ER stress marker CHOP were significantly reduced in the renal cortex of albuminuric mice compared to the 20 week old mice (P<0.05), which had similar CHOP expression to 34 week old non-albuminuric mice. A similar trend was observed for GRP94, but this did not reach statistical significance.

Conclusions: These findings do not support a major role for ER stress in the early stages of the development of renal injury in SLE, as defined by onset of albuminuria. Whether ER stress contributes to the further progression of renal injury in lupus nephritis once albuminuria has developed remains to be investigated.

Funding: Private Foundation Support

SA-PO383
Effect of Pioglitazone on the Shedding of Urinary Angiotensin Converting Enzyme (ACE) 2 and Nephrilysin (NEP) in db/db Mice and Their Role as Urinary Biomarkers for Diabetic Kidney Disease

Podocytes

ACE2 precedes albuminuria. Depletion of tubular renal ACE2, NEP, could lead to CKD: Risk Factors for Incidence and Progression - III

Podocytes

Angiotensin II Induces Cholesterol Accumulation and Injury in Podocytes. Treatment of Ang-II-treated podocytes with simvastatin indicated that simvastatin did not improve Ang-induced cholesterol accumulation and podocyte apoptosis.

Podocytes

Excess cholesterol induces podocyte injury.

Funding: Government Support - Non-U.S.

SA-PO385
Phosphate Nilosamide Mitigates Renal Fibrosis through Inhibiting HPK2 Expression

Xin Zhen, Xiaoyan Chang. Nanfang Hospital Southern Medical University, Guangzhou, China.

Background: Renal fibrosis is the final common pathway of all kinds of progressive chronic kidney disease (CKD). However, there are no effective therapies to prevent or slow the progression of renal fibrosis. Recently, homedomain interacting protein kinase 2 (HIPK2) has been identified as a key regulator in kidney fibrosis and idiopathic pulmonary fibrosis (IPF) that acts upstream of several major pro-fibrotic and pro-inflammatory pathways including TGF-β/Smad, Wnt/β-catenin, Notch pathway and NF-κB pathway, indicating that HIPK2 might be a potential target for anti-fibrosis therapy. Nilosamide is a Food and Drug Administration (FDA) approved oral antithemlthic drug used for treating most tapeowm infections. It has been shown that P-NICLO exerts antitumor function by targeting multiple signaling pathways including NF-κB, Wnt/β-catenin, and Notch pathways. Given the critical role of the above pathways in the pathogenesis of renal fibrosis, the aim of the present study is to explore the potential therapeutic effect of P-NICLO on renal fibrosis.

Methods: In vivo, male BALB/c mice were injected with ADR (12mg/kg). P-NICLO (30mg/kg/d) was injected 2 weeks after ADR for 3 weeks. U/M mice received intraperitoneal injection of P-NICLO (30mg/kg/d) from day 7 after operation for 7 days. In vitro, NRK-52E or HK-2 cells reached approximately 60% confluence, pre-incubated with indicated amount of P-NICLO for 1 h followed by coinoculation with recombinant TGF-β1. WT-HPK2 construct was transfected into HK-2 cells by using Lipofectamine 2000 Reagent 24 h after TGF-β1 (10ng/ml) and P-NICLO (0.4 μM) treatment.

Results: 1.P-NICLO attenuates glomerular injury and interstitial fibrosis induced by ADR. 2.P-NICLO ameliorates established renal fibrosis and interstitial inflammation induced by 3.P-NICLO inhibits multiple pro-fibrotic signaling pathways including TGF-β/Smads, Wnt/β-catenin, NF-κB and Notch pathways in vitro and in vivo 4.P-NICLO inhibits HPK2 transcription through interfering the binding of Smad3 to the promoter region of HPK2 gene to inhibit the expression of pro-fibrosis markers

Conclusions: In summary, we have shown here that P-NICLO is effective in slowing the progression of renal fibrosis. Mechanistically, P-NICLO directly attenuated the activation of multiple pro-fibrotic and proinflammatory signaling pathways through suppressing TGF-β1-induced HPK2 expression.

SA-PO386
FGF23 Promotes Progression of CKD by Directly Activating Pro-inflammatory Signaling in Renal Epithelial Cells

Olena Andrukhova1, Lukas Endler1, Birgitt Strobl1, Reinhold Erben2. 1University of Veterinary Medicine, Vienna, Austria; 2University of Veterinary Medicine of Vienna, Vienna, Austria.

Background: There is solid evidence from clinical and epidemiological studies that fibroblast growth factor 23 (FGF23) is a strong predictor of disease progression and adverse clinical outcomes in patients with chronic kidney disease. However, the mechanisms underlying the association between FGF23 and CKD progression are unclear.

Methods: To gain more insight into the signaling mechanisms induced by FGF23 in renal epithelial cells, we treated 3-month-old wild-type (WT) mice, Fgf23−/−/Vdr−/− (VDR/FGF23) and Fgf23−/−/Vdr+/− (VDR−/FGF23) as a disease model. CKD mice were characterized by high circulating concentrations of intact FGF23, activation of renal JAK/STAT signaling, and renal interstitial fibrosis, 8 weeks after 5/6-Nx. Treatment of CKD mice with low doses of neutralizing anti-Fgf23 antibody (50 μg per mouse, two times per week) over 8 weeks largely prevented CKD progression, and profoundly reduced the Jak/STAT-mediated pro-inflammatory and pro-fibrotic pathways in a Klotho independent manner.

Results: RNA-Seq analysis revealed that FGF23 treatment led to strong activation of the Janus kinase/signal transducer and activator of transcription (Jak/STAT) pathway in proximal and distal renal epithelial in a Klotho independent fashion. This unexpected and striking finding was confirmed by qRT-PCR and immunohistochemical analysis of several key pro-fibrotic and pro-inflammatory pathways. We next performed RNA-Seq analysis to identify differentially expressed genes and identified that FGF23 treated kidney upregulated IL-6, IL-8, TGF-β1, β-catenin, NF-κB, TNFα, the Notch pathway. Given the critical role of the above pathways in the pathogenesis of chronic kidney disease (CKD), elevated Ang-II levels can lead to podocyte injury. However, it has no effect on urinary NEP and KIM-1.

Conclusions: Our data is consistent with the critical role of FGF23 in the pathogenesis of chronic kidney disease (CKD) through direct activation of pro-inflammatory pathways in renal epithelial cells.
suPAR induces proteinuria in solitary functioning kidney models

Methods: SuPAR transgenic models or littermate controls. Minipumps with three different concentrations of LPS were implanted subcutaneously in B6 mice only. Proteinuria and/or suPAR were followed weekly for 4 weeks. In the HSRA spontaneous one-kidney rat model, suPAR on proteinuria development in three different rodent models of SFK.

Results: We first found that LIGHT infusion induced persistently elevated HIF-1a protein levels in endothelial cells of capillary lumen of glomeruli in the control HIF-1α−/− mice. Then we identified that LIGHT-induced HIF-1α gene expression is crucial for prolonged accumulation of HIF-1α in the endothelial cells in hypertensive CKD by inducing a series of potent vasoactive components. As such, we further found that LIGHT-induced hypoxia, proteinuria, decreased urinary osmotic pressure and renal fibrosis. Next, we found that endothelial HIF-1α gene expression was induced by LIGHT in a NF-κB-dependent manner. Finally, we discovered reciprocal positive transcriptional regulation of endothelial HIF-2α and HIF-1α genes is a key mechanism for their persistent activation and disease progression. Overall, our findings revealed that the stimulation of HIF-1α in endothelial cells is detrimental to kidney injury, hypertension and disease progression.

Conclusions: Our findings highlight early diagnostic opportunities and therapeutic approaches for hypertensive CKD.

SA-PO390

Blocking the phosphorylation of ribosomal protein S6 inhibits focal segmental glomerulosclerosis

Background: The pathogenic mechanism of focal segmental glomerulosclerosis (FSGS) remains poorly understood. Renal hypertrophy is largely mediated by phosphorylated ribosomal protein S6 (pS6), a downstream effector of the mTORC1-S6K1 pathway.

Methods: We created pS6−/− mouse models expressing non-phosphorylatable pS6 (pS6+) and generated matched wild-type littermates.

Results: pS6−/− mice were markedly increased in the renal glomeruli of both FSGS patients and ADR-induced FSGS mice. Podocyte specific pS6 hyper-phosphorylation induced by genetic deletion of Tsc1, an upstream negative regulator of mTORC1, induced striking hypertrophy of surviving podocytes and recapitulated many features of human FSGS, including podocyte loss and segmental glomerulosclerosis, which were blunted by low-dose rapamycin treatment (0.5 or 1 mg/kg). Similarly, treatment with the phosphatase inhibitor, Tautomycin, also increased p-rpS6 and significantly promoted podocyte hypertrophy.

Conclusions: pS6 hyperphosphorylation plays a key role in adaptive podocyte hypertrophy and progressive podocyte loss in response to initial podocyte injury during the development and progression of FSGS.

Funding: Private Foundation Support, Clinical Revenue Support
in renal vascular resistance (RVR) in response to mild but not severe RVP elevation. This suggested a possible mechanism. However, with greater RVP elevation, this would increase renal sympathetic nerve activity (RSNA) and that severe RVP elevation leads to vasoconstriction and diminished GFR via activation of the RAS.

### Methods
Blood pressure, RVP and RSNA were measured in anesthetized rats (300-400 g, n=25). Separately, renal arterial blood flow (RBF) and GFR were assessed in rats (n=11) supplemented with 6% NaCl (2 weeks). In all rats, following baseline, RVP was increased to 10 or 20 mmHg by partial occlusion of the left renal vein for 120 min.

### Results
RSNA was maintained in response to RVP 10 mmHg (frequency: 12.3±12.4%; amplitude: 0.06±0.2µV). RVP 20 mmHg induced a significant and sustained reduction in RSNA (-50.3±11.3%, p<0.05) and spike amplitude (-0.68±0.2µV, p<0.05). After 30 min, RVP 10 or 20 mmHg did not elicit a change in RBF (RVP 10: -0.8±0.4ml/min; RVP 20: -1.0±0.4ml/min). High salt did not alter GFR response to RVP increase (RVP 10 GFR: -0.9±0.2ml/min; RVP 20 GFR: -1.1±0.2ml/min).

### Conclusions
Mild RVP elevation sustains RSNA while severe RVP elevation suppresses RSNA and reduces recruitment of nerve fibres. High salt-suppression of the RAS abolishes RVP-induced modulation of renal hemodynamics, indicating that the RAS, rather than RSNA mediates the renal response to acute RVP elevation.

### SA-PO394

#### Alterations in Notch Signaling Pathway Activity and Its Potential Role in Kidney Damage in Carriers of APOL1 Risk Alleles

**Background:** The association between apolipoprotein L1 (APOL1) gene variations and the increased incidence of chronic kidney disease (CKD) in individuals of African ancestry has been well established. Despite their importance, little is known about how these variants contribute to renal dysfunction, and better understanding of this mechanism could yield new diagnostic and treatment options.

**Methods:** To address this shortcoming, we studied kidney tissue obtained before the development of parenchymal damage in order to identify any pathway alterations that create a milieu that promotes the later development of kidney injury. We focused on glomerular changes, given the association of APOL1 variations with several glomerular disease phenotypes. Kidney samples were stratified according to APOL1 genotype, including high risk alleles (G0G0), one risk allele (G0G1, G0G2) and two risk alleles (G1G2). Gene expression profiling was performed using Affymetrix microarrays with RNA extracted from laser capture micro-dissected glomeruli, and biological pathways that are coordinately regulated between the G0G0 and G1G2 groups were identified using Gene Set Enrichment Analysis (GSEA).

**Results:** Our data shows that genes related to the Notch signaling pathway (NSP) are significantly coordinately upregulated in the G1G2 group compared to the G0G0 group (FDR q < 0.25).

**Discussion:** Given that the NSP is already implicated in other glomerular diseases, the altered NSP activity in carriers of APOL1 risk alleles may be a precursor to future disease before overt kidney injury is apparent. This also suggests that genetic variation in APOL1 may have indirect effects on other genes relevant to glomerular function.

### SA-PO395

#### Albuminuria and Podocytopathy Induced by Podocyte-Specific Deletion of Acid Ceramidase α Subunit

**Background:** Acid ceramidase (AC) as a lysosomal enzyme has been shown to be critical in the metabolism of sphingolipids, ceramides, which regulate lysosome function and related cellular activities such as autophagy and vesicle or molecular trafficking. It remains unknown whether AC is involved in the control of podocyte function and in the development of glomerular disease. In the present study, we generated a mouse line with podocyte-specific deletion of α subunit in Asah1 gene (AC gene code in mouse), a main subunit for its activity in lysosomes using Cre-Lox recombination technology. This AC flox/podocyte Cre (Asah1fl/fl/podoCre) mouse colony was characterized by several genetic, molecular and biochemical approaches. By PCR genotyping, detection of both homozygous floxed gene Asah1 and Cre recombinase gene was considered as homozygous mice with Cre expression. If neither floxed Asah1 gene nor Cre recombinase gene was detected, mice are wild type (WT/WT). If only floxed Asah1 gene was detected without Cre recombinase gene, the mice were Asah1 flox control without Cre specific deletion (Asah1flox/WT). Immunofluorescent staining and immunohistochemistry showed that ACα was not detectable in podocytes in glomeruli of Asah1fl/fl/podoCre mice, compared to Asah1flox/WT and WT/WT mice. Although Periodic acid-Schiff staining showed no significant increase in glomerular damage index in Asah1fl/fl/podoCre mice compared with other two types of mice, there were severe proteumia and albuminuria found in Asah1fl/fl/podoCre mice even started at 6 weeks old. Correspondingly, compared Asah1flox/WT and WT/WT mice at the same ages, hypoalbuminemia and edema were observed in Asah1flox/WT and podoCre mice when they grew to 5 weeks old. Under electron microscopy analysis, Asah1fl/fl/podoCre mice showed foot process effacement, vacuolization, and microvillus formation in podocytes. In cultured mouse podocytes, we also found that inhibition of AC activity by carmofur, a selective AC inhibitor, remarkably decreased the expression of podocin. These results suggest that ACα associated metabolism of ceramide are essential for the maintenance of podocyte structural and functional integrity and that the defect or deficiency of AC expression and function may result in podocytopathy and related glomerular disease such as minimal change disease.

**Methods:**

**Results:**

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

Underline represents presenting author.

577
Sex Differences in the Exacerbating Effects of Chronic Nicotine on Angiotensin II-Induced Renal Injury

Rogério Maranon, Kiran B. Chandrashekar, Luis A. Juncos, UMMC, Brandon, MS; University of Mississippi Medical Center, Jackson, MS.

Results:

Conclusions: 

Chronic Nicotine Mediated Accentuation of Angiotensin-II-Induced Renal Injury Is Prevented but Not Readily Reversed by Sildenafil

Kiran B. Chandrashekar, Rodrigo Maranon, Arnoldo E. Lopez-Navarrete, Arany, L. A. Juncos; Dept. Pediatrics, Div. Pediatric Nephrology, UMC, Jackson, MS; 'None, Rochester, MN; 'UMMC, Brandon, MS; 'University of Mississippi Medical Center, Jackson, MS.

Conclusions: 

Sildenafil treatment was very effective at decreasing Ch-Nic mediated exacerbation of AngII-induced renal dysfunction, inflammation, injury, and pro-apoptotic and pro-fibrotic signaling while increasing HO activity. In contrast, late sildenafil decreased blood pressure, but was much less effective at improving renal parameters of injury.

Results: 

Chronic Nicotine Mediated Accentuation of Angiotensin-II-Induced Renal Injury Is Prevented but Not Readily Reversed by Sildenafil

Kiran B. Chandrashekar, Rodrigo Maranon, Arnoldo E. Lopez-Navarrete, Arany, L. A. Juncos; Dept. Pediatrics, Div. Pediatric Nephrology, UMC, Jackson, MS; 'None, Rochester, MN; 'UMMC, Brandon, MS; 'University of Mississippi Medical Center, Jackson, MS.

Background: Chronic Nicotine (Ch-Nic) exacerbates angiotensin II (AngII)-induced renal injury in murine models via various mechanisms that alter hemodynamics and oxidative stress. Because females may regulate these factors differently, and also metabolize nicotine than males, we tested whether Ch-Nic exacerbates AngII-induced renal injury in females to the same extent as in males. For this, we tested male and female Sprague-Dawley rats aged 60 days with Ch-Nic (12 mg/ml) or vehicle in drinking water, and then randomized into 4 groups each, which received either AngII (200ng/kg/min) or vehicle via SQ osmotic minipumps for an additional 28 days. Systolic blood pressure (SBP) was measured by tail-cuff plethysmography twice weekly and parameters of renal function and injury were assessed at the end of the experiments. See Table below.

Methods: 

Conclusions: 

Heterogeneity and Clinical Relevance of Tertiary Lymphoid Tissue in Murine and Human Kidneys

Yuki Sato, Peter Boor, Jürgen Flöge, Motoko Yanagita; Medical Innovation Center TMKF, Graduate School of Medicine, Kyo University, Kyoto, Japan; 'Department of Nephrology, Graduate School of Medicine, Kyo University, Kyoto, Japan; 'Institute of Pathology, RWTH University of Aachen, Aachen, Germany; 'Department of Nephrology, RWTH University of Aachen, Aachen, Germany.

Background: Unlike reversible AKI in the young, AKI in the elderly often leads to end-stage renal disease. We previously demonstrated that after AKI aged but not young mice developed multiple renal tertiary lymphoid tissues (TLTs), which comprised mainly lymphocytes and fibroblasts. These promoted aberrant inflammation and underlined the “AKI to CKD sequence”. We also showed that aged (~ 60 yrs old) but not young (4 yrs old) humans exhibited renal TLTs (Sato Y et al. JCI insight 2016). Although TLTs are closely involved in the pathophysiology of various chronic inflammatory diseases in human, the developmental stages and clinical relevance remain ill defined.

Results: 

Heterogeneity and Clinical Relevance of Tertiary Lymphoid Tissue in Murine and Human Kidneys

Yuki Sato, Peter Boor, Jürgen Flöge, Motoko Yanagita; Medical Innovation Center TMKF, Graduate School of Medicine, Kyo University, Kyoto, Japan; 'Department of Nephrology, Graduate School of Medicine, Kyo University, Kyoto, Japan; 'Institute of Pathology, RWTH University of Aachen, Aachen, Germany; 'Department of Nephrology, RWTH University of Aachen, Aachen, Germany.

Methods: 

Conclusions: 

Male SD rats were given intraperitoneal injection of fludrocortisone 2.5 mg/kg BW/day. A1, 2, 4, 6 and 72 hr, the kidney was removed and RNA was extracted for real time PCR. We also used tubule suspensions of renal cortex to test the direct effects of aldosterone. Because sildenafil can preserve cGMP levels and increase heme oxygenase activity, it may offer a novel strategy to evaluate the CKD patients and potentially improve their therapeutic approaches.

Conclusions: 

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

Underline represents presenting author.
mL/min (n=5, p<0.05) at 6 hr after the injection of fludrocortisone, but was decreased to 1.62 ± 0.43 mL/min (n=10, p>0.05) at 72 hr.

Conclusions: Aldosterone may regulate Epo production by the nephron via stimulation of a HIF2α pathway. HIF2α is regulated not only by hypoxia but also by RAS.

Funding: Commercial Support - Takeda Research Support, Government Support - Non-U.S.

SA-PO400

Current Nephrology Practices for Slowing CKD Progression – The Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps) Bene_fd Ge_reeka,1,2 Charlotte T.,1, Celine Lange,1 Lindsay Zepel,1 Danilo Fiser,6 Roberto Pecotits-Filho,1 Izzy Massy,12 Bruce M. Robinson,11 Inserm-CESP, Villejuif, France; 1Univ Paris-Saclay, Villejuif, France; 2Arbor Research Collaborative for Health, Ann Arbor, MI; 3Biomedicine Agency, La Plaine Saint-Denis, France; 4Pontifícia Universidade Católica do Pará, Parauapebas, Brazil; 5Saarland University Medical Center, Homburg/Saar, Germany; 6Ambroise Paré University Hospital, Boulogne Billancourt/Paris cedex, France. Group/Team: CKD-REIN and CKDopps.

Background: The 2012 KDIGO guideline for the management of CKD recommends several measures for preventing CKD progression, including blood pressure (BP) control, use of renin-angiotensin system inhibitors (RASi), and dietary advice. Whether these recommendations are followed in current nephrology practice is unknown.

Methods: We used baseline data from CKDopps (2013-17), a prospective cohort study of adult patients (pts) with eGFR < 60 ml/min/1.73m² from national samples of nephrology clinics in Brazil (BR), France (FR), Germany (GER), and the United States (US) to describe success rates in achieving recommended measures by albuminuria category (using either spot or 24-hour urinary albumin or protein equivalent) or eGFR, and by country

Results: Median age ranged from 67 yrs in BR to 77 yrs in GE. Albuminuria or proteinuria was routinely measured in 42%, 44%, 43% of pts in BR, GER, and the US, respectively, and 39% in FR (where this was requested per study protocol). Proteinuria was more commonly measured than albuminuria in all countries. Percentages of pts with BP <140/90 were lower at higher UAP, and higher in the US and GER than in BR and FR. RASi use did not vary by albuminuria level, but was lower at lower eGFR in BR, GER, and the US. Receiving dietary advices was slightly more common in pts with low eGFR, and better for salt than protein intake, but dietician visit was not common practice.

Conclusions: Monitoring albuminuria as recommended is not a standard practice in nephrology. BP control and RASi use vary substantially by country, and expert dietary advice remains poor across participating countries. The effects on clinical outcomes, and reported variation in incidence of kidney failure by country, will be evaluated during follow-up.

Funding: Commercial Support - CKDopps Brazil supported by AbbVie, CKDopps US by Keryx, and CKD-REIN by Amgen, Baxter, GSK, Fresenius, Lilly, MSD, Otsuka, Government Support - Non-U.S.

SA-PO401

Nomograms for Evaluating the Long-Term Prognostic Risk of IgA Nephropathy Xiangmei Chen. Chinese PLA General Hospital, Beijing, China.

Background: IgA nephropathy(IgAN) shows strong heterogeneity between individuals. The prognosis of IgAN is associated with lesions of Oxford classification and many clinical indicators. However, simple tools for evaluating the prognosis for clinicians remains limited. Our objective was to develop an intuitive estimation tool for predicting the prognosis of IgAN.

Methods: Patients with IgAN diagnosed by renal biopsy at Chinese PLA General Hospital were retrospectively analyzed. The endpoint was a decrease in estimate Glomerular filtration rate (eGFR) ≥ 0.43 U/ml (n=10, p>0.05) at 72 hr. Using COX regression coefficients, nomograms was developed to predict the risk of endpoints.

Results: In the modeling cohort, 98 among 274 patients developed into endpoints during 81 months followed- up. Nomograms was established, of which mesangial lesions, tubulointerstitial lesions as well as baseline 24hr urinary protein content>1g, baseline eGFR<90ml/min/1.73m² and baseline mean arterial pressure were included. Additional 117 IgAN patients were retrospectively followed as validation cohort at a mean of 79 months.[s1] The nomograms showed good discrimination and goodness of fit in the modeling cohort (C-index=0.86,r²=0.72) and in the validation cohort (C-index=0.89,r²=0.72) respectively.

Conclusions: The nomograms involving clinical and pathological parameters can predict the prognosis of IgAN effectively and intuitively

Funding: Government Support - Non-U.S.

SA-PO402

Impact of Inter-Laboratory Variability of Serum Creatinine Assays on KFRE Risk Scores Divvanshi Jalan,1 Elizabeth S. Lee,2 Christine P. Collier,3 Ayub Akbari,4 Christine A. White,1 Queen’s University School of Medicine, Kingston, ON, Canada; 2University of British Columbia, Vancouver, BC, Canada; 3University of Ottawa, Ottawa, ON, Canada.

Background: Inter-laboratory variation in creatinine (Cr) measurement exist and result in inter-laboratory variability in eGFR-EPI and chronic kidney disease (CKD) diagnosis. We aim to examine the impact of inter-laboratory variability in Cr measurement on the Kidney Function Risk Equation (KFRE).

Methods: Split serum samples from 33 patients with eGFR-EPI between 10 and 60 ml/min/1.73m² were sent to 12 laboratories for Cr measurement. For each patient and laboratory we calculated the 5 year risk of ESKD using the KFRE equation (KFRE-5) assuming 65 year old non-African American woman and three ACR levels (27, 266, 885 mg/g). For each patient and ACR value we calculated the KFRE-5 all method mean (AMM), coefficient of variation (CV) and range. For the cohort, we determined the mean KFRE-5 range, CV, and the mean ratio of minimum and maximum KFRE-5 scores.

Results: Figure 1 shows individual patients’ mean, minimum and maximum KFRE-5 scores (ACR 266 mg/g). There is substantial variability in KFRE scores which are more pronounced with higher albuminuria and when KFRE values are between 5% and 80% [Table 1, Figure 1].

Conclusions: Inter-laboratory variability of serum Cr measurement results in variability in KFRE scores which is more pronounced when eGFR is moderately-severely reduced and ACR is high. This needs to be considered when using KFRE cut-offs for referrals, clinical discharge, vascular access placement and suitability for CKD funding. Manufacturers need to improve assay specificity in order to reduce KFRE variability between laboratories.

Funding: Private Foundation Support

Table 1: Mean ± SD KFRE-5 range and mean/min ratios

<table>
<thead>
<tr>
<th>KFRE-5 range (mean ± SD) (CV) (%)</th>
<th>ACR 27 mg/g</th>
<th>ACR 266 mg/g</th>
<th>ACR 885 mg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>KFRE-5 range (mean ± SD) (%)</td>
<td>2.7 ± 2.4</td>
<td>6.2 ± 4.5</td>
<td>8.4 ± 5.7</td>
</tr>
<tr>
<td>KFRE-5 (mean ± SD) (%)</td>
<td>20.4 ± 3.3</td>
<td>59.9 ± 31.1</td>
<td>90.0 ± 27.4</td>
</tr>
<tr>
<td>KFRE-5 (mean ± SD) (%)</td>
<td>3.4 ± 1.2</td>
<td>3.3 ± 1.2</td>
<td>2.3 ± 1.2</td>
</tr>
</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
SA-PO403

GFR Measurement Method: A Critical Determinant in Estimation Equation Assessment Céline M. Allen,1 Ayub Akbari,2 Greg A. Knoll,2 Christine P. Collier,1 Christine A. White,1 Queen’s University, Kingston, ON, Canada; 2University of Ottawa, Ottawa, ON, Canada.

Background: Multiple equations exist to translate various serum analyte concentrations into estimates of the glomerular filtration rate (eGFR). Validation studies of these estimates often yield differing results. This is likely the result of differing patient populations and characteristics, analytic assay manufacturer biases, and GFR measurement protocols. This study aimed to examine the impact of GFR measurement methodology on the performance of the creatinine CKD-EPI equation (eGFRCr-EPI).

Methods: Cr was measured and eGFRCr-EPI calculated in 85 research subjects. GFR was measured (mGFR) simultaneously using different methodologies: renal inulin clearance, plasma 99mTc-DTPA clearance (2-4 hour clearance) and plasma iohexol clearance (2-10 hour sampling). For each method, bias (eGFR - mGFR), precision (standard deviation of mean bias) and accuracy (P30-the percent of all eGFRCr-EPI within 30% of the mGFR) were determined. Bias and accuracy were compared using paired t-tests and McNemar’s test respectively.

Results: Mean age 60 ± 14 yrs, mean BSA 1.98 ± 0.30 m², 95% non-black and 40% female sex. Mean inulin GFR 39.3 ± 28.8 ml/min/1.73m² while mean eGFRCr-EPI was 38.7 ± 28.5 ml/min/1.73m². Performance results are shown in Table 1.

Conclusions: eGFRCr-EPI performance results differ significantly depending on how GFR is measured (tracer, clearance strategy and sample timing). Short-plasma-based strategies yield the highest biases and worse accuracies for the eGFRCr-EPI equation. These discrepancies need to be considered when interpreting validation data and designing validation studies.

Funding: Government Support - Non-U.S.

Table 1: eGFRCr-EPI performance by GFR methodology

<table>
<thead>
<tr>
<th>Method</th>
<th>Bias (mGFR- eGFRCr) (±SDmmol/min/1.73m²)</th>
<th>Precision (SD of mean bias) (±SDmmol/min/1.73m²)</th>
<th>Accuracy (P30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal inulin</td>
<td>0.5</td>
<td>0.5</td>
<td>78</td>
</tr>
<tr>
<td>Plasma 99mTc-DTPA (2-4 hr)</td>
<td>8.8 ± 3.3</td>
<td>13.6</td>
<td>57 ± 6</td>
</tr>
<tr>
<td>Plasma iohexol (2-10 hr)</td>
<td>-5.9 ± 4.6</td>
<td>11.4</td>
<td>59 ± 6</td>
</tr>
</tbody>
</table>

* p = 0.0001 compared to inulin, ** p = 0.08 (NS) compared to inulin, ▲ p = 0.0012 compared to inulin, ▲ p = 0.06 compared to inulin

SA-PO404

The Spectrum of CKD in China: A National Study Based on 64.7 Million Hospitalized Patients from 2010 to 2015 Yu-ming Huang,1 Damin Xu,3 Jianyan Long,1 Ying Shi,1 Luxia Zhang,3 Haibo Wang,1 Adera Levin,1 Ming Hui Zhao,2 China Standard Medical Information Research Center, Shenzhen, China; 2St. Paul’s Hospital and University of British Columbia, Vancouver, BC, Canada; 3Renal Division, Peking University First Hospital, Beijing, China.

Background: Chronic kidney disease (CKD) is a significant public health burden worldwide. Previous studies demonstrated that diabetes and hypertensive kidney disease became the leading cause of CKD in China, but the transition of other causes was still unclear.

Methods: We utilized a national in-patients database covering 878 class 3 hospitals (which provide primary, secondary and tertiary care to nationwide patients) and involving 64.7 million adult patients from 2010 to 2015. The specific causes of CKD were extracted from International Classification of Diseases-10 codes of discharge diagnoses.

Results: Altogether 4.5% of hospitalized patients (1.8 million) were identified as having CKD, with an annual incidence rate from 2010 (3.7%) to 2015 (4.7%). Increasing trends of diabetic kidney disease and hypertensive kidney damage were observed from 2010 to 2015, especially for northern urban areas. The percentage of obstructive nephropathy also increased gradually and constituted an important cause of CKD for southern rural residents.

Conclusions: The spectrum of etiologies of CKD is changing in China, and varies over time and geographic regions.

Funding: Other NIH Support - the World Health Organization (WHO Reference 2014/435380-0); the National Key Technology R&D Program of the Ministry of Science and Technology (2011BAI10B01); the Beijing Science and Technology Committee (D131100004713007); and the University of Michigan Health System-Peking University Health Science Center Joint Institute for Translational and Clinical Research (BMU20140479), Government Support - Non-U.S.

SA-PO405

Regional Differences in Prevalence and Determinants of CKD among Individuals with Hypertension in Rural Communities in South Asia Liang Feng, Tazeen H. Jafar. Duke-NUS Medical School, Singapore, Singapore.

Background: The objectives of the study were to determine the regional burden and differences in prevalence and determinants of chronic kidney disease (CKD) in rural Bangladesh, Pakistan, and Sri Lanka.

Methods: We conducted a cross-sectional study on 2349 participants aged ≥40 years with hypertension in 30 randomly selected rural communities, 10 each in Bangladesh, Pakistan, and Sri Lanka. The primary outcome was CKD defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m² estimated by CKD Epidemiology Collaboration (CKD-EPI) or urinary albumin to creatinine ratio ≥ 30 mg/g.

Results: The mean (SD) age of participants was 58.8 (11.3) years, and 36% were men, 27% had diabetes, and 10% were current smokers. The age-standardized prevalence (95% CI) of primary outcome of CKD was 38.4% (34.1 to 42.8%) in Bangladesh, 19.1% (15.7 to 22.5%) in Pakistan, and 49.8% (45.1 to 54.6%) in Sri Lanka. The factors independently associated with CKD were older age (OR=1.06,95%CI(1.03,1.09) for every 1 year increase), diabetes (OR=2.03,95%CI(1.03,2.25)), elevated systolic blood pressure (OR=1.06,95%CI(1.04,1.09)), per 5 mm Hg increase, current vs non-smoker.
Prevalence of CKD in the Healthy Elderly Using the Aspirin in Reducing Events in the Elderly (ASPREE) Study Cohort

**Table 1. Crude prevalence of CKD (n=2349)**

<table>
<thead>
<tr>
<th>Country</th>
<th>CKD Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>23.4%</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>18.4%</td>
</tr>
<tr>
<td>Pakistan</td>
<td>22.6%</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>24.2%</td>
</tr>
</tbody>
</table>

**Results:**

The prevalence of CKD in this healthy elderly population was 19%, substantially higher than the prevalence of 9.5% reported in the next closest country.

**Conclusions:**

CKD is common among individuals with hypertension in rural South Asia with alarmingly high rates of reduced kidney function in Sri Lanka. Our findings underscore the urgency of addressing the key determinants of CKD, and establishing CKD detection and management programs as a public health priority in the South Asian region.

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

**SA-PO406**

Prevalence of CKD in the Healthy Elderly Using the Aspirin in Reducing Events in the Elderly (ASPREE) Study Cohort

**Background:** The diagnosis & definition of CKD in the elderly is controversial. GFR declines with age such that reduced eGFR is common in the elderly but may not reflect true underlying kidney related disease. The ASPREE study is an international (Australia, US, United Kingdom), 15,588 subjects (15,588 Australia, 2,343 USA) had complete data from baseline to follow-up. Estimated GFR was calculated using each 3 equations: MDRD, CKD-Epi and CKD-Epi Cr. Our

**Results:**

CKD prevalence was calculated using each equation and compared. Predictors of CKD were assessed by logistic regression.

**Conclusions:**

CKD prevalence was calculated using each equation and compared. Predictors of CKD were assessed by logistic regression. The elderly-specific GFR equation BIS1 doubled the prevalence of CKD with the majority reclassified from stage 2 to stage 3a CKD.

**Funding:** Other NIH Support - National Institute on Aging and National Cancer Institute

**SA-PO407**

A Comparison of Different Equations for Estimating GFR in 29 US Health Care Organizations

**Background:** The KDIGO 2012 guidelines recommend reporting eGFRcreat in adults using the 2009 CKD-EPI creatinine equation to diagnose and stage CKD with known risk relationships. Some health care organizations use different equations, with common alternatives being the MDRD and Mayo Clinic Quadratic (MCQ). Electronic health record (EHR) data provide the opportunity to estimate the impact of using these three common equations to estimate GFR to a health care organization and its patient population.

**Methods:** This study uses EHR data from 29 AMGA member organizations who are using the Optum One population health analytics platform. Data from 2.3 million patients age 18-90, with a history of hyperglycemia, at least 1 ambulatory office visit and a serum creatinine recorded between 01/01/2013 and 12/31/2016 were included. Estimated GFR was calculated for each patient using the CKD-EPI, MDRD, and MCQ equations.

**Results:** The 2.3 million patients had mean age 62.3 years, were 52.8% female, 10.7% black race, and 51.1% had a diagnosis of type 2 diabetes (on a claim or the patients problem list in the EHR). The average (standard deviation) eGFR from the CKD-EPI, MDRD, and MCQ equations were 77.4 (25.4), 76.3 (28.9), and 88.8 (25.4) ml/min/1.73 m², respectively. Distributions of eGFR for the three equations differed markedly (Figure 1). In the CKD G3+ range (<60 ml/min/1.73m²) the MCQ estimates gave a much lower prevalence compared to the CKD-EPI and MDRD equations (23.2 and 24.8 vs. 12.7%, summing the prevalence in range below 60 in Figure 1). Only 48.7% of patients were classified in the same CKD GFR categories with all three equations.

**Conclusions:** Compared to the CKD-EPI equation which is currently recommended and stages CKD with a known relationship to risk, the MDRD equation produces similar results at low eGFR, while the MCQ equation yields a dramatically lower prevalence of CKD.

**Funding:** Private Foundation Support

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

781
Comparison of eGFR with Creatinine and Cystatin C by eCKD-EPI in CKD Patients with and without Hypoalbuminemia

Background: Serum cystatin C (CysC) could be a better predictor than serum creatinine (Cre) in comorbid patients with CKD. Differences between CysC and Crea eGFR in patients with and without hypoalbuminemia (hypoA) were poorly understood.

Methods: We estimated GFR by the new CKD-EPI equations based on CysC and Crea. The CKD stage was determined by the Crea-based eGFR. HypoA was defined by serum albumin ≤3.5 g/L. In each CKD stage, differences between average of CysC and Crea-based equation and concordance to assign the same CKD stage were calculated.

Results: We included 1054 patients (64.5% female) aging 63±18 years. 50.9% were elderly. Mean Cre was 143.4±48 µmol/L and CysC was 3.52±1.05 g/L. In each CKD stage, differences between mean eGFR of CysC and Crea were poorly understood.

Conclusions: Differences between CysC and Crea-based equation could be affected in the setting of low serum albumin values. Patients with hypoA showed higher differences.

SA-PO409

Estimated Glomerular Filtration Rate by Serum Creatinine Lacks Accuracy and Precision in Older Adults with and without Type 1 Diabetes:

Results: The prevalence of chronic kidney disease (CKD) in the elderly is high. Serum cystatin C (CysC) can be a better predictor than serum creatinine (Crea) in comorbid patients with CKD. Differences between CysC and Crea eGFR in patients with and without hypoalbuminemia (hypoA) were poorly understood.

Methods: We estimated GFR by the new CKD-EPI equations based on CysC and Crea. The CKD stage was determined by the Crea-based eGFR. HypoA was defined by serum albumin ≤3.5 g/L. In each CKD stage, differences between average of CysC and Crea-based equation and concordance to assign the same CKD stage were calculated.

Results: We included 1054 patients (64.5% female) aging 63±18 years. 50.9% were elderly. Mean Cre was 143.4±48 µmol/L and CysC was 3.52±1.05 g/L. In each CKD stage, differences between mean eGFR of CysC and Crea were poorly understood.

Conclusions: Differences between CysC and Crea-based equation could be affected in the setting of low serum albumin values. Patients with hypoA showed higher differences.

Reference:
1. Varela, Federico Carlos; Varela, Graciela; Jimenez, Griselda; Bratti, Maria L.; Ocampo, Gustavo; Grez, Guillermo; Dios, Rosa. *Nephrology*. Hospital Italiano de Buenos Aires, CABA, Argentina; *Nephrology*. Hospital Italiano Buenos Aires, CABA, Argentina.

SA-PO410

Estimated Glomerular Filtration Rate by Serum Creatinine Lacks Accuracy and Precision in Older Adults with and without Type 1 Diabetes:

Methods: Sixty-six adults with at least 50 years of age/sex-matched subgroups (65% male and 35% female) were underalcoholized with a mean age of 60.9±20.7 years. The prevalence of chronic kidney disease (CKD) in the elderly is high. Serum cystatin C (CysC) can be a better predictor than serum creatinine (Crea) in comorbid patients with CKD. Differences between CysC and Crea eGFR in patients with and without hypoalbuminemia (hypoA) were poorly understood.

Methods: We estimated GFR by the new CKD-EPI equations based on CysC and Crea. The CKD stage was determined by the Crea-based eGFR. HypoA was defined by serum albumin ≤3.5 g/L. In each CKD stage, differences between average of CysC and Crea-based equation and concordance to assign the same CKD stage were calculated.

Results: We included 1054 patients (64.5% female) aging 63±18 years. 50.9% were elderly. Mean Cre was 143.4±48 µmol/L and CysC was 3.52±1.05 g/L. In each CKD stage, differences between mean eGFR of CysC and Crea were poorly understood.

Conclusions: Differences between CysC and Crea-based equation could be affected in the setting of low serum albumin values. Patients with hypoA showed higher differences.

Reference:
1. Varela, Federico Carlos; Varela, Graciela; Jimenez, Griselda; Bratti, Maria L.; Ocampo, Gustavo; Grez, Guillermo; Dios, Rosa. *Nephrology*. Hospital Italiano de Buenos Aires, CABA, Argentina; *Nephrology*. Hospital Italiano Buenos Aires, CABA, Argentina.
SA-PO413
A Novel Equation Using Low-Invasive Test Items to Estimate the Severity of Interstitial Fibrosis in IgA Nephropathy
Keita Inui,1 Kosuke Yamaka,1 Yusuke Yamada,1 Yuji Kamijo,2 Shishu University, Matsumoto, Japan; 2Shishu University School of Medicine, Matsumoto, Japan.

Background: In IgA nephropathy, tubulointerstitial fibrosis is said to be very important in predicting whether or not renal dysfunction is progressive. Until now, however, invasive renal biopsy has been the primary means of determining the severity of fibrosis in IgA nephropathy. A formula to estimate tubulointerstitial fibrosis severity using such low-invasive parameters as physical findings, serology, and urinalysis is therefore needed.

Methods: Masson Trichrome-stained renal biopsy specimens of 51 patients diagnosed as having IgA nephropathy at Shinsu University Hospital were collected. The severity of interstitial fibrosis as calculated by the percentage of area stained blue in the cortex tubulointerstitium (Fib%) was quantitatively measured by ImageJ analysis software (Figure) and its correlation with various factors was examined. A formula for estimating interstitial fibrosis was then derived by multiple regression analysis using parameters whose correlation with Fib% was strong.

Results: Fib% increased proportionally to Oxford classification T-score (P<0.001) and accurately reflected the severity of interstitial fibrosis. Fib% also correlated strongly with serum creatinine (sCr) (mg/dL) (correlation coefficient R²: 0.61, P<0.01), urinary N-acetyl-β-D-glucosaminidase (uNAG) (U/gCre) (R: 0.44, P<0.01), and body mass index (BMI) (kg/m²) (R: 0.44, P<0.01). The estimation formula of Fib% from these 3 parameters was determined as: Fib% = 16.84 + 17.15(sCr) + 0.51(BMI) + 0.59(uNAG) (correlation coefficient of determination R²: 0.70). The correlation coefficient of determination R²: 0.70.

Conclusions: Interstitial fibrosis in IgA nephropathy can be estimated using data obtained from low-invasive tests. A prospective study is being planned to validate our novel formula.

SA-PO414
Prediction of Urinary Creatinine Excretion and of Renal Function in CKD Patients from Body Composition Analysis
Carlo Donadio, University of Pisa, Pisa, Italy.

Background: The utility of creatinine clearance (CCr) to measure renal function is greatly reduced by its low accuracy and by the need for a timed collection of urine. Different formulas have been proposed to predict CCr or GFR from serum creatinine. However, the validity of these formulas is greatly reduced by their low accuracy and by the need for a timed collection of urine.

Methods: In a total of 692 participants (age: 56±13 years, BMI: 26±4 kg/m²), 24-hour urinary creatinine (UCr) excretion was measured by an automated analyzer (Beckman Coulter, Brea, CA) and its determinants were BCM, age, and PCr. UCr predicted from MR equation (MR-BCM-CCr) and UCr predicted from C&G equation (C&G-CCr). Regression analysis was performed to correlate the determined parameters with MR-BCM-CCr and with C&G-CCr.

Results: Between MR-BCM-CCr and mCCr was better than that of C&G CCr. 32.1 mL/min, NS), with a closer correlation than C&G CCr (r=0.61, NS). The most relevant determinant of UCr was BCM, age, and PCr. UCr predicted from MR equation (MR-BCM-CCr) and UCr predicted from C&G equation (C&G-CCr) were strongly correlated with 24h-UCr and BCM (r=0.780). Multiple linear regression (MR) modeling was used to find the best correlation between 24h-UCr and BCM (r=0.780), which was closer than that between 24h-UCr and BW (r=0.626). The correlation coefficient of determination R²: 0.70.

Conclusions: In CKD patients at the different stages of GFR impairment, urinary creatinine excretion can be more accurately estimated, and creatinine clearance can be predicted from the value of body cell mass combined with anthropometric data and with serum creatinine.

Funding: Government Support - Non-U.S.

SA-PO415
Usefulness of Repeated Measurement of Casual Urine Sodium-to-Potassium Ratio in Patients with CKD
Yuka Okuyama,1 Haruhito U. Uchida,1 Toshiyuki Iwahori,1 Hiidemi Takeuchi,2 Nozomo Otaka,3 Masashi Kitagawa,4 Hitoshi Sugiya4, Katsuyuki Miura,5 Hirotsugu Ueshima and EPOCH-JAPAN Group,6 Jun Manaka,7 Okayama University, Okayama, Japan; 2Okayama University School of Medicine, Okayama, Japan; 4Okayama University Graduate School, Okayama, Japan; 5Shiga University of Medical Science, Otsu, Shiga, Japan.

Background: Lowering sodium-to-potassium ratio has been reported to benefit people for hypertension prevention and control in epidemiological studies. Four to seven repeated measurements of casual urine sodium-to-potassium ratio is known to provide high correlation and good agreement quality with less bias to estimate 7-day 24-hour urinary Na/K ratio in normotensive and hypertensive individuals. However, little is known about urinary Na/K ratio in patients with chronic kidney disease (CKD). The aim of this study was to clarify the relationship of the repeated measurement of casual and 24-hour urinary sodium-to-potassium ratio in patients with CKD.

Methods: A total of 61 inpatients with CKD in stages 1-3 (eGFR ≥ 30 ml/min/1.73m²) was recruited in Okayama University Hospital. Na/K ratio in casual urine at 4 points/day (first void after rising, each urine after breakfast, lunch or dinner) for 2 days and 2-day 24-hr urine at the same day were measured. Correlation and the quality of agreement by Bland and Altman between casual urine and 24-hour urine samples were analyzed.

Results: Mean 24-hour Na and K excretion was lower in participants in stage 4-5 (Na: 99.0 mmol/24h, K: 26.1 mmol/24h), whereas mean 24 hour Na/K ratio was higher in participants in stage 4-5 (5.1) than in participants in stage 1-3 (4.1). Casual urine Na/K ratio was strongly correlated with 24-24-day 24-hour urinary Na/K ratio by sampling 2 casual urine specimens per day for 2 days in participants in stage 1-3 (r = 0.49-0.78), but not in stage 4-5 (r = 0.12-0.19). The bias for mean Na/K ratio between 24-hour urine and 24-hour casual urine for the 2 days 2-days 24-hour urine per day in participants in stage 1-3 ranged from -0.86 to 0.16, and the quality of agreement for the mean of this casual urine sampling was similar to that of all 8 points of casual urine samples for estimating 2-day 24-hour values.

Conclusions: Repeated casual urine Na/K ratio measurement is useful to estimate 24-hour urine Na/K ratio in stage 1-3 CKD patients as well as normotensive and hypertensive people; however, not in stage 4-5 CKD patients.

SA-PO416
Metabolic Syndrome, Inflammation, and Risk of Developing CKD in Rheumatoid Arthritis
Masako Kochi, Kentaro Kohagura, Yusuke Ohya. University of the Ryukyus, Nishihara-cho, Japan.

Background: Inflammation is a risk factor for progression of CKD in patients with rheumatoid arthritis (RA) as well as general population. High incidence of metabolic syndrome (MetS) has been reported in RA. MetS is associated with both inflammation and developing CKD. However, the combined effects of MetS and inflammation on the risk of developing CKD are not known in RA. This study aims to examine the relationship between MetS, C-reactive protein (CRP; a marker of inflammation), and the incidence of CKD in RA patients.

Methods: We retrospectively examined a total of 345 RA patients. The outcome of interest was incidence of CKD which was defined as an eGFR<60 ml/min/1.73 m² and/ or positive dipstick testing for proteinuria for ≥3 months. MetS was defined as the presence of ≥3 of the following criteria: obesity, hypertriglyceridemia, high low-density lipoprotein cholesterol, high blood pressure, and high fasting glucose level. CRP was used as an inflammation marker, and a high CRP was defined as persistently CRP value of >3 mg/L during the first 6 months of follow-up. Patients were categorized into four subgroups by the presence of MetS and high CRP at baseline: non-MetS with low CRP, non-MetS with high CRP, MetS with low CRP, and MetS with high CRP.

Results: Mean baseline patient age was 57 years, and mean eGFR was 87 ml/min/1.73 m². Over a median follow-up of 8 years, 47 (14%) patients developed CKD. MetS and high CRP were independently associated with the incidence of CKD. Subgroup analysis showed that the cumulative incidence of CKD was the highest in patients with MetS / high CRP group compared with all other groups (P < 0.0001, log-rank test). In a multivariate analysis, MetS / high CRP group was significantly associated with increased risk for incident CKD (adjusted HR, 5.35; 95% confidence interval, 2.27–12.71; P < 0.0001, log-rank test). In a multivariate analysis, MetS / high CRP group was significantly associated with increased risk for incident CKD.

Conclusions: Independent of confounding factors, MetS had an inflammation-augmented association with increased risk of incident CKD in patients with RA.
SA-PO417

Association of Estimated Glomerular Filtration Rate and Gestational Complications Sehoon Park,1,2 Ho Jun Chim,1 Ki Young Na,1 Dong Ki Kim,2 Yon Su Kim,2 Hajoeong Lee.1 1Seoul National University Bundang Hospital, Seongnam, Republic of Korea; 2Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea.

Background: Glomerular filtration rate elevation represents the intrarenal hemodynamic changes in pregnant women, yet, estimated glomerular filtration rate (eGFR) during gestation and its association with pregnancy outcomes remains to be investigated.

Methods: We collected pregnancy cases in two tertiary teaching hospitals in Korea from 2001 to 2015. With eGFR during pregnancy, estimated by CKD-EPI method, we calculated time-averaged eGFR considering the value as a time-dependent variable. Adverse pregnancy outcome was the composition of preterm birth, low birth weight and preeclampsia.

Results: Among total of 12,900 mothers, a number of 4,028 (31.2%) mothers experienced composite adverse pregnancy outcomes. Gestational eGFR showed a non-linear U-shaped association with the risk of gestational complication, which was most prominent with the midterm eGFR values. The adjusted odds ratio (aOR) and associated 95% confidence interval of an adverse pregnancy outcome for eGFR levels below and above the reference level of 120–150 mL/min/1.73 m² were as follows: 1.150 mL/min/1.73 m², aOR 1.86 (1.56–2.22), P<0.001; 90–120 mL/min/1.73 m², aOR 1.18 (1.06–1.31), P=0.003; and 60–90 mL/min/1.73 m², aOR 1.72 (1.12–2.65), P=0.014. Moreover, gestational eGFR additively elevated power to predict gestational complications [AUROC with eGFR 0.733 (0.717-0.740) vs AUROC without eGFR 0.728 (0.722-0.744), P for AUROC comparison = 0.006].

Conclusions: We demonstrated a non-linear, U-shaped relationship between eGFR during gestation and the risk of adverse pregnancy outcome. Appropriate interpretation of eGFR values in pregnancy might be helpful for risk prediction of gestational complications.

SA-PO419

Oral Iron Therapy and Serum Hepcidin in Children with CKD Ameneh Amini,1,2 Richa Gautam,2 Eduardo M. Perelson,2 Stefano Rivella,1 Mary E. Choi,2 Juli Kim,2 Oleh M. Akchurin,2 Chirag Patel.1 1Children’s Hospital of Philadelphia, Philadelphia, PA; 2Weil Cornell College of Medicine, New York, NY.

Background: Hepatic peptide hepcidin, a major regulator of iron homeostasis, is up-regulated in adults and children with chronic kidney disease (CKD). Hepcidin blockade ameliorates renal anemia in experimental CKD. Iron and inflammation contribute to hepcidin over-production in animal models and in adult patients with CKD. However, the relationship between oral iron therapy and hepcidin in children with CKD has not been characterized.

Methods: Cross-sectional single center study. Serum hepcidin was measured by ELISA (Intrinsic Lifesciences, USA). Clinical data were abstracted from medical records of children with stages 2-5 CKD. Platelet-to-lymphocyte ratio (PLR) was used as a marker of inflammation. Glomerular filtration rate (GFR) was estimated using the Schwartz formula. Normally distributed data are shown as mean±SD. T-test and linear regression were used for data analysis.

Results: Hepcidin was measured in 36 children (60% males, median age 12.5). Hepcidin levels were higher in girls compared with boys (median, 18.3 vs. 10.6 pg/mL, p=0.015). There was a trend toward correlation between hepcidin and hemoglobin (r=0.29, p=0.05) and with total iron binding capacity (TIBC) (r=0.43, p=0.005) and with gestational age (r=0.43, p=0.005). There was a trend toward correlation between hepcidin and hemoglobin (r=0.29, p=0.05). No correlation was observed between serum hepcidin and PLR (r=0.1). Oral iron therapy was prescribed to 14 children (Fe²⁺ group) and not prescribed to 22 (Fe³⁺). GFR was 34.6 and 47.4 mL/min/1.73m² in the Fe²⁺ and Fe³⁺ groups, respectively (p=0.03). Fe³⁺ group had a lower hepcidin compared to Fe²⁺ group (11.7±1.3 vs. 13.6±2.0, p=0.04), but similar serum iron, ferritin, TIBC, and transferrin saturation. Serum hepcidin was higher in the Fe²⁺ group than in Fe³⁺ group (94.6±41 ng/mL vs. 44.7±88, p=0.015). This difference remained significant after adjusting for age, sex, CKD etiology (glomerular vs. non-glomerular) and PLR (adjusted p=0.017) and was attenuated after additional adjustment for GFR (adjusted p=0.03).

Conclusions: In this pediatric CKD cohort, serum hepcidin levels were associated with iron therapy status, independently of PLR. Additional analyses of inflammatory markers in this cohort are ongoing. Further investigations of the impact of iron-mediated hepcidin elevation on clinically relevant outcomes in children with CKD are warranted.

SA-PO420

Assessment of Renal Impairment on the Prognosis of Newly Diagnosed Multiple Myeloma Veronica T. Costa e Silva,1 Elsa J. Costalonga,1 Marcella M. Frediani,1 Renato A. Caires,2 Fernanda O. Coelho,2 Estefany A. A. Burdam,2 Antonio A. Portela Silva,2 Adriel G. B. FHC-FM/USP, São Paulo, Brazil; 3Saint Joseph’s Hospital, University of Sao Paulo, São Paulo, Brazil; 4USP, São Paulo, Brazil; 5University of São Paulo School of Medicine, São Paulo, Brazil; 6University of São Paulo School of Medicine, São Paulo, Brazil.

Background: Severe Renal Impairment (RI) is associated with early death in patients (pts) with multiple myeloma (MM). The new criteria from the International Myeloma Working Group (IMWG) defined RI as serum creatinine (Scr) ≥ 2.0 mg/dL or estimated glomerular filtration rate (eGFR) < 40 mL/min/1.73 m². If these definitions are associated to overall survival (OS) is still debatable.

Methods: All pts with newly diagnosed MM (up to three months) admitted for treatment at the Hematology Outpatient Service from the Sao Paulo State Cancer Institute, between February 2012 and January 2014, were prospectively followed. Exclusion criteria were: age < 18 years; pts on maintenance dialysis; follow up < 3 months. Chronic Kidney Disease (CKD) was diagnosed as eGFR < 60 mL/min/1.73 m². GFR was estimated by the CKD Epidemiology Collaboration formula. International Staging System (ISS) relied on serum albumin (Alb) and β₂-microglobulin (ß2M).

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

784
Results: One hundred twenty pts were enrolled. Pts characteristics were age 62.02 ± 11.2 years, 56.2% male. MM type was IgG kappa in 59% of cases and 21% of pts had light chain MM. The clinical stages included Durie-Salmon stage III (DS-III) in 81% and ISS stage III (ISS-III) in 30% of pts. Serum exams were: 43% hemoglobin (Hb) < 10 g/dL; 14.3% total calcium (CaT) > 11 mg/dL; 39.2% SAA < 3.5 g/dL; 54.5% BSM = 3.5 mg/L; 18.3% lactate dehydrogenase (LDH) > normal value. At the moment of enrollment, SCR was 1.05 (0.74 – 1.43) mg/dL and eGFR was 69.8 (42.7 – 97.1) ml/min/1.73 m2. Thirteen percent of pts had RI with SCR > 2.0 mg/dL. CKD stage 3 was detected in 43% pts. Overall survival (OS) was 3.70 (1.97 – 4.44) years. No pts characteristics, CaT, Hb or DS-III stage were related to reduced OS. Neither was RI (P=0.31) or eGFR < 40 ml/min/1.73 m2 (P=0.19). Conversely, CKD stage 3 was associated to reduced OS (3.26 [1.56 – 4.41] vs 3.72 [2.69 – 4.96] years, P=0.032) as well as ISS-III (P=0.022). On Cox regression model, only BSM = 3.5 mg/L (Hazard Ratio: 2.14 [1.03 – 4.42] and LDH > normal value (Hazard Ratio: 2.74 [1.45 – 5.18]) were associated with lower OS.

Conclusions: Currently used KDIGO CKD definitions seem to be superior than the new IMWG criteria to assess the impact of RI on the prognosis of newly diagnosed MM pts.

SA-PO421

Results from the Cross-Sectional Evaluation of Clinical Symptoms and Epidemiologic Parameters in Patients with TMA, Differentiated Results from the Cross-Sectional Evaluation of Clinical Symptoms

Background: Atypical hemolytic uremic syndrome (aHUS), thrombotic thrombocytopenic purpura (TTP) and HUS caused by Shiga toxin-producing Escherichia coli (STEC-HUS) are diseases with thrombotic microangiopathy (TMA) and similar clinical presentations. Epidemiological data on TTP and aHUS in Germany are lacking.

Methods: CESAR is a German prospective, multicenter, cross-sectional, epidemiological study of the relative incidences (RI) of UHUS, TTP and STEC-HUS in patients (pts) presenting with TMA. ADAMTS13 activity and presence of STEC were tested. Treating clinicians diagnosed pts as either aHUS, TTP, STEC-HUS or “other”.

Results: From 04/2014 to 03/2017, 232 pts were enrolled in 22 German centers. RIs and clinical data are shown in the table. 104 (74%) pts with AHUS had at least one complement-amplifying condition.

Conclusions: aHUS was the most common diagnosis in pts with clinical TMA. Less frequent differential diagnoses including TTP should be rapidly ruled out through specific diagnostic tests. Pts with aHUS or STEC-HUS were less thrombocytopenic and experienced more severe acute kidney injury than pts with TTP.

Funding: Commercial Support - Alexion Pharma Germany GmbH

SA-PO423

Evolution of HIV-Associated Glomerulonephritis with Treatment and Time: A Study of Serial Biopsies

Background: At the spectrum of HIV-associated glomerular disease is well described, the impact of treatment on evolution of these diseases, both clinically and histologically, is less clear. In the era of widespread antiretroviral therapy (ART) use, many patients with renal disease will be identified and investigated after a period of suppressed viral replication, potentially complicating interpretation of the renal biopsy. Serial biopsies are rarely performed so histological progression is as yet not well understood. Our aim was to examine the histologic evolution of HIV-associated glomerular disease with time and improvement through study of patients who had undergone serial kidney biopsies.

Methods: Patients with HIV and serial biopsies were identified through local database searches in two UK renal units. Patients whose first biopsy was considered non-diagnostic (n=2) were excluded. Histology data was obtained from structured departmental reports; all repeat biopsies had been reported with reference to the initial biopsy. Clinical data and drug treatments were obtained by review of notes and pathology databases.

Results: 13 patients with glomerular disease and serial biopsies were identified (n= HIV-associated nephropathy (HIVAN)=3, immune complex kidney disease (ICKD)=6, IgA nephropathy=4). Typical collapsing glomerulopathy was not identified on the second biopsy of any patient with HIVAN, all of whom had received ART in the intervening period. 3 patients with ICKD had cellular segmental lesions with crescents in their index biopsy; all had resolved on serial biopsy leaving segmental sclerosis (n=2, both received ART and hyperplasia (n=1, received steroids). Glomerular appearances showed no improvement on serial biopsy in IgA patients; 1 patient with crescentic IgA showed no improvement on 2 serial biopsies despite robust control of viral replication.

Conclusions: In this small and unique study, it was demonstrated that the morphology of established HIV-associated glomerular disease can change over time. Healed segmental proliferative lesions in ICKD may simulate ‘primary’ FSGS, while typical collapsing glomerulopathy in HIVAN may be reversed, or obscured by glomerular obsolescence. On the other hand, viral control did not impact on histological activity of HIV-associated IgA.

SA-PO424

Performance of a Pure Metabolite Panel Estimate of GFR

Background: We showed that panels of metabolites can provide an accurate estimate of glomerular filtration rate (GFR) without creatinine and demographic characteristics. We present a Laboratory Developed Test (LDT) to estimate GFR (accuGFR) and estimate intrapatient variability in subgroup analyses. GFR estimation by our panel was shown to be accurate. Study Population: GFR measurements (mgFR) on 3,236 individuals in the AASK, MDRD, AGES and the CRISP studies were divided randomly into a development sample (50%) and validation samples (25% complete, 25% unused backup).

Methods: Laboratory Methods: Stored (-70°C) serum specimens were subjected to targeted UPLC-mass spectrometry assays for 4 metabolites and serum creatinine (CV <5%). Data Analysis: accuGFR estimated using linear regression of log mgFR on log metabolites in the development sample. Performance measured using large errors (1-P30

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

Underline represents presenting author.
and 1-P20, the percentage of estimates deviating from the mGFR by >30% and >20%

Results: mGFR spanned a wide range (mean 55, SD 26 ml/min/1.73m²). accuGFR based on 4 metabolites without demographics had substantially better accuracy than eGFRcre and eGFRcys but similar performance to eGFRcre-cys in the accuGFR development and validation samples. In subgroups where there is concern that eGFRcre may be inaccurate, accuGFR often outperformed even eGFRcre-cys, particularly for 1-P20.

Conclusions: accuGFR based on four metabolites without serum creatinine or demographics nearly halved the rate of large errors compared to eGFRcre and appears to be robust across a range of relevant subgroups. The utility of the accuGFR test based on a single blood draw should be tested in diverse clinical and research populations.

**Table 1: Improved performance by accuGFR vs. CKD-EPI equations, eGFRcre, eGFRcys, and eGFRave**

<table>
<thead>
<tr>
<th>Method</th>
<th>Age ≥75%</th>
<th>BMI ≥36</th>
<th>eGFRcre (mGFR)</th>
<th>eGFRcys (mGFR)</th>
<th>eGFRave (mGFR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>accuGFR Development (n=1617)</td>
<td>45.8%</td>
<td>34.7%</td>
<td>43%</td>
<td>41%</td>
<td>44%</td>
</tr>
<tr>
<td>accuGFR Age ≥75% (n=660)</td>
<td>35.6%</td>
<td>33.6%</td>
<td>40%</td>
<td>39%</td>
<td>41%</td>
</tr>
<tr>
<td>accuGFR BMI ≥36% (n=660)</td>
<td>36.1%</td>
<td>34.9%</td>
<td>40%</td>
<td>39%</td>
<td>41%</td>
</tr>
</tbody>
</table>

**SA-PO425**

**Molecular Re-Classification of CKD Based on Kidney Transcriptomics**

Profiles Anna Remichienko,1 Viji Nair,1 Scan Eddy,1 Tao Wei,1 Tim Slidel,1 Wenjun Ju, James Conway,1 Shawn S. Badaroon,2 Johnna D. Wesley,2 John T. Liles,3 Uptal D. Patel,3 Matthew D. Breyer,3 Kevin L. Duffin,2 Carol P. Moreno Quinn,3 Maria chiara Magnone,4 Matthias Kretzler,3 1AstraZeneca, Gothenburg, Sweden; 2Eli Lilly and Company, Indianapolis, IN; 3Gilead Sciences, Inc., Foster City, CA; 4Novo Nordisk Research Center, Seattle, Seattle, WA; 5University of Michigan, Ann Arbor, MI; 6MedImmune, Cambridge, United Kingdom; 7MedImmune, Gaithersburg, MD. Group Team: Renal Pre-Competitive Consortium (RPC2).

**Background:** The CKD population is highly heterogeneous and includes a wide range of etiologies with a multitude of underlying molecular processes in the kidney. Current clinical classification of CKD into five stages based on GFR and albuminuria is agnostic to the disease heterogeneity and intrarenal biology, and thus is antithetical to the personalized medicine (PM) concept. We re-classified a CKD patient population based on the kidney molecular profiles, consistent with PM initiatives.

**Methods:** From clinically indicated renal biopsies in 165 ERCB cohort participants, transcriptomics profiles were generated using Affymetrix U133 platforms. Self-Organizing Maps (SOM), an unsupervised neural network machine learning algorithm, was used to stratify CKD population by clustering cases with similar transcriptomics profiles. Gene Ontology, pathway, and Gene Set Enrichment analyses were performed to identify key molecular mechanisms per SOM cluster.

**Results:** Using SOM, we identified four distinct patient clusters within the topological map of renal transcriptomics data structure. Relating these molecular clusters back to the current classification revealed the lack of overlap with CKD stages, thus demonstrating that SOM clusters represent a novel characterization beyond clinical classification. The SOM clusters were also not explained by CKD etiology, thus demonstrating that SOM clusters represent a novel characterization beyond clinical classification. Analyses showed that the SOM clusters differed in terms of biological pathways in the kidney including inflammation, metabolism, cell signaling and apoptosis.

**Conclusions:** Molecular re-classification may help realize the potential of PM for CKD. Elucidation of the molecular drivers of population clustering can lead to new biological hypotheses, therapeutic targets, and cluster-specific biomarkers that would enable PM-based regimens.

**SA-PO426**

**Quest for Simple and Accurate Estimate of Kidney Function for Chemotherapy Dosing: A Comparison of Commonly Used GFR Estimates and Inulin Clearance**

Fumiaki Ishii,1 Eriko Nakano,2 Yasuhiro Komatsu,1 Nephrology, St. Luke's International Hospital, Tokyo, Japan; 2Medical oncology, St. Luke's International Hospital, Tokyo, Japan.

**Background:** The increase in the number of oncology patients with renal impairment demands the accurate estimate of kidney function to avoid unnecessary adverse effects caused by overdose of chemotherapy. However, dose accuracy after renal function assessment calculated using eGFR equations based on creatinine measured by enzymatic assay and/or cystatin C remains unclear.

**Methods:** In this single-center study, we collected data from all adult patients whose inulin clearance was measured between January 2009 and March 2017. Renal function and consequent dose of renally-excreted chemotherapy, including carboplatin, were calculated by estimated creatinine-based GFR (eGFRcre) developed by the Japanese Society of Nephrology (JSN), estimated cystatin C-based GFR (eGFRcys) developed by JSN, averaged value of eGFRcre and eGFRcys (eGFRave), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Cockcroft-Gault (CG), Wright, and Jelliffe formulae. Logistic regression analysis was conducted to determine factors associated with overdose.

**Results:** The concordance of renal function estimates according to the CKD classification with measured inulin clearance (67±32 ml/min/1.73m²) in 187 adults (age 52±16, 58.3% men) for eGFRcre, eGFRcys, eGFRave, CKD-EPI, CG, Wright, and Jelliffe formulae was 53.5%, 56.6%, 58.5%, 52.9%, 49.2%, 52.4%, and 52.9%, respectively. Concordance for recommended dosage of chemotherapy using each respective formulae was 71.1%, 64.8%, 74.8%, 68.9%, 65.2%, 67.9%, and 67.4%. Especially concordance for carboplatin was 64.2%, 57.2%, 69.8%, 57.2%, 43.9%, 40.6%, and 47.6%, respectively. Hypoalbuminemia was an independent factor for overdose (OR 3.14, 95% CI 1.75-5.61).

**Conclusions:** For accurate chemotherapy dosing, eGFRave appears to be the most appropriate estimate of renal function. Patients with hypoalbuminemia may need actual measurement of inulin clearance.

**CKD molecular re-classification**

**Poster/Saturday**

**Underline represents presenting author.**
SA-PO427

Serum Creatinine from 29 US Health Care Organizations: The Case of Imprecise Measurement

Nikia Stempniewicz,1 Shoshana Ballew,2,3 Elizabeth Ciemins,4 Morgan Gramps,3 Kunihiro Matsuhashi,2 Jerry Penso,1 Jose Coresh,1,2,4 AMGA, Alexandria, VA; Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; Welch Center for Prevention, Epidemiology & Clinical Research, Baltimore, MD; Johns Hopkins School of Medicine, Baltimore, MD.

Background: For precise measurement of estimated GFR (eGFR), KDIGO 2012 guidelines recommend clinical laboratories report serum creatinine to the nearest 0.1 mg/dL. Rounding serum creatinine measurements to 0.1 mg/dL reduces the precision of eGFR, e.g., a female with a serum creatinine of 1.0 mg/dL, and ages of 60, 70, or 80 would report eGFR (CKD-EPI) in the ranges of 58-64, 54-60, and 51-56 mL/min/1.73 m², respectively. However, many laboratories still round to 0.1 mg/dL.

Methods: We analyzed 2.3 million patients with serum creatinine measurements from the electronic health record (EHR) data of 29 AMGA member organizations who use the Optum One population health analytics platform. We used the most recent serum creatinine recorded between 01/01/2013 and 12/31/2016 for patients age 18-99, with a history of hyperglycemia, and at least one ambulatory office visit. Imprecision in serum creatinine reporting was quantified using the proportion of values with a 0 in the second place after the decimal (e.g., 0.90, 1.00). With precise measurement we expect ~10% of patients to end in each digit including 0.

Results: Overall, 36% of serum creatinine measurements had 0 for the second decimal place (e.g. X.00, blue in Figure 1). This proportion varied among organizations, ranging from 10%-100%. Over the last 4 years the proportion with 0 in the second place after the decimal decreased from 51% (2013) to 24% (2016).

Conclusions: Imprecise measurement of serum creatinine by clinical laboratories in the US is improving but is still a prevalent practice which should be eliminated to meet with guidelines and improve the quality of health care.

SA-PO428

Existing Creatinine Based Estimating Equations Overestimate GFR in Indian Subjects

Vivek Kumar,1 Ashok K. Yadav,1 Vinod Kumar,2 Krishnan Lal L. Gupta,2 Masaru Horio,2 Vivekanand Jha,3 George Institute for Global Health, New Delhi, India; 2Osaka University Graduate School of Medicine, Ashiya, Japan; 3Nagoya University Post Graduate School of Medicine, Nagoya, Japan; 4Postgraduate Institute of Medical Education & Research, Chandigarh, India; 5Postgraduate Institute of Medical Education and Research, Chandigarh, India; 6Fiirstien Institute for Medical Research, New York, NY.

Background: Ethnic differences, predominantly vegetarian diet and poor representation in derivation and validation cohorts for eGFR equations call for assessment of accuracy of current eGFR equations in Indian population.

Methods: This study was done at PGIMER, Chandigarh, India. Stable adult prospective living renal donors or subjects with CKD were eligible for enrolment. GFR was measured (mGFR) by urinary clearance of inulin. eGFR were calculated using CKD-EPI, Japanese coefficient-modified CKD-EPI, MDRD and CKD-EPI Pakistan equation. Bias (mGFR-eGFR), 95% limits of agreement, precision (95% CI of mGFR-eGFR) and accuracy (RMSE of mGFR-eGFR, and % of subjects with eGFR within ±10% of mGFR) of each eGFR equation were compared.

Results: After excluding 5 subjects with incomplete data, 130 subjects were included for final analyses (63 prospective donors and 67 subjects with previously diagnosed CKD). 50% were strict vegetarian and average meat intake among meat eaters was only 3.8 times/month. The average creatinine (Cr) excretion was 14.7 mg/kg/day (95% CI: 13.5 to 15.9 mg/kg/day) and 12.4 mg/kg/day (95% CI: 11.2 to 13.6 mg/kg/day) in males and females, respectively. The average daily protein intake based on 24-hour urea nitrogen excretion was 46.1 g/day (95% CI: 43.2 to 48.8 g/day), respectively. Bias, precision and accuracy of eGFR equations are shown in table 1. All Cr based eGFR equations overestimated GFR with CKD-EPI, and MDRD being the poorest.

Conclusions: Cr based eGFR equations significantly overestimate GFR in the predominantly vegetarian Indian population. Lower Cr excretion suggest that this overestimation is likely linked to lower muscle mass. There is need of an appropriately powered study to develop either a correction factor or a new equation for accurate assessment of kidney function in Indian population.

Funding: Private Foundation Support

Table 1: Performance of GFR estimating equations as compared to measured GFR by urinary inulin clearance

<table>
<thead>
<tr>
<th>Equation</th>
<th>Bias (mGFR-eGFR)</th>
<th>95% Limits of agreement</th>
<th>Precision (95% CI)</th>
<th>Accuracy (RMSE)</th>
<th>GFR agreement (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD-EPI</td>
<td>-4.49 ± 7.19</td>
<td>-15.75 to 6.81</td>
<td>10.7 (5.9 to 15.5)</td>
<td>33.3 ± 26.4</td>
<td>47 ± 24</td>
</tr>
<tr>
<td>Japanese C-M</td>
<td>-4.25 ± 6.73</td>
<td>-12.46 to 4.00</td>
<td>7.1 (5.7 to 8.5)</td>
<td>48 ± 22</td>
<td>56 ± 28</td>
</tr>
<tr>
<td>MDRD</td>
<td>-3.69 ± 10.10</td>
<td>-20.37 to 12.98</td>
<td>10.4 (7.9 to 12.9)</td>
<td>41 ± 29</td>
<td>51 ± 24</td>
</tr>
<tr>
<td>CKD-EPI</td>
<td>-3.52 ± 10.10</td>
<td>-20.22 to 13.18</td>
<td>10.4 (7.9 to 12.9)</td>
<td>41 ± 29</td>
<td>51 ± 24</td>
</tr>
</tbody>
</table>

SA-PO430

Prevalence of Hyperkalemia in Medicare Patients

Keith Betts,1 J. Michael Woolley,1 Fan Mu,1 Wenzhu Tang,1 Yao Wang,1 Eric Wu,1 Analysis Group, Inc., Los Angeles, CA; 2ZS Pharma Inc., San Mateo, CA.

Background: The objective of this study was to estimate the prevalence of hyperkalemia in the Medicare patient population.

Methods: Adults with at least one medical service were selected from the 5% random Medicare sample (01/01/2010-12/31/2014). Patients with at least one calendar year of data with continuous enrollment throughout the year were included. Hyperkalemia was defined as a serum potassium level ≥5.5 mmol/L.

Results: Of the 13,617,971 adults, 3,030,300 (22.1%) had at least one hyperkalemia event. The prevalence of hyperkalemia increased with age, from 7.6% for those aged 65-69 years to 30.2% for those aged 85 years or older. Women were slightly more likely to have hyperkalemia than men (22.2% vs. 21.9%). Hyperkalemia was more common in patients with diabetes (24.5%) than in those without (20.7%). The prevalence of hyperkalemia was highest in patients with kidney disease (64.4%) and lowest in patients without kidney disease (20.7%).

Conclusions: The prevalence of hyperkalemia in Medicare patients is high, with a prevalence of 22.1% among adults aged 65 years or older. Hyperkalemia is more common in patients with diabetes and kidney disease.

Funding: Private Foundation Support
Results: A total of 4,418 matched cases and controls were included in the analysis. Cases had higher rates of inpatient admissions (1.00 vs. 0.41), emergency department visits (1.98 vs. 1.13), and outpatient visits (49.60 vs. 38.93) compared to controls in the 1-year study period (all p<0.001). Cases incurred $33,120 higher 1-year total all-cause costs ($71,322 vs. $38,203), and higher costs within each quarter (Q1: $23,615 vs. $12,041; Q2: $16,466 vs. $9,241; Q3: $16,630 vs. $8,560; Q4: $14,611 vs. $8,361) compared to controls (all p<0.001). Among patients with CKD and/or heart failure, cases had $33,827 higher 1-year total costs than controls ($76,971 vs. $43,143; p<0.001).

Conclusions: The results indicate that hyperkalemia-related hospitalizations are associated with significant economic burden during the 1-year post-discharge period.

SA-PO433
Development of a Predictive Model for Hyperkalemia Keith Betts,1 J. Michael Woolley,2 Fan Mu,1 Iryna Bocharova,3 Arielle G. Bensimon,4 Eric Wu,1 Analysis Group, Inc., Boston, MA; 2ZS Pharma Inc., San Mateo, CA

Background: The objective of this study was to develop and validate a predictive model for the risk of hyperkalemia (HK) in US adults.

Methods: Adults were selected from a large US commercial claims database (2013-2014) if they were continuously enrolled from 7/1/13-12/31/13 (baseline) and 1/1/14-12/31/14 (follow-up) and had at least one serum potassium (K+) lab result during follow-up. The resulting sample was partitioned into two subsamples to train (60%) and validate (40%) the model. HK was defined as having in 2014: two elevated K+ values (>5.0 mEq/L); or one diagnosis for HK (ICD-9=276.7); or one prescription fill of sodium polystyrene sulfonate. In the training sample, multivariate logistic regression was used to develop a model estimating the 1-year probability of HK as a function of baseline covariates. Receiver operating characteristic (ROC) curve analysis of the validation sample was used to assess the predictive performance of the model.

Results: HK was identified in 4,815 (1.6%) of 295,511 adult patients in the training sample. Some important baseline predictors of HK included: CKD stages 3-5 (e.g., odds ratio 3.6 for stage 3 without dialysis vs. stage 4 with dialysis); adding dialysis vs. no dialysis (OR=1.95; 95% CI: 1.61-2.36); an additional year in age (OR=1.028; 1.025-1.030); history of HK (e.g., number of HK-related hospitalizations OR=1.65; 1.20-2.26); type II diabetes (OR=1.65; 1.53-1.77); and use of renin-angiotensin-aldosterone system inhibitors (RAAS, OR=1.38; 1.29-1.47). ROC curve analysis in the validation sample showed good predictive accuracy (area under the curve=0.78). The figure shows the probability of HK for a RAAS patient as a function of CKD stage, age, and history of hyperkalemia.

Conclusions: This study developed a HK prediction model with the most important predictors being CKD stage, age, and history of HK. More frequent K+ monitoring may be warranted for patients at elevated risk.

SA-PO434
Indirect Comparison of Sodium Zirconium Cyclosilicate versus Patiromer in the Treatment of Hyperkalemia through 48 Hours Keith Betts,1 J. Michael Woolley,2 Yan Song,1 Wei Gao,1 Eric Wu,1 Analysis Group, Inc., Boston, MA; 2ZS Pharma Inc., San Mateo, CA

Background: Two agents have completed phase 3 trials for treatment of hyperkalemia: patiromer which was approved by US FDA in 2015 and sodium zirconium cyclosilate (ZS) which is an investigational medication. An indirect treatment comparison was conducted to compare efficacy of ZS and patiromer in lowering serum potassium [K+] after 48 hours of treatment.

Methods: To compare mean [K+] after 48 hours of treatment, a matching-adjusted indirect comparison (MAIC) was conducted using patient-level data for patients treated with 10g ZS from the ZS-003 and ZS-004 trials and published aggregate data of patiromer from the OPAL-HK trial. Indirect/exclusion criteria of the OPAL-HK trial were applied to ZS trials to derive a subset of patients comparable to those in the OPAL-HK trial. To adjust for cross-trial differences, patients from ZS trials were reweighted using the method of moments to exactly match baseline characteristics reported in OPAL-HK. By applying inclusion/exclusion criteria=8:11 crits/C16:10:11:13:6:7; adding a 1-year additional year and 243 patiromer treated patients were included in the analysis. After matching, all baseline characteristics were balanced between the two treatments. The mean baseline [K+] of both sets of patients was 5.60 mmol/L; and, after 48 hours of treatment, the mean [K+] achieved by ZS treated patients was significantly lower than those treated with patiromer (4.60 vs. 5.15 mmol/L; difference = -0.55 mmol/L; p-value <0.01; Figure 1). As a sensitivity analyses, the exclusion criteria were varied and the results remained consistent.

Conclusions: After adjusting for baseline differences, at 48 hours after the initiation of treatment, patients treated with ZS had a statistically significantly lower mean [K+] than those treated with patiromer.
Management of Hyperkalemia in Veterans with Advanced CKD

Enrica Fang,1 Chun Thomas,1 Manjula Kurella Tamura.1,2 Stanford University, Palo Alto, CA; 1Veteran Affairs Palo Alto Health Care System, Palo Alto, CA.

Background: Hyperkalemia is a serious complication among patients with advanced chronic kidney disease. The frequency and success of hyperkalemia management strategies are not well described.

Methods: We assembled a national cohort of veterans with advanced CKD not on dialysis, defined by an outpatient eGFR ≤30 ml/min/1.73m² and at least one episode of hyperkalemia (potassium ≥5.5 mEq/L), using administrative, laboratory and medication data from the Department of Veterans Health Affairs.

Results: Among 76,021 veterans with advanced CKD, 25,227 (33.2%) had at least one episode of hyperkalemia during 5 years of follow-up. The majority of patients (57.3%) were on at least one medication that can potentiate hyperkalemia, and 18.1% had one episode of hyperkalemia during 5 years of follow-up. The majority of patients data from the Department of Veterans Health Affairs.

Conclusions: Among patients with advanced CKD and hyperkalemia, discontinuation of RAAS inhibitors and beta blockers resulted in higher serum K+ levels (p=0.42/mL, 95% CI 0.14 - 0.71, p=0.01) compared with participants who used neither in the subgroup of 75 yo or older.

Funding: NIDDK Support, Veterans Affairs Support

Management strategies and recurrence of hyperkalemia within 90 days (n, %)

<table>
<thead>
<tr>
<th>Medications</th>
<th>Total cohort</th>
<th>No recurrence</th>
<th>Recurrence to K ≤3.5-4.1 mEq/L</th>
<th>Recurrence to K ≤4.5 mEq/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>5580 (27.7%)</td>
<td>2560 (45.9%)</td>
<td>307 (5.5%)</td>
<td>199 (3.6%)</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>1177 (5.5%)</td>
<td>46 (3.9%)</td>
<td>72 (6.0%)</td>
<td>55 (4.7%)</td>
</tr>
<tr>
<td>Potassium/sodium sulfate</td>
<td>2579 (12.6%)</td>
<td>172 (6.7%)</td>
<td>251 (9.7%)</td>
<td>198 (7.7%)</td>
</tr>
<tr>
<td>Initiation of K conserving drug</td>
<td>7577 (36.9%)</td>
<td>216 (2.9%)</td>
<td>742 (9.7%)</td>
<td>541 (7.2%)</td>
</tr>
</tbody>
</table>

SA-PO435

Beta Blockers as the Cause of Hyperkalemia in Near-End Stage Renal Disease Patients: A Cross-Sectional Study

Kazuhiko Okamura,1 Masahide Furusho,2 Shogo Sasaki,1 Masahide Furusho,1 Makoto Hirakawa,1 Iizuka Hospital, Iizuka-city, Japan; 1Department of Healthcare Epidemiology, Kyoto University Graduate School of Public Health, Kyoto city, Japan. Group/Team: JOINT-KD.

Background: Although there are several case reports on hyperkalemia caused by beta blockers so far, few studies have verified its causal relationship based on epidemiological methods. The objectives of this study were to assess the association between beta blocker use and risk of hyperkalemia among patients with near end-stage renal failure (ESRD).

Methods: Design and participants: We performed a cross-sectional study at seven Japanese teaching hospitals. Consecutive adult patients with eGFR <15 ml/min/1.73m² that visited outpatient departments from April 1 to June 30, 2013, were enrolled. Patients with dialysis, post-transplantation, or hospitalization within 30 days after discharge, were excluded.

Exposure: We set the usage of beta blockers as the exposure to be tested. Outcomes: Serum K+ concentration was taken as the outcome. Statistical analysis: Descriptive analysis was done. Next, multivariate analysis adjusted for age, sex, eGFR, presence of diabetes mellitus, RAAS inhibitors use, concomitant diuretics use, loop diuretics use, K absorption drugs use was conducted. In addition, analysis stratified by age (cut off: 75 yo) and RAAS inhibitor use was performed.

Results: Of 517 patients (56.9% male) who were at a median age of 72 (interquartile range 62 to 80), with median eGFR 11.1 ml/min/1.73m² (interquartile range 9.2 to 13.1) included, 239 (46.2%) had diabetes mellitus, 305 (59%) used RAAS inhibitors, and 148 (28.6%) used beta blockers. In the results of the multivariate analysis adjusted for possible confounders, there was no significant difference in the serum K+ value between the group using the beta blockers and the group not using the beta blockers (+0.07 mEq/L; 95% confidence interval [-0.59 to 0.73]).

Conclusions: In patients with near ESRD who were 75 years of age or older, it was suggested that the use of beta blockers may raise the serum K+ value.

Funding: Other U.S. Government Support

SA-PO436

End-of-Life Care in Advanced Kidney Disease Treated and Not Treated with Maintenance Dialysis

Susan P. Wong,1 Margaret K. Yu,2 Chuan-fen Liu,3 Paul L. Hebert,4 Ann M. O’Hare.2 1VA HSR&D Puget Sound Healthcare System, Seattle, WA; 2VA Puget Sound Health Care System, HSR&D, Seattle, WA; 3Stanford University, Stanford, CA.

Background: Little is known about the clinical course of patients with chronic kidney disease (CKD) who do not receive maintenance dialysis. We examined the association between death and end-stage renal disease (ESRD) in patients with advanced CKD not on dialysis.

Methods: We followed a national cohort of 28,568 patients receiving care in the US Department of Veterans Affairs (VA) from the date of their second estimated glomerular filtration rate ≤15 mL/min per 1.73m² occurring between 2000-2009 through October 1, 2011. We linked a combination of national registry data on dialysis, VA and Medicare files, and medical record review to identify a subset of 18,051 patients who were treated with dialysis, 851 patients in whom there was a decision not to pursue dialysis, and 640 patients...
who were preparing for dialysis (HR 2.39, 95% CI 2.19-2.62); hospitalization (57.3% vs. 76.8%; OR 0.40, 95% CI 0.34-0.46), receipt of an intensive procedure (3.5% vs. 24.6%; OR 0.15, 95% CI 0.10-0.22) and in-hospital death (41.4% vs. 57.3%; OR 0.78, 95% CI 0.72-0.83) were less common and palliative care consultation (52.6% vs. 21.6% OR 4.19, 95% CI 3.58-4.90) and hospice enrollment (38.5% vs. 18.2%; OR 3.32, 95% CI 2.83-3.89) more common among patients who did not pursue dialysis than in those who received dialysis. For patients who were preparing for dialysis, hospitalization, receipt of an intensive procedure, and in-hospital death were less common but palliative care consultation and hospice referral similar as compared with patients treated with dialysis.

Conclusions: Patients with advanced CKD not treated with dialysis had more limited survival and received less intensive end-of-life care than those treated with dialysis.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO439

Ethnic Differences in Mortality among Veterans with Kidney Disease: A 13-Year National Longitudinal Cohort Study

Mukonso N. Ozieh,1,6 Mulgatega Gebregeziabher,1,6 Ralph Ward,1 David J. Taber,1 Leonard Egede,2
1Medical University of South Carolina, Charleston, SC; 2Nephrology, Medical College of Wisconsin, Milwaukee, WI; 3Internal Medicine, Medical College of Wisconsin, Milwaukee, WI; 4Nephrology, Zablocki VAMC, Milwaukee, WI; 5Center for Patient Care and Outcomes Research (PCOR), Medical College of Wisconsin, Milwaukee, WI; 6Health Equity and Rural Outreach Innovation Center, Ralph H. Johnson VAMC, Charleston, WI.

Background: To assess the association between ethnic differences and mortality among Veterans with chronic kidney disease (CKD) over a 13-year period.

Methods: We examined all-cause mortality among Veterans with CKD from Jan 2000 to Dec 2012, including 3,015,318 Veterans using a unique algorithm to identify CKD, which was defined as estimated glomerular filtration rate (eGFR) of >60ml/min/1.73m2 and presence of proteinuria for ≥3 months for stage 1 and 2 CKD or eGFR <60 ml/min/1.73m2 for ≥3 months for stage 3 CKD or higher. Cox proportional hazards models were used to assess the relationship between mortality and racial/ethnic groups, and the models were developed in a sequential fashion. Hazard ratios (HR) and corresponding 95% CI were reported overall. All analyses were performed in SAS 9.4.

Results: The mean age for the cohort was 76.7 ± 11 years, which varied by ethnicity: 70.8 ± 12 years in Non-Hispanic blacks (NHB); 74.5 ± 11.7 years in Hispanics and 78.0 ± 10.3 years in non-Hispanic whites (NHW)]. The unadjusted all-cause mortality rate was 52.0% in NHB, 42.7% in NH and 41.3% in Hispanics. After adjusting for demographic variables, NHBs and Hispanics had statistically significant lower CKD mortality risk relative to NHW (HR 0.92; 95% CI, 0.91 - 0.92) and (HR 0.73, 95% CI, 0.72 - 0.74) respectively. In the fully adjusted model (adjusting for race/ethnicity and age), mortality was not different between NHB and NH, while NH had a higher mortality rate than NHW (HR 0.73, 95% CI, 0.72 - 0.74) respectively.

Conclusions: This is the first national longitudinal cohort study among Veterans which uses a robust algorithm to identify CKD. Non-Hispanic blacks and Hispanic Veterans with CKD have a survival advantage relative to NHW after adjusting for demographic, CKD stage and comorbidities.

SA-PO440

Treatment of Depression Symptoms Is Associated with Attenuated Risk of All-Cause Mortality among Patients with CKD

Delphine S. Tuot,1 Keith Shardlow,2 Jennifer J. Gassman,1 Elaine K. Cleveland, Cleveland, OH; 1UCLA, Marina Del Rey, CA; 2University of California, San Francisco, San Francisco, CA.

Background: Depression is common, under-recognized, and undertreated among patients with CKD, especially among racial/ethnic minorities. We examined whether the relationship between depressive affect and mortality differs by antidepressant use or race/ethnicity among patients with CKD.

Methods: We assessed the presence of depressive symptoms among Chronic Renal Insufficiency Cohort (CRIC) participants, defined by a Beck Depression Inventory II (BDI) score of ≥14 at baseline enrollment. Cox regression was used to associate baseline depressive symptoms with risk of all-cause mortality (before or after ESRD) adjusted for socioeconomic factors, baseline CKD severity, time-updated comorbid conditions including ESRD status, and baseline anti-depressant use. We tested for the presence of interaction between race/ethnicity and depressive symptoms. Confirmatory analyses were performed using long-term follow-up data from the African American Study of Kidney Disease and Hypertension Cohort (AASK).

Results: Among 3725 CRIC participants, 23.3% had a baseline BDI of ≥14 with 17.0% prevalence of anti-depressant use. Crude mortality rate was 3.37/100-person years (PY) during 6.7 years of median follow-up. Baseline BDI ≥14 was associated with higher risk of all-cause mortality, attenuated by antidepressant use (Table). Differences in the relationship between BDI score and mortality were noted by race/ethnicity (Pinteract = 0.04, Table). Results were consistent among 652 AASK study participants, among whom 30.3% had BDI ≥14 with a crude mortality rate of 6.8/100-PY. Baseline BDI ≥14 in AASK was not associated with greater risk of mortality during 5.1 years of median follow-up (HR=0.84; 0.61-1.18).

Conclusions: Treatment of depressive symptoms was associated with attenuated risk of mortality among individuals with CKD. Further investigation is needed to better understand differences in mortality by depressive risk by symptoms among racial/ethnic subgroups.

Funding: NIDDK Support
SA-PO442

Body Mass Index, Waist Circumference, and Risk of Kidney Function Decline in a Global Consortium Alex R. Chang. CKD Prognosis Consortium, Baltimore, MD.

Background: Limited data exist on the association between body mass index (BMI) or waist circumference (WC) with kidney function decline.

Methods: We performed collaborative meta-analyses to examine the association between BMI and WC with kidney function decline (ESKD or eGFR decline ≥40%) in 26 general population (GP) (n=712748) cohorts, of which 17 (n=238210) cohorts had WC data. Secondary meta-analyses were done in 12 CKD cohorts (n=22587), and in 6 high-risk population cohorts (n=135054). References were set at BMI 25 kg/m² and sex-specific WC values of 92 cm (men) and 78 cm (women).

Results: In GP cohorts, mean values for BMI, eGFR, and sex-specific WC were 27.8 (6.3) kg/m², 90.1 (22.5) ml/min/1.73m², and 92.2 (11.5) cm for men and 84.3 (13.2) cm for women, respectively. Within the 26 cohorts, 26,424 individuals developed kidney function decline over a mean follow-up of 6.9 (4.2) years. In analyses adjusted for age, sex, race, and current smoking, a BMI of 30 kg/m² vs. 25 kg/m² was associated with a hazard ratio (HR) of 1.20 (95% CI: 1.14-1.26) for kidney function decline (Figure). For the same outcome, WHO-recommended cut-points of waist circumference of 102 cm (men) and 88 cm (women) were associated with an HR of 1.15 (95% CI: 0.99-1.34) relative to the sex-specific references. The relationship between BMI and kidney function decline did not significantly differ by age, gender, diabetes, or baseline eGFR category. Associations were attenuated in high-risk and CKD cohorts, and when models were additionally adjusted for baseline diabetes, cardiovascular disease, hypertension, and eGFR.

Conclusions: Elevated BMI and WC are risk factors for ESKD and eGFR decline ≥40% in individuals with normal and reduced eGFR.

Funding: NIDDK Support, Private Foundation Support

SA-PO443

Why Select Conservative Management? A Qualitative Study of Patient-Identified Factors and Influences Contributing to Advanced Kidney Disease Patients’ Decisions to Choose Non-Dialysis Care Emily Lu,1 Jeffrey I. Silberzweig,2 Anna M. Hennon,3 Nathaniel E. Berman,2 Ronald D. Adelman,3 Megan J. Shen,3 Katherine Lamp,a3 Manney C. Reid,3 1Nephrology and Hypertension, Weill Cornell Medicine/New York Presbyterian Hospital, New York, NY; 2The Rogosin Institute, New York, NY; 3Geriatrics and Palliative Medicine, Weill Cornell Medicine/New York Presbyterian Hospital, New York, NY.

Background: Conservative management (CM) of advanced chronic kidney disease (CKD) continues to be an area of growing interest. However, in the United States, little is known about why and how patients decide to pursue CM. The purpose of this study is to...
better understand why American patients with advanced CKD select CM and to identify factors or influences important to them in this decision-making process.

Methods: Patients with estimated glomerular filtration rate (eGFR) <30 ml/min who had previously made the decision to select CM—non-dialysis care—for their CKD were recruited. Semi-structured interviews of 15 patients were conducted, audiotaped, and transcribed. Data were analyzed inductively using grounded theory to identify common themes in patients’ narratives.

Results: Four emerging themes were identified: 1) Choice of CM remains ultimately fluid, provisional, or circumstance-dependent (patients would consider dialysis if specific situations were developed, e.g. imminent danger/death, nephrologist recommendation, no longer felt well); 2) Importance of quality of life (negative impact of time required for dialysis, wish to live without restriction/limitation); 3) Currently feeling well (selected CM because does not feel sick); 4) Gaps in knowledge of and/or discussion with nephrologist regarding CKD care options (lack of recollection of discussion or content, difficulty describing anticipated symptoms of CM progression).

Conclusions: Understanding how advanced CKD patients select CM as a treatment option for their CKD provides insight regarding the beliefs/values, motivations, and concerns they take into account during the decision-making process. Further interviews will be conducted to reach methodological saturation. The identified themes will inform a future longitudinal study of treatment decision-making in advanced CKD.

SA-PO444
Polycystic Kidney Disease Is Significantly Associated with Alzheimer Dementia Risk:

Propensity Score Matched Analysis of a Nationwide, Population-Based Cohort

Tung-Min Yu, Ya-Wen Chuang, Misaki Morishii, Shinichiro Tsuchiya. Taichung Veterans General Hospital, Taichung ---, Taiwan.

Background: Data on the risk of neurodegenerative diseases, including Alzheimer disease and Parkinson disease, in patients with polycystic kidney disease (PKD) are lacking.

Methods: A total of 4229 patients who were aged ≥20 years and had received a diagnosis of PKD were included in the PKD cohort. For each PKD case identified, 1 participant aged ≥20 years without a history of PKD, dementia, or PD was selected from the comparison cohort. For each patient with PKD, the corresponding controls were selected 1:1 on the basis of the nearest propensity score calculated using logistic regression.

Results: The incidence density rates of dementia were 4.31 and 2.50 per 1000 person-years in the PKD and control cohorts, respectively. A 2.04-fold higher risk of dementia was observed in patients with PKD than in controls (adjusted hazard ratio [aHR] = 2.04; 95% confidence interval [CI] = 1.46–2.85). Regarding the risk of different dementia subtypes including AD and vascular dementia (VD), the aHR for AD and pre-senile dementia was 2.71 (95% CI = 1.08–6.75) and that for VD was 0.90 (95% CI = 0.43–1.87) in patients with PKD compared with controls, after adjustment for age, sex, and comorbidities. Compared with controls, the risk of PD increased by 1.78-fold (95% CI = 1.14–2.79) in patients with PKD.

Conclusions: In clinical practice, health care providers should be aware of the risk of these neurodegenerative diseases in patients with PKD.

SA-PO445
Cognitive Function and Hyponatremia: Baseline Data from the SPRINT Trial

Daniel E. Weiner, S. Gausson, Manjula Kurella Tamura, Alfred K. Cheung, William C. Cushman, Anthony A. Kellen, Maulviy Rahamani, Brian M. Wall, Jamie P. Dwyer, Kausik Saha, Case Western Reserve University, Cleveland, OH; "Memphis VA Medical Center, Memphis, TN"; "Stanford University, Palo Alto, CA"; "Tufts Medical Center, Boston, MA"; "University of Minnesota, Minneapolis, MN"; "University of Utah, Salt Lake City, UT"; "Vanderbilt University Medical Center, Nashville, TN"; "Wake Forest, Winston-Salem, NC"; "Henry Ford, Detroit, MI".

Background: Hyponatremia is stated as a reversible cause of cognitive impairment despite very limited data exploring this association.

Methods: To explore the relationship between serum sodium concentration and cognitive function, we evaluated baseline data from the Systolic Blood Pressure Intervention (SPRINT) cognition study, SPRINT-MIND. Five cognitive domains were defined from 11 cognitive tests using z-scores, and the association of serum sodium with cognitive performance and brain abnormal white matter volume quantified by MRI were evaluated using linear and quartile regression, respectively.

Results: Among 9361 SPRINT-MIND participants, 2853 were administered an expanded cognitive battery at baseline, 664 of whom had brain MRI. Mean age was 68 years; 29% had known CVD and 29% eGFR <60 ml/min/1.73m². There were 120 participants with serum sodium ≤135 mEq/L, 485 with sodium 136-138, 983 with 139-140, 891 with 141-142, and 374 with ≥143 mEq/L. In analyses adjusted for age, sex, SPRINT network, education, race, diabetes, CVD, BMI, smoking, ACEi/ARB use, systolic and diastolic BP, lipids, eGFR, and albuminuria, lower serum sodium was associated with significantly worse executive function (p = 0.002) and a trend to worse attention (p = 0.08) and global cognitive function (p = 0.12). Associations were unchanged following adjustment for thiazide and anti-depressant use. When examining thresholds, participants with Na ≥143 mEq/L demonstrated worse cognitive test performance in most domains, consistent with a 3-shaped relationship between sodium and cognition. In the MRI subgroup, sodium was not associated with brain abnormal white matter volume in adjusted analyses (p = 0.77).

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

Poster/Saturday
SA-PO447

Metabolomics Study Identifies Several Metabolites Associated with Uremic Symptoms in Advanced CKD

Jiun-Huey Hu,1,3 Andrew S. Levey,3 Josef Coresh,1,4 Morgan Grans,1,4 Eugene P. Rhee,3 Tariq Shafi,1,4
1Epidemiology, Johns Hopkins School of Public Health, Baltimore, MD; 2Massachusetts General Hospital, Boston, MA; 3Tufts Medical Center, Boston, MA; 4Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins University, Baltimore, MD; 1Vanderbilt University School of Medicine, Nashville, TN.

Background: Uremic symptoms are common in patients with advanced CKD, but the toxins that cause these symptoms are unknown.

Methods: We measured metabolites in participants of the Modification of Diet in Renal Disease (MDRD) with measured GFR < 20 ml/min/1.73 m² (N=216), using an untargeted LC/MS/MS platform. We determined the association of 667 metabolites with uremic symptom scores using linear regression adjusting for clinical factors and accounting for multiple comparisons.

Results: The mean age of the participants was 52 years and 81% were white. Uremic symptoms were common. 80% of participants had at least 1 uremic symptom. Metabolites associated with uremic symptoms are presented in the accompanying table.

Conclusions: We identified several metabolites associated with uremic toxins. Metabolomics has the potential to identify toxins that cause uremic symptoms.

---

SA-PO448

Near-Infrared Spectroscopy Measured Muscle Haemoglobin O2 Saturation Kinetics and Physical Performance in CKD

Thomas J. Wilkinson,2 Alice c. White,2 Daniel Nixon,2 Douglas W. Gould,2 Emma L. Watson,2 Alice C. Smith,1 1John Walls Renal Unit, Leicester General Hospital, Leicester, United Kingdom; 2University of Leicester, Leicester, United Kingdom.

Background: CKD patients have poor exercise capacity. A possible factor may be an imbalance in muscle oxygen (O2) supply and utilisation, moderated by mitochondrial and endothelial dysfunction. Near-infrared spectroscopy (NIRS) can be used to measure in vivo muscle oxidative metabolism. Using NIRS we investigated gastrocnemius skeletal muscle O2 kinetics in non-dialysis CKD patients during exercise.

Methods: 30 patients (59±16 yrs; 11 female; eGFR: 54±26 ml/min/kg/1.73m²) completed the incremental shuttle walk test. NIRS measured light attenuation in the near-infrared spectrum and determined chromophores, primarily % of oxygenated haemoglobin present in the muscle (SMO2%). SMO2% was assessed before, during, and after (recovery) exercise. Resting cardiac parameters were assessed, along with habitual physical activity (PA). Patients were divided into aerobic capacity tertiles to determine SMO2% differences.

Results: From baseline, SMO2% declined by 12±7% during exercise before rapidly recovering upon cessation (Fig 1). Controlled for age, sex and eGFR, patients with higher aerobic capacity took 258 (56-461) secs (55%) longer (P=.016) to reach minimum SMO2% and recovered 49 (2.96) secs (75%) quicker (P<.040) than those with lower aerobic capacity. Better SMO2% kinetics were associated with higher stroke volume and PA levels, and lower peripheral resistance.

Conclusions: Superior SMO2% kinetics (i.e. slower deoxygenation rate, quicker recovery) are associated with greater exercise capacity, better vasculature, and higher PA in CKD. The dysfunctional kinetics observed may indicate endothelial dysfunction and an inability of mitochondria to efficiently carry out oxidative phosphorylation. Accordingly, NIRS is a low-cost and non-invasive means to evaluate O2 kinetics and could be a useful tool to measure oxidative metabolism mechanisms in CKD.

Funding: Private Foundation Support

---

SA-PO449

Exercise Improves Self-Reported Physical Symptom Burden and Fatigue in Non-Dialysis CKD

Thomas J. Wilkinson,1 Soteris Xenophontos,2 Douglas W. Gould,1 Amy L. Clarke,3 Barbara P. Vogt,2 Joao L. Viana,4 Emma L. Watson,3 Alice C. Smith.1 1John Walls Renal Unit, Leicester General Hospital, Leicester, United Kingdom; 2University of Leicester, Leicester, United Kingdom; 3Univesidade Estadual Paulista UNESP, Botucatu, Brazil; 4University of Leicester, Leicester, United Kingdom; 5University Institute of Maia, Porto, Portugal.

Background: CKD patients suffer from a variety of physical symptoms due to the disease and its treatments. Symptoms include fatigue, muscle weakness, pain, and sleep disruption, and these can negatively affect quality of life (QoL) and discourage physical activity. Whilst intradialytic exercise may help ameliorate some symptoms in dialysis patients, research on whether exercise can reduce symptom burden in non-dialysis patients is lacking.

Methods: 36 patients (62±12 yrs; 22 female; eGFR: 26±8 ml/min/kg/1.73m²) completed supervised aerobic exercise (AE) (n=18) or combined aerobic plus resistance exercise (A+RE) (n=18) 3x/week for 12 weeks. Self-reported symptom burden and fatigue measures were taken pre- and post-exercise. The Leicester Uremic Symptom Scale (L USS) measured the frequency and intrusiveness of 11 symptoms. Fatigue was measured using the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F); the total FACIT-F score and Trial Outcome Index (TOI) were used.

Results: AE reduced the total mean number of symptoms from 6.3 to 5.4 (14% (P=.014) and the frequency of itching by 35% (P=.004). AE also reduced the intrusiveness of sleep disturbance by 14% (P=.001) and experience of muscle spasm/stiffness by 29% (P=.021). In the A+RE group, only a reduction in the frequency (41% (P=.001) and intrusiveness (39% (P=.001) of a feeling in loss of muscular strength/power was seen. Exercise improved fatigue; total FACIT-F score was improved in the AE and A+RE groups by 9% (P=.028) and 23% (P=.068) respectively, whilst the TOI was improved by 10% (P=.067) and 27% (P=.048).

---

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
**Conclusions:** Exercise can significantly reduce physical symptom burden and fatigue in patients with CKD. Patients performing AE reported less symptoms overall, with itching, sleep disturbance, and muscle stiffness symptoms improving specifically. Unsurprisingly, patients performing additional strength training felt stronger. Fatigue was improved following both exercise modalities. Symptom burden contributes to physical inactivity as a reduction in QoL, and as such exercise should be encouraged to help improve patients’ health status.

**Funding:** Private Foundation Support

**SA-PO450**

“It’s Opened Up My Eyes to How Much I Can Actually Do”: A Mixed Methods Study Exploring the Feasibility of a Physical Activity Education Programme in CKD


**Background:** Physical activity (PA) can improve the quality of life (QoL) and health of patients with chronic kidney disease (CKD). However, patients exhibit minimal PA, and currently, no specific pathways exist to target physical inactivity in CKD. “PACT” is a 3.5-hour structured group education programme designed to initiate PA by eliciting illness perceptions, providing basic disease education, highlighting health risks, and promoting the benefits of PA and self-regulation.

**Methods:** A mixed methods ‘before and after’ feasibility study of the PACT intervention to explore recruitment, retention and engagement; and patient acceptability of intervention and outcome measures. Semi-structured interviews were conducted to gain an understanding of patient experience.

**Results:** Overall, 75 non-dialysis CKD patients were approached and 19 (25%) were consented. 17 (90%) attended the group session, and 4 withdrew due to unrelated reasons, resulting in a 68% completion rate. Engagement with step monitoring was good during the 8 weeks of walking:11 returned PA diaries completed at a rate of 61-100%. There was a mean (CI 95%) increase in daily steps from pre-to post-intervention of 1947(445, 4349) which produced a small-moderate effect (d=0.47). Positive changes were observed for physical function, QoL, activation and knowledge. Our qualitative analysis found that participants enjoyed the interactive session and would recommend it; outcome assessments were for the most acceptable, and self-monitoring steps enhanced engagement. However, some participants felt that real time monitoring on a mobile app, further guidance for exercise intensity, and a greater emphasis on psychological strategies related to disease adjustment and PA motivation could improve the intervention.

**Conclusions:** The purpose of this trial was to determine acceptability of and engagement with the PACT protocol. Findings were positive, with some areas for refinement indicated. The trial was not powered to assess efficacy, but demonstrated potential to improve PA, and domains related to QoL. This approach to lifestyle management has great promise in CKD and deserves further attention.

**SA-PO451**

Prevalent Depression and Associated Factors in a Disadvantaged CKD Population

**Carol P. Walther,** Jingbo Niu, Sai Kaumudi Saridie, Wolfgang C. Winkelmayr, Sankar D. Navaneethan. Baylor College of Medicine, Houston, TX.

**Background:** Depression is common among individuals with CKD and associated with adverse outcomes. In the US population, prevalence is lower in older persons and varies with race/ethnicity. We studied factors associated with depression in a diverse non-dialysis CKD cohort, which could help to identify high-risk patients and disparities.

**Methods:** We identified adults with eGFR <60 for a0 days who received care through a safety-net health system from 2006-16. Depression was determined from ICD codes prior to or within 2 weeks of cohort entry. Comorbidities were identified using a similar method. We categorized CKD into stages 3A, 3B, 4, and 5. Race/ethnicity was recorded in 5 mutually-exclusive categories. We used multivariate logistic regression to analyze associations with demographics, comorbidities, and CKD stage, and calculated predicted probabilities and 95% CIs.

**Results:** We included 13678 CKD patients of whom 39.4% were Hispanic, 40.9% black, 11.5% white, 5.9% Asian/Pacific Islander, and 2.2% other/unknown race. Depression prevalence was 11.6% overall, and 23.9% among whites, 11.1% among blacks, 9.8% among Hispanics, and 5.3% among Asians/Ps. Interactions between age and race/ethnicity, and between age and number of comorbidities were observed.

**Conclusions:** Depression prevalence varied with race/ethnicity, age, and comorbidities. Depression decreased markedly with age in blacks and whites, but not Hispanics. The association of comorbidities with depression decreased with age.

**Stratified Odds Ratios [95% CI] for Depression**

<table>
<thead>
<tr>
<th>Age category (years)</th>
<th>Hispanic versus Black or White1</th>
<th>One additional comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-34</td>
<td>0.65 (0.59-0.73)</td>
<td>2.43 (2.06-2.88)</td>
</tr>
<tr>
<td>35-49</td>
<td>0.70 (0.63-0.78)</td>
<td>1.79 (1.45-2.22)</td>
</tr>
<tr>
<td>50-64</td>
<td>0.76 (0.69-0.84)</td>
<td>1.59 (1.30-1.94)</td>
</tr>
<tr>
<td>65-79</td>
<td>0.87 (0.79-0.97)</td>
<td>1.55 (1.36-1.77)</td>
</tr>
<tr>
<td>80 or older</td>
<td>1.01 (0.84-1.21)</td>
<td>1.23 (1.04-1.45)</td>
</tr>
</tbody>
</table>

*Adjusted for CKD stage, sex, cohort year, continuous age, and either 1comorbidity count or 1race/ethnicity

**SA-PO452**

Prevalence and Associated Factors of Depressive Symptoms among Predialysis CKD Patients in China: Results from the Chinese Cohort Study of CKD (C-STRIDE)

**Lei Pu, Li Wang, Guisen Li.** Renal Division and Institute of Nephrology, Sichuan Academy of Medical Sciences; Sichuan Provincial People’s Hospital, Chengdu, China; Sichuan Provincial People’s Hospital, Chengdu, China. Group/Team: C-STRIDE study group.

**Background:** Depression was reported to be the most common mental disorder in patients with chronic kidney disease (CKD). Previous studies found that depression could accelerate the progression of CKD disease, and was an independent risk factor of hospitalization and death among patients with CKD. The objective of this study is to investigate the prevalence of depression in Chinese patients with predialysis CKD, and to identify factors associated with depression.

**Methods:** Baseline data of a multicenter prospective cohort study, Chinese cohort study of chronic kidney disease(C-STRIDE)study were used. Altogether 2995 participants with CKD stage 1 to 4 who completed a survey of depressive symptoms were included. The depressive symptoms were assessed by Zung Self-Rating Depression Scale (ZSDS). ZSDS <50 was used as the cutoff score of the presence of depressive symptoms. MultivariableLogistic regression models were used to identify factors associated with depression.

**Results:** Mean eGFR level was 51.59±29.49ml/min/1.73m2. The prevalence of depressive symptoms was 37.8% and increased significantly with advanced CKD stages. Female, higher education level, low income, larger economic impact of disease cost, comorbid cardiovascular disease, anemia, lower physical activity ability were independently associated with depressive symptoms.

**Conclusions:** Our study revealed that depressive symptoms were common among Chinese predialysis CKD population. Socioeconomic factors and clinical characteristics of severity of disease were strongly associated with the depressive symptoms.

**SA-PO453**

The Impact of CKD on Disability and Health-Related Quality of Life (HR-QOL) of Children and Adolescents

**Anna Francis,** Natasha Nassar, Allison Tong, Tonya Kara, Anna Francis, Natasha Nassar, Allison Tong. University of Sydney, Westmead, NSW, Australia; Centre for Kidney Research, Westmead, NSW, Australia; None, Amunie, NSW, Australia; Princess Alexandra Hospital, Brisbane, QLD, Australia; Children’s Hospital, Auckland, New Zealand; Princess Children’s Hospital, Auckland, New Zealand; Sydney Children’s Hospital, Newtown, NSW, Australia; The University of Sydney, Westmead, NSW, Australia; University of Sydney/Children’s Hospital, Sydney, NSW, Australia; Children’s Health Queensland, Brisbane, QLD, Australia.

**Background:** Children with CKD suffer from reduced HR-QOL. The extent of impairment and risk factors for poorer HR-QOL and disability are under-studied. The study aimed to compare overall HR-QOL and severity of disability in children and adolescents with different stages of CKD and to determine factors associated with lower HR-QOL scores.

**Methods:** HR-QOL data were collected from children and adolescents (age 6-18 years) across five paediatric units in Australia and New Zealand. The Health Utilities Index 3 survey was used to measure overall utility based HR-QOL (where 0 represents being dead and 1 represents full health). A score of 1.00 represents no disability, 0.89-0.99 represents mild disability, 0.70-0.88 represents moderate disability and less than 0.70 represents severe disability. HR-QOL scores and disability stages were compared between CKD stages using the Mann-Whitney-U test. Multivariable linear regression assessed factors associated with decline in HR-QOL.

**Results:** There were 377 children with CKD (median age 12.6 years). The median unadjusted HR-QOL score for those with CKD stages 1-4 was 0.88 (interquartile range
SA-PO454

Posttraumatic Stress Disorder and Outcomes among US Veterans Who Transition to Renal Replacement Therapy: A Transition of Care in CKD Study Vanessa A. Ravel,1 Elani Streja,1 Connie Rhee,1 Csaba P. Kovesdy,2 Kamyar Kalantar-Zadeh.1 1UC Irvine, Orange, CA; 2University of Texas Health Science Center, Memphis, TN.

Background: End stage renal disease (ESRD) patients starting dialysis treatment often experience worse mental health and quality of life. While poor mental health has been associated with a higher risk of mortality and hospitalization in studies of veteran patients, there is a dearth of research specifically evaluating the association of posttraumatic stress disorder (PTSD) and these outcomes in veterans transitioning to dialysis.

Methods: From a nationwide contemporary cohort of 79,331 US veterans transitioning to dialysis between 10/2007 and 3/2014, we identified 5,464 (6.9%) veterans with a PTSD diagnosis prior to transition. The association between pre-ESRD (prelude) PTSD and 1-year all-cause mortality was examined via adjusted Cox regression, and Poisson regression was used to evaluate the association between PTSD and 1-year hospitalization rate. Models were hierarchically adjusted for case-mix and laboratory covariates.

Results: Patients were 71±12 years old and included 5% women, 24% African-Americans, 61% diabetics and 9% were homeless. Patient with prelude PTSD had a higher risk of 1-year all-cause mortality [aHR: 0.89 (0.84-0.95)], but a lower 1-year hospitalization rate. Models were hierarchically adjusted for case-mix and laboratory covariates.

Conclusions: While prelude PTSD is associated with reduced risk of post-ESRD mortality in veterans transitioning to dialysis, it is also associated with a higher hospitalization rate. Studies are warranted to examine the role of psychosocial factors between prelude PTSD and post-ESRD outcomes, and whether an increased hospitalization rate mediates better survival for veterans with PTSD transitioning to ESRD.

Funding: NIDDK Support

SA-PO455

Impact of Multimorbidity on Patient-Reported Quality of Life – Analysis of a Real World CKD Patient Population James Jackson,1 Anna Hadfield,2 Rebecca Moon.1 Adelphi Group, Macclesfield, United Kingdom; 2Adelphi Real World, Macclesfield, United Kingdom.

Background: It is widely accepted that the prevalence of anemia, secondary hyperparathyroidism (SHPT) and hyperkalemia amongst chronic kidney disease (CKD) patients increases as CKD worsens. The objective of this analysis was to determine whether an increase in the number of CKD related comorbidities has an impact on patient quality of life (QoL).

Methods: Data were drawn from the Adelphi CKD Disease Specific Programme (DSP), a real-world, cross-sectional survey of consulting non-dialysis (ND) and dialysis CKD patients across EU and USA. Patients were segmented according to the number of physician-reported, CKD-related comorbidities (anemia, SHPT and/or hyperkalemia) experienced and patient-reported QoL was assessed using EuroQol-5D-3L-SL (EQ-5D).

Results: Results from 1758 CKD patients showed that as CKD worsened, patients were more likely to experience multiple comorbid conditions (Figure 1). An increase in multimorbidity at Stage 3-ND and Stage 4-ND was associated with a decrease in patient-reported QoL. For Stage 4-ND patients, a significant reduction was observed in the mean EQ-5D score for patients with 3 conditions compared with those who have 0 conditions (Figure 1). Although a similar trend was not observed amongst the Dialysis population, the QoL scores were lower overall than those patients at an earlier stage (Figure 1).

Conclusions: Multimorbidity increases as CKD progresses. Increased multimorbidity is associated with a poorer quality of life for CKD patients. Slowing disease progression could help prevent the onset of anemia, SHPT and/or hyperkalemia leading to maintenance of better QoL for longer.

Figure 2: Proportion of patients with 0, 1, 2 or 3 comorbidities commonly associated with CKD and related EQ-5D utility scores

Funding: Other NIH Support - Patient-Centered Outcomes Research Institute

SA-PO456

Association between Peer Mentoring and Quality of Life among Patients with CKD Hafiz Z. Mahmodoo, Awais Ammar, Emily J. Wasserman, Tara Liaghat, Umar Farooq, Nasrollah Ghalhrami. Penn State College of Medicine, Hershey, PA.

Background: Health related quality of life (HRQOL) has been increasingly recognized as an important medical outcome in patients with chronic kidney disease (CKD). Peer mentoring (PM) has been proposed as an effective model for active patient engagement and subsequent improvement in HRQOL. This study evaluates the preliminary effects of face-to-face peer mentoring on HRQOL among patients with chronic kidney disease.

Methods: Sixty-one patients with CKD were assigned to trained peer mentors with whom they had weekly phone contact and at least monthly face-to-face contact for a six-month period. All participants completed a baseline Short Form Kidney Disease Quality of Life (KDQOL) instrument, developed as a self-report, health-related QOL tool designed specifically for patients with CKD. Currently, 25 patients have also completed the 12-month assessment. The Wilcoxon Signed Rank Test was used to evaluate paired differences in patient outcome measures for patients receiving face-to-face mentorship between the baseline and 12-month assessments (Change = Difference of 12-month assessment minus baseline assessment). All reported p-values are two-sided with a significance level of 0.05.

Results: There was a significant difference in the ‘Symptoms/Problems’ subscale (p=0.003; Median Change=-6.25, IQR = 20.83, N=25) and the ‘Effects of Kidney Disease’ subscale (p=0.01; Median Change=-12.50, IQR=-25.00, N=25) of the KDQOL between the baseline and 12-month assessments. No significant differences were noted in the assessment of Kidney Disease (p=0.73, N=25), Physical Component Summary (p=0.89, N=15) and Mental Component Summary (p=0.30, N=15).

Conclusions: Face-to-face peer mentoring is associated with improved symptoms and problems subscale, as well as the effects of kidney disease subscale of the KDQOL instrument.

Funding: Other NIH Support - Patient-Centered Outcomes Research Institute

SA-PO457

Depression, Anxiety, and Stress – Before and After Dialysis Initiation: A Pilot Study Ciccio I. Bezerra, Bruno C. Silva, Rosilene M. Elias. Universidade de Sao Paulo, Sao Paulo, Brazil.

Background: Chronic kidney disease (CKD) affects psychological and emotional aspects that are particularly critical while choosing the renal replacement therapy (RRT) modality. Anxiety, depression and stress are common yet frequently overlooked among these patients. We have examined the behavior of these emotional components pre- and post-RRT and hypothesized that there will be an improvement of symptoms after starting dialysis, regardless of chosen modality.

Methods: This is a prospective observational study in which patients were approached two months before starting dialysis (within the first 3 months). Scales of anxiety, depression and stress (Hospital Anxiety and Depression Scale and Perceived Stress Scale, respectively) were applied. Demographic and clinical characteristics were also assessed.

Results: Out of 67 patients, 16 have already started RRT by April 2017 (50% men, age 56±15 years, 58% Caucasian, 42% diabetic). Scores of depression, anxiety and stress reduced significantly from pre to post RRT initiation (Table 1), with no difference between patients who chose peritoneal dialysis or hemodialysis. Before RRT, anxiety scores correlated significantly with depression (r=0.75) and stress scores (r=0.79); after RRT initiation, anxiety scores correlated significantly with depression (r=0.59) and stress scores (r=0.62).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: Although decision-making on RRT is a process associated with high scores of anxiety, depression and stress, these symptoms are attenuated at the end of this process, with patients already on dialysis. This finding identifies the importance of targeting psychological symptoms on RRT modality choosing process, and highlights that an improvement might occur after RRT initiation.

Table 1 - Anxiety, Depression and Stress scores before and after RRT initiation

<table>
<thead>
<tr>
<th></th>
<th>Before RRT</th>
<th>After starting RRT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety scores</td>
<td>6.1 ± 2.3</td>
<td>9.1 ± 1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depression scores</td>
<td>7.8 ± 2.0</td>
<td>11.2 ± 2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stress scores</td>
<td>29.4 ± 7.5</td>
<td>11.1 ± 6.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SA-PO458 Enhanced Evaluation of Human Renal Biopsies Using Multicolor Flow Cytometry and Cytokine Analysis: A Focus on Transplanted Kidneys

Background: Virtually all renal disease is due to an immune response. Examination of renal biopsies with light, immunofluorescence and electron microscopy provide limited information about immune mechanisms causing kidney injury and disease activity. In addition, information is often insufficient to direct therapy with specific agents, which becomes a frustration with new immune modulating agents being developed.

Methods: To enhance the information available from a biopsy we developed a technique for reducing a fraction of a renal biopsy to single cells for multicolor flow cytometry and for capture and quantitation of secreted cytokines present within the biopsy. As proof of concept, after evaluation of over 400 biopsies, we use our technique to suggest new criteria for evaluating rejection and renal inflammation that are clinically useful for directing therapy.

Results: A ratio of CD4+ to CD4lymphocytes of greater than 1.2 within the biopsy of transplanted kidneys is associated with rejection, even before it is apparent by microscopy. Elevated numbers of CD45 leukocytes and higher levels of IL-6, IL-8 and IL-10 within the kidney indicate more severe injury. Antibody binding to microvascular endothelial cells can be measured and corresponds to antibody-mediated forms of allograft rejection. Eculizumab binding to endothelial cells suggests complement activation, which may be independent of bound antibody. A comparison of intrarenal leukocyte subtypes and their activation states to those of peripheral blood from the same donor at the time of biopsy identify significant differences supporting the need to develop techniques which interrogate the immune system within the kidney.

Conclusions: Our use of cytometry to assess intrarenal leukocyte subsets, microvascular endothelial cell properties and secreted cytokines from a fragment of a standard renal biopsy provide useful information about the immune processes in the kidney. After evaluation of over 400 biopsies we find results reliable indicators of disease activity. This information is not available from peripheral blood. While we have focused on biopsies from transplanted kidneys (due to their availability), our techniques are equally applicable to native kidneys. Cytometry can enhance renal biopsy evaluation in a clinically significant manner.

Funding: Private Foundation Support

SA-PO459 Outcomes of Kidney Transplant Recipients with G3 Glomerulitis

Background: Glomerulitis is one of the pathological features of AMR. However, the natural history of kidney allografts with G3 lesions (glomerulitis in >75% of glomeruli) is poorly defined.

Methods: We sought to determine the concomitant immunopathologic findings and outcomes in a case series of kidney transplant recipients with G3 lesions. Results: Thirty seven consecutive kidney transplant recipients with G3 lesions in diagnostic biopsies performed 6.2 ± 6.7 years after transplant were included. At the time of biopsy, mean age was 45.5 years and all patients were on triple therapy with CNI, MPA, and prednisone. The majority were Caucasian (90%), male (60%), and had transplant glomerulopathy (68%), with kidney function and immunopathological findings (mean values) at the time of biopsy displayed in Table 1. Treatment after the biopsy included pulse steroids/VIG (70%), Rituximab (50%), and plasma exchange (10%). Patients were followed up for a mean of 1.6 ± 1.1 years. The incidence of graft loss and death was 11 (30%) and 3 (10%), respectively. Univariate regression analyses including demographic, functional, and immunohistological variables determined that t score (HR = 2.7, 95% CI: 1.3 to 5.8), eGFR score (HR = 2.1, 95% CI: 1.009 to 4.7), Scar score (HR = 1.6, 95% CI: 1.1 to 2.2), and live donor status (HR = 0.18, 95% CI: 0.3 to 0.9) were significantly associated with graft loss. Multivariable stepwise Cox regression analyses only retained Scar (HR = 1.8, 95% CI: 1.2 to 2.7) and live donor status (HR = 0.14, 95% CI: 0.02 to 0.8). Notably, C4d staining and DSA were not retained as significant predictors.

Conclusions: In this largest case series of patients with G3 lesions, 30% of the grafts were lost in 2 years. Scar score and live donor status were the most important variables associated with graft loss. Future studies are needed to determine preventive and treatment strategies to improve outcomes in patients with G3 lesions.

SA-PO460 Eosinophil-Rich Inflammation in Allograft Renal Biopsies: An Analysis of Clinical Significance and Correlation with Rejection

Background: In this study we investigate the significance of interstitial eosinophilic inflammation in renal allografts and its association with rejection, response to treatment, risk of subsequent rejections, and allograft outcome.

Methods: We studied 26 kidney transplant pts between 2012-17 with AKI who underwent biopsies. The biopsies showed clusters of interstitial eosinophils histologically, with or without evidence of ACR, AMR, or both. Allograft function at the time of the biopsy was assessed by SCr and by its change from baseline. After initial treatment, pts were categorized as, “Complete Responders (CR): SCr returned to baseline - Partial Responders (PR): SCr decreased to a level that was greater than 50% of SCr at the time of biopsy, but never returned to baseline. - Non Responders (NR): SCr remained or above SCr at the time of biopsy.

Results: 22 out of the 26 biopsies with eosinophils had rejection [Borderline 10 (45%), 1A 1 (5%), 1B 5 (23%), 2A 1 (5%), 2B 2 (9%), AMR+ACR 3 (14%)]. Allograft response to treatment of underlying and incidents of subsequent rejection is shown in Table 1. Of 13 of 22 pts with eosinophilia and rejection had subsequent rejection (64%, 95%CI: 44-84%), 30% of the pts (2 of 7) progressed to needing RFT, of which 2 lost allograft within 2 yrs, 22% (5) of pts with eosinophilic rejection had h/o BK viremia, 22% (5) had h/o CMV viremia, of which 75% were NR. 50% (11) of the pts who had eosinophilic rejection had history of recurrent UTIs. One pt with HIV had severe rejection with plasma cells and allograft loss within a year of transplantation. 61% (16) pts were on drugs that are shown to be associated with AIN especially PPIs. Only 34% (3) pts had peripheral eosinophilia.

Conclusions: Of the 26 pts with eosinophilic inflammation in the allograft biopsy we note a higher incidence of ongoing rejection and risk of developing subsequent rejection and allograft loss. As eosinophilia remains a marker of ongoing rejection, UTIs, BK, CMV had higher incidence of underlying rejection with eosinophilic infiltrates.

Table 1: Allograft response to treatment of underlying and incidents of subsequent rejection

<table>
<thead>
<tr>
<th></th>
<th>% of Patient</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>PK</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>NR</td>
<td>3</td>
<td>36</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>13</td>
</tr>
</tbody>
</table>

SA-PO461 Angiotensin-2 Expression Is Increased in Macrophages during Acute Cellular Rejection of Human Allografts

Background: The renin-angiotensin system (RAS) is well known to involve in hemodynamic changes in the kidney, but recent in vivo studies imply immunologic effects of RAS to cause damages in kidneys, partially through stimulating Interleukin-1 production by macrophages. We previously demonstrated that macrophages are one of dominant cellular components in acute cellular rejection (ACR). This study was to investigate whether there was an expression of angiotensin-2 (Ang2), the effector molecule in RAS, in macrophages involving ACR.

Methods: The study included 3 groups. The group 1, as the negative controls, was composed of 15 normal parenchyma sections away from renal cell carcinoma in nephrectomy specimens. The group 2, as the study group, consisted of 20 human allograft explant cases with ongoing ACR. As Ang2 is a small 8-peptide molecule being difficult for targeted staining, we selected 20 sarcoidosis cases (composed of aggregated and fused macrophages into giant cells), mostly known to have elevated serum angiotensin-converting enzymes, as the positive controls (4 in kidneys, and others in tonsil, liver and hilar lymph nodes). All paraffin embedded sections were stained for Ang2 by immunohistochemical staining method and cytoplasmic staining of Ang2 was graded 0 to 3 (0 - no staining, 1+ - weak fmal granular staining, 2+ - moderate granular staining and 3+ - strong granular staining).

Results: All negative controls (group 1) stained negatively for Ang2, as no or minimal inflammatory cells were present. All sarcoid granulomatous cells (macrophages and giant cells) in positive controls demonstrated prominent (2+ to 3+) positive staining for Ang2 in the cytoplasm. In macrophages involved in ACR of group 2, there was diffuse granular expression of Ang2 in macrophages with intensity ranging from 1+ to 3+. In the group 2, lymphocytes with scant cytoplasm appeared to stain weakly for Ang2 as well.

Conclusions: Using sarcoid granulomas as positive controls for Ang2 expression, the data indicate that Ang2 expression can be highly present in the activated macrophages involving in ACR of human allografts, implying Ang2 as a potential therapeutic target against ACR. In addition, the results from human specimens also support a notion that the RAS may affect some immunologic activities in the kidneys, based on previously in vitro and in vivo experiments.
Molecular Diagnosis of Rejection in Formalin Fixed Paraffin Embedded Kidney Transplant Biopsies Is Feasible but Extensively Compromises the RNA

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO465


Background: Tissue analysis of intragraft immunological processes remains an essential, but often underestimated tool as an early prognostic determinant of humoral changes and graft loss in kidney transplantation. This is particularly true for the growing population of sensitized recipients with an increased risk of immunological graft loss.

Methods: We retrospectively studied all eligible 213 allograft biopsies from 104 standard-risk and sensitized patients transplanted between 2006 and 2012, obtained in the first year after transplantation. We compared the effect of macrophage infiltration on long-term-allograft function and death-censored graft loss in both risk populations, analyzing the impact on the development of acute and chronic changes.

Results: Organ recipients from deceased donors had a higher CD68-positive cell infiltration one month after transplantation compared to living donor ones. Strong CD68 positivity in the first month after transplantation was associated with the occurrence of delayed graft function in sensitized patients. High number of CD68 positive cells one month after transplantation was a valid predictor of death censored graft loss in standard-risk patients. In sensitized patients, the number of tissue infiltrating CD68-positive cells in biopsies obtained between day 90 and 360 of transplantation was inversely correlated with the kidney function 1, 2 and 3 years after transplantation. Moreover, each CD68-positive cell increased the risk in 1.024 for the further development of antibody mediated rejection in this collective.

Conclusions: Macrophage tissue infiltration represents a potential additional tool for the analysis of kidney transplant biopsies and may predict worse outcomes especially in sensitized patients, irrespective of the histological diagnosis.

SA-PO467


Background: Patients (pts) awaiting kidney transplant (ktx) with pre-formed donor specific anti-HLA antibodies (DSA) have been subjected to aggressive desensitization or long wait times for a compatible donor. Anti-DP DSA may represent a unique situation amenable to ktx without desensitization. Since 2014, we have done 16 ktxs with isolated pre-formed anti-DP DSA with Mean Fluorescence Intensity (MFI) >5000 without desensitization.

Methods: We performed a chart review to assess the incidence of antibody mediated rejection (AMR) and graft survival at 6 months post ktx in this pt population.

Results: 16 pts with DP DSA >5,000 MFI and cPRA ranging from 75-100% underwent ktx. All pts have completed 6 month follow up. Virtual crossmatch was used in all pts; 8 had a positive B cell flow crossmatch. All pts received 2 g/kg IVIG in the immediate post- ktx period. There was a significant decrease in DP DSA MFI (figure). During six month follow up period, 14 pts had allograft biopsy. Six pts were diagnosed with AMR. There was no graft loss. Mean eGFR (MDRD equation) at 6 months was (63.9 ml/min). eGFR for the 10 patients without AMR was 71.5 ml/min versus 43.1 ml/min in those patients with AMR (P=0.02). There was no difference between those with AMR vs no AMR wrt sex (P=0.12), race (P=0.28), cPRA (P= 0.65), or positive flow x match (P=1).

Pts with AMR were younger (P=0.03) and displayed a trend toward higher pre-ktx DP DSA MFI compared to those without AMR (16097 vs 17119; P= 0.16).

Conclusions: We have been successfully transplanting pts with high levels of DP DSA (even with positive FXM) without aggressive desensitization. At 6 months, 10 out of 16 patients with anti DP DSA MFI >5000 experienced no AMR and there was no graft loss. Further investigation is needed to identify definitive risk factors for AMR in ktx with anti-DP DSA. Higher MFI pre-ktx may be a risk factor for AMR in this population and should be further investigated.

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

798
SA-PO468

Differential Outcomes in Patients with De Novo Donor-Specific Antibodies (DSA) Compared to Patients with Preformed DSAs

Abstract: The Natural History of De Novo Donor-Specific Antibodies (dnDSA):

Methods: This is a prospective study including 664 non-HLA-identical patients who received a kidney transplant between January 2009 and December 2014. Protocol testing for DSA via LAbScreen single antigen beads was done before and at 1, 3, 12 months, and then annually. Patients with preformed DSAs received a transplant with anti-thymocyte globulin and IVIG induction treatment if CDC cross-match was negative and MFI value was < 5,000 for HLA-A, B, DR and < 10,000 for HLA-C, DQ and DP.

Results: 108 (16%) patients had preformed DSA before transplantation. During a median follow-up of 13.8 months, de novo DSA developed in 95 patients (17%) at a mean of 20.3±13.3 months after transplantation. Those patients were compared to 461 patients without any DSA. There was no difference between incidences of acute antibody (AMR) or T cell mediated rejection (ACR), chronic rejection, transplant glomerulopathy (TG), serum creatinine levels, graft and patient survival when preformed DSA patients compared to no DSA patients. While there was no significant difference in patient survival, de novo DSA group had lower graft survival (61.4% ± 92.7%), higher AMR (17.3% vs. 1.6%), ACR (14.1% vs. 4.3%) and TG/CAMR (16.3% vs. 3.3%). Of the 108 patients with preformed DSA, 67 patients lost DSA and 41 showed persistent DSA. Persistent DSA patients had more class II antibodies (56% vs. 36%) and higher MFI values (4608±4150 vs. 2235±1283). For de novo DSA patients, 49% had persistent DSA, 40% lost their DSA and 11% had their DSA MFI decreased by more than 50%. The mean follow-up of de novo DSA in the persistent DSA group was higher than the patients who lost their DSA (4063.3±3487) or DSA MFI decreased by more than 50% (8768.7±8455.4).

Conclusions: 17% of our transplant recipients develop de novo DSA after kidney transplantation and associated with significantly higher allograft rejection and lower allograft survival. Low level pre-DSAs do not increase the risk of graft loss in patients who receive thymoglobulin/IVIG induction therapy.

SA-PO469

The Natural History of De Novo Donor-Specific Antibody (dnDSA): Results from Systemic Monitoring of DSA at ECMC

Methods: We performed a single centre retrospective cohort study with the hypothesis that patients identified as having BPAR or dnDSA at any timepoint would have a greater mean IPV than those who did not. Patients transplanted in our centre between 2009-2014 and receiving standard preparation Tacroliumus based immunosuppression were included. Patients receiving other primary immunosuppression, who were in receipt of organs other than kidneys and who did not have a functioning transplant at 2 years were excluded. One hundred and seventy one patients were identified if IPVA data collected at 2 predetermined time points: 6-12 months post-transplant (T1) and the most recent 12 months (T2).

Results: IPVA values were compared using Mann Whitney U tests between patients developing a) BPAR and b) dnDSA with those who did not, at both T1 and T2. The results are shown in table 1. There is a clear association between BPAR and high IPVA at T1 which reverses at T2 but fails to reach statistical significance. For dnDSA, we observe a higher IPVA for both T1 and T2 although in both cases it is not statistically significant.

Conclusions: As most episodes of BPAR occur early post-transplant, it is possible that observed reversal in IPVA at T2 reflects more precise monitoring and control of Tacrolimus exposure in these patients following rejection. In respect of the observation of higher IPVA at both T1 and T2 for dnDSA, the small sample size who developed antibodies may have contributed to the failure to reach significance and it is anticipated that this analysis will be expanded to a multicentre cohort in the future.

Table 1: Mann Whitney U Test to compare BPAR and DnDSA

SA-PO470

De Novo Donor Specific Antibody (dnDSA) and Biopsy Proven Acute Rejection (BPAR) Are Associated with Higher Intrapatient Variability (IPV) in Tacrolimus Trough Levels Following Renal Transplant

Background: High IPV in Tacrolimus trough levels has been associated with poorer kidney transplant outcomes, including the occurrence of BPAR. However, there is a paucity of information in the published literature about any association between high IPV and the development of dnDSA.

Methods: We performed a single centre retrospective cohort study with the hypothesis that patients identified as having BPAR or dnDSA at any timepoint would have a greater mean IPV than those who did not. Patients transplanted in our centre between 2009-2014 and receiving standard preparation Tacroliumus based immunosuppression were included. Patients receiving other primary immunosuppression, who were in receipt of organs other than kidneys and who did not have a functioning transplant at 2 years were excluded. One hundred and seventy one patients were identified if IPVA data collected at 2 predetermined time points: 6-12 months post-transplant (T1) and the most recent 12 months (T2).

Results: IPVA values were compared using Mann Whitney U tests between patients developing a) BPAR and b) dnDSA with those who did not, at both T1 and T2. The results are shown in table 1. There is a clear association between BPAR and high IPVA at T1 which reverses at T2 but fails to reach statistical significance. For dnDSA, we observe a higher IPVA for both T1 and T2 although in both cases it is not statistically significant.

Conclusions: As most episodes of BPAR occur early post-transplant, it is possible that observed reversal in IPVA at T2 reflects more precise monitoring and control of Tacrolimus exposure in these patients following rejection. In respect of the observation of higher IPVA at both T1 and T2 for dnDSA, the small sample size who developed antibodies may have contributed to the failure to reach significance and it is anticipated that this analysis will be expanded to a multicentre cohort in the future.

Table 1: Mann Whitney U Test to compare BPAR and DnDSA
SA-PO472

Altered Kynurenine 3-Monoxygenase May Mediate Rejection and Tubular Cell Injury in Pig Kidney Transplants Youli Wang,1 Xueci Fang,1 Daniel T. Klevén,1 Chak-Sum Ho,2 Stanley Rahman,3,4 Todd D. Merchen.3 1Augusta University, Evans, Columbia; 2Gift of Life Michigan, Ann Arbor, MI; 3Medical College of Georgia at Augusta University, Augusta, GA; 4Northwood VAMC, Augusta, GA.

Background: The indoleamine 2,3-dioxygenase (IDO) transprotein prevents rejection (RJ) in rodent solid organ transplantation, including kidney transplant (KTs). Thus, the increase in IDO activity in RJX seen in our pig KTx model and in KTx patients (KTI; 77:60) is paradoxical. Kynurenine (KYN) 3-monoxygenase (KMO) is a downstream enzyme of IDO generating 3-OH-KYN which is both pro-tolerant and cytotoxic. On this basis, we theorized that RJX would blunt KMO activity from rejecting pig kidneys, and in particular, silence tubular epithelial cell (TEC) KMO expression.

Methods: Pigs underwent allogeneic (Allo) (n=9) or auto renal transplants (Auto) (n=10 and as a control for ischemia), as we described (Transplantation, in press). For Allo, pairs of mismatched pigs operated simultaneously with L kidneys exchanged. All Autos were also the L kidney. All pigs then had right nephrectomy (control tissue (RTx)) prior to closure, and left Nx at sacrifice after 72 hrs. No immunosuppression was used in all kidneys. RJX was assessed using Banff criteria; IDO and KMO gene expressions quantitated with qPCR; tissue IDO activity measured by HPLC, and tissue KMO localized and quantitated with immunohistochemistry (IHC).

Results: Postop creatinine was higher in Allo vs Auto (8.1±2.5 vs 2.8±0.6 mg/dL, respectively, P<0.006). Auto had mild tubular injury, and no changes in IDO mRNA or activity vs RTx (n=16). Allo showed acute rejection (Banff I to III), with a 6 fold (X) increase in allograft IDO mRNA, and 19.5X increase in tissue IDO activity vs Auto. KMO showed a 2X reduction in Auto, and 5X decrease in Allo RJX kidneys. By IHC KMO activity was constitutively in Auto and RTx NEC, but silent in TEC from rejecting Allo.

Conclusions: KMO gene activity and TEC expression are blunted in KTx rejection. KMO may be an important downstream mediator of IDO activity and function in a protolerant and cytotoxic protective capacity. This may help explain the paradoxical increase in IDO activity seen in KTI rejection.

SA-PO473

Association of HLA-DR and DQ Mismatches and Acute Rejection in Living Donor Kidney Transplant Recipients Daniel Onete,1 Qingyong Xu,2 Rita Sun,3 Lakshman Gunaratnam.1 1London Health Sciences Centre, Oakville, ON, Canada; 2Université de Montréal, Montréal, QC, Canada; 3Physiology and Pharmacology, Western University of Canada, London, ON, Canada.

Background: Previous studies show that HLA-incompatibility is associated with greater risk of graft failure in deceased-donor kidney transplant patients. However, whether HLA-mismatches are important in low-risk recipients of living donor kidneys in the era of modern immunosuppression is unclear. Given that de novo, donor specific antibodies against Class II HLA (DQ or DR) are associated with poor long-term outcomes in deceased donor transplant recipients, we hypothesized that having 3-4 vs. 0-2 HLA DQ/DR mismatches would be associated with acute rejection in low-risk, living donor kidney transplant recipients.

Methods: We conducted a retrospective cohort study of all cross-match negative, transplant-naive, living donor kidney transplant recipients at our center from 2006-2016. Electronic charts were reviewed for demographics, comorbidities, HLA genotype and outcomes. HLA genotyping was performed using molecular typing. The primary outcome was acute rejection (RJ) within 1-year post-transplant, and was defined as either: definite biopsy-proven T-cell mediated rejection (TCMR) (Banff criteria), or as borderline TCMR on biopsy that was treated with pulse steroids and/or anti-thymocyte globulin. The secondary outcome was serum creatinine at 1 year post-transplant. Outcomes were compared between patients with 0-2 vs. 3-4 HLA-DQ/DR mismatches.

Results: Of the 178 recipients transplanted with living donor kidneys from 2006-2016, 6 were excluded due to incomplete follow-up data. In total, 124 (72%) and 48 (28%) received 0-2 and 3-4 HLA-DQ/DR mismatched kidneys, respectively. We observed 27 definite RJ (10%). Of these, 25 treated borderline rejections within 1-year post-transplant. Patients with 3-4 HLA-DQ/DR mismatched kidneys had a statistically significant greater risk of acute rejection (odds ratio = 3.43 [95% CI 1.69-6.94]; p=0.0008). This association persisted when we limited the primary outcome to definitive rejection (odds ratio = 3.39 [95% CI 1.45-7.89]; p=0.0053). There was no significant difference between groups in the mean 1-year serum creatinine (122.4 ± 5.889 vs. 117.0 ± 4.035; p=0.59).

Conclusions: In this single-center study, we found that greater HLA-DR and DQ mismatches were associated with increased risk of acute rejection at 1-year after living donor kidney transplant. Funding: Government Support - Non-U.S.

SA-PO474

Highly Sensitized Patients at Miami Transplant Institute: An Update Camilo Cortesi,1 Mai Sedki,2 Gillesse Guerra,3 Gabriel Contreras,4 Adela D. Mattiazzi.2,4 1University of Miami, Miami, FL; 2University of Miami/Jackson Memorial Hospital, Miami, FL; 3University of Miami/Miller School of Medicine, Miami, FL.

Background: Highly sensitized (HS) patients are defined as transplant candidates sensitized against human leukocyte antigen (HLA) antibodies with a panel reactive antibody (PRA) greater than 80%. This has been a major obstacle to kidney transplantation (KT). Major causes are blood transfusions, pregnancy and prior transplants. HS patients have an increased risk of rejection, worse graft survival, and less annual transplant rates. There are different strategies available for desensitization including intravenous immunoglobulin (IVIG), Rituximab (R), and Thymoglobulin (Thy). We provide an update of our experience comparing patients undergoing desensitization.

Methods: This is a retrospective analysis of 50 HS KT recipients categorized into 2 groups based on induction immunosuppression received at transplantation. The control group (CG) received standard induction. The Rituximab group (RG), 38 HS KT, received standard induction as well as R and IVIG. KT graft failure, and death. Secondary outcomes assessed graft function via serum creatinine at various times post-transplant.

Results: The number of HLA mismatches was not statistically different between the 2 groups. In the CG, 75% had prior transplants compared to 53% in the RG. Mean waiting time for KT was 7.6 years and 5.4 years for the CG and RG, respectively (p=0.007). The cumulative proportion of patients who remained free of death or allograft failure was significantly higher in the RG (87%) compared to the CG (60%) (p=0.039). The probability of rejection was similar in both groups (p=0.36). The mean serum creatinine at 1 year was 1.35 ± 0.54 and 1.36 ± 0.64 mg/dL for the CG and RG, respectively.

Conclusions: Desensitization strategies are fundamental for the management of the HS population. Our study confirms that the addition of R continues to improve allograft survival and decrease death rates.

SA-PO475


Background: Acute rejection is a significant cause of morbidity, and transplant biopsy remains the gold standard to diagnose the failure of rejection. Guidelines published by KDIGO recommend biopsy for “persistent, unexplained increase in serum creatinine.” To our knowledge there have been few studies defining the magnitude of decline in renal function that should trigger a biopsy to rule out rejection.

Methods: We performed a retrospective analysis of patients at a single center who underwent diagnostic transplant biopsy (excluding surveillance biopsies) between 2006-2016 at least three months post-transplant. We evaluated for association between pre-biopsy decline in renal function (mean of renal function measured between 6 months prior to biopsy and day of biopsy) and pathologic findings of rejection using logistic regression models (adjusted for age, race, sex, diabetes, donor type and transplant year). Absolute rise in serum creatinine and percent change in estimated glomerular filtration rate (eGFR) by CKD-EPI equation were examined as predictors of the outcome of rejection (cellular or antibody-mediated).

Results: 1,224 biopsies were included for analysis. Mean age was 46.3 years, 58.3% were female, and 18% were black. Overall, 53.5% of biopsies demonstrated evidence of rejection. Declines in eGFR of ≥20% were associated with higher odds of rejection in both unadjusted and adjusted analyses compared to a <5% decline in eGFR [Table]. Risks in absolute serum creatinine by ≥0.3 mg/dL also corresponded with a higher risk of rejection compared to rises <0.3 mg/dL.

Conclusions: In this single-center study, decline in eGFR ≥20% or rise in serum creatinine by ≥0.3 mg/dL were associated with higher risk of rejection. Changes in renal function of this magnitude may warrant prompt prompt arrangement of biopsy given the high risk of rejection.
Thresholds of decline in renal function and risk of rejection

<table>
<thead>
<tr>
<th>Precentage Change in eGFR</th>
<th>Number of biopsies</th>
<th>Unadjusted Odds Ratio (95% CI)</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5%</td>
<td>220</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>5-20%</td>
<td>248</td>
<td>0.41 (0.36-0.47)</td>
<td>0.42</td>
<td>0.05</td>
</tr>
<tr>
<td>&gt;20-40%</td>
<td>202</td>
<td>1.53 (1.06-2.20)</td>
<td>0.02</td>
<td>0.06</td>
</tr>
<tr>
<td>&gt;40%</td>
<td>543</td>
<td>2.41 (1.73-3.32)</td>
<td>0.001</td>
<td>2.20</td>
</tr>
</tbody>
</table>

SA-PO476

Ultrasound and CT Guided Kidney Transplant Biopsies: Evaluating Complications

Camillo Cortesi,1 Karla G. Carias martinez,2 Mai Sedki,1 Giselle Guerra,1 David Roth,3 Adela D. Mattiazzi,1 Jackson Health System, Miami, FL; None, Miami, FL; University of Miami Miller School of Medicine, Miami, FL; University of Miami/Jackson Memorial Hospital, Miami, FL; University of Miami/Miller School of Medicine, Miami, FL.

Background: Kidney transplant (KT) rejection is one of the main indications for KT biopsy (KTB). The ultrasound (US)-guided approach is the preferred method however the computed tomography (CT)-guided approach offers an excellent alternative when the yield is low. We sought to evaluate the incidence of complications in both techniques.

Methods: We identified 646 KTb performed to rule out rejection, 32 of those were CT-guided and the rest were US-guided. Data were collected in an electronic registry. Complications were divided into major and severe where moderate complications included: hematoma, hydrenephrosis, arteriovenous fistula, hemoglobin drop >2 g/dL, and need for blood transfusions; severe included the former events associated with a kidney dysfunction. Page kidney or the need for nephrectomy. Descriptive analysis was used for the CT-KTb and a logistic regression was conducted for the US-KTb.

Results: The logistic regression was statistically significant, indicating that the predictors as a set did reliably predict complication occurrence (chi square=51.044, p<0.05, df=34). Prediction success overall was 81.2%. The Wald criterion demonstrated that blood pressure control, BUN, and use of anticoagulants prior to biopsy had a statistically significant impact in predicting complications (p<0.001, p<0.007, p<0.027, respectively). Patients on anticoagulants prior to biopsy were 4 times as likely to have complications (odds ratio 4.167). In CT-KTb only one patient had complications. This patient had uncontrolled blood pressure, BMI ≥ 35, platelet count of 93 K/uL and INR was 1.21 at the time of biopsy.

Conclusions: Our data shows that uncontrolled blood pressure, defined as ≥160/90, uncontrolled anticoagulants were the main predictors of negative outcomes. The presence of these risk factors, particularly in combination, could be of great value in weighing the necessity of a procedure. Additionally, CT-KTb was shown to be a safe alternative for obtaining renal tissue. We highlight the need to achieve adequate control of blood pressure prior to KTb.

Demographics

<table>
<thead>
<tr>
<th>Age</th>
<th>US-KTb</th>
<th>CT-KTb</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>575 ± 15</td>
<td>575 ± 15</td>
</tr>
<tr>
<td>40-60</td>
<td>273 ± 15 female</td>
<td>151 (41.6%) male</td>
</tr>
<tr>
<td>60-80</td>
<td>101 ± 15</td>
<td>88 (28.2%)</td>
</tr>
<tr>
<td>&lt;40</td>
<td>60 ± 77</td>
<td>61 ± 37</td>
</tr>
<tr>
<td>40-60</td>
<td>21.7 ± 20.3</td>
<td>21 ± 15</td>
</tr>
<tr>
<td>60-80</td>
<td>313 ± 25</td>
<td>313 ± 25</td>
</tr>
<tr>
<td>&lt;40</td>
<td>0.9 ± 0.9</td>
<td>1.0 ± 0.9</td>
</tr>
<tr>
<td>40-60</td>
<td>11 (2.2%)</td>
<td>11 (2.2%)</td>
</tr>
</tbody>
</table>

Complications (n=14)

<table>
<thead>
<tr>
<th>Complications (n)</th>
<th>Status</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (n=1)</td>
<td>Normal</td>
<td>0.92 (95% CI)</td>
</tr>
<tr>
<td>1 (n=1)</td>
<td>Moderate</td>
<td>1.0 (95% CI)</td>
</tr>
<tr>
<td>1 (n=1)</td>
<td>Severe</td>
<td>1.5 (95% CI)</td>
</tr>
</tbody>
</table>

Format is mean ± SE unless otherwise specified

SA-PO477

Evaluation of C1q status and Titre of Donor Specific Antibodies as Predictors of Allograft Survival

Osama Attia,1,2 Emma Yaqoob,3, Alex Ashman,4 Karla Gupta,3,4 Mai Sedki,1 Giselle Guerra,1 David Roth,3 Adela D. Mattiazzi,1 Jackson Health System, Miami, FL; None, Miami, FL; University of Miami Miller School of Medicine, Miami, FL; University of Miami/Jackson Memorial Hospital, Miami, FL; University of Miami/Miller School of Medicine, Miami, FL.

Background: Donor-specific antibodies (DSA) either developed as de-novo or preformed before renal transplantation are independent predictors of allograft loss. However, it is unknown if DSA and C1q status post transplantation can independently predict allograft loss. Serologically emergence of de-novo or rising titres of preformed DSA is used as surrogate markers of impending graft dysfunction and rejection. However sensitivity and specificity of this approach is not robust enough to escalate immunosuppression. However recent evidence suggests that complement binding DSA may identify clinically important It is also associated with poor graft survival. C1q status may help clinician in the identification of patients who may be at high of losing graft following rejection and help in optimization of immunosuppression therapy.

Funding: Government Support - Non-U.S.

SA-PO478

Genome-Wide Association Meta-Analysis for Acute Rejection of Kidney Transplant

Karen E. Iwarsson,1,2,3 Pamala A. Jacobson,1,10,11 Welthua Guan,11 Casey D. Dorf,1,2 Martin H. De Borst,3 Caragh P. Stapleton,1,2 Paul J. Phelan,1,3 Peter J. Conlon,1 Kelly A. Birdwell,4 Stephan J. Bakker,3 Gianpiero Cavalleri,3 William S. Oetting,1 David P. Schladt,3 Jessica Van setten,3 Pui-Yan Kwok,2 Michael Eikmans,1,4 Harold Snieder,1 Baloon Wu,11 Laia Bassaganyas,1 Jinxin Yang,7,12 Brendan Keating,7 Beaumont Hospital, Dublin 9, Co Dublin, Ireland; UCSF, San Francisco, CA; Hennepin County Medical Center, Minneapolis, MN; Minneapolis Medical Research Foundation, Minneapolis, MN; RCSI, Dublin, Ireland; UMC Utrecht, Utrecht, Netherlands; University Medical Center Groningen, Rondern, Netherlands; University Medical Center Utrecht, Utrecht, Netherlands; University of California, San Francisco, San Francisco, CA; University of Groningen, Groningen, Netherlands; University of Minnesota, Minneapolis, MN; University of Pennsylvania, Philadelphia, PA; Vanderbilt University, Nashville, TN; Leiden University, Leiden, Netherlands; NHS Lothian, Edinburgh, United Kingdom.

Background: Acute rejection (AR) is associated with worse kidney allograft survival. Methods: We performed a genome-wide association study (GWAS) meta-analysis of AR in recipients and donors after kidney transplantation using the Affymetrix exome plus chip. AR was defined by treating physician at anytime post-transplant.

Funding: The interim meta-analysis of 5 GWAS cohorts participating in GeneTRAIN included 4,437 Caucasian kidney transplant recipients with 999 (23%) AR events (Table 1). Twenty-five recipient single-nucleotide polymorphisms (SNPs) reached GWAS significance (p ≤ 1E-7) for their association with AR. The top four recipient SNPs with strongest AR association include two located in introns of MAN5C1 rs15278158 (ρ=1.53E-9) and rs15280693 (ρ=1.75E-9). Another is located 7.5 kb upstream of UGT2B10 rs294768 (ρ=1.24E-8). The fourth SNP is located in the 3‘UTR of NUB1 rs54414806 (ρ=4.81E-8). Furthermore, 14 of the 25 top recipient SNPs are located in or near UGT2B10, including rs2942857, which is an mRNA splice acceptor. The donor analysis identified 66 SNPs reaching GWAS significance for their association with AR. The top two of these SNPs are rs8108030 (ρ=2.90E-9) and rs7439859 (ρ=3.69E-9) which are 79 kb and 58 kb upstream, respectively, of HERPUD2. Another donor SNP associated with AR is rs79865478 (ρ=4.62E-8), located in an intron of SOX3.

Conclusions: We identified several novel susceptibility loci associated with AR, which can be validated by independent cohorts.

Funding: Other NIH Support - AI U19 AI070119

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

Underline represents presenting author.
SA-PO479

Rituximab in Late Antibody-Mediated Kidney Transplant Rejection – A Double-Blind Randomized Placebo-Controlled Trial (BORTEJECT Study) Farsad A. Eskandary,1 Heinz Regele,2 Gregor Bond,1 Nicolas Kozakowski,2 Markus Wahrmann,3 Luis G. Hidalgo,3 Helmut Haslacher,4 Christopher Kaltenecker, Bernadette Aretin,4 Rainer Oberbauer,1 Jeff Reeve,1 Philip F. Halloran,4 Georg Bohling,1 1Nephrology and Dialysis, Medical University Vienna, Vienna, Austria; 2Clinical Pathology, Medical University Vienna, Vienna, Austria; 3Alberta Transplant Applied Genomics Centre, University of Alberta, Edmonton, AB, Canada; 4Laboratory and Pathology, University of Alberta, Edmonton, AB, Canada; 5Pharmacy, AKH-Wien, Vienna, Austria.

Background: Antibody-mediated rejection (ABMR) is a leading cause of long-term kidney transplant loss. Optimal treatment of late ABMR is unclear, and our current knowledge is mostly based on uncontrolled studies.

Methods: In this randomized, double-blind, placebo-controlled, single-center phase 2 trial (NCT01873157), we investigated whether two cycles of the proteasome inhibitor bortezomib (each cycle: 1.3 mg/m^2 on days 1, 4, 8, and 11) are able to halt the progression of late ABMR, using eGFR slope (over 0, 3, 6, 12, 18 and 24 months) as primary endpoint (44 patients; 1:1 randomization). Secondary outcomes were mGFR at 24 months, donor-specific antibody (DSA) course and morphological/molecular results of 24-month follow-up biopsies.

Results: Upon systematic cross-sectional HLA antibody screening of 741 recipients [inclusion criteria: age >18a, eGFR >20 ml/min/1.73 m^2 at a180 days post-transplantation] we identified 111 recipients with DSA. Forty-four DSA+ recipients with morphological evidence of ABMR were included in the trial. Twenty-one patients were allocated to receive bortezomib, and 23 placebo. Despite a trend in reduction of DSA levels, bortezomib neither affected eGFR decline (bortezomib vs. placebo: +4.7 vs. -6.8 ± 2.5 ml/min/1.73 m^2/year), nor median mGFR at 24 months [33mL (IQR: 28-40) vs. 43mL (26-51), p=0.02]. There were also no differences regarding two-year overall graft survival (81% vs. 96%, p=0.1) and morphological (ABMR category, g, ptc score, FTA score, C4d) and molecular results (Molecular-ABMR score, MMDx) of 24-month follow-up biopsies. Bortezomib treatment was associated with a higher rate of GI adverse events (diarrhea: 67% vs. 22%, p=0.005) and thrombo- and leukocytopenia.

Conclusions: The BORTEJECT trial demonstrates that proteasome inhibition does not ameliorate the two-year course of late ABMR. Our results underscore the need for randomized trials to disentangle the efficiency and safety of new treatment strategies in this context.

Funding: Government Support - Non-U.S.

SA-PO480

Hospitalization Trends for CMV Disease in Kidney Transplant Recipients in the United States, 2004–2014 Neetika Garg,1 Nilay Kumar,2 Sandesh Parajuli,3 Tripti Singh,1 Fahad Azziz,4 Maha A. Mohamed,5 Brenda L. Muth,3 Arjang Djamali,6 Didier Mandelbrot,7 1None, Madison, WI; 2School of Medicine and Public Health, Madison, WI; 3U of Wisconsin Hospital, Madison, WI; 4UW Health, Middleton, WI; 5University of Wisconsin, Madison, WI; 6University of Wisconsin School of Medicine and Public Health, Madison, WI; 7University of Wisconsin, Madison, Madison, WI.

Background: CMV infection is a frequent complication of kidney transplantation, especially with increasing use of more aggressive immunosuppressive regimens. How the burden of inpatient hospitalization related to this diagnosis has changed over time in the United States is not known.

Methods: We used the National Inpatient Sample 2004 – 2014 to identify hospitalizations with primary or secondary diagnosis of CMV disease (ICD-9 code: 078-5) in the setting of known history of kidney transplantation. Survey analysis techniques were used to generate national estimates. Data regarding prevalent kidney transplant recipient population was obtained from OPTN/STRTR. Linear and logistic regressions were used to test trends in hospitalization rate, acute kidney injury (AKI), diabetes-requiring AKI, length of stay (LOS) and cost.

Results: 2,126 hospitalizations over the 11-year study period were representative of 10,213 hospitalizations for CMV disease nationally. Mean age was 52 years; 44.3% were women. Rate of hospitalization remained stable during the study period (6.3 to 5.3 per thousand prevalent recipient population, p-trend=0.75). However, a trend towards increasing in-hospital mortality (1.8% to 2.9%, p-trend=0.07) along with significant increases in rates of AKI, diabetes-requiring AKI, LOS and cost were noted (Table 1). This was accompanied by an increase in comorbidity burden as measured by Mean Charlson Comorbidity Index (0.80 to 2.02, p=0.001) during the study period.

Conclusions: Our study findings may reflect a shift towards outpatient management of CMV disease with hospitalization only for the sickest patients in the United States. Patient outcomes were worse and resource utilization (duration and cost of hospitalization) was higher for those admitted in more recent years.

Table 1

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization rate per 1000 prevalent kidney transplant recipients</td>
<td>9.29</td>
<td>9.76</td>
<td>8.48</td>
<td>8.45</td>
<td>6.54</td>
<td>7.25</td>
<td>6.01</td>
<td>5.31</td>
<td>5.09</td>
<td>6.03</td>
<td>5.30</td>
<td>0.75</td>
</tr>
<tr>
<td>In-hospital mortality (%)</td>
<td>1.4</td>
<td>0.5</td>
<td>2.2</td>
<td>1.9</td>
<td>1.8</td>
<td>3.5</td>
<td>1.8</td>
<td>5.6</td>
<td>3.7</td>
<td>1.8</td>
<td>2.0</td>
<td>0.07</td>
</tr>
<tr>
<td>Dialysis-/hospitalization (%)</td>
<td>9.4</td>
<td>11.0</td>
<td>7.0</td>
<td>8.7</td>
<td>7.1</td>
<td>3.5</td>
<td>2.5</td>
<td>3.5</td>
<td>2.1</td>
<td>3.5</td>
<td>2.0</td>
<td>0.001</td>
</tr>
<tr>
<td>LOS days, mean</td>
<td>7.7</td>
<td>5.3</td>
<td>6.9</td>
<td>8.1</td>
<td>8.2</td>
<td>8.8</td>
<td>8.9</td>
<td>9.9</td>
<td>9.6</td>
<td>8.4</td>
<td>9.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Infection-related cost ($, mean)</td>
<td>[4,021 - 16,213]</td>
<td>[6,689 - 21,660]</td>
<td>[25,258 - 25,363]</td>
<td>[26,645 - 25,709]</td>
<td>[29,064 - 25,249]</td>
<td>[22,236 - 26,725]</td>
<td>[41,000 - 49,000]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SA-PO482

Long-Term Outcomes of Valganciclovir versus Valacyclovir for Cytomegalovirus Prophylaxis in Renal Transplantation: A Parallel Group, Open-Label Randomized Controlled Trial Tomas Reischig,1 Martin Kacer,2 Petra Hruza,3 Daniel Lysaök,4 Pavel Jindra,5 Ondrej Hes,6 Mirko Bouda,7 1Charles Univ. Medical School and Teaching Hospital, Pilsen, Czech Republic; 2Institute for Clinical and Experimental Medicine, Prague, Czech Republic.

Background: Both valganciclovir and high-dose valacyclovir are recommended for cytomegalovirus (CMV) prophylaxis after renal transplantation. Less early acute rejection was observed with valganciclovir, however long-term comparison is lacking.

Methods: In a randomized, open-label, single-center trial, renal transplant recipients (recipient or donor CMV seropositive) were randomly allocated (1:1) to 3-month prophylaxis with valganciclovir (900mg daily) or valacyclovir (2g four times daily). The

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

802
primary outcome was moderate to severe interstitial fibrosis and tubular atrophy (IFTA) associated by protocol biopsy specimens. Analysis was by intention-to-treat.

Results: A total of 119 patients were assigned to valganciclovir (n=60) or valacyclovir prophylaxis (n=59). At 3 years, the incidence of CMV DNAsemia (36% vs 42%, P=0.272) and CMV disease (9% vs 2%, P=0.199) was comparable in both groups. Among the 101 patients with a protocol biopsy specimen available, 11 (22%) of the 51 patients in the valganciclovir group and 17 (34%) of the 50 patients in the valacyclovir group had moderate to severe IFTA. The risk of moderate to severe IFTA was significantly lower with valganciclovir after adjusting for baseline recipient and donor characteristics (adjusted hazard ratio, 0.45; 95% confidence interval [CI], 0.25–0.81). No trend toward less acute rejection (24% vs 32%, adjusted hazard ratio [AHR], 0.53; 95% CI, 0.25–1.01; P=0.087) and more polyoma BK virus viremia (42% vs 26%; AHR, 1.91; 95% CI, 0.95–3.82; P=0.069) at 3 years was observed in the valganciclovir group. 4-year patient survival and graft survival were not significantly different among the two groups.

Conclusions: Valganciclovir prophylaxis compared to high-dose valacyclovir is associated with reduced risk of moderate to severe IFTA in late protocol biopsy recipients in renal transplant recipients. (Trial registered at Australian New Zealand Clinical Trials Registry: ACTRN12608000166303.)

Funding: Government Support - Non-U.S.

SA-PO483

Use of Body Surface Area Corrected GFR results in Inappropriate Valganciclovir Dosing in Kidney Transplant Recipients Rohan S. Paul, Chethan M. Puttarajappa, Sundaram Harthanar. University of Pittsburgh Medical Center, Starzl Transplant Institute, Pittsburgh, PA.

Background: Clinicians generally use the MDRD or CKD-EPI equations to gauge renal function, which normalize GFR to a body surface area (BSA) of 1.73 m². We hypothesized that since absolute GFR is rarely measured and used, prophylactic valganciclovir is being dosed inappropriately in certain renal transplant recipients which may predispose to leukopenia and or CMV infections. The ATHENA trial was designed to compare everolimus (EVR) in de novo kidney transplant recipients. 225 renal transplant recipients from 10 institutions were randomized to EVR (3–8 ng/ml M1–M12) + TAC (4–8 ng/ml M1–M3; 3–5 ng/ml M3–M12) or EVR (3–8ng/ml M1–M12) + CyA (75–125ng/ml M1–M3; 50–100ng/ml M3–M12) or control TAC regimens (4–8ng/ml M1–M3; 3–5ng/ml M3–M12) with MPA. All pts continued on steroids. Herein we report M12 outcomes on infections and CMV events from ITT with 205 EVR group pts and 205 TAC-MPA pts.

Results: From randomization to M12 total incidences of infections were 73% in EVR+TAC and 72% in EVR+CyA treated pts vs 82% in TAC-MPA pts. Whilst incidences of bacterial infections were similar between the three treatment groups (44% EVR+TAC, 42% TAC-MPA and 45% CyA), EVR+TAC-MPA major differences were seen for viral infections with incidences of 41% in TAC-MPA vs only 26% in EVR+TAC and 12% in EVR+CyA groups. Incidence of BKV events was 23% in TAC-MPA vs 17% in EVR+CyA vs 9% in EVR-Cya pts (p=0.01). CMV events occurred two thirds less in EVR treated pts and EVR+CyA +pts had an incidence of 21% in TAC-MPA vs 6% for EVR+TAC and 3% for EVR+CyA treated pts (p=0.001).

Conclusions: ATHENA as largest European KTx study confirmed comparable efficacy and safety together with less viral infections for EVR-based treatment groups with EVR+CyA vs TAC-MPA being significantly protective effect of EVR-based regimens vs EVR+CyA treated pts was robustly confirmed.

Funding: Commercial Support - Novartis Pharma GmbH, Germany; Government Support - Non-U.S.

SA-PO485

Peptide Vaccination against Cytomegalovirus (CMV) Induces Cellular Immune Response in CMV Seronegative ESRD Patients Claudia Sommerer,1 Anita Schmitz,1 G. Zeier,2 Michael Schmitz,1 Thirolgie; University Hospital Heidelberg, Heidelberg, Germany; 1Nephrology, University Hospital Heidelberg, Heidelberg, Germany; 2Internal Medicine V, University Hospital Heidelberg, Heidelberg, Germany.

Background: Cytomegalovirus (CMV) reactivation occurs particularly in patients after solid organ transplantation (SOT) from seropositive donors. CMV reactivation is associated with a high risk of disease and mortality. The nonameric peptide NLPVMATV derived from CMV phosphoprotein 65 (CMVpp65) is highly immunogenic. Here we report on a clinical phase I peptide vaccination trial with this peptide in a water-oil emulsion and an oil-in-oil (water-in-oil) emulsion (Alduram™) as adjuvant.

Methods: Four vaccines were administered subcutaneously at a biweekly interval to ten CMV seronegative endstage renal disease patients waiting for kidney transplantation. The clinical course, CMVpp65 antigenaemia and CMV replication were monitored. CMV-specific T cells were characterized by multi-color flow cytometry and IFN-γ ELISPOT (ELISPot) and correlated to clinical parameters.

Results: Peptide vaccination was well tolerated and no drug-related serious adverse events were detected except from local skin reactions. In four patients, specific CD8+ T cell responses against CMV could be elicited by prophylactic vaccinations. In responders an increase of CMV-tetramer positive CD8+ T cells and interferon gamma secretion was detected. Interestingly a shift from CCR7+CD45+ naïve T cells towards CCR7-CD45RA+ effectors was observed suggesting an effective immune response against the virus.

Conclusions: In ten CMV seronegative endstage renal disease patients on the waiting-list for kidney transplantation we demonstrated that administration of CMVpp65 peptide vaccination was safe, well tolerated and clinically encouraging. Imiquimod can serve as an adjuvant with a similar efficacy.

Funding: Commercial Support - Novartis Pharma GmbH, Germany.
Conclusions: Intensive BKV screening in the 1st year post kidney transplant allows for early intervention to guide IS management with excellent graft outcomes. This strategy reduces risk of over-treatment or risk of acute rejection. Larger trials are needed to determine the optimum frequency of BKV monitoring.

SA-PO487

Targeted Sequencing of BKPyV in Urothelial Carcinomas in Transplant Recipients

Evans A. Farkash, Edward S. Harake. University of Michigan, Ann Arbor, MI.

Background: Some urothelial carcinomas arising in transplant recipients show strong, universal expression of BKPyV Large T antigen (LTA). BKPyV is closely related to known oncoviruses SV40 and MCMV; we hypothesize that BKPyV acts as oncovirus in immunosuppressed transplant recipients. Determining the genomic structure of BKPyV in urothelial tumors may provide clues to the mechanism of oncogenesis.

Methods: We designed 26 sets of fully nested 5' and 3' primers using the BKPyV DlK strain and validated on a DlK isolate. DNA was extracted from paraffin blocks of 2 urothelial carcinomas with diffuse LTA expression (QAMP FFPE). The BKPyV genome was amplified by 2x overlapping nested PCRs and Sanger sequenced. Sequences were aligned and compared to 312 full length BKPyV sequences from the NCBI database, as well as 1 tumor previously sequenced by a different method (Megalign, Figgtree).

Results: Tumor 1 (fatal) arising 9.7 years after transplant in 59 year old male harbors a clade IV virus (31.2% sequenced). Tumor 2 (nonfatal) arising 8.9 years after transplant in a 68 year old female harbors a clade IV virus (84.8% sequenced). Tumor 2 (previous work) contains a clade 1a virus. Clade I has a worldwide distribution, and clade IV is enriched in Asian and Japanese regions.

Conclusions: A targeted amplification strategy was partially successful at sequencing BKPyV from urothelial carcinoma tumors from FFPE tissue. Identification of viruses from clades 1a, 1b1 and IV provides evidence that potential oncogenicity from BKPyV in transplant recipients is not restricted to a single clade. No viral integration sites or flanking DNA were identified, and a linker DNA technique is likely needed to map potential integration sites.

Funding: Other NIH Support - NIAID, Clinical Revenue Support

SA-PO488

Shotgun Cellfree DNA Sequencing to Evaluate Renal Allograft Damage in Recipients with BKVN

Darshana Dadhania,1 Philip Burnham,1 John R. Lee,2 Catherine Snopkowski,1 Carol Y. Li,1 Hua Yang,1 Thangamani Muthukumar,2 Manikkam Suthanthiran,2 Iwijn De Vlaminck,1 Cornell University, Ithaca, NY; 2Weill Cornell Medical College, New York, NY; 3Weill Medical College of Cornell University, New York, NY.

Background: BKV replication is frequent and is associated with graft loss in 20-50% of cases. Existing non-invasive assays to detect BKV replication fail to correlate with the extent of renal allograft damage. Advances in the measurement of cellfree (cf) DNA in allograft recipients may be useful to identify allograft damage associated with BKVN.

Methods: In 16 recipients with stored urine supernatants, we studied cf DNA of BK virus DNA & donor DNA fractions. Analysis was performed in sex-mismatched individuals with normal protocol biopsy (n=4) & biopsy proven BKVN diagnosis (n=12). We performed shotgun metagenomic sequencing on an Illumina NextSeq (2 x 75 bp) using a single-stranded library preparation. In patients who received organs from the opposite sex, a comparison of the depth of sequencing coverage of the sex chromosomes was used to determine the cf donor DNA fraction and associated with graft injury.

Results: Urine cellfree BKV DNA correlated with urine cell pellet BKV VP1 copies (Fig 1) and Figure 2 demonstrates the correlation between serum creatinine at the time of biopsy and cf donor DNA fraction. Female recipients (n=4) receiving a male donor kidney had significantly lower cf DNA fraction compared to male recipients (n=12) receiving female kidney (Fig 3a). Among the male recipients, those with BKVN diagnosis had significantly higher urine cf donor DNA fraction compared to those with normal protocol biopsy & stable graft function (Fig 3b).

Conclusions: Our data on sex mismatched allograft recipients demonstrates that urinary cf DNA measurement in recipients offers a noninvasive measure of the burden of viral disease & allograft damage. Additional studies are needed to apply this technology to study the dynamic changes in cf donor DNA fraction with increasing/decreasing allograft damage & changes in renal function.

SA-PO489

A Universal Real Time Quantitative Multiplex PCR Assay for the Non-Invasive Diagnosis of BK Polyomavirus Associated Nephropathy

Catherine Momot,1 Carol Muthukumar,2 Hua Li,1 Perry,1 Hua Yang,1 John R. Lee,1 Thangamani Muthukumar,2 Manikkam Suthanthiran,1 Well Cornell Medical College, New York, NY; 2Weill Medical College of Cornell University, New York, NY.

Background: BK Polyomavirus associated nephropathy (BKVN) is an important cause of kidney allograft failure. Early detection & reduction of immunosuppression is the best strategy for mitigating BKVN associated graft dysfunction. Use of sensitivity DNA PCR and neighbor-joining method, a phylogenetic tree of BKV has been developed & population specific prevalence of BK has been emphasized. Existing BKV PCR assays fail to account for BKV subtypes, we designed & developed a multiplex quantitative PCR assay for detection of clinically significant subtypes.

Methods: We designed 3 sense & 3 antisense primers and 3 TaqMan probes, which in combination, amplified 7 BKV subtypes- BKV Dunlop, Ia, IC, III, I V , and VI. Total RNA was isolated from 205 biopsy matched urine specimens reverse transcribed to cDNA and real-time quantitative multiplex PCR assays were established. All biopsies were stained for SV40: 36 were SV40 positive & classified as BKVN biopsies; remaining 169 were SV40 negative & classified as acute rejection (n=56); Normal (n=53); acute tubular injury (n=50); Other (n=10). Receiver-operating- characteristic curve analysis was used to calculate area under the curve (ROC-AUC), sensitivity and specificity for distinguishing BKVN biopsies from other biopsy diagnoses.

Results: Analysis involving ROC curve demonstrated that BKVN diagnosis can be predicted with a sensitivity of 100% & a specificity of 95% with the use 4.54 x 10 copies of BKV mRNA per microgram of RNA as the cutpoint (ROC-AUC=0.98, 95% CI, 0.97 to 1.0, P<0.0001). (Figure 1)

Conclusions: We have designed and developed real time quantitative multiplex PCR assays for the detection of major subtypes of BKV and demonstrate its utility for the noninvasive diagnosis of BKVN. In view of population specific prevalence of BKV subtypes, the newly developed assay should have universal appeal.
Predictive Value of the Combination of Peripheral Blood Lymphocyte Count and Urinary Cytology in the Diagnosis of Polyomavirus BK Nephropathy

Background: Screening of Polyomavirus BK (BK) infection is recommended for kidney transplant (KT) patients. Graft biopsy is the gold standard for the diagnosis of BK nephropathy (BKVN), and polymerase chain reaction for viral DNA is the most specific screening technique. However, the identification of non-invasive, and cost-effective marker is still important and can improve monitoring. Thus we investigated the predictive value of the peripheral blood lymphocyte (PBL) count and urinary cytology for the diagnosis of BKVN.

Methods: From July 2008 through May 2014, 492 adult patients received KT at Kyushu University Hospital. We investigated the PBL count and cytology results at graft biopsy in the patients with BKVN (BKVN group, n=21), acute T-cell mediated rejection (TCMR group, n=79), and no evidence of rejection (No AR group, n=149). We performed univariate and multivariate logistic regression and receiver operating characteristics analyses to compare the test performance of PBL count alone, cytology alone, and their combination in the diagnosis of BKVN.

Results: PBL count (mean ± SD) at graft biopsy was significantly lower in BKVN group than those in TCMR and No AR groups (959 ± 290, 1433 ± 673, and 1531 ± 549 µL, respectively, p<0.01). PBL count increased after the treatment of BKVN (at diagnosis, after 1, 2, and 3 months were 959 ± 290, 1123 ± 377, 1238 ± 419, and 1292 ± 491, respectively, p<0.05). On univariate logistic regression analysis, the area under the curve for the prediction of BKVN was significantly higher in the combined model that includes PBL and cytology alone (0.90, 0.797 and 0.875, respectively, p<0.01). The improvement of predictive performance in the combined model remained significant after adjustment for the classical risk factors of BKVN (0.972, 0.844, and 0.928, respectively, p<0.01).

Conclusions: Dropped PBL count was found in the patients with BKVN. Although PBL count alone showed moderate accuracy, the predictive performance of the combination of PBL count and urinary cytology is significantly enhanced in the diagnosis of BKVN.

SA-PO490

Urinary Exosomal Viral miRNA as a Marker of BK Virus Nephropathy after Kidney Transplantation

Background: Penicillin is the most common cause of virus-associated nephropathy (VAN) in kidney allografts. However, immunosuppression (IMMS) can result in reactivation. With renal tropism BK virus is the most common cause of virus associated nephropathy (VAN) in kidney allografts while JC VAN is a rare complication with a higher proportion of patients receiving high doses of cyclosporine A (CsA).

Methods: From October 2007 to December 2014, 5 cases of JCVAN were detected in our institution. We report on the variable presentation and histologic findings for JCVAN in these patients. Multivariate logistic regression analysis was performed to identify factors associated with development of JCVAN.

Results: Among the 5 cases of JCVAN, 3 were male and 2 were female. The mean age at presentation was 69 years (range 41-81 years). The mean time from transplantation to JCVAN diagnosis was 15 months (range 6-36 months). The mean CsA dose at JCVAN diagnosis was 6.5 mg/kg/day (range 2.5-8 mg/kg/day). The mean DME score at JCVAN diagnosis was 8.5 (range 6-10). The mean serum creatinine at JCVAN diagnosis was 3.2 mg/dL (range 2.0-5.0 mg/dL).

Conclusions: JCVAN is a rare complication of immunosuppression in kidney transplantation. The use of CsA in high doses has been associated with the development of JCVAN. Future studies are needed to determine the optimal CsA dose to prevent JCVAN.
inflammation as rejection activity should be exercised, as intensified IMMS likely contributes to KC VAI.

SA-PO494


Background: In patients with hematological malignancy who are intended to receive rituximab, hepatitis B virus (HBV) serology screening and viral reactivation monitoring are recommended. However, the effect of single-dose rituximab on HBV reactivation in kidney transplant (KT) patients with previous HBV infection is still unclear.

Methods: In this retrospective cohort study of 1,284 KT patients, we identified 76 who were negative for preoperative hepatitis B surface antigen and HBV DNA, and positive for hepatitis B core antibody. A rituximab dose of 200 mg/body was administered to 48 patients; 46 of whom did not receive prophylaxis (rituximab + group). Twenty-eight patients received neither rituximab nor prophylaxis (rituximab - group). We monitored HBV DNA by polymerase chain reaction every 1–3 months, and HBV reactivation was defined as detectable HBV DNA.

Results: HBV reactivation was found in one patient in the rituximab + group (2.2%) and in the rituximab - group (3.6%) at 6 weeks and 5.5 years post-KT, respectively, but it was spontaneously cleared. Both patients were positive for hepatitis B surface antibody (anti-HBs) preoperatively. HBV reactivation was not found in six patients lacking anti-HBs preoperatively.

Conclusion: Low-dose rituximab administration in KT patients without prophylaxis is associated with a low incidence of HBV reactivation. However, the sequential monitoring is necessary for many years to detect viral reactivation and prevent novo hepatitis.

SA-PO495

Comparison of Renal Safety and Efficacy of Tenofovir and Entecavir Treatment in Chronic Hepatitis B Patients with Kidney Transplantation Seonghoon Kim, Hyosang Kim, Soo Ya Bae. Asan Medical Center, University of Ulsan College of Medicine, SEOUL, Republic of Korea.

Background: Nucleotide reverse transcriptase inhibitor is used for the treatment of chronic hepatitis B (CHB). Preemptive antiviral therapy can improve the survival of HBsAg-positive renal allograft recipients. But there are concerns about the potential risk of nephrotoxicity with long-term use. This study aims to assess the efficacy and safety of tenofovir and entecavir in kidney transplant patients.

Methods: We performed a single center based retrospective study of 55 patients with CHB treated with tenofovir (n=34) and entecavir (n=21) after kidney transplantation. Patients with a decrease ≥20% in eGFR at 1 year from treatment were tenofovir (adjusted odds ratio, 18.477; 95% CI, 1.123-275.953; p=0.034).

Conclusions: Patients who received KT and treated with tenofovir were likely to have decline in renal function than patients who treated with entecavir at 1 year from transplantation. Tenofovir was insufficiently associated with decrease in eGFR at 1 year from treatment. There was no significant difference in an efficiency between tenofovir and entecavir at the end of treatment.

SA-PO497

Effectiveness of Direct-Acting Antiviral Regimens in the Treatment of Hepatitis C Virus (HCV) in Kidney Transplant Recipients. Karolyn S. Horn, Maya Campara, Michelle T. Martin, Ignatius Y. Tang. University of Illinois Hospital and Health Science System, Chicago, IL; University of Illinois Hospital and Health Science System / University of Illinois at Chicago College of Pharmacy, Chicago, IL.

Background: The AASLD Hepatitis C Virus (HCV) guideline document does not offer recommendations for the treatment of kidney transplant recipients. Real-world data are needed to evaluate the effectiveness of direct-acting antivirals (DAAs) in this underrepresented population.

Methods: Authors performed a retrospective chart review of kidney transplant recipients (KTRs) who were treated for HCV at an urban medical center from January 1, 2014 to December 1, 2016. This report [M1] our single-center, retrospective analysis of the efficacy and safety of DAA-based regimens in kidney (K), kidney-pancreas (KP) and kidney-pancreas (KP) transplant patients.

Results: Of 28 KTRs were treated for HCV, 54% were K, 32% KL, and 14% KP. Patients had a mean age of 60 (±7) years, 50% were male, 71% were treatment naïve, 25% had cirrhosis, and all GT 1. Pre-treatment and end-of-treatment levels did not differ for serum creatinine (n=22 patients, 1.5mg/dL vs 1.7mg/dL, p=0.4); or urine microalbumin to creatinine ratio (n=15 patients, 337.3 vs 311.1, p=0.3). 18% had dose changes in immuno-suppression (IMSS) levels during and after HCV treatment, but the mean daily tacrolimus levels did not differ from baseline and 12 weeks after treatment completion (4.6 mg vs 4.8 mg, respectively, p<0.05). The overall SVR rate was 86%. SVR did not differ by regimen; 50% with sofosbuvir/ribavirin, 90.9% with sofosbuvir/simeprevir, and 90% with elbasvir/grazoprevir achieved SVR (p=0.55). SVR did not differ by type of transplant (92.9% vs 80% vs 75% KP p = 0.54). SVR also did not differ by genotype, female, ethnicity, BMI, baby-boomer status, cirrhosis, treatment history, adherence, or diabetes (p>0.05). SVR did differ by primary IMSS agent, SVR rates were 100% for paritaprevir (n=1), 91.7% for tacrolimus (n=24), 100% for sirolimus (n=1), and 85.7% for cyclosporine (20%), tacrolimus (55%), or other (25%); adjustments in IS dosing were minor.

Conclusions: DAA regimens were highly effective in treating HCV in KTRs. Renal allograft function was stable throughout and 12 weeks after DAA therapy. Comparison

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

Underline represents presenting author.
across groups was limited due to small numbers. IMS levels should be monitored closely during HCV treatment as many patients required dose adjustments.

**SA-PO498**

**Impact of Early Ureteric Stent Removal on Urinary Tract Infection and Ureteric Complication after Kidney Transplantation – A Single Centre Experience**

**Authors:** Stephanie Chang,1 Yiyanan Mahalingasivam,1 Sajeda Youssouf,1 Mark Blunden,1 1Barts Health NHS Trust, London, United Kingdom; 2Mid Essex Hospitals NHS Trust, Harrow, United Kingdom; 3Royal London Hospital, London, United Kingdom.

**Background:** Recurrent urinary tract infection (UTI) is a common cause of renal allograft dysfunction as well as a burden on patient quality of life and the health economy.

**Methods:** We performed a retrospective study of consecutive deceased donor transplants undertaken at our centre between January 2012 and June 2016 to determine the effectiveness of strategies which had been established to reduce rates of UTI in our patient cohort. These included changing pre-operative antibiotic prophylaxis from co-amoxiclav to meropenem in January 2014, whilst a cohort of patients underwent the intra-operative tying of ureteric stents to indwelling urinary catheters, in order to allow for early concurrent removal on day 5. The remaining patients continued to undergo standard cystoscopic stent removal after six weeks. Our aim was to determine the difference these changes made to the incidence of UTI in the first three months after transplantation. 555 adult deceased donor transplants were studied of which 23 were excluded due to early explantation. 115 underwent early stent removal whilst 418 underwent later cystoscopic removal.

**Results:** There was no difference in the number of patients with at least one UTI between with groups (37.0% with early stent removal, 38.3% with later stent removal, \(p=0.83\)) or with more than two UTIs (15.6% vs 14.8%, \(p=0.83\)). There was no difference in the average number of UTIs per patient (1.02 vs 1.05, \(p=0.43\)). There was also no difference in the incidence of extended-spectrum beta-lactamases (ESBL) (6.09% vs 7.42%, \(p=0.58\)) or hospital admission (10.5% vs 6.09%, \(p=0.15\)). There was no difference in the rate of ureteric complication (6.9% vs 5.7%, \(p=0.85\)). There was however, an increase in the rate of UTI per patient after the antibiotic protocol was switched from co-amoxiclav to meropenem (0.68 to 1.35, \(p=0.05\)). The rate of ESBL was similar (5.49% vs 8.36%, \(p=0.20\)) in both groups.

**Conclusions:** Early ureteric stent removal does not appear to reduce the incidence or frequency of UTI and there was no significant difference in ureteric complication rates in our patient cohort. These findings suggest that early stent removal is a potentially viable and cost effective surgical strategy in renal transplantation but further prospective randomised controlled trials are needed for validation.

**SA-PO500**

**Gut Microbiota Disturbances and Urinary Tract Infections in Kidney Transplant Recipients**

**Authors:** John R. Lee,1 Matthew Magruder,2 Lisa T. Zhang,2 Darshana Dadhania,2 Thangamani Muthukumar,2 Lilan Ling,1 Eric Pamer,1 Manikkam Suthanthiran,2 Memorial Sloan Kettering Cancer Center, New York, NY; 3Well Cornell Medicine, New York, NY.

**Background:** Diarrhea is a common complication in kidney transplant recipients, but its etiology is unknown. In a prior gut microbiota profiling study, we found a link between the abundance of pathogenic gut microbiota and urinary tract infections (UTI) in kidney transplant recipients.

**Methods:** Herein, we perform a validation study using an independent cohort of 71 kidney transplant recipients. We collected 199 serial fecal specimens from this population in the first 3 months of transplantation and profiled their gut microbiota using 16S rRNA deep sequencing of the V4-V5 hypervariable region. Among the 71 subjects, 13 developed Proteobacteria UTIs and 58 subjects did not. We compared the gut microbial profiles in the 11 fecal specimens collected at the time of Proteobacteria UTI (Proteobacteria UTI Group) to the gut microbiota profiles of 135 fecal specimens collected at the same time urine cultures were negative for Proteobacteria UTI (No Proteobacteria UTI Group).

**Results:** The fecal abundance of Proteobacteria, the phylum that contains gram negative pathogens like *Escherichia*, was significantly higher in the 11 fecal specimens from the Proteobacteria UTI Group than in the 135 fecal specimens from the No Proteobacteria UTI Group (1.3% vs 0.2%, \(P=0.03\)). Predicted bacterial genes based on the 16S rRNA data (using PICRUSt) revealed lower metabolism related genes in the fecal specimens from the Proteobacteria UTI Group than in those in the No Proteobacteria UTI Group (Fig B). In a pilot gut microbial profiling study, we found a link between the abundance of pathogenic gut microbiota and urinary tract infections (UTI) in kidney transplant recipients.

**Conclusions:** Disturbances in the gut microbiota has been linked to infectious complications beyond *C. difficile*. In a pilot gut microbial profiling study, we found a link between the abundance of pathogenic gut microbiota and urinary tract infections (UTI) in kidney transplant recipients.

**Funding:** Other NIH Support - NIAID K23 AI 124464
SA-PO52
Prevalence and Clinical Outcomes in Kidney Transplant Patients with Viral and Fungal Opportunistic Infections and Malignancies
Michelle L. Lubetzkyy, Nicole A. Hayde, Layla Kamal, Maria Ajajmy, Puneet Bedi, Enver Akalin. Brookdale University Hospital Medical Center, Brooklyn, NY; Transplantation, Montefiore Medical Center, New York, NY; Montefiore Medical Center, Bronx, NY.

Background: Opportunistic infections (OI) and malignancy after kidney transplantation (KTx) are associated with increased morbidity and mortality. We aimed to assess clinical outcomes in patients with these complications.

Methods: We performed a single-center retrospective review of KTx patients from January 2009 until December 2014. Patients with opportunistic viral infections (BK virus or cytomegalovirus (CMV)), fungal infections, or malignancies were reviewed and compared to patients without these complications.

Results: During a median follow-up of 3.8 years (2.4-5.3), out of a total 677 patients, 222 developed OI or malignancy (32.8%); 19.2% had BK viremia, 1.5% BK nephropathy, 9.5% CMV viremia, 2.1% invasive CMV infection, 2.5% fungal infection, and 5.6% had malignancies. There was no difference between the groups in terms of age, race, gender, induction type, or etiology of kidney disease (Table). One year and most recent serum creatinine levels were significantly higher in the OI/Malignancy group (p=0.01). There were significantly higher rates of acute rejection in the OI/Malignancy group (p=0.01). There was significantly more graft loss (22.5%) in the OI/malignancy group compared to only 4.2% in the non OI group (p=0.01). Additionally patient survival was lower in the OI/malignancy group (p=0.05). Graft loss in the OI/malignancy group was more likely to be due to chronic rejection (58% vs. 31.6% p=0.08); in most cases rejection occurred in the setting of reduced immunosuppression. Conclusion: Opportunistic infections and malignancies develop in 33% of kidney transplant recipients, and are associated with lower graft and patient survival and increased risk of acute rejection.

SA-PO503
A Randomized Controlled Trial Comparing Belatacept to Tacrolimus in De Novo Kidney Transplantation

Background: Belatacept (bela) allows for calcineurin-inhibitor-free immunosuppressive therapy after kidney transplantation but is associated with a higher acute rejection risk than ciclosporin. We compared clinical outcomes in a randomized-controlled trial comparing bela to tacrolimus (tac) in de novo kidney transplantation.

Methods: Forty kidney transplant recipients were 1:1 randomized to a bela- or tac-based immunosuppressive regimen combined with basiliximab, mycophenolate, and prednisolone. One-year graft- and biopsy-proven acute rejection (BPAR) free survival were assessed, as well as the development of de novo donor-specific anti-HLA antibodies (DSA), the incidence of adverse events (AEs) and eGFR (in mL/min/1.73m²).

Results: Three graft losses occurred on days 12, 59, and 161 after transplantation, resulting in a 1-year death-censored graft survival of 85% in the belatacept group vs. 100% in the tacrolimus group (p=0.08). All were the result of glucocorticoid-resistant
rejection. The incidence of BPAR was higher in the bela-treated than in the tac-treated patients, n=11 (55%) vs. n=2 (10%), p=0.006, respectively, and rejections were of a more severe grade. In the first year, 2 patients, of which 1 rejected, developed DSA, both in the bela group. Total AE were similar between groups; means of 10.3 and 11.9 per patient in the bela- and tac-groups, respectively, p=0.57. However, graft-loss censored eGFR in bela-treated rejectors (n=8) was 36 (28-76) mL/min at month 12, excluding graft losses, was not different between bela-treated and tac-treated patients on month 12: 54 (28-89) and 50 (33-84) mL/min, respectively, p=0.57. However, graft-loss censored eGFR in bela-treated rejectors (n=8) was 36 (28-76) mL/min at month 12, which was lower than the eGFR of 58 (37-84) mL/min in the bela-treated non-rejectors, p=0.001.

Conclusions: Bela-based immunosuppressive therapy results in a higher rejection rate and severity compared to standard, tac-based therapy, and shows similar graft function 1 year after transplantation.

SA-PO504

Single-Dose (SD) Pharmacokinetics (PK), Pharmacodynamics (PD), and Safety of Belatacept (Bela) in Adolescent Kidney Transplant Recipients (KTRs) Asha Moudgil,1 Vikas D. Raghunathkaria,2 Daniel Feig,3 Barry L. Warshaw,2 Vidya Pereira,2 Bindu Murthy,2 Martin Polinsky,2 Robert B. Ettenger,4 Washington University, St Louis, MO; 5Bristol-Myers Squibb, Princeton, NJ; 6Children’s National Medical Center, Washington, DC; 7University of Alabama, Birmingham, AL; 8Emory University & Children's Healthcare of Atlanta, Atlanta, GA; 9University of California, Los Angeles, CA.

Background: Bela blocks CD86-CD28 co-stimulation between antigen presenting cells and T-cells. It is approved for rejection prophylaxis in KTR >18 yrs old. A phase III study in adolescent KTRs showed SD therapy with bela was safe and efficacious and was used to evaluate efficacy, rejection rate, graft survival and DGF during the 2-year follow-up period: Basiliximab (n=39) vs Thymoglobuline (n=32) at a fixed 1D and 2D group respectively. Rejection-free survival was similar in both groups (Log rank=NS).

Methods: A preliminary report is presented. This preliminary report suggests that there is no difference in rejection-free survival and graft function at the end of follow-up with the 20 mg dose of basiliximab compared to 40 mg in patients with renal transplantation and low immunological risk. Should confirm this results with a large number of patients.

SA-PO506

Induction Therapy with Low Dose Thymoglobulin versus Standard Therapy with Basiliximab: A Comparative Study of Safety and Effectiveness in Marginal Donor Kidney Transplant Recipients Giorgia Comai, Olga Baralid, Vania Cuna, Matteo Ravaioli, Maria Cappuccilli, Gaetano La Manna. University of Bologna, Bologna, Italy.

Background: In renal transplant the most commonly administered induction immunosuppressive therapy is based on Basiliximab, a chimeric non depleting anti-IL2-receptor monoclonal antibody, or Thymoglobulin, a polyclonal depleting agent. The use of Thymoglobulin in the recipients of marginal kidney transplants is an attractive opportunity, since besides the known anti-rejection effect, it has a protective potential against ischemia/reperfusion injury and the subsequent delayed graft function (DGF), thus allowing the reduction of maintenance therapy.

Methods: We retrospectively analyzed 71 patients who received a kidney transplant from marginal donors in the period 2013-2015 to assess the safety (incidence of infections, new onset diabetes after transplantation-NODAT, cardiovascular events) and efficacy (rejection rate, graft survival, DGF, graft function) of two different induction regimens during the 2-year follow-up period: Basiliximab (n=39) vs Thymoglobuline (n=32) at a very low dose (with a cumulative dose of 2 mg/kg).

Results: The two groups were similar for donor and recipient age, but there were different frequencies of double renal transplants: 4/39 (10.3%) in Basiliximab group and 18/32 (56.2%) in Thymoglobulin group (p<0.01). Likewise, ischemia interval and Karpsinski score were higher in the Thymoglobulin group (p<0.05). The safety of the two induction regimens was comparable, as no significant differences were found in the incidence of infections, NODAT and cardiovascular events. Concerning the parameters used to evaluate efficacy, rejection rate, graft survival and DGF did not differ significantly between the groups, while serum creatinine (sCreat) and proteinuria were higher in Basiliximab group that in Thymoglobulin group (sCreat: 1.8 ± 0.3 vs 1.6 ± 0.4 mg/dL; p=0.019; urine protein levels: 37 ± 21 vs 17 ± 18 mg/dL; p<0.01).

Conclusions: Induction therapy with low dose thymoglobulin has been shown to have a comparable efficacy with Basiliximab, also showing an excellent safety profile. This finding appears to be promising, also in view of unfavourable characteristics of the transplanted patients included in the Thymoglobulin group, namely double kidney transplant, longer cold ischemia time and higher Karpsinski score.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Whereas <10% get IL-2 receptor blockade (Basiliximab). Our center has historically used ATG induction but has more recently favored Basiliximab for simultaneous pancreas kidney transplants (SPK). We sought to retrospectively compare the graft and patient outcomes of SPK and pancreas transplant alone (PTA) recipients treated with either ATG or Basiliximab induction.

**Methods:** We reviewed all 242 cases of PTAs at our institution between 2003 and 2014. Patients who received a pancreas after kidney (51) and those who did not receive induction (15) were excluded. From the remaining 176 patients, 105 received ATG induction at 4.5 mg/kg and 71 got Basiliximab 20mg on POD 0 and 4. Outcomes included 1 and 3-year graft survival, patients’ survival, incidence of rejection episodes, time to first rejection episode, viral infections (CMV, BK, and EBV viremias), and malignancies.

**Results:** Mean duration of follow up was 81.6 ± 3.8 months for the ATG group and 63.6 ± 3.4 for Basiliximab (p=0.01). All patients in the Basiliximab group had received an SPK whereas 44% of those who received ATG induction had a PTA (p=0.01). Maintenance immunosuppression was similar in both groups. Graft survival at 1 and 3 years were 96 and 88% for Basiliximab and 90 and 81% for the ATG group (p 0.05). Patients’ mean survival was not different between both groups (121 ± 6 for Basiliximab and 142 ± 5 for ATG, p=0.7). There was no statistically significant difference in the incidence of rejection, infections, or malignancies (Table 1).

**Conclusions:** Basiliximab appears to be a reasonable alternative for induction following SPK, and does not seem to be associated with a higher incidence of rejection, graft failure, or viral infections.

**SA-POS08**

Low Dose Rituximab and Thymoglobulin Induction in a Steroid Free Protocol Involving Protocol Biopsies Improves Patient and Graft Survival at 11 Years after Kidney Transplantation

**Vivek Pathak,** Nephrology, Kovai Medical Center and Hospitals, Coimbatore, India.

**Background:** The purpose of this study is to document long term patient and graft survival in a steroid free regime with a different induction protocol.

**Methods:** 1069 patients, who underwent renal transplantation at our institute in eleven years since July 2005 till Jan 2017 were studied. Thymoglobulin was used for induction at a dose of 1.5mg/kg 3 doses in the first 5 days. Rituximab 200 mg was given to those patients who were considered to be at high risk for rejection and approximately 60 to 65% of the cohort received it. Maintenance immunosuppression was Tacrolimus and Mycophenolate mofetil. Prednisolone was rapidly discontinued by fifth post operative day. All patients underwent protocol biopsies at 3 months, 1 year, 5 years and 10 years and indicated biopsies were done whenever required.

**Results:** The Patient and graft survival rates at 11 years were 92% and 85.4 % respectively. Biopsy proven acute rejection free graft survival was 78.1% at 11 years including subclinical rejections. The cumulative incidence of graft loss was 8.07%. The incidence of death was 5.3%. This is an improvement over the data published by Rizzardi et al(CASN 2012) where patient and graft survival rates were 70% and 61% respectively at 10 years. The OPTN data in AFT December 2016 showed all cause graft failure > 20% in 10 years whereas our all cause graft failure is 14.6% at 11 years. 79.07% patients were prednisolone free at 11 years.

**Conclusions:** The reasons for the improved patient and graft survival in our study in comparison to published literature could have been the addition of low dose pre-operative Rituximab, steroid withdrawal and aggressive cardiovascular screening resulting in low post transplant mortality due to ischemic heart disease, decreased incidence of BK virus induced graft loss, reduced death due to malignancy and reduction in fatal infections.

**SA-POS09**

Reassessing Thymoglobulin Induction in Kidney Transplantation (RETHINK): An Analysis of the Scientific Registry of Transplant Recipients (SRTR)

**Isa Ashoor,** 1 Robbie A. Bely,2 Vikas R. Dharnidharka,

1Pediatrics, LSU Health Sciences Center, New Orleans, LA; 2Pennington Biomedical Research Center, Baton Rouge, LA; 3Washington University School of Medicine, St Louis, MO.

**Background:** Recent single center studies suggest lower dose Thymoglobulin (TMG) for induction in kidney transplant (KT) provides effective rejection prophylaxis comparable to higher dose TMG with less infectious morbidity. We sought to determine whether less TMG exposure is effective in a large national cohort of KT recipients.

**Methods:** All first time KT only recipients in SRTR on MMF and tacrolimus based immunosuppression who received TMG induction were analyzed. Recipients of expanded criteria donor kidneys or with delayed graft function were excluded. TMG exposure days were analyzed. Primary outcome was graft failure due to acute rejection or infection by 12 mo post KT. Logistic regression was used to identify covariates affecting primary outcome.

**Results:** 27,808 KT recipients met inclusion criteria (56% male, 52% Whites, 39% Living donor source). Most were adults (92% >21 years old) and transplanted in past 10 years since 2007 (70%). Recipients received a median of 4 days of TMG with 45% receiving 3 days or less. Low (<3 days) and high (>3 days) TMG exposures differed in gender, transplant year, peak PRA, and HLA mismatch (Table). The primary outcome of graft failure due to acute rejection or infection within 12 mo post KT was seen in 197 recipients. Logistic regression identified worst odds of graft failure in relation to non-white race (OR 2.2), younger age ≤21 years (OR 3.7), and older transplant era prior to 2007 (OR 2.1) with p-value <0.0001. Low TMG exposure was not detrimental to graft outcome and just missed significance for benefit (OR 0.76, p-value 0.06).

**Conclusions:** In this large cohort of first time KT recipients on contemporary immunosuppression with TMG induction, graft failure due to acute rejection or infection within 1 year was rare, and not influenced by TMG exposure days. Further studies are needed to confirm results using granular dosage information.

**Funding:** Other NHI Support - “Supported in part by 1 U54 GM104940 from the National Institute of General Medical Sciences of the National Institutes of Health, which funds the Louisiana Clinical and Translational Science Center. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.”, Clinical Revenue Support

Comparison of Low and High Thymoglobulin Exposure Groups

<table>
<thead>
<tr>
<th>Baseline Characterization</th>
<th>Sub-category</th>
<th>Low Thymoglobulin Exposure (≤3 days)</th>
<th>High Thymoglobulin Exposure (&gt;3 days)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male/Female</td>
<td>788/112 (78%/12%)</td>
<td>805/120 (78%/12%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Race</td>
<td>White/Non-White</td>
<td>664/70 (95%/5%)</td>
<td>709/61 (95%/5%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Age</td>
<td>21 years old</td>
<td>1142/92 (94%/6%)</td>
<td>1215/72 (94%/6%)</td>
<td>0.018</td>
</tr>
<tr>
<td>Disease Type</td>
<td>Living Donor/Deceased Donor</td>
<td>1367/26 (85%/15%)</td>
<td>1522/18 (85%/15%)</td>
<td>0.5</td>
</tr>
<tr>
<td>PRA</td>
<td>0-20/≥20</td>
<td>1000/895 (74%/26%)</td>
<td>972/115 (74%/26%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HLA mismatch M/M</td>
<td>0-4/5</td>
<td>3002/636 (47%/53%)</td>
<td>2977/641 (47%/53%)</td>
<td>0.083</td>
</tr>
</tbody>
</table>

**SA-POS10**

Everolimus [EVR]-Based versus Tacrolimus [TAC]-MPA Regimen in De Novo Kidney Transplant Recipients: 12 Months Safety and Efficacy Data from the AthenA Duska Dragan,1 Claudia Sommerer,1 Ingeborg A. Hauser,1 Barbara M. Siewelak,2 Peter Schenker,1 Oliver Witzke,2 Christian Hugo,1 Nissim Kamar,2 Pierre Merz3,1 Martina Jung,2 Björn Nashan,1 Friedrich Thaiss,1 Bundesärztekammer, Hamburg, Germany; 2University Clinic Frankfurt (UKF), Frankfurt Main, Germany; 3Muenster, Germany; 4Novartis Pharma GmbH Germany, Nuremberg, Germany; 5Pellegrin Hospital, Bordeaux, France; 6Ruhr-University Bochum, Bochum, Germany; 7Toulouse University Hospital, Toulouse, France; 8University Duisburg-Essen, Essen, Germany; 9University Hospital Hamburg, Hamburg, Germany; 10University Hospital Charity, Campos Virchov, Berlin, Germany; 11University Hospital of Heidelberg, HEIDELBERG, Germany; 12University of Dresden, Dresden, Germany, Dresden, Germany. Group/Team: AthenA Study Group.

**Background:** The ATHENA study was set up to compare EVR combined with TAC or cyclosporine A [CyA] vs. mycophenolic acid [MPA] combined with TAC in de novo kidney transplant [KTX] recipients.

**Methods:** In this 12 months [M] prospective, open-label, multi-center study 612 patients [pts] were randomized 1:1:1 at time of Tx to either EVR (3-8ng/ml M1-M12) + TAC(4-8ng/ml M1-M3; 3-5ng/ml M3-M12), or EVR (3-8ng/ml M1-M12) + CyA (75-125ng/ml M1-M3; 50-100ng/ml M3-M12) or TAC(4-8ng/ml M1-M3; 3-5ng/ml M3-M12) + MPA, all with steroids. HCs report M12 efficacy and safety (208 EVR + TAC, 199 EVR+CyA, 205 TAC+MPA pts).

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

Underline represents presenting author.

810
Results: M12 Kaplan Meier estimates for treated BPAR were 6.7% in EVR+TAC, 17.6% in EVR+CyA and 3.9% in TAC+MPA group, with most events graded BANFF IA (1.9%, 9.5%, 1.5%), few (1.5%, 2% vs 0.5%) BANFF II/III. 5 pts in EVR+TAC, 5 in EVR+CyA and 6 in TAC+MPA died. Few graft losses occurred: 10 pts (4.8%) in EVR+TAC, 13 (6.5%) in EVR+CyA, 6 (2.9%) in TAC+MPA arm, including 5 primary non-functioning grafts in each EVR-group and 1 in TAC+MPA arm. Safety profiles were comparable, incidences of AE/Infections leading to study discontinuation or dose adjustment/interruption were 56.7% in EVR+TAC, 55.5% in EVR+CyA vs 61.3% in TAC+MPA arm. Main reasons for changes were infections (7.1% EVR+TAC, 4.5% EVR+CyA, 23.8% TAC+MPA control) and lympho-leucopenia (3.3%, 3.5%, 13.2%). No differences in AEs on wound complications were seen (sum-incidences: 41.9% EVR+TAC, 38.9% EVR+CyA, 43.2% TAC+MPA).

Conclusions: ATHENA as largest European KTx study confirmed good efficacy and comparable safety as International standards for all 3 groups with no unexpected safety events for this pts population. There were no differences in reported AEs wound healing and less leucopenia with EVR-based regimens.

Funding: Commercial Support - Novartis Pharma GmbH, Germany

SA-PO511

Randomized Controlled Trial Assessing the Impact of Conversion to Everolimus with Ultra-Low Tacrolimus Exposure on Graft Outcomes in Kidney Transplant Recipients

Background: Despite low rate of acute rejection, the triple regimen of tacrolimus (FK), mycophenolate (MMF) and prednisone can increase the risk of late graft loss due to nephrotoxicity and opportunistic infections.

Methods: Single-center, randomized, controlled trial assessing the impact of a three month conversion to EVR with ultra-low FK exposure, compared to the regimen of full exposure FK with MMF (NCT 02096107). Adult, solitary kidney transplant recipients with a functioning graft at 3 months were eligible for inclusion. Goal trough levels in the intervention arm were 2-5 ng/mL for FK and 3-8 ng/mL for EVR, while FK was maintained at 5-12 ng/mL in the control arm.

Results: 60 patients were randomized (30 in each arm). Groups were well matched at baseline (3 months post-transplant), except there were fewer females in the intervention arm. FK levels were significantly lower in the EVR arm (Figure 1). At 12-months post-transplant, acute rejection rates (7% FK/MMF vs. 3% FK/EVR, p=0.554, Table 1) and graft function (mean eGFR FK/MMF 59±15 vs FK/EVR 59±14 mL/min/1.73 m², p=0.465; Figure 2) were similar between arms. The EVR/ultra-low FK arm had significantly lower rates of CMV infection, severe BK infection and improved BK viral clearance kinetics (Figure 3). All safety measures, including immunosuppression discontinuation, hospitalizations, and graft and patient loss were similar between arms (Table 1).

Conclusions: An immunosuppression conversion regimen of EVR with ultra-low exposure FK provides equally sufficient immunosuppression prophylaxis efficacy as varying methodologies: thus it is unclear how comparable tacrolimus levels and hence IPVs are between centres and studies.

Methods: A retrospective study was undertaken in five UK transplant centres using a unified methodology. Renal databases in all centres were interrogated to provide demographic details and laboratory results for all renal transplant recipients (RTR) between 1 January 2009 and 31 December 2014 who received tacrolimus therapy. RTR were excluded if they received dual-organ transplants or if death or graft loss occurred within two years of transplantation, or if their immunosuppression regimens included modified release tacrolimus. IPV was calculated from trough levels taken during the 6-12 month post-transplant period (T1) and the last 12 months of follow-up (T2).

Results: A total of 1070 eligible RTR across the five centres were included (Table 1). Despite variation in ethnic make-up and median age across centres, median tacrolimus IPV at both T1 and T2 was similar at around 14-16%. Across all centres male gender and non-Caucasian ethnicity were not associated with increased IPV. Increasing age did not correlate with IPV. There was no correlation between duration of transplant follow-up and T2 IPV.

Conclusions: In the first national retrospective study of this kind, we report that despite variation in population demographics between centres, median tacrolimus IPV is remarkably consistent. Increased IPV does not appear to be associated with age or ethnicity. This data will be pooled to enable formulation of a ‘national standard’ IPV, which will allow further study to assess whether RTR with an above median IPV have poorer transplant outcomes.

Funding: Commercial Support - Astellas Educational Grant

Table 1: Tacrolimus IPV in UK Transplant Centres

<table>
<thead>
<tr>
<th>Centre</th>
<th>Median IPV</th>
<th>IQR IPV</th>
<th>Min IPV</th>
<th>Max IPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>London</td>
<td>0.0074</td>
<td>0.0007</td>
<td>0.0000</td>
<td>0.241</td>
</tr>
<tr>
<td>Manchester</td>
<td>0.0078</td>
<td>0.0008</td>
<td>0.0000</td>
<td>0.241</td>
</tr>
</tbody>
</table>

SA-PO513

Is There a Relationship Between HLA Mismatch and Intra-Patient Tacrolimus Variability in Kidney Transplant Patients? A Comparative Multi-Centre Retrospective Study

Background: Tacrolimus (Tac) is a critical component of immunosuppressive therapy after kidney transplantation (tx). It has been previously reported that high Tac Intrapatient Variability (IPV) (patient’s trough level variability over time) is associated with higher rejection episodes and poor long term outcome after kidney tx. The relationship between HLA mismatch (MM) and Tac IPV has not been previously evaluated.

Methods: 1068 kidney transplant recipients in 5 UK centres between 2009-2014 and who were taking standard release Tac preparations were included in the study. IPV data was retrospectively collected from 2 time points – 6-12 months post-transplant (T1) and the last 12 months of follow up (T2). Patients were divided into a high immunological risk HLA MM (HLA MM 4-6) and a low risk HLA MM group (HLA MM 0-3). Association between HLA MM and IPV was evaluated for each centre.

Results: Table 1 describes the results of 1068 patients included from 5 UK centres. When comparing IPV<20% and IPV>20%, there was no significant correlation with the high risk HLA MM group or the low risk HLA MM group (p=0.1 for all comparisons). The relation between HLA mismatch and Tac IPV did not reach significance in T1 and T2 periods in all centres.

Conclusions: This study represents the first and largest population based evaluation of the relationship between HLA mismatch and Tac IPV. Our results demonstrate a clear evidence that HLA mismatch does not affect Tac IPV in either early or late post operative periods. This finding is consistent between 5 UK tx centres. Therefore, HLA mismatch should not be considered as a factor that affects Tac IPV for kidney transplant patients.

Funding: Commercial Support - Astellas Pharma LTD, Government Support - NHS U.S.

Table 1: Relationship between HLA MM and Tac IPV

<table>
<thead>
<tr>
<th>HLA MM</th>
<th>IPV&lt;20%</th>
<th>IPV&gt;20%</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>0.05</td>
<td>0.07</td>
<td>0.1</td>
</tr>
<tr>
<td>4-6</td>
<td>0.06</td>
<td>0.08</td>
<td>0.1</td>
</tr>
</tbody>
</table>

SA-PO512

Median Intrapatient Tacrolimus Variability Is Comparable between Renal Transplant Centres: A Multicentre UK Retrospective Study

Background: Tacrolimus is an immunosuppressant with a narrow therapeutic window and regular serum trough level monitoring is necessary. Increased intrapatient variability (IPV) in these levels has been identified as a risk factor for graft rejection and loss after renal transplant. Previous reports have been from single centre studies with
High Calcineurin Inhibitor (CNI) Intra Patient Variability (IPV) Is Associated with Early Renal Allograft Inflammation, Chronicity, and Loss Akhil Sharma,1 Aravind Cherukuri,1 Rajil B. Mehta,1 Puneet Sood,2 Sundaram Harirahan.1 1UNIVERSITY OF PITTSBURGH, Pittsburgh, PA; 2University of Pittsburgh Medical Center, Pittsburgh, PA; 3University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA.

Background: High CNI IPV has been associated with poor kidney allograft outcomes, albeit in small limited studies.

Methods: We evaluated effect of CNI IPV (the degree of fluctuation of CNI levels in all patients over 2-12M post-transplant) on early allograft inflammation, subsequent chronicity, graft loss (GL) and a composite end-point (CEP) of GL and impending GL (GLi defined as eGFR<30m/min & 30% decline). 286 patients transplanted between 01/13-11/14 were enrolled with 2 Protocol Bx and any For-Cause Bx. The mean CNI values tested per patient was 37±15. The trough level < 6 ng/ml was considered as sub-therapeutic.

Results: CNI-IPV: The mean CNI-IPV was 28.5% and 1/4 of them had IPV>35% (High IPV). High IPV was associated with more sub-therapeutic CNI levels (29% vs.11%, p<0.0001). Baseline demographic differences between those with high IPV and acceptable IPV were similar with a trend towards more non-Caucasian patients in the high IPV group. Allograft Histology: High IPV was associated with a higher incidence of subclinical & clinical acute rejection (AR) at 3mos (40.9% vs. 19.5%, p<0.0001), more persistent/recurrent AR at 1yr (18.2% vs 6.2%, p=0.002) and high-grade AR (aBanff IB, 27.5% vs 7.3%, p < 0.0001). Patients with denovo DSA & high IPV had more AR (24.6% vs. 9.1%, p=0.001). High IPV was associated with worse IFTA (p = 0.005) and IF+’i (p < 0.0001) on 1yr protocol Bx. Graft Outcomes: High CNI-IPV was associated with increased GL (Fig1A) and GLi (Fig1B). Sub-analysis of patients with DGF and IF+’i: High IPV was associated with worse IFTA (p= 0.005) and IF+’i’ (p < 0.0001) on 1yr protocol Bx. The mean CNI values tested per patient was 37±15. The trough level < 6 ng/ml was considered as sub-therapeutic.

Conclusions: High CNI-IPV within 1 year post-transplant is associated with worse allograft outcomes including more severe acute rejection, allograft chronicity, GL, and GLi. Thus, this represents an early simple modifiable risk factor for allograft loss.
a greater reduction in Pneumococcal IgG coverage than the ABOc group and this did not recover at 12 months. Our findings reveal the impact of IAR on protective antibodies and suggest an opportunity to revisit the timing of vaccination schedules.

**Funding:** Private Foundation Support

**SA-POS17**

**Weaning Immunosuppression in Patients with Failing Kidney Grafts: When and How?**

Hyunjin Ryu, Yong Chul Kim, Mi-yeon Yu, Yon Su Kim, Hajeong Lee. Seoul National University Hospital, JongNo-Gu, Seoul, Republic of Korea.

**Background:** Immunosuppressant (ISA) weaning protocol in failing allograft has not been established. Maintaining ISA would preserve residual renal function (RRF) and prevent graft intolerance syndrome (GIS) and sensitization, although it would increase risk of infection, malignancy and cardiovascular disease. However, there is no optimal ISA weaning protocol after GF.

**Methods:** We retrospectively reviewed graft failure (GF) cases after kidney transplantation (KT) in a single center. After excluding 424 patients with age under 19, death within 6 month after KT or 1 month after GF, and lost follow-up, a total of 131 GF patients were analyzed. Maintaining ISA was defined as either a10 mg of prednisolone (Pd) or combination treatment including Pd with calcineurin inhibitors or antimetabolites at 6 month after GF. ISA weaning was defined as either all ISA discontinuation or using <10mg of Pd at 6 month after GF. Duration of low dose steroid usage after GF, which is <10mg of Pd, were also reviewed. Outcomes were infection-related hospitalization, death, GIS, nephrectomy, and RRF represented as duration of diuretics usage.

**Results:** Among 131 cases, 34 (26%) were female and mean age at GF was 44.9±11.1 years. At the time of GF, 72 (55%) patients were maintaining ISA but 6 month after, only 22 (16.8%) patients were maintaining ISA. With low dose steroid usage, 60 (45.8%) and 33 (25.2%) patients maintained Pd at 6 and 12 months after GF. There were total 68 events of infection related hospitalization, 11 GIS, 20 graft nephrectomy (9 GIS, and 3 graft kidney cancers), and 17 deaths (8 Cardiovascular disease, 5 infection, and 4 malignancy) during median 216 months (range: 15-375 months) follow up. ISA maintaining significantly lowered patient survival rate (log rank P=0.027) than weaning. Moreover, it was an independent risk factor for mortality even after adjustment (odds ratio of 3.36, 95% CI 1.06-10.64, P=0.04). Infection related hospitalization, GIS and nephrectomy was not affected by ISA weaning protocol. However, low dose steroid maintaining at 6 and 12 months after GF, was protective in RRF preservation (P=0.002 and P<0.001, respectively).

**Conclusions:** In this study, we suggested that ISA should be maintained less than 6 months after GF if possible and decrease mortality risk. However, low dose steroid continuation up to 1 year after GF could be advantageous for preserving RRF.

**SA-POS18**

**Non Melanoma Skin Cancer Risk Following Graft Failure in Renal Transplant Recipients in Ireland, 1994-2015: Does the Hazard Vary during Periods of Dialysis?**

Donal J. Sexton, Patrick O'Kelly, Sandra Deadly, Peter J. Conlon. Beaumont Hospital, Dublin 9, Co Dublin, Ireland; *National Cancer Registry, Ireland, Cork, Ireland; *The Irish Longitudinal Study on Ageing (TILDA), Trinity College Dublin., Dublin, Ireland; *Beaumont Hospital, Dublin, Ireland.

**Background:** Non melanoma skin cancer (NMSC) is common after renal transplant. Whether the risk of skin cancer development varies as treatment for ESKD varies is not well described. We evaluated whether this risk is attenuated during periods of graft loss with a return to dialysis.

**Methods:** The National Kidney Transplant Service (NKTS) database was accessed for the years 1994-2015 and all recipients with available data were included in the analysis. This data was linked with the national Irish Cancer Registry (NCRI) to capture episodes of malignancy over follow up. In our analysis we considered end stage kidney disease (ESKD) treatment modality as a time varying covariate and calculated incidence rates, which may fluctuate between transplant and dialysis over follow up. Limitations include: difficulty in capturing the lag between exposure and diagnosis, which may vary by treatment period.

**Results:** 3,672 deceased and living donor adult kidney transplants were assessed comprising 2,310 (62.9%) male and 1,362 (37.1%) female recipients. Periods of treatment with functioning transplant had a higher incidence of skin cancer diagnosis [adjusted incidence rate ratio IRR 2.41 (1.72, 3.38), P<0.001]. Other risk factors for skin cancer included male sex, the number of transplants, and episodes of acute rejection. Tacrolimus was associated with a lower risk compared to cyclosporin however this may be due to a period effect, with longer follow up and ascertainment with ciclosporin.

**Conclusions:** The incidence of skin cancer was higher during periods defined by a functioning renal transplant and lower during subsequent periods of dialysis following graft failure. It is likely that periods defined by graft failure lead to lower overall immunosuppressive burden over follow up.

**Non-Melanoma skin cancer incidence with ESKD treatment modality as a time-varying covariate.**

**SA-POS19**

**The Incidence and Predictors of Post-Transplant Lymphoproliferative Disease (PTLD) after Kidney Transplantation**

Anna Francis, David W. Johnson, Jonathan C. Craig, Germaine Wong, Princess Alexandra Hospital, Brisbane, QLD, Australia; 2University of Sydney/Children’s Hospital, Sydney, NSW, Australia; 3University of Sydney, Sydney, NSW, Australia.

**Background:** PTLD is well described, but the long-term incidences and risk factors for PTLD for adult and paediatric renal transplant recipients remain unclear.

**Methods:** Using data from the Australian and New Zealand Dialysis and Transplant Registry (1963-2015), the cumulative incidence of PTLD in all kidney transplant recipients was calculated using a competing risk of death model and compared with age-matched population-based data using standardized incidence ratios (SIR). Risk factors for PTLD in the modern era of immunosuppression (from year 2000) were assessed using competing risk Cox regression.

**Results:** Among 23, 477 patients (92% adult, 60% male) followed for a median time of 8.5 years, 505 developed PTLD with 50/505 occurring in childhood (age at transplant under 20 years) recipients. The 25-year cumulative incidence of PTLD was 3.3% (95%CI 2.9-3.6%) for adult recipients and 3.6% (95%CI 2.7-4.8%) for child recipients (figure 1). Childhood transplant recipients had a 30-fold increased risk of developing lymphoma compared to the general population (SIR 29.5, 95%CI 21.9-38.8), higher than for adult transplant recipients (SIR 8.4, 95%CI 7.7-9.2). EBV negative recipient serology (adjusted hazard ratio [aHR] 2.85, 95%CI 1.69-4.81), year of transplantation (aHR 0.89 for each year after the year 2000, 95%CI 0.82-0.95) and having diabetes (aHR 2.53, 95%CI 1.37-4.67) were independently associated with PTLD, when adjusted for race, gender, age group and induction agent.

**Conclusions:** Lymphoproliferative disease in transplant recipients occurs at higher rates than in the general population, particularly in paediatric recipients. EBV-negative patients and those with diabetes are at increased risk of PTLD, however PTLD rates have been decreasing over the last 15 years.

**Funding:** Private Foundation Support
A 44 year old male was suffering from end stage kidney failure without any calculi. There was no family history of renal calculus disease. He underwent dialysis for 3 months and received kidney from his mother. He received triple immunosuppression. He had non-oliguric AKI post operatively and then renal function started worsening 4 weeks later. A renal biopsy was done and it showed brown crystals favoring 2,8 DHA crystals. He was started on haemodialysis. Primary hyperoxaluria work up was negative. He was started on tab. Febsuxostat 80mg a day due to suspicion of recurrent DHA nephropathy. A blood spot test showed very low level of APRT (courtesy Dr. Dawn Milliner, mayo Clinic) and a DNA analysis showed mutation of APRT gene. Patient gradually became better and creatinine came down from 7.8mg/dL to 2.7mg/dL in 4 months and is stable two-and-half years later.

Results:

Conclusions: This patient illustrates the importance of recurrent crystalline nephropathy in a post transplant patient. 2,8 DHA is an under-recognized cause of ESRD and can be prevented by correct diagnosis. This patient’s diagnosis was not recognized pre-operatively. A repeat renal biopsy gave the first clue for the diagnosis. The diagnosis was confirmed by measurement of APRT activity in red blood cells and DNA analysis showed mutation consistent with APRT deficiency. This patient responded well perhaps due to early start of therapy with Febsuxostat even before confirming the diagnosis. The disease must be considered in the differential diagnosis of crystalline nephropathy even in the absence of history of nephro lithiasis (Nasr et al NDT 2010).

BR-Q145

Post-transplantation de novo crystalline nephropathy due to 2,8-Dihydroxyadenine

SA-PO520

Kidney Cancer after Renal Transplant: 9 Year Review

Dennis Hu, Suresh K. Rijhwani, Harlan C. Rust, Usama T. Hussein, Sandeep Magoon, Thomas R. McCune. Department of Nephrology, Norfolk, VA; Department of Nephrology, Tidewater, Virginia Beach, VA; Department of Nephrology, Sentara Norfolk General Hospital, Norfolk, VA; Department of Nephrology, Nephrology Associates of Tidewater, Virginia Beach, VA.

Background: Renal transplant patients are at increased risk of renal cell carcinoma (RCC). The overall incidence of RCC following renal transplantation from 1987-2010 is 5.68 times higher than in the general population. Possible explanations include immunosuppression leading to DNA repair impairment, decreased host immune surveillance with resulting unchecked tumor development, and increased oncogenic viral infections. Due to the rapid growth and metastasis of RCC, renal ultrasounds (US) have been used as a screening tool; however, there is no guideline on the frequency of US after renal transplantation.

Methods: Retrospective chart review of 543 renal transplant recipients (age 21-75 at transplant) at Sentara Norfolk General Hospital from 1/1/07-10/31/16 was performed. All patients received similar immunosuppression regimens and serial routine post-transplant renal ultrasounds. Patient characteristics including gender, race, age at transplant, underlying cause of ESRD, and US at 1, 3, 5, 7, and 9 years post-transplant were collected. If renal malignancy was found, tumor characteristics including timing of development, mass location, pathology, staging, and outcome was assessed. RCC incidence was calculated based on timing of US post-transplant.

Results: RCC incidence was 2.2% and found in 92% males and 8% females. RCC was found in patients aged 30-40 (16%), 40-50 (25%), 50-60 (16%), and 60-70 (41%) years old at transplant. Incidence on 0-1, 1-3, 3-5, 5-7, and 7-9 year ultrasounds post-transplant were 0.18%, 0.73%, 1.29%, 0%, and 0%, respectively. Median time of RCC diagnosis was 3 years post-transplant. Tumor characteristics were clear cell (33%), papillary (33%), oncocytoma (13%), tubulocystic (6%), and unclassified (13%). Staging was T1a(1%), T1b(20%), and T3a(6%). 3 patients had different RCC in the same kidney. 1 patient had RCC 4.5 years after previous RCC. All patients had radical nephrectomies. Etiology of ESRD was HTN (33%), Diabetes (50%), and unspecified glomerulonephritis (16%).

Conclusions: US at 1, 3, 5, and 7 years post-transplant identified all RCCs and remained localized within the kidney. Men are at increased risk of RCC. PCKD is not associated with developing RCC. Multicentric development of RCC suggests that follow-up of remaining kidney after nephrectomy is required.

SA-PO521

Recurrent 2,8 DHA Nephropathy Reversal in a Renal Allograft Recipient

Vivek Pathak, Nephrology, Kovai Medical Center and Hospital, Coimbatore, India.

Background: APRT deficiency is a rare autosomal recessive inherited disorder of purine metabolism. In the absence of APRT, adenine is oxidized to 2,8 DHA and forms crystals resulting in nephro lithiasis and progressing to ESRD. This disease can cause recurrent renal allograft failure in post transplant patients. DHA stones are radiolucent and misdiagnosed as uric acid stones.

Methods: A 44 year old male was suffering from end stage kidney failure without any calculi. There was no family history of renal calculus disease. He underwent dialysis for 3 months and received kidney from his mother. He received triple immunosuppression. He

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Frequent Histologic Recurrence of Lupus Nephritis after Kidney Transplantation

M. Lourdes Gonzalez Suarez, Fernando G. Cosio, Lynn D. Cornell, Tomoki Kato, Andrea G. Kattah, Andrea G. Kattah, M. Lourdes Gonzalez Suarez

Background: Frequent occurrence of aHUS and TBMID in a small proportion of LN recipients has been reported. aHUS is a rare condition and the incidence of graft loss due to aHUS is not known. The aim of this study was to assess the incidence and clinical outcome of aHUS in a non-selected group of kidney transplant recipients.

Methods: Retrospective cohort of 306 kidney transplant recipients (KTR) from September 2012 to September 2016 at a single brazilian center. PT-TMA was diagnosed by a panel of experts in consultation. PT-TMA was diagnosed by a panel of experts in consultation.

Results: The incidence of PT-TMA was 3.9% (n = 12). Of these, two were diagnosed with early or no response. Median time from transplant to aHUS diagnosis was 81 (35.5 – 134.5) days. Median time from diagnosis to graft survival was 17 (4.5 – 134) days and was not significantly different between those who improved renal function or those who did not. The aHUS improved in five patients, three remain on dialysis and one suffered sudden death after two doses. Of those who improved renal function, died, one from gastrointestinal bleeding and one from sepsis of cutaneous infection. Death censored graft survival was 50% at 1 year and 46% at 2 years.

Conclusions: aHUS occurred in 6 months PT-TMA and was related to late graft survival leading to a very poor prognosis. Time from diagnosis to treatment with eculizumab did not correlate to better graft survival, but the small sample size should be considered when interpreting these results.

SA-POS25

Incidence and Treatment of Recurrent FSGS Following Kidney Transplantation in Patients with Pre-Emptive Plasmapheresis

Meredith Harris, David K. Hooper. Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.

Background: Focal Segmental Glomerulosclerosis (FSGS) is a leading cause of end stage renal disease (ESRD) in children. Unfortunately, it recours in up to half of patients following kidney transplantation. Pre-emptive therapeutic plasma exchange (TPE) has been suggested as a way to prevent recurrent FSGS, although few studies have evaluated its’ efficacy. Once FSGS does recur, therapies such as rituximab and cyclophosphamide have been tried in combination with TPE to induce remission, but few studies report the efficacy of these therapies.

Methods: We performed retrospective chart review of 258 patients transplanted at CCHMC from May 2003 through November 2016 and identified patients with FSGS as the primary diagnosis. We reviewed medical records of all patients who received more than 1 TPE treatment prior to kidney transplantation and evaluated the risk of FSGS recurrence. FSGS recurrence was compared between patients with 1 TPE treatment and ≥ 3 treatments. For patients with recurrent FSGS, we compared treatment in patients with early vs. late remission.

Results: 35/258 (14%) transplants had FSGS as the primary diagnosis, 20 of which had received pre-emptive TPE. 11/20 (55%) patients with pre-emptive TPE experienced FSGS recurrence at a median of 3 days (range 1-690) post-transplant. 2/5 patients (40%) who had received more than 1 pre-emptive TPE had recurrent disease compared 9/15 (60%) patients who received ≥ 3 TPE treatments (p = 0.62). Of the 11 patients with FSGS recurrence, 10 (90%) achieved remission within a median of 9 months (range 1 – 24 mos). 8/11 patients received rituximab, 9/11 were switched from tacrolimus to cyclosporine, and all patients remained on TPE until remission was achieved. 5 patients experienced early remission (≤ 3 months) and 6 patients experienced late remission (> 3 months). Of 5 patients with early remission 100% switched to cyclosporine within 5 days of recurrent disease, compared to only 1/6 (17%) patients with late or no remission (p = 0.015). 4/5 patients with early remission received rituximab compared to 0/6 patients with late remission (p = 1).

Conclusions: Pre-emptive TPE does not prevent FSGS recurrence regardless of the number of treatments. Rapid switch to cyclosporine was associated with faster time to remission.

SA-POS26

Evolution of Post-Transplant Atypical Hemolytic Uremic Syndrome (aHUS)

Sylvana Maria C. Miranda,1 Pedro Augusto M. Souza,2 Gerson M. Pereira jr,1 Carlos Rafael A. Felpie,1 Vanessa B. Souza,1 Izabela L. Piana,2 Andre S. Alvarenga,2 Claudia Ribeiro,2 Hospiital Santa Casa de Belo Horizonte, Belo Horizonte, Brazil; 3None, Belo Horizonte, Brazil; 4Santa Casa de Belo Horizonte, Belo Horizonte, Brazil.

Background: The incidence of post-transplant thrombotic microangiopathy (PT-MTA) ranges from 1-5% and causes reduction of graft survival. Nevertheless, diagnosis of aHUS is difficult due to multiple potential triggers. Timely treatment of aHUS can improve prognosis.

Methods: Retrospective cohort review of 306 kidney transplant recipients (KTR) from September 2012 to September 2016 at a single brazilian center. PT-MTA was diagnosed by a graft biopsy and/or hemolytic microangiopathic syndrome.

Results: The incidence of PT-MTA was 3.9% (n = 12). Of these, two were diagnosed with acute antibody-mediated rejection, one tacrolimus induced and nine with aHUS by excluding secondary causes. The etiology of renal disease was unknown in six patients of aHUS group. The other three cases were attributed to diabetic nephropathy, malignant arterial hypertension and membranous nephropathy. Fifty five percent of aHUS patients received prednisone, tacrolimus (TAC) and mycophenolate while the remaining received prednisone, tacrolimus and everolimus. Six had TAC trough levels greater than 10 ng/ mL, two greater than 20 ng/mL and none had everolimus trough levels greater than 6 ng/ mL. All nine patients received eculizumab, two of which received plasmapheresis with no response. Median time from transplant to aHUS diagnosis was 81 (35.5 – 134.5) days. Median time from diagnosis to graft survival was 17 (4.5 – 134) days and was not significantly different between those who improved renal function or those who did not.

Conclusions: aHUS occurred until 6 months PT-MTA and was related to late graft survival leading to a very poor prognosis. Time from diagnosis to treatment with eculizumab did not correlate to better graft survival, but the small sample size should be considered when interpreting these results.

SA-POS27

Monoclonal IgG Deposits on Tubular Basement Membrane in Renal Allograft: Is This Significant for Chronic Allograft Injury?

Shinagawa-ku, Tokyo, Japan; 2St.Marianna University, Kawasaki, Kanagawa, Japan; 3Tokyo Women’s Medical University, Shinjuku-ku, Japan; 4University of California, San Diego, La Jolla, CA; 5Nippon Medical School, Tokyo, Japan.

Background: In renal allografts, tubular basement membrane immune deposit (TBMD) has often been observed. Such deposits are usually found in association with BK virus nephropathy and immune complex glomerulonephritis; however, their significance is not well-understood. In recent years, monoclonal immunoglobulin (Ig) G deposition on the renal glomeruli has also been observed. However, the clinical significance of IgG TBMID has not been studied until now. Therefore, we conducted a retrospective clinicopathological study on mononclonal IgG TBMD.
Methods: In total, 7177 biopsy specimens obtained in our institution from 2007 to 2012 were studied. Conventional light and electron microscopic studies and indirect fluorescence immunostaining for Ig heavy and light chains and complements C1q and C3c were performed. Monoclonal IgG TBMID was diagnosed if an IgG subclass or light-chain restriction was present and all other antibodies were absent in TBMID. Of these, seven showed monoclonal IgGk TBMID and three showed monoclonal IgGλ, IgG2k, and IgG3k TBMID, respectively. In all patients with monoclonal IgGk TBMID, abundant and large granular electron-dense deposits (EDD) were detected in the tubular basement membrane (TBM). In patients with polyclonal IgGk, IgG2k, and IgG3k TBMID. On the other hand, eight patients showed polyclonal IgG TBMID. Progression of interstitial fibrosis and tubular atrophy (IFTA) was significantly higher in patients with monoclonal IgG and IgGk TBMID compared with that in those with polyclonal IgG TBMID (P < 0.05). There were no significant differences in the other clinical parameters between monoclonal IgG and IgGk and polyclonal IgG TBMID.

Conclusions: This is the first study on patients with monoclonal IgG TBMID in renal allografts. We found that monoclonal IgGk TBMID was associated with EDD formation in TBM and the progression of IFTA.

SA-PO528
Allograft Crescent Predicates Graft Failure in Recurrent IgA Nephropathy Patients

Sohon Park, Hyunjung Cho, Mi-yeon Yu, Yae-jeong Kim, Yo Su Kim, Hae-jong Lee. Seoul National University Hospital, SEOUL, Republic of Korea.

Background: Recent studies demonstrated the predictive value of crescent in IgA nephropathy (IgAN) prognosis. However, it remains unclear whether allograft crescent is associated with worse graft prognosis in patients with recurrent IgAN.

Methods: We reviewed 376 IgAN patients who received kidney transplantation from 1979-2016 in a university hospital in Korea. Allograft biopsies were performed when patients had a significant proteinuria, hematuria, or a progressive deterioration of renal function. Clinical and pathologic characteristics at the time of biopsy were collected in recurrent IgAN cases. The degree of the crescent formation was classified into prominent (> 10%), mild (0-10%), and none (0%). The renal outcome was death-censored graft failure (DCGF).

Results: During the follow-up duration of 7.0 (3.7-14.3) years, 122 (32.3%) patients were diagnosed as recurrent IgAN by allograft biopsy. Median time to recurrence was 4.1 (1.9-8.1) years. Recipients who received their IgAN were younger. They were donated allograft from younger donor and received less induction immunosuppressive treatment. Among the recurrent IgAN patients, 36 (29.5%) reached graft failure after 9.3 (3.7-12.2) years from their transplantation. Moreover, IgAN recurrence itself was a strong time-dependent risk factor for DCGF (adjusted HR 2.703, 95% CI 1.608-4.545, P < 0.001). Regarding the pathologic findings, crescent was identified in 20 patients with recurrent IgAN, in those with relatively old graft age, decreased renal function at the time of IgAN recurrence, and higher MEST scores. All five patients with prominent (>10%) crescent formation in their allograft biopsies progressed to consequent DCGF within from 0.4 to 4.6 years after the IgAN recurrence. Also, the presence of prominent (>10%) crescent in transplanted kidney was a strong risk factor for DCGF when compared with other recurrent IgAN patients without crescent formation (adjusted HR 6.313, 95% CI 1.699-23.458, P=0.006), even after adjustment of MEST scores and coexisting rejection.

Conclusions: Despite its rarity, a prominent allograft crescent (>10%) was demonstrated to contribute to renal deterioration in recurrent IgAN patients. Treatment strategies for those patients should be investigated.

SA-PO529
When Post-Transplant IgA Deposition Is Not Recurrence

Claire Kennedy,1,2 Darren McMahon,3 Orna Waldron,2 Andrea M. Fitzmaurice,3 Patrick O’kelly,2 Megan R. Finan,2 Brendan Doyle,1 Anthony M. Dormain,1 Peter J. Conlon,2 Beaumont Hospital, Dublin 9, Ireland; 2Beaumont Hospital, Dublin 9, Co Dublin, Ireland; 3Royal College of Surgeons in Ireland, Dublin, Ireland.

Background: Immunglobulin A (IgA) deposition in the post-transplant setting usually represents disease recurrence but can occasionally represent donor-related or de novo disease. We aimed to examine post-transplant outcomes in the setting of donor-related or de novo IgA deposition and compare patient and graft outcomes in these cohorts to those in all other renal transplant recipients during a similar time period.

Methods: Ten renal biopsy records from 1/1/1995 to 31/12/2012 (n=7296) were reviewed to identify those with post-transplant IgA deposition. Detailed chart review was performed to identify those in whom the IgA deposition was deemed donor-related (>6 months post-transplant) or de novo (>6 months post-transplant) as opposed to recurrent. A retrospective review of research MEST score (0-7) was assigned to each biopsy. The National Kidney Transplant Service database was accessed to facilitate a comparison of patient and graft outcomes in these cohorts and all other renal transplant recipients.

Results: Fifteen cases of post-transplant IgA deposition were deemed to be donor-related (fourteen deceased donors) and had a mean research MEST score of 1.65 (range 0.3-3.9). Eleven cases of de novo IgA deposition were identified across all kidney transplant recipients. One of these cases showed resolution of the deposits over time. Eight cases were deemed to represent de novo IgA deposition. The mean research MEST score, which is less specific in this setting, was 2.60 (range 1-4). There were no differences in patient and graft survival rates in these groups compared to all other transplants performed during a similar time period. Cox regression multivariate analysis did not identify either donor-related or de novo IgA deposition as a contributing factor to patient or graft survival.

Conclusions: Cases of donor-related or de novo IgA deposition were infrequently encountered in our review of ‘for-cause’ biopsies. Neither condition, when histologically mild/moderate was found to impact on patient or graft survival rates. These results cannot be extrapolated to the setting of living donation. This information is important for prognostication and counselling purposes in selected future cases.

SA-PO530
Long-Term Prognosis of Kidney Transplant Patients with Rapidly Progressive Glomerulonephritis (RPGN)

Talar Kharadjian,1 Brad C. Astor,1 Sarah E. Panzer,2 Tripti Singh,2 1University of Wisconsin, Madison, WI; 2School of Medicine and Public Health, University of Wisconsin, Madison, WI.

Background: ANCA associated vasculitides (AAV) and anti-GBM are the leading cause of ESRD due to RPGN. We report our institution’s experience with renal transplant patients in patients with ESRD due to RPGN.

Methods: We compared the outcomes for patients with ESRD due biopsy proven AAV and anti-GBM with patients with ESRD due to IgA nephropathy (IgAN) and autosomal dominant polycystic kidney disease (ADPKD) who underwent kidney transplant between 1994 to 2013.

Results: 72 patients with biopsy proven RPGN (AAV N=46, anti-GBM N=26) underwent kidney transplant between 1994-2013. The mean follow up time was 7.2 years (± 4.7 years). The incidence of graft loss was 2.9/100 person years for AAV and 5.2/100 persons year for anti-GBM. The incidence of patient death was 3.8/100 person years for AAV and 3.2/100 person years for anti-GBM. The risks of graft loss and patient death were similar to those for IgAN (2.8 and 2.2/100 person years) in multivariable analysis (Table 1). 10-year death censored graft survival for AAV and anti-GBM was similar to IgAN and ADPKD (Fig1).

Conclusions: Long-term patient and graft survival for patients with ESRD due to AAV and anti-GBM after kidney transplant was good and similar to ESRD due to IgAN and ADPKD post transplantation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
His immunosuppression included anti-thymocyte globulin (ATG) induction therapy, and methylprednisolone, mycophenolate mofetil, and tacrolimus. At the time of transplant he presented with a creatinine of 2.2 mg/dL in the setting of likely medication nonadherence. A renal transplant biopsy revealed acute cellular rejection (ACR) grade 2R, peritubular capillaritis with C4d positivity in 50% of glomeruli, and a serum donor specific antibody (DSA) positivity. There was also PLA2R positive membranous nephropathy. His infectious workup was negative. He was treated with pulse methylprednisolone, ATG, plasma exchange, intravenous immunoglobulin (IVIG) and tacrolimus. His cr decreased to 1.03 mg/dL at hospital discharge. His interval follow up demonstrated stable renal function. At nineteen months post-transplant his cr was 1.57 mg/dL, he had negative DSA and undetectable tacrolimus trough level. He was next seen 3 months later with allograft pain and a cr of 7.0 mg/dL. Renal biopsy was consistent with ACR, microcapillaritis inflammation suspicion for AMR (negative C4d, positive DSA) and no evidence of membranous nephropathy. He was treated with ATG, methylprednisolone, rituximab, plasma exchange, and IVIG and his cr decreased to 3.7 mg/dL.

Results: 
Conclusions: While the pathophysiology of dnMN remains to be elucidated, this disease entity is currently viewed as an alloimmune disease mediated by chronic AMR. In contrast to idiopathic MN, dnMN associated with AMR has not been found to be PLA2R positive. Although rare, the presence of PLA2R positive dnMN should be considered in the setting of AMR. Further study and long term follow up of these patients will help us gain a better understanding.

SA-PO532
Characteristics of Donor Transmitted Membranous Nephropathy in Kidney Transplantation
Yasuhiro Otsuka, Yoshikiko Watarai, Asami Takeda, Nagoya Daini Red Cross Hospital, Nagoya, Japan.

Background: Donor transmitted membranous nephropathy (MN) is a unique entity that shows histological features of MN even though donor urinalysis is negative for protein before kidney transplantation (KTx). Donor transmitted MN is rarely seen in KTx, but its prognosis and histological changes are unclear.

Methods: Retrospective data were collected from 2002 to 2016. Out of 1113 KTx cases, eight patients were diagnosed with donor transmitted MN by 1 hour biopsy. All eight cases were living KTx, and posttransplant renal function and urinary protein of both donor and recipient were analyzed. Protocol renal allograft biopsies were performed one hour, three weeks, and one year after KTx, and light microscopy, immunofluorescent study for IgG, C3, C4d, and IgG subclass, and electron microscopy were performed.

Results: 
Donor age was 61.1 ± 13.1 years, and four were male. Urinalysis was negative for protein in all eight donors. Donor eGFR and urinary albumin creatinine ratio (UACR) before KTx were 83.0 ± 11.2 mg/mmol/1.73m² and 38.0 ± 38.7 mg/dL. Donor eGFR and UACR one year after KTx was 51.5 ± 9.1 mg/mmol/1.73m² and 3.5 ± 0.9 mg/dL. Donor follow up period was 43.1 ± 43.9 months, latest eGFR and urinary protein was 50.6 ± 10.1 mg/mmol/1.73m² and 0.08 ± 0.12 mg/dL. Recipient age was 38.6 ± 7.0 years, five were male, and all eight cases were AB0 compatible KTx. Recipient eGFR and urinary protein were performed one hour, three weeks, and one year after KTx, and light microscopy, immunofluorescence study for IgG, C3, C4d, and IgG subclass, and electron microscopy were performed. Four out of five were positive for C4d on capillary wall at one year biopsy. IgG subclass stain revealed that one case was negative for IgG4. By light microscopy, bubbling appearance was observed at one hour and one year biopsy in all available cases. By electron microscopy, stage did not change at one year biopsy except one case from electron microscopy stage III to stage IV.

Conclusions: 
This study suggest that deposition of IgG in donor transmitted MN decreases within one year after KTx. Clinical data showed a good renal function and urinary protein within normal limit at latest follow-up in both donor and recipient.

SA-PO534
Successful Remission of Recurrent FSGS Following Lipid Apheresis in Renal Transplant Recipients
Lokesh N. Shah,1,2 Christopher J. LaRosa,2 Justine Speckhals,2 Carolyn Lokesh,2 and 7 Lokesh,6 Nemours/ Alfred I. DuPont Hospital for Children, Wilmington, DE;1 Nemours/ Alfred I. DuPont Hospital for children, Avondale, PA;4 Nemours/ Alfred I. duPont Hospital for Children, Wilmington, DE; Nemours/ Alfred I. duPont Hospital for children, Wilmington, DE; Nemours/ Alfred I. duPont Hospital for Children, Wilmington, DE; Nemours/ Alfred I. duPont Hospital for Children, Wilmington, DE; Nemours/ Alfred I. duPont Hospital for Children, Wilmington, DE; Thomas Jefferson University, Philadelphia, PA; 8 Alfred I. duPont Hospital for Children, Wilmington, DE.

Background: The Liposorber® LA-15, a lipoprotein apheresis device, has been used as a rescue therapy in patients with recurrent primary focal segmental glomerulosclerosis (FSGS). Using a protocol of weekly lipid apheresis in combination with IV methylprednisolone, we describe the remission of recurrent FSGS in two pediatric kidney transplant recipients.

Methods: Both patients were diagnosed with steroid-resistant biopsy-proven FSGS at age 2. They failed to respond to multiple interventions (high dose steroids, high dose calcineurin inhibition, mycophenolate, and rituximab). They eventually underwent renal transplantation due to ensuing ESRD. Both post-transplantation courses were complicated by immediate recurrence of FSGS with urine protein/creatinine (U/cre) ratios > 50. Again, both failed to respond to high dose steroid and calcineurin inhibition; nor did they respond to 3 months of thrice weekly standard plasmapheresis. As a rescue therapy both patients underwent weekly lipid apheresis using the Liposorber® LA-15 system with a treatment volume of 60 mL/kg along with a 10 mg/kg dose of IV methylprednisolone. The final cycle of lipid apheresis occurred approximately 80 days after its initiation in both patients. In both cases there was a dramatic decrease in the urine protein to creatinine ratios (FIGURE). After stopping lipid apheresis both patients have remained in clinical remission without further treatment.

Results: 
Conclusions: Lipid apheresis has shown promise in the treatment of both primary and recurrent FSGS; however, experience with this modality is limited. Our successful use of lipid apheresis in combination with methylprednisolone to induce remission in treatment-resistant recurrent FSGS provides a protocol for future studies, and provides a better understanding of the ill-defined pathophysiology of hyperlipidaemia and nephrotic syndrome.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO535
Clinical Findings, Pathology, Treatment, and Outcomes of PGNMID after Kidney Transplantation
Hassan A. Salameh, Hatem Amer, Ladan Zand, Fernando C. Fervenza, Nelson Leung. Mayo Clinic, Rochester, MN.

Background: Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is a rare form of glomerular disease caused by monoclonal immunoglobulin (Ig) deposition localized to the glomeruli. The outcome of PGNMID is in renal allograft recipients is unknown.

Methods: Between 2000 and 2016 we identified 20 patients with PGNMID who underwent kidney transplantation (KTx). We describe their clinical findings, laboratory data, recurrence rates, biopsy findings, treatment and outcomes during the study period.

Results: The median age at the time of native kidney biopsy-proven PGNMID was 54 (range 23-74) years. Median time between the initial kidney biopsy to ESRD (KTx or dialysis) was 36 (range 2-146) months. PGNMID recurred in 18 out of 20 patients (90%). The median time to recurrence in the kidney biopsy was 4 (range 1-48) months (Figure 1). Four patients did not receive targeted treatment for the PGNMID recurrence and no graft loss was noted with median follow-up of 48.5 months. Three patients were treated with additional immunosuppressive agents including steroids and cyclophosphamide and 33% (n=7) had graft loss in this group. Seven patients received B-cell targeted therapy with Rituximab with graft loss rate of 28% (n=2). Four patients received plasmapheresis in addition to immunosuppressive therapy; graft lost in 75% (n=3); however, only 25% (n=1) was attributed to PGNMID with the other two losses due to rejection.

Conclusions: In our experience, PGNMID was associated with a very high rate of recurrence in all grafts reaching 90%. Graft loss occurred in 33% of recurrent cases. The median time to graft loss was 67 (range 31-132) months. Graft loss incidence due to PGNMID was similar between the immunosuppression, Rituximab and plasmapheresis groups; however, the plasmapheresis group had more aggressive disease that lacked response to other treatment options.

Figure 1. Kaplan-Meier plots of (A) Cumulative incidence of PGNMID recurrence in grafts and (B) Graft loss in recurrent PGNMID.

SA-PO536
Determinants of Renal Progenitor Cell Responsiveness to the Inductive Wnt9b Signal from the Ureteric Bud
Kyle Dickinson, Thomas J. Carroll, Paul R. Goodyer.1 McGill University, Montreal, QC, Canada; 2UTSW Medical Center, Dallas, TX

Background: The canonical Wnt-signalling pathway is essential for kidney development as fully primed renal progenitor cells (RPC) appear in the metanephric mesenchyme. RPCs receive inductive Wnt9b signals from the adjacent ureteric bud to initiate a proliferative program. Specificity of Wnt ligand binding is determined by the co-receptor complex consisting of a Fzd and Lipoprotein-related receptor protein (Lrp)5/6, however, the specific molecular components conferring responsiveness in RPCs have yet to be identified. The receptor complex is stabilized by R-spondin1 and R-spondin3 (Rspo1 and Rspo3), amplifying the Wnt signal.

Methods: We obtained M15 cells, derived form E10.5 mesonephric mesenchyme (Hastie et al, 1999) and systematically analyzed Wnt receptor/signalling components required for a canonical Wnt response. To measure activation of the canonical Wnt pathway, we transfected our M15 cells with reporter plasmid 4X TOPFlash and measured luciferase activity using a luminometer. RNA was analyzed by qRT-PCR.

Results: Exposing M15 cells to external Wnt9b resulted in minimal luciferase activity suggesting a signalling component is missing. We analyzed M15 cells for components of the β-catenin/TCP pathway and found mRNA expression of Fzd5-6, Lrp6 but neither Rspo1/3. To ascertain whether absence of R-spondin accounts for the lack of response, we transfected M15/TOPFlash cells with Wnt9b and added recombiant Rspo1 or Rspo3 and observed a 4.8-fold and 7.8-fold increase in luciferase activity, respectively. In the presence of Rspo1, we transfected the cells with Fzd1-10 and observed an additional 5-fold increase in the presence of Fzd5 but not the other Fzds. Knockdown of LpR6 with siRNA (60% reduction in mRNA level) resulted in a 60% reduction in luciferase activity which was not rescued by Lrp5.

Conclusions: Our results suggest that early RPCs must acquire a specific receptor complex consisting of Fzd5, Lrp6 and Rspo1/3 before they can transduce an optimal β-catenin/TCP signal in response to Wnt9b during nephrogenesis. We speculate that putative RAPCs lacking these components are incompetent for primitive nephrogenesis and/ or regeneration of damaged adult kidneys.

Funding: Government Support - Non-U.S.

SA-PO537
DNMT1-Dependent Cytosine Methylation Is Essential for the Control of Progenitor Cell Differentiation in Early Nephron Development
Szu-Yuan Li,1,2 Jhijwark Park,1 Rojesh Shrestha,1 Katalin Szustak.1 University of Pennsylvania, Philadelphia, PA; 2Medicine, Taipei Veterans General Hospital and Yang-Ming University, Taipei, Taiwan.

Background: The basic functional units of the mammalian kidney, nephrons, are generated repetitively during kidney organogenesis. Six2 positive cells represent a monolayer of nephron progenitor population within which knowledge has been generally acquired in only 12 patients. We describe a single centers’ experience with PGNMID after kidney transplantation (KTx).

Methods: Between 2000 and 2016 we identified 20 patients with PGNMID who underwent kidney transplantation (KTx). We describe their clinical findings, laboratory data, recurrence rates, biopsy findings, treatment and outcomes during the study period.

Results: The median age at the time of native kidney biopsy-proven PGNMID was 54 (range 23-74) years. Median time between the initial kidney biopsy to ESRD (KTx or dialysis) was 36 (range 2-146) months. PGNMID recurred in 18 out of 20 patients (90%). The median time to recurrence in the kidney biopsy was 4 (range 1-48) months (Figure 1). Four patients did not receive targeted treatment for the PGNMID recurrence and no graft loss was noted with median follow-up of 48.5 months. Three patients were treated with additional immunosuppressive agents including steroids and cyclophosphamide and 33% (n=7) had graft loss in this group. Seven patients received B-cell targeted therapy with Rituximab with graft loss rate of 28% (n=2). Four patients received plasmapheresis in addition to immunosuppressive therapy; graft lost in 75% (n=3); however, only 25% (n=1) was attributed to PGNMID with the other two losses due to rejection.

Conclusions: In our experience, PGNMID was associated with a very high rate of recurrence in all grafts reaching 90%. Graft loss occurred in 33% of recurrent cases. The median time to graft loss was 67 (range 31-132) months. Graft loss incidence due to PGNMID was similar between the immunosuppression, Rituximab and plasmapheresis groups; however, the plasmapheresis group had more aggressive disease that lacked response to other treatment options.

Figure 1. Kaplan-Meier plots of (A) Cumulative incidence of PGNMID recurrence in grafts and (B) Graft loss in recurrent PGNMID.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO538
HIF Prolyl-4-Hydroxylation in FOXD1 Lineage Cells Is Essential for Normal Kidney Development
Hanako Kobayashi.1 Volker H. Haase.2 1Vanderbilt University Medical Center, Nashville, TN; 2Vanderbilt University Medical Center, Nashville, TN.

Background: Hypoxia in the embryo is a frequent cause of intra-uterine growth retardation, low birth weight and multiple organ defects. In the kidney this can lead to low nephron endowment predisposing to chronic kidney disease and arterial hypertension. A key component in cellular adaptation to hypoxia is the hypoxia-inducible factor (HIF) pathway, which is regulated by prolyl-4-hydroxylase domain (PHD) dioxygenases PHD1, PHD2 and PHD3. In the adult kidney, PHDs function as oxygen-sensors, are differentially expressed in a cell type-dependent manner and control the production of erythropoietin in interstitial cells. The role of interstitial cell PHDs in renal development, however, has not been examined.

Methods: In order to examine the role of intestinal HIF oxygen sensing in renal development and homeostasis, we used the Cre-loxP system to target all 3 HIF-PHDS in conjunction with Hif-1α or Hif-2α in FOXD1-expressing stromal cells.

Results: PHD2 and PHD3 are essential for normal kidney development as the combined inactivation of stromal PHD2 and PHD3 resulted in renal failure that was associated with reduced kidney size, decreased numbers of glomeruli and abnormal postnatal nephron formation. In contrast, PHD1 inactivation was normal in animals with individual PHD inactivation. We furthermore demonstrate that the defect in nephron formation in PHD2/PHD3 double mutants required intact HIF-2 signaling and was dependent on the extent of stromal HIF activation.

Conclusions: The ability to regulate HIF prolyl-4-hydroxylation in FOXD1 stroma-dependent cells is essential for normal nephron formation. Our data have implications for the therapeutic use of HIF prolyl-4-hydroxylase inhibitors, which are currently in phase 3 clinical development for renal anemia.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO539
Hedgehog-TGFβ Signaling in Foxd1+ Stromal Cells Controls Stromal Patterning and Nephron Formation
Christopher Rowan, Norman D. Rosenblum. The Hospital for Sick Children, Toronto, ON, Canada.

Background: In the embryonic mammalian kidney, signals from Foxd1+ stromal cells are critical in establishing a full complement of nephrons. Yet, the molecular mechanisms that control stromal-nephrogenic cell interactions are largely unknown. Previously, we demonstrated that hypoxogenic deficiency of SMO, a cell surface Hedgehog signaling effector, in the stromal lineage (Smoo-/-foxd1mice) results in a 42% decrease in nephron number. Remarkably, low nephron number is preceded by expansion of SIX2+ nephron progenitors into a relative lack of mesenchymal epithelial canonisation [ASHG 2014]. Here, we identify molecular mechanisms that control nephron number in Smoo-/-foxd1mice.
**Methods:** RNA expression was assayed by RNASeq, quantitative (q)PCR, and in situ hybridization. Preparations were performed on whole mouse embryos at defined stages using neutralizing antibodies and in situs. TGFβII receptor II (Tgfb2) expression was demonstrated in the extracellular matrix of in situ hybridization. The TGFβII receptor II (Tgfbr2) ligands were visualized using TGFβII receptor II (Tgfbr2) mutant kidney tissue and in FACS-isolated mutant Foxd1+ and stromal cells. 

**Results:** RNASeq of wild type and Smo-null**+** E13.5 kidney tissue demonstrated decreased expression of Tgfb2 in mutant tissue. qPCR showed a 30% decrease in Tgfb2 in Smo-null**+** mutant kidney tissue and in FACS-isolated mutant Foxd1+ and stromal cells. In situ hybridization demonstrated decreased Tgfb2 expression, and immunostaining demonstrated decreased expression of the TGFβII receptor II (Tgfbr2) ligands within Foxd1+ and stromal cells. Smo-null**+** mutant kidneys. Treatment of wild type embryonic kidney explants with neutralizing antibody or MO specific to TGFβII resulted in 65% (P=0.017) and 35% (P=0.003) fewer nephrons, respectively (n=3 per group). CRE-dependent deletion neutralizing antibody or MO specific to TGFβII resulted in 65% (P=0.017) and 35% (P=0.003) fewer nephrons, respectively (n=3 per group). CRE-dependent deletion neutralizing antibody or MO specific to TGFβII resulted in 65% (P=0.017) and 35% (P=0.003) fewer nephrons, respectively (n=3 per group). CRE-dependent deletion neutralizing antibody or MO specific to TGFβII resulted in 65% (P=0.017) and 35% (P=0.003) fewer nephrons, respectively (n=3 per group).

**Conclusions:** We conclude that HI-TGFβII signaling exerts both cell autonomous and non-cell autonomous effects to control nephron formation and stromal patterning.

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

---

**Methods:** We identified Unc5c as a receptor for the ligand Ntn1 (Ntn1) which has roles in axon guidance as well as vascular, lung, and mammary gland development. In situ analyses show that Ntn1 expression is restricted to the stromal progenitors. Other receptors for Ntn1 such as Unc5b are expressed in the vascular endothelium and medullary collecting ducts. Therefore, we focused on assessing the knockout phenotype of their common ligand Ntn1. We utilized the Floxed line to conditionally ablate Ntn1 in the stromal progenitors.

**Results:** Ntn1 mutant kidneys are hypoplastic. At E15.5, immunostaining for Smo2, cytotkeratin, and Wnt1 reveals relatively normal nephron progenitor and ureteric tree organization with developing nephrons and glomeruli present despite kidneys being smaller. Since Ntn1 has roles in vascular development and axon guidance, we also stained kidneys for CD31 (endothelium) and Tuj1 (neuron). Mutant kidneys often had additional endothelial and neuronal projections extending over the outer cortex. Subsets of P0 mutant collecting ducts showed extensive dilation. Numbers of each genotype were assessed at P14 and indicate that most conditional Ntn1 mutants die postnatally.

**Conclusions:** We identified a novel signaling pathway acting in the embryonic kidney. Stromal progenitor-derived Ntn1 may play several roles including regulating the nephron progenitor population through Unc5c as well as guiding vascular and neuronal cell networks. Current studies are underway to assess cell type numbers, proliferation, and differentiation of vascular and neuronal networks. Additionally, we are analyzing Unc5c mutant kidneys. Our studies will help shed light onto new signaling pathways controlling mammalian kidney development and may have implications on vascularization and innervation of the kidney where much less is known about their development and regulation during morphogenesis.

**Funding:** NIDDK Support

---

**Methods:** The kidney is a complex organ that is made of many different cell types. In an effort to better understand the cell diversity within the developing kidney we have performed single cell RNA-seq on embryonic day 14.5 mouse kidneys. Of particular interest is the apparent lack of a Hox code within the developing kidney. Previous studies have determined that Hox 10 and 11 paralogous groups are functioning within kidney development. Interestingly, thirty-six of the thirty-nine mammalian Hox genes are expressed during kidney development.

**Methods:** Analysis of wild type and mutant E14.5 kidneys was performed using data obtained through Drop-seq. Additional data sets were gathered using Fluidigm and Chromium Drop for wild type validation. Hox9,10,11, Hoxd9,10,11 mutants were used to determine the functional role of the Hox genes during kidney development. Altogether and Seurat based analyses are being used to determine the normal and mutant expression profiles.

**Results:** Single cell genotypes were identified in the wild type data set; medullary collecting duct, cortical collecting duct, ureteric bud tip, loop of Henle, distal comma shaped body, podocyte, mid S-shaped body, early proximal tubule, pre-tubular aggregate, three cap mesenchyme groups, endoderm, nephrogenic zone stroma, cortical stroma, and medulla.

**Background:** Kidney morphogenesis is driven by reciprocal signaling between progenitor populations. However, novel signaling pathways may remain unknown. We recently uncovered targets of SIX2 in the nephron progenitors of mouse and human kidneys through a combination of ChIP-seq and RNA-seq. We analyzed these lists to identify novel signaling pathways acting in the developing kidney.

**Results:** Smo-null kidney tissue showed extensive dilation. Numbers of each genotype were assessed at E14.5 and indicate that most conditional Smo-null mutants die postnatally.

**Conclusions:** We conclude that HI-TGFβII signaling exerts both cell autonomous and non-cell autonomous effects to control nephron formation and stromal patterning.

**Funding:** Government Support - Non-U.S.
Chemical Genetic Screen Reveals Novel Role for PPAR Signaling in Renal Progenitor Development

Joseph M. Chambers, Rebecca A. Wingert. University of Notre Dame, Notre Dame, IN

Background: The genetic and molecular mechanisms directing nephron segmentation during kidney development are not well understood. Deregelation of genes involved in kidney development results in a variety of diseases broadly categorized as Congenital Anomalies of the Kidney and Urinary Tract (CAKUT). Embryonic zebrafish have a simplified kidney, the pronephros, comprised of proximal and distal segments that display conservation with mammalian nephrons, including humans, thus enabling CAKUT modeling.

Methods: Through novel chemical genetic screen, we discovered that peroxisome proliferator-activated receptor (PPAR) signaling is essential for normal nephron segment development. PPARs are a group of nuclear receptor proteins that are activated by ligands such as thiazolidinediones and act as transcription factors by heterodimerization with retinoid X receptor (RXR) to regulate cell differentiation and perform diverse roles in metabolism. We found that treatment with the PPAR agonist bezafibrate during nephrogenesis alters the balance of proximal and distal cells. Interestingly, pparg co-activator, pparcg1a1, which binds to activated PPARs to regulate transcription of target genes, is dynamically expressed in renal progenitors.

Results: To test the functional role of this co-activator during nephron segmentation, we examined nephron development in pparcg1a1 knockout and knockdown models development renal cysts, a hallmark of dysplastic CAKUT. Interestingly, there is a decrease in cilia within the nephrons of mutant and knockdown examples. Assessment of essential nephron regulators revealed that pparcg1a1 acts to inhibit irx3b and promote thx2b.

Conclusions: Taken together, our studies suggest a novel mechanism by which PPAR signaling coordinates lineage choices during nephrogenesis. These findings may lead to a better understanding of the therapeutic potential of PPARs in relation to renal birth defects and cystic disease conditions as a core, conserved pathway of PPARs in relation to renal birth defects and cystic disease conditions of MCC development separate from

Genetic Mechanisms of Multiciliated Cell Development in Renal Progenitors

Amanda N. Marr, Rebecca A. Wingert. University of Notre Dame, Notre Dame, IN

Background: Multiciliated cells (MCCs) are found in a wide variety of species and tissues, ranging from the embryonic kidney of frogs and fish to the reproductive and respiratory systems of mammals. Differentiation of MCCs has become an increasingly attractive area of research due to their association with fluid flow and disease. There is evidence for a core, conserved pathway of MCC development that includes the Notch signaling pathway as a negative regulator of MCC fate.

Methods: The embryonic zebrafish kidney, or pronephros, has emerged as a useful tool to study MCC development due to the availability of lineage markers and the ease of investigating the effects of genetic and chemical perturbations. In this study, we have used a combination of gene and chemical perturbations to investigate the role of Notch signaling in MCC development.

Results: We found that inhibition of Notch signaling resulted in an expansion of the pronephric domain, suggesting a role for Notch signaling in the regulation of MCC fate. Moreover, we observed a decrease in the number of MCCs in Notch mutants, indicating that Notch signaling is required for MCC development.

Conclusions: Our findings suggest that Notch signaling plays a crucial role in the regulation of MCC development. Further studies are needed to determine the specific mechanisms by which Notch signaling regulates MCC development.
neon- nephrons. Furthermore, we generated rat neo-nephrons in the mouse nephrogenic zone by conditional elimination and replacement.

Methods: We used Cre-loxP technology in combination with diphtheria toxin receptor-loxP (DTDR-loxP) and Six2-Cre mice for Diphtheria Toxin (DT)-mediated NPC elimination. Metanephros (MN) was isolated from the Six2-DTR +/- mouse embryos. We generated NPC-enriched kidney rudiments transplanted into the Six2-DTR +/- mouse nephrogenic zone and simultaneously administered DT, followed by co-culture in an organ culture dish for seven days. We examined donor NPCs differentiation into neo nephrons by immunostaining of nephron markers (WT1, PAX8, GATA3, Cytokeratin8, E-cadherin, LTL).

Results: Donor rat NPCs were observed in the broad graftenfassment in host mouse cap mesenchyme, which eliminated native mouse NPCs on DT administration. The interspecies chimeric nephrons expressed glomerular and tubular markers. We also observed direct connections between host collecting ducts and the neo-nephrons.

Conclusions: Using progenitor cells conditional elimination system, we demonstrated that donor rat NPCs replaced host mouse NPCs in the mouse nephrogenic zone, and that generation of neo-nephrons is possible by other species. Thus, this technique enables the differentiation of progenitor cells into nephrons, providing insight into the nephrogenesis and organ regeneration processes. We believe that this technique could effectively be used to evaluate the differentiation of NPCs from pluripotent stem cells (PSCs).

Funding: Other NIH Support - Grants-in-Aid for Scientific Research, Grant-in-Aid for Young Scientists (B)

SA-PO549

Regeneration of Rat Nephrons in the Mouse Metanephros: In Vivo Regeneration of Nephrons between Different Species under the Administration of Optimal Immunosuppressive Agents

Takashi Yoshinari, Susumu Amanaka, Kei Ajiri, Keiko Fukunaga, Takashi Yokoko. Division of Nephrology and Hypertension, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan.

Background: The transplant of exogenous nephron progenitor cells(NPCs) to a nephrogenic niche has demonstrated very low engraftment efficiency, possibly due to the competition with existing native host NPCs occupying the niche. Previously, we generated a transgenic mouse model with ablation of NPCs by using a drug for induction. We demonstrated that host mouse NPCs were replaced with donor mouse NPCs by eliminating existing native host NPCs, and that donor cells regenerate neo nephrons that connect with host collecting ducts. In the future, we aim to regenerate human nephrons in different species using the NPCs elimination and replacement system, and apply this novel strategy to the treatment of kidney failure. As a first step, we needed to examine the possibility of interspecies regeneration of nephrons. We succeeded in regenerating rat nephrons in the mouse metanephros(MN) on an organ culture dish using this system. In this work, we verified the in vivo regeneration of nephrons between rat and mouse models.

Methods: In the transgenic mouse, diphtheria toxin receptor cDNA is specifically expressed on Six2-positive NPCs. The MN was isolated from the E13 embryo, following which donor rat NPCs that were not affected by the diphtheria toxin were transplanted into the MN. Diphtheria toxin was simultaneously added to the MN for the elimination of native NPCs only. Subsequently, the mouse MN-implanted rat NPCs were transplanted into the abdominal para-aortic area of an adult rat under the administration of tacrolimus and Mycophenolate mofetil. After 3 weeks, regeneration of rat nephrons in the transplanted mouse MN was examined through immunohistological analysis.

Results: Donor rat NPCs were noted engraftment in the host mouse cap mesenchyme, which ablated native NPCs using diphtheria toxin. Additionally, donor rat NPCs differentiated into neo nephrons in the host mouse metanephros transplanted into the adult rat.

Conclusions: We demonstrated interspecies regeneration of nephrons within a living organism under the administration of optimal immunosuppressive agents by using the NPCs elimination and replacement system. This system strategy is considered an effective method for kidney regeneration.

SA-PO550

Maintenance of Mature Collecting Duct Principal Cells Is Dependent on Notch Signaling

Malini Mukherjee, Jennifer DeRiso, Kameswaran Sunderran. Sanford Research, Sioux Falls, SD; Pediatrics, University of South Dakota, Sioux Falls, SD.

Background: During kidney development Notch signaling endows the collecting ducts with proper urine concentrating capacity by ensuring that a sufficient number of collecting duct cells differentiate into mature principal cells instead of selecting intercalated cells fates. Based on the continued expression of Notch ligands in intercalated cells adjacent to mature principal cells we tested the hypothesis that Notch signaling is required for the maintenance of the mature principal cell state.

Methods: To study the role of Notch signaling in the mature collecting ducts: (i) ectopic expression of dominant-negative mastermind like-1 (dnMaml), a known inhibitor of Notch/RBPJ-mediated transcriptional activation, in mature mouse kidney epithelial cells, (ii) conditional genetic inactivation of Notch1 and Notch2 in the mature principal cells of mouse kidneys during three weeks of age, and (iii) conditional genetic inactivation of the down-stream Notch signaling target Hes1 in the renal epithelium starting at three weeks of age.

Results: Inhibition of Notch signaling in the adult mouse kidneys resulted in a significant regeneration of urine concentrating capacity when compared with that of control normal ureteral littersmates in all three mouse models. Induction of dnMaml expression in the renal epithelia of three week old mice for three days reduced expression of Uoop, a gene known to be induced in a Notch1/RBPJ-mediated signaling, along with principal cell specific genes such as Agg2 and Aqp2, while expression of intercalated cell specific genes, Fox11 and Slc4a9, were increased. Genetic inactivation of Notch1 and Notch2 or Hes1 in the mature epithelial cells of the mouse kidneys resulted in reduced number of principal cells and increased number of intercalated-like cells as determined by immunohistochemistry.

Conclusions: Notch signaling is required for maintaining mature principal cells in a functional state by ensuring continued expression of critical principal cell specific genes, and repressing essential intercalated cell specific genes. Lineage tracing of principal cells in Notch1/RBPJ inactivation of Notch signaling development of Notch signaling into intercalated-like cell transdifferentiation. Similarly, Notch signaling appears to prevent transdifferentiation of mature principal cells in the adult mouse kidneys.

Funding: NIDDK Support, Other NIH Support - NIGMS

SA-PO551

Human Missense Variants in Integrin-Linked Kinase Agonrate Renal Branching Morphogenesis by Disrupting MAPK Signaling

Dana Kablawi, Kirsten Y. Renkema, Nine V. Knors, Norman D. Rosenblum. The Hospital for Sick Children, Toronto, ON, Canada; University Medical Center Utrecht, Utrecht, Netherlands.

Background: Integrin-linked kinase (ILK) is required for murine renal branching morphogenesis and acts via p38MAPK/ATF2 signaling. Yet, its contribution to human congenital kidney-urinary tract anomalies (CAKUT) is undefined. The objective of these studies is to identify ILK variants in CAKUT and define their functional consequences.

Methods: Patients with CAKUT were analyzed by exome sequencing. Variants were verified by Sanger sequencing. Cells stably expressing human ILK variants were generated, and inhibition of ILK signaling was performed. The proliferation and transcription factor activation were analyzed using immunoblotting. Subcellular localization of transcription factors was imaged by immunofluorescence. Gene expression and pathway enrichment were assessed using whole genome microarray and quantitative (q) PCR. In vivo assays were conducted using lentivirus-based transduction of mouse embryonic kidney explants.

Results: Exome sequencing of 208 CAKUT candidate genes in 453 probands with CAKUT identified ILK3613V (1 proband) and ILK3640V (4 probands), both of which are missense variants in ILK ankyrin repeat domains. Stimulation of IMCD3 cells stably expressing ILK3613V (versus ILK3640V) with EGF (15 minutes) revealed dysregulation of each of JNK, P-JNK and AKT (P<0.05, n=3), as well as increased nuclear translocation of P-JNK (P<0.05, n=3). c-Jun, RNA signaling target, was increased 1.5 fold (P<0.05). EGF (15 minutes) (P=0.05, n=6, qPCR). Pathway enrichment analysis of genome-wide RNA expression after 1 hour of EGF stimulation revealed dysregulation of AKT/MTOR target genes (n=3). In contrast to ILK3613V, EGF mediated stimulation of mIMCD3 cells expressing ILK3640V increased ERK phosphorylation (P<0.05, n=3). Treatment of E12.5 kidney explants with lentivirus expressing ILK3613V resulted in hypoplasia with a 45% decrease in ureteric bud (UB) tip number (P=0.025, n=9 kidneys). Treatment with lentivirus expressing ILK3640V generated a spectrum of phenotypes including reduced number of UB tips (n=6 kidneys, P<0.009, increased (1.5-fold) number of UB tips (n=6 kidneys, P=0.048), and ectopic branching of the main ureter (n=3 kidneys).

Conclusions: ILK ankyrin-repeat domain missense variants associated with human CAKUT cause distinctive abnormalities in MAPK signaling and variable patterns of disrupted kidney explant development.

Funding: Government Support - Non-U.S.

SA-PO552

Loss of Zeb2 in Ureteric Mesenchymal Cells Causes CAKUT Phenotype in Mice

Sudhir Kumar, Richa Sharma, Xiaping Fan, Weining Lu. Boston University Medical Center, Boston, MA.

Background: Congenital anomalies of the kidney and urinary tract (CAKUT) are major causes of renal failure in children. ZEB2 is a SMAD-interacting transcription factor that causes Mowat-Wilson Syndrome (MWS), a congenital disorder with an increased risk for CAKUT phenotype including hydrourter and hydrenephrosis. However, no defined underlying cellular and molecular mechanisms for hydrourter and hydrenephrosis in MWS have been established.

Methods: We generated Zeb2 conditional knockout mice (Zeb2 cKO) by crossing Zeb2 flox mice with Th11Cre mouse. Urinary tract phenotypes in Zeb2 cKO mice and their wild-type littermate controls were analyzed by gross and histological examination. Zeb2 expression in developing ureter was analyzed by in vivo immunohistochemistry staining. Uretoral cellular and molecular phenotypes were studied using cell specific markers, apoptosis assay, and anti-SMAD antibodies.

Results: We found that Zeb2 is highly expressed in the ureteral mesenchymal cells and is co-localized with TBX18 in developing mouse ureter at E14.5. Deletion of Zeb2 causes severe mesenchymal cell loss and downregulation of mesenchymal mesenchyme development. We also found increased apoptosis and upregulation of pSMAD1/5/8 expression in ureteral mesenchyme cells in E14.5 Zeb2 cKO, suggesting loss of ureteral mesenchymal cells and abnormal SMAD signaling in developing ureter. The phenotype in adult Zeb2 cKO mice: ZEB2 is involved in mesenchymal cell development. Loss of Zeb2 in ureteric mesenchymal cells leads to reduced TBX18+ mesenchymal cells
and abnormal ureteral smooth muscle formation due to aberrant SMAD signaling, which eventually causes the loss of ureteric epithelium in ureteral buds of E14.5 cKO mice.

Funding: NIDDK Support, Private Foundation Support

SA-PO553

A Morphogenetic Study of Murine Renal Collecting System Based on 3D Visualization Ling Gu,1 Jie Zhang,1 Shi-Jie Chang,1 Kaiyue Wang,1 Jesper S. Thomsen,2 Arme A. Andreassen,2 Erik I. Christensen,2 Xiao-Yue Zhai,2 1Department of Histology and Embryology, China Medical University, Shenyang, China; 2Department of Biomedical Engineering, China Medical University, Shenyang, China; 3Department of Biomedicine – Anatomy, Aarhus University, Aarhus, Denmark.

Background: The iterative bifid branching of ureteric bud (UB) lays basis for formation of the collecting system (CS), and for generation of nephrons as the tip of the UB induces nephrogenesis at the nephrogenic zone (NZ). A low nephron number is associated with adult defect, such as hypertension. Therefore, a full knowledge of the morphogenesis and the connections of CS with nephrons is crucial to understand the development of such adult defects. The present study provides a spatial morphologic transformation of UB branching into adult CS based on 3D reconstruction.

Methods: Serial paraffin and epoxy sections of 3 mouse kidneys from each of different embryonic (E) and postnatal (P) days were prepared. The branching paths of UB at E14.5, E17.5, and CS from P7 and adult kidneys were traced on aligned micrographs using custom-made software. The architecture of adult CS was first established for comparison of UB branching trees.

Results: 1) The morphology of cortical CS was asymmetric. One ICT rapidly bended down into the juxta-medullary cortex from the main CD at the middle to superficial cortex forming an abrupt arc. The other ICT went straight outwards to the superficial cortex and ran a certain distance beneath the renal capsule. 2) The connection of nephrons with CS in a specific temporospatial order. The earlier formed nephrons connected with the arc in distal to proximal order along the trunk, while the later formed nephrons, connected with the ICT in proximal to distal order. 3) The association of UB branching morphology with the primitive bladder. This was established when the first mature nephrons appeared, the UB bifurcations reached up to 7 to 10 cycles, laying basis for adult CS formation. With time until P3, the tips at NZ increased in number, consistently inducing nephrogenesis instead of branching.

Conclusions: The CS is formed by more than one type of branching: 1) the traditional bifurcation for formation of CD; 2) lateral branching along the arc for formation of the ICT and connecting segments; and 3) sprouting for formation of the CNT connecting directly with individual nephrons. This suggests that the number of the nephrons is closely associated not only to the iterative branching, but also to the formation of lateral and sprouting branches, the latter mainly occurred near NZ.

Funding: Government Support - Non-U.S.

SA-PO554

Loss of the Planar Cell Polarity Gene Fuzzy Leads to Defective Branching Morphogenesis and Cystogenesis in Embryonic Kidneys Yanran Wang,1,2 Elena Torban,2 1Division of Experimental Medicine, Department of Medicine, McGill University, Montreal, QC, Canada; 2McGill University Health Centre, Montreal, QC, Canada.

Background: The PCE effector gene Fuzzy is essential for organogenesis. In Drosophila, it is critical for establishing planar cell polarity via controlling the actin cytoskeleton. In vertebrates, the role of Fuzzy is less clear, but it appears to control some aspects of trafficking protein cargos to the basal body. Fuzzy has been designated as a Ciliogenesis and PCE effector (CPLANE) gene. Disruption of Fuzzy in mice results in severe malformations, including neural tube defects, polydactyly, facial defects andect, suggesting its participation in various signaling pathways.

Methods: To study kidney development, homozygous E14.5 and E16.5 embryos carrying a gene-trap Fuzzy mutation and wildtype littermates were harvested for immunofluorescence and in situ hybridization (ISH) studies.

Results: Fuzzy-/- mutants exhibited profound renal hypoplasia at E14.5. Although Six2-positive progenitor cells and their differentiation into early nephron structures were unaffected, the number of the ureteric buds was decreased to 50% of control. This was accompanied by a ~ 50% reduction in the number of glomeruli without a decrease in the number of podocytes per glomerulus. ISH studies indicated that GDNF expression was unaffected, but e-Ret expression was upregulated in Fuzzy-/- mutant mice. The expression of the Hippo kinase pathway effector Yap was decreased significantly in ureteric buds. At E11.5, when the first mature nephrons appeared, the UB bifurcations reached up to 7 to 10 cycles, laying basis for adult CS formation. With time until P3, the tips at NZ increased in number, consistently inducing nephrogenesis instead of branching.

Conclusions: The number of the nephrons is closely associated not only to the iterative branching, but also to the formation of lateral and sprouting branches, the latter mainly occurred near NZ.

Funding: Government Support - Non-U.S.

SA-PO555

Robo2 Mediated Raldh2 Signaling in Bladder Mesenchyme Is Crucial for Urerter Development Qinggao Li,1 Xiangmei Chen,1,2 Chinese PLA General Hospital, Beijing, China; 1Chinese PLA general Hospital, Beijing, China.

Background: Congenital anomalies of urinary-tract are a significant cause of morbidity in infancy, many of the congenital anomalies are linked to ureter development. Despite the frequent occurrence of the ureter abnormalities, little is known about their causes. A recent study revealed that the uroplakins play a crucial role in the generation of the ureteral-tract abnormalities of the urinary-tract, with ureter defect and viscousureal reflux. While mechanistic aspects of this pathway are increasingly well defined, it remains unclear how Robo2 modulation impacts ureter development.

Methods: We performed in immunofluorescence on mouse embryonic whole mount kidney and section with E-cadherin, and Co-IP and Mass spectrometry analysis on mouse embryonic kidneys and urogenital tracts with a specific ROBO2 polyclonal antibody. Laser scanning confocal microscopy and real time RT-PCR were used to observe expression of Robo2 in frozen section and urogenital tract samples. Kidney explants dissected from E12.5 embryo were cultured in DMEM/10%FCS.

Results: Robo2 is expressed in common nephric duct (CND) and primitive bladder, and interact with Raldh2. Moreover, the ureter elongation is depend on signaling in Robo2, but not kidney morphogenesis, reveals how Robo2 impact ureter cell fate decisions. Delayed apoptosis due to failure of CND fusion with primitive bladder in Robo2/-/-embryo, resulting in the abnormal ureter remain connected to CND. Analysis of Robo2-/- mice reveals hydropnephrosis and defective ureter development by the CND remodeling defects and delayed fusion with primitive bladder. Using retinoic acid rescued ureter anomalies in Robo2/-/-embryo.

Conclusions: We found Robo2 impacts CND migration and fusion with primitive bladder via its novel protein partner Raldh2 signaling, this may have relevance for diverse disease conditions, associated with altered signaling from primitive bladder.

Funding: Government Support - Non-U.S.

SA-PO556

Tubular Immaturity Underlies Erythropoietin-Deficiency Anemia of Prematurity Nariaki Asada,1 Keio University School of Medicine, Tokyo, Japan.

Background: Kidneys are physiologically hypoxic and produce erythropoietin (EPO) after birth by sensitively detecting oxygen levels. Preterm neonates, especially those less than 32 weeks of gestation, develop EPO-deficiency anemia, known as anemia of prematurity (AOP). In AOP, immature kidneys cannot produce sufficient EPO in response to anemia even when renal injuries are absent. It remains unclear how kidneys start to produce EPO after birth.

Methods: Neonatal mice were used as AOP model since they are physiologically born premature. To confirm factors associated with AOP in human, correlation of hemoglobin levels with fraction excretion of sodium (FENa), urinary creatinine to 2-microglobulin ratio (uCr/u2MG), and hematocrit at P7, were evaluated in prospective observational study of 18 preterm patients at age 14 days and 21 days.

Results: Mice at postnatal day 14 (P14) showed physiological anemia and elevated renal sodium reabsorption. Mice at P7 showed a reduced expression of EPO, tubular reabsorption and delayed fusion with primitive bladder. Using retinoic acid rescued ureter anomalies and delayed fusion with primitive bladder. Using retinoic acid rescued ureter anomalies and delayed fusion with primitive bladder.

Conclusions: AOP is caused by insufficient hypoxic environment due to low oxygen consumption by immature tubules. Kidneys start to produce EPO as tubules mature and renal oxygen levels decrease. PHDi can be a therapeutic option for AOP in preterm patients.

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

SA-PO557

DNA Hydromethylation Is Altered by Maternal Nutrient Restriction in the Kidney Mariko Hida,1 Mayumi Oda,1 Midori Awazu,1 1Department of Pediatrics, Keio University School of Medicine, Tokyo, Japan.

Background: DNA hydromethylation is an epigenetic modification that oxidizes 5-methylcytosine (5mCt) into 5-hydroxymethylcytosine (5hmC). Increasing evidence suggests that the role of DNA hydromethylation is different from DNA methylation in various organs but that in the kidney is unclear. We previously showed that the global DNA methylation was reduced and the gene-specific DNA methylation was altered in kidney of rat embryos from nutrient-restricted mothers. In the present study, we investigated DNA hydromethylation in the same model.

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

822
Methods: The kidneys of embryonic day 18 fetuses (E18) from dams given food ad libitum (CON) and those subjected to 50% food restriction throughout pregnancy (NR) were examined (n=3 litters for each group). Global hydroxymethylation levels were assessed by ELISA. The local 5mC detection by Hi-MeSeal method followed by high throughput sequencing (5mC-seq) was used to analyze the changes in hydroxymethylation patterns by NR. 5mC-seq matched regions (5mC peaks) were identified using a peak finding algorithm (MACS2.1.4) and then annotated to the nearest genes.

Results: Global hydroxymethylation levels in E18 metanephros were significantly increased in the CON (p < 0.05). At glomerular tuft regions, 3/α3 vs 20% hydroxylation was noted, whereas in the loop stage of glomerulus, two layers of GBM showed 3/α3 vs 20% hydroxylation (p < 0.05). Global hydroxymethylation levels in E18 metanephros showed a progressive increase relative to stage of development. Global hydroxymethylation levels were significantly increased in NR compared with CON (p < 0.05). The hydroxymethylated peaks (5mC-seq) were noted in the glomerular tuft, which consists of podocytes, glomerular basement membrane (GBM) and capillary network. Among the identified local 5mC sites reside in intergenic regions, followed by introns, whereas the sites near the transcriptional start sites were few. Among genes with CON-specific hydroxymethylated peaks, some genes were related to the kidney development (Amphl, Glccl, Gli3, Igfbp5, Cdh11, FGF10, Ihh, and Agt1α, in descending order of peak score). Genes with NR-specific hydroxymethylated peaks also had a few kidney development genes (Gfap, and Fst). Protein expression of Amphi and Cdh11 was upregulated in NR. The transcript level of Agt1α assessed by PCR was not different between CON and NR.

Conclusions: Maternal nutrient restriction increased the global DNA hydroxymethylation and changed the local hydroxymethylation in genes involved in kidney development.

Funding: Government Support - Non-U.S.

SA-PO558

Intrauterine Growth Restriction (IUGR) by Maternal Protein Undernutrition Disrupts the Transcriptional Networks of Energy Metabolism in Nephrin Progenitors

Francesca Edgington-Giordano, Hongbing Liu, Sylvia Hilliard, Jiao Liu, Yuwen Li, Renfang Song, Zhubaida R. Saifuldeen, Samir S. El-Dahr. Tulane University School of Medicine, New Orleans, LA, USA.

Background: Fetal IUGR from maternal undernutrition is linked to reduced nephron endowment, resulting in a suboptimal renal function and a predisposition towards hypertension and chronic kidney disease. Using an established protein-deficiency mouse model of IUGR, we examined the impact of maternal undernutrition on nephrin progenitor cell (NPC) maintenance and gene expression.

Methods: CD1 mice were fed isocaloric low-protein (6%) or control (20%) diet from day 1 to 18 of gestation. At each visit we selected 10 to 20 to assess NPC pool size (Six2, NCAM) and differentiating nephrons (NCAM, Lhx1, Wt1) by IF. RNA-Seq was performed on RNA isolated from native NPC of P0 kidneys (n=3), and data analyzed by IPA and GO-Panther. Bonferroni correction was applied.

Results: Significantly reduced (p<0.0001) P0 body and kidney weight were observed. However, kidney/body weight ratios are not significantly changed in 6% vs 20% pups. 6% pups show diminished nephrogenic zone, a smaller Six2+ NPC pool and nascent nephron structures. Cellular processes and metabolism are profoundly altered at the nephron formation stage of development. Wnt9b mRNA. Global hydroxymethylation levels in E18 metanephroi was significantly increased in NR vs CON (0.31 ± 0.05). Global hydroxymethylation levels in E18 metanephroi was significantly increased in NR vs CON (0.31 ± 0.05).

Conclusions: IUGR by maternal protein undernutrition disrupts key transcriptional networks of energy metabolism in nephrin progenitors. More specifically, the repression of Wnt9b is accompanied by a reprogramming of metabolic pathways in NPCs, which may impact the formation of functional nephrons. These findings suggest potential therapeutic targets to improve kidney development and to prevent postnatal progression of kidney disease.

Funding: NIDDK Support

SAQ-059

The Quantitative and Qualitative Characteristics of Glomerular Basement Membrane in Rat Kidney Development and Glomerulonephritis

Shinya Nagasaka, Akira Shimonaka. Department of Histology and Embryology, China medical university, Shenyang, China; Department of Analytic Human Pathology, Nippon Medical School, Tokyo, Japan; First Affiliated Hospital of Xi’an Jiaotong University, Xi’an, China.

Background: The renal glomerulus is filter function of primary urine through glomerular tuft, which consists of podocytes, glomerular basement membrane (GBM) and endothelial cells. Mature GBM is mainly composed of α3/α4/α5 chain of type IV collagen (IV). In order to clarify the maturation process of renal glomerular tuft during renal development, and injured and recovery of glomerular tuft from injuries in glomerulonephritis (GN), we evaluated the pathology and c chains (IV) of GBM and glomerular capillaries of 1-day-old and 10-week-old rat kidneys, as well as experimental thy-1 GN on day 7 and 10 (n=3) and clinical biopsy cases of membranoprolifenerative GN (MPGN) type II.

Results: In the development, glomerular capillaries with endothelial cells migrated from interstitium into the cleft of S-shaped body to form the glomeruli. The basement membrane (BM) of S-shaped neuron and glomerular capillaries formed GBM, which were composed of α3/α4/α5 chain (IV) in S-shaped stage. In the early capillary loop stage of glomerulus, the cleft of the S-shaped body was occupied by a primitive capillary network. GBM was composed of two BMs, such as continuous GBM of primitive podocytes with α3/α4/α5 chain (IV) and discontinuous capillary BM with α1/α2 chain (IV). At late capillary loop stage of glomerulus, two layers of GBM such as continuous podocytes’ BM and discontinuous or continuous capillary BM change to one layer of GBM with only α3/α4/α5 chain (IV). In early to late capillary stage, formation of foot processes and fenestrated structures was found in podocytes and endothelial cells, respectively. In experimental and biopsy cases of GN, injured glomerular tuft showed double contour of GBM, α3/α4/α5 chain (IV) of podocytes’GBM and α1/α2 chain (IV) of capillary BM, with irregular effacement of foot processes of podocytes and irregular loss of fenestrae of endothelial cells, resembling the pathology of glomerular tuft of early capillary stage. However, after recovery, glomerular tuft showed one layer of GBM with α3/α4/α5 chain (IV) and mature podocytes and endothelial cells.

Conclusions: Our findings suggest that injured glomerular tuft was accompanied by quantitative and qualitative alterations of GBM in GN, and recovery of glomerular tuft after injuries may be following similar processes in the development of glomerular tuft.
choleretic efflux. Further, given the known role of choleretic as a regulator of Rac1 signaling, we postulated that ABCA13 KD may induce inappropriate activation of Rac1 and promote podocyte motility through the Rac1-mediated upregulation of JNK/Paxillin signaling.

**Methods:** Whole-exome sequencing, direct sequencing, lentivirus-mediated siRNA gene silencing, scratch wound healing assays, and immunoblotting.

**Results:** ABCA13 KD induced an upregulation of JNK activation (p < 0.01) and an increase in Rac1 membrane recruitment in podocytes. Additionally, cell migration in ABCA13 KD podocytes was significantly increased (p < 0.01) relative to scramble siRNA control. Rac1 membrane recruitment and motility was significantly attenuated by the Rac1 inhibitor extracting agent methyl-b-cyclohexdin (p < 0.03) and the JNK inhibitor tanszetanib (p < 0.01). Additionally, ABCA13 KD enhanced Paxillin phosphorylation at the JNK target site Ser178 in podocytes.

**Conclusions:** ABCA13 KD enhances podocyte motility possibly through the dysregulation of Rac1/JNK/Paxillin signaling axes. These data suggest that 1: Rac1/JNK/Paxillin signaling may play an important role in the pathogenesis of FSGS, and that 2: targeting this signaling pathway may be a novel therapeutic approach for the treatment of FSGS.

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

**SA-PO562**

A Homozygous Missense Mutation in VWA2, Encoding an Interactor of the Fraser-Complex, as a Likely Cause of Vesi, Uter, Kielbassa, Shirlie, Shril, Amir et al.

**Background:** Congenital anomalies of the kidney and urinary tract (CAKUT) are the most common cause of chronic kidney disease in the first 3 decades of life. About 30% of cases causing CAKUT are known so far, explaining <20% of CAKUT cases.

**Methods:** To identify additional monogenic causes of CAKUT, we performed whole exome sequencing in a consanguineous patient with CAKUT from Indian origin.

**Results:** We identified a homozygous missense mutation (c.1356C>T, p.Arg446Cys) in the gene Von Willebrand factor A domain containing 2 (VWA2). By immunohistochemistry on kidney sections of newborn mice, we show that Vwa2 and Fraser extracellular matrix complex subunit 1 (Francis) co-localize in the nephrogenic zone of the renal cortex. There was pronounced staining for Vwa2 in the basement membrane of the UB and derivatives of the MM (comma-shaped and S-shaped bodies). By applying cell-based assays, we demonstrate that VWA2 expression levels are regulated by cis-regulatory elements. In vitro Arg446Cy mutation decreases secretion of the VWA2 protein into the extracellular space in vitro: Lack of secretion is most likely due to increased intracellular aggregate formation of VWA2 secondary to the additional, unpaired cysteine residue in the mutated protein. Recombinant mutant VWA2 additionally forms disulfide-linked higher aggregates in vitro.

**Conclusions:** VWA2 is a known, direct interactor of FRAS1 of the Fraser-Complex (FC). FC-encoding genes FRAS1, FREM1, FREM2 and interacting proteins GRIP1 and ITGA8 have previously been implicated in the pathogenesis of syndromic and isolated CAKUT phenotypes in humans (Kohl JASN 25, 2014). The results from in vitro experiments indicate a dose-dependent, gain-of-function effect of the Arg446Cys homozgyous mutation in VWA2. VWA2 therefore constitutes a very strong candidate for the search for novel CAKUT-causing genes.

**Funding:** NIDDK Support, Other NIH Support - DK088767

**SA-PO563**

Mutations of GAPVD1 and ANKFY1 Are Novel Causes of Nephrotic Syndrome Tobias H. Herrell, Ronen Schneider, David Schapira, Shiri M. Eliyahu, Jamiea A. Kari, Daniela A. Braun, Friedhelm Hildebrandt, Boston Children’s Hospital/Harvard Medical School, Boston, MA; King Abdul Aziz University Hospital, Jeddah, Saudi Arabia.

**Background:** Steroid resistant nephrotic syndrome (SRNS) is a frequent cause of end-stage renal disease within the first 3 decades of life. The discovery of more than 50 different monogenic causes has helped to elucidate the pathogenesis of SRNS.

**Methods:** To identify novel monogenic causes of SRNS we performed exome sequencing (WES) in a worldwide cohort of ~600 SRNS individuals with nephrotic syndrome. Co-immunoprecipitation using HEK cells was employed to analyze protein interaction.

**Results:** By WES we identified two homologous missense mutations of GAPVD1 (c.1240C>G, p.L414V and c.2810G>A, p.R937Q) in two patients from unrelated families with early-onset nephrotic syndrome. Both mutated amino acids are conserved in *C. intestinalis*. One patient did not respond to steroids while the other showed the unusual combination of congenital nephrotic syndrome and spontaneous remission. This has only been observed in few alleles of NPHS1. The biology in both cases was characterized by mesangial hypercellularity while electron microscopy revealed podocyte foot process effacement. GAPVD1 is a known regulator of endosomal trafficking and interacts with RAB5. GAPVD1 harbors both, a GTPase activating and an inactivating domain. We further identified a mutation of ANKFY1 (c.284G>T, p.R95L), conserved in *D. melanogaster* in a patient with SRNS and FSGS with an affected sibling sharing the mutation. ANKFY1 is also an interaction partner of RAB5 and serves as a RAB5-effector. Western blotting revealed expression of GAPVD1 and ANKFY1 in a human podocyte cell line. Using co-immunoprecipitation we observed physical interaction between both proteins. We further found interaction of GAPVD1 and the slig diamorph protein NPHS1. Novel experiments suggest that both functional domains of GAPVD1 bind to NPHS1.

**Conclusions:** We discover mutations of GAPVD1 and ANKFY1 as novel monogenic causes of nephrotic syndrome. Interestingly, both proteins interact with each other and RAB5. GAPVD1 further interacts with NPHS1, mutations in which cause SRNS.

**Funding:** Other NIH Support - DK076683, Government Support - Non-U.S.

**SA-PO564**

Whole Exome Sequencing Identifies a Monogenic Cause in ~43% of Families with Hypertension from Midaortic Syndrome Jillian K. Warejko, Markus Schueler, Asaf Vivante, Jennifer A. Lawson, Weizhen Tan, Ankana Daga, Shirlie Shril, Shrikant M. Mane, Deborah R. Stein, Michael A. Ferguson, Friedhelm Hildebrandt, Boston Children’s Hospital, Boston, MA; Genetics, Yale University, New Haven, CT.

**Background:** Midaortic syndrome (MAS) is a cause of severe hypertension in children with narrowing of the abdominal aorta. It involves the renal vessels in ~80% of cases (Ped Nephrol 24:2225, 2009). Treatment requires antihypertensive medications and/or operative or endovascular interventions. Morbidity is high with hypertensive encephalopathy, stroke, heart failure and renal dysfunction. MAS may occur as part of a genetic syndrome, such as neurofibromatosis 1. However, most cases have been considered idiopathic until now.

**Methods:** We hypothesized that in patients with MAS, a monogenic cause of disease may be detected in one of 38 candidate genes of syndromic or non-syndromic vasculopathies. We studied 36 individuals from 35 different families by whole exome sequencing (WES).

**Results:** Patients were recruited at Boston Children’s Hospital from 1/2014 to 12/ 2016. Individuals included in WES if MAS was diagnosed before age ≤25 years with evidence of narrowing of the abdominal aorta on imaging. We examined WES data for mutations in all 38 candidate genes. In 15/35 families (42.9%), we identified a causative, dominant or recessive mutation. Mutations were identified in five candidate genes: NIF, kidney fibroblast, JAG1 (4/15), ELN (3/15), and one each for GATA3 and RNF213. A total of 15 different mutations were detected, 10 of which were novel. In 2/6 families with NIF mutation and 1/4 families with JAG1 mutation the appropriate diagnosis of NF or Alagille syndrome respectively, had not yet been made by clinical criteria.

**Conclusions:** We demonstrate that WES in combination with an a priori candidate gene approach can provide a conclusive molecular genetic diagnosis in a high fraction of individuals with syndromic or isolated MAS. We present data that there may be genotype/phenotype correlations between the severity of the mutation and the phenotype observed.

**Funding:** Other NIH Support - DK076683, DK007726-31A

**SA-PO565**

New Interaction between Galectin-3 and Cystinosin Reveals a Role of Inflammation in Kidney Pathogenesis in Cystinosis Tatiana V. Lobry,4 Roy Miller,1 Nathalie Nevo,2 Celine Rocca,3 Marie-Claire Gubler,1 Tristan Y. Montier,1 Corinne Antignac,1 Stephanie Cherqui,1 Faculté de médecine de Brest, Brest, France; INSERM, Paris, France; Imagine Institute, Paris, France; ‘None, Paris, France; UCSD, San Diego, CA; ‘University of California, San Diego, La Jolla, CA.

**Background:** Cystinosis is a lysosomal storage disorder caused by mutations in the CTNS gene, encoding a lysosomal cystine transporter, leading to cystine accumulation. Affected individuals typically present with proximal tubulopathy, end-stage renal disease and multi-organ failure. Cystinosis has now been shown to have other cellular functions and an unbiased screen revealed a direct interaction of cystinosin with a member of the galectin’s family, galectin-3. This protein is implicated in different biological processes like cell death, cell cycle and inflammation.

**Methods:** We generated a murine model deficient for both cystinosis and galectin-3, the Ctns+/− mice.

**Results:** We showed that cystinosis enhances galectin-3 lysosomal localization and degradation. In the Ctns−/− mouse model, expression of galectin-3 was increased compared to wild-type. Moreover, absence of galectin-3 in cystinotic mice led to a better renal function and preservation of kidney morphology. Less inflammatory cell infiltration was observed in kidneys of Ctns−/− mice compared to Ctns+− mice, suggesting that galectin-3 mediated inflammation is involved in progression of the kidney disease in cystinosis.

**Conclusions:** We are currently investigating the mechanism by which galectin-3 induces recruitment of inflammatory cells in the kidney of cystinosis and we already found an interaction between galectin-3 and a chemokine implicated in the recruitment of monocytes/macrophages. This work brings new insights on the pathogenesis of the disease and may lead to the identification of new drug targets to delay its progression to renal failure.

**Funding:** NIDDK Support, Private Foundation Support
Whole Exome Sequencing Identifies the Causative Mutation in 50% of Families with Adult-Onset CKD

Methods: We conducted whole exome sequencing (WES) in 16 Irish families (27 cases with CKD). Selection criteria were: A positive family history of CKD (n=12 families) and/or history of extra-renal disease manifestations (n=8 families). Individuals with autosomal dominant polycystic kidney disease or Alport’s syndrome were excluded.

Results: WES identified a causative mutation in one of 250 known monogenic CKD genes in 50% of families (n=8/16 families, 12 individuals). Six of the 8 families had no prior diagnosis of the cause of CKD. The 8 families in whom a causative mutation was identified included nephropathies (n=4), IFT140, NPH1, BBS9, DYNC2H1, autosomal recessive polycystic kidney disease (n=3), PKHD1, congenital abnormalities of the kidneys and urinary tract (n=1, PAH2), Lowe’s syndrome (n=1, OCL1) and interstitial nephritis (n=1, FAN1). In 3 families, in whom known CKD genes were excluded, 3 different potential novel candidate genes were identified.

Conclusions: This study establishes that WES can detect specific causative mutations in 50% of families with adult-onset CKD. Furthermore, WES allows the identification of novel candidate genes. WES is therefore an important diagnostic tool to establish an etiologic diagnosis in an adult-onset CKD.

Funding: Other NIH Support - NIH DK088767 to F.H.

SA-PO567

The ANLN R431C FSGS Mutation Alters AKT and Rac1 Activation in Podocytes

Methods: The incidence and phenotypes of patients with ADCK4 mutations were investigated in a cohort of Chinese pediatric patients with SRNS non-nephrotic proteinuria, or CKD. We identified 12 patients from 11 families with bi-allelic mutations of ADCK4. Patients with ADCK4 mutations showed a largely renal-limited phenotype, with three subjects exhibiting occasional seizures, two subject exhibiting mild mental retardation, and one subject exhibiting retinitis pigmentosa. ADCK4 nephropathy presented during adolescence (median age, 7.6 years) with nephrotic-range proteinuria in 58.3% of patients and advanced CKD in 63.6% of patients at time of diagnosis. Renal biopsy specimens uniformly showed FSGS. ESRD occurred almost after age of 6 in patients with ADCK4 nephropathy. CoQ10 supplementation was administered following genetic diagnosis. Median estimated glomerular filtration rate (eGFR) just before CoQ10 administration was 120.4 (IQR 69.5-135.9) ml/min/1.73m²; proteinuria was evaluated using a Urine Protein creatinine ratio (UP/cre) showing 3.9 (IQR 2.4-6.0). After a median follow-up of 21 (range 12–24) months following CoQ10 administration, proteinuria was significantly decreased (median UP/cre 2.2, IQR 1.5-2.5), whereas the eGFR preserved (median 117.1, IQR 82.2-137.4).

Conclusions: ADCK4 mutations are one of the most common causes of adolescent-onset albuminuria and/or CKD of unknown etiology in China. CoQ10 supplementation appears efficacious at reducing proteinuria, and may thereby be neuroprotective.

Funding: NIDDK Support
SA-PO570
Recessive Mutation in CD2AP Causes Focal Segmental Glomerulosclerosis in Humans and in Mice
Tomoaki Takano,1 Lamие Aoudjit,2 Cindy Baldwin,1 Jasmine El andaloussi,1 Lina Muhtadi,3 Indra R. Gupta.2 1Medicine, McGill University Health Centre, Montreal, QC, Canada; 2Pediatrics, Montreal Children’s Hospital, Montreal, QC, Canada; 3Medicine, Lakeshore General Hospital, Montreal, QC, Canada.

Background: CD2-associated protein (CD2AP) is an adaptor protein expressed in podocytes. CD2ap−/− mice develop early-onset severe nephrotic syndrome and die at 6 weeks old, while CD2ap+ mice show susceptibility to insults and glomerulosclerosis at 9 months old. However, only a few patients have been described with mutations in CD2AP.

Methods: Whole exome sequencing (WES) was performed on genomic DNA. C57/B6 mouse-derived ES cells were electroporated with Cas9, two guide sequences and a donor oligo to allow CRISPR-mediated insertion of 4 base pairs into the CD2AP gene. One ES clone with the desired insertion was used to generate chimeric mice that were crossed to C57/B6 mice for germline transmission.

Results: Three siblings (2 males and 1 female) born of consanguineous parents developed FSGS in their teens and progressed to ESRD by 20 years of age. WES identified an insertion of 4 nucleotides in the CD2AP gene, causing a frameshift at Ser198, resulting in a stop codon (p.Ser198fs). All three siblings were homozygous for the mutation, while the unaffected father was heterozygous. Mother’s DNA was not available. When homozygous mice carrying the insertion were bred, wild-type (WT), heterozygous, and homozygous mice were born at the expected Mendelian frequency. By 2-3 weeks, homozygous mice showed heavy albuminuria, glomerulosclerosis, tubular atrophy, and interstitial leukocyte infiltration. By 4-6 weeks, histological changes worsened and were accompanied by elevated serum creatinine and BUN and hypoalbuminemia. These changes were not seen in heterozygotes or WT. Homozygous mice died at 7-8 weeks, likely from kidney failure.

Conclusions: CRISPR/Cas9 gene editing has been utilized to generate a mouse model with a recessive mutation in CD2ap, p.Ser198fs that results in FSGS, nephrotic syndrome, and kidney failure in mice. The results prove that this recessive mutation in CD2AP is causal in human FSGS.

Funding: Government Support - Non-U.S.

SA-PO572
OXGR1 Mutations Present a Novel Cause of Nephrotic Syndrome
Amir J. Majmudar,1 Ankana Daga,2 Daniela A. Braun,3 Heon Yung Gee,2 Shirlee Shirl,1 Jan Halbritter,2 Shrikant M. Mane,4 John A. Syer,5 Hanan Fatth,1 Michelle A. Baum,1 Friedhelm Hildebrandt.1 1Medicine, Div Nephrology, Boston Children’s Hospital, Boston, MA; 2University Clinic Leipzig, Leipzig, Germany; 3El Shatty Children’s Hospital, Alexandria, Egypt; 4Newcastle University, Newcastle, United Kingdom; 5Yonsei University College of Medicine, Boston, Republic of Korea; 6Yale University School of Medicine, Yale Center For Mendelian Genomics, New Haven, CT.

Background: Nephrotic syndrome (NS) affects 1 in 11 individuals worldwide and causes significant morbidity and cost including surgical intervention. There are >30 genes, for which causative mutations have been identified in 11% of adult and 17-20% of pediatric NL cases (Halbritter JASN 26:543, 2015; Braun eJASN 11:664, 2016). Identifying novel NL genes can reveal new pathogenic mechanisms.

Methods: We employed whole exome sequencing (WES) to identify novel genes in familial NL cases.

Results: By WES, we identified a heterozygous missense variant (c.3717T>G, p.L1245R) in the gene OXGR1 that segregated in 4 affected children and 1 affected mother from an Egyptian family with an autosomal dominant inheritance pattern of calcium oxalate containing NL and/or nephrocalcinosis (NC). OXGR1 encodes oxoglutarate receptor 1, a G-protein coupled receptor (GPCR) that is expressed in the distal nephron and promotes urinary alkalinization (Tokonami JCI 123:3166, 2013). The affected amino acid residue is conserved through vertebrate orthologues and in 72% of human GPCR sequences. The predicted protein change showed strong SIFT and PolyPhen-2 scores. In the ExAC Exome Database, the allele is not found in the nephrotic state and found occasionally in 60/632 individuals. Targeted sequencing of OXGR1 in 599 additional families with calcium oxalate containing NL and/or NC identified 3 additional alleles (c.649T>C, p.C217R; c.697A>C, p.S233R; c.860C>T, p.S287F) in 4 additional families (0.8% of cohort).

Conclusions: We identified OXGR1 mutations as novel monogenic cause of NL. As OXGR1 is implicated in urine alkalinization, further study of the disease mechanisms may provide insight into novel therapeutic options for NL.

Funding: NIDDK Support, Other NIH Support - NIH DK086360, NIH T32-AR053461-04

SA-PO573
Acute Regulation of the Proximal Tubule Endocytic Pathway in Cell Culture and Ex-Vivo Kidney Slices
Catherine J. Batty,1 Kimberly R. Long,2 Ora A. Weiss.3 1University of Pittsburgh, Pittsburgh, PA; 2University of Pittsburgh School of Medicine, Pittsburgh, PA.

Background: The proximal tubule (PT) of the kidney is highly specialized for apical endocytosis of megalin/cubilin ligands that pass through the glomerular filtration barrier into the tubule lumen. Impaired uptake of these ligands results in tubular proteinuria, which is observed in genetic diseases such as Lowe syndrome, Dent disease, and sickle cell disease. Despite the critical role of endocytosis for PT function, we know little about how the apical endocytic pathway is regulated in these cells. Studies in PT cells demonstrate that endocytosis of megalin/cubilin ligands is rapidly responsive to changes in fluid shear stress (FSS). However, currently available PT cell culture models lack many features that are present in vivo.

Methods: We have established an OK cell culture system that dramatically enhances apical endocytic capacity compared with OK cells cultured under standard conditions. Additionally, endocytosis of megalin/cubilin ligands is rapidly and reversibly modulated by changes in FSS. Consistent with our studies in cell culture, endocytic uptake was enhanced in slices exposed to shear stress. Studies are in progress to assess the mechanism of FSS-mediated uptake in PT cells and whether this is impaired in diseases that result in tubular proteinuria.

Conclusions: Together, these complementary models offer a useful approach to dissect the effect of physiologically-relevant stimuli on the PT apical endocytic pathway and its disruption in genetic and other diseases that result in tubular proteinuria.

Funding: NIDDK Support

SA-PO574
TBC1D8B Mutations Are a Novel Cause of Nephrotic Syndrome
Ronen Schneider,1 Tobias F. Hermle,1 David Schaprio,2 Aigl Berdel,2 Reynier F. Loza,3 Daniela A. Braun,3 Friedhelm Hildebrandt.1 1Boston Children’s Hospital, Brookline, MA; 2Boston Children’s Hospital, HMS, Boston, MA; 3Boston Children’s Hospital/Harvard Medical School, Boston, MA; 4Nephrology, Boston Children’s Hospital, Boston, MA; 5Ege University Medical Faculty, Izmir, Turkey; 6Cayetano Heredia Hospital, Los Olivos, Peru.

Background: Nephrotic Syndrome (NS) is the second most frequent cause of end-stage renal disease in the first 3 decades of life. RAB proteins are regulators of endocytosis, and several important features of podocyte function are dependent on RAB proteins that if mutated cause NS, has rendered first insights into disease mechanisms of NS. To date no monogenic mutations affecting RAB proteins or related proteins have been implicated in the pathomechanism of NS.

Methods: To identify novel monogenic causes of NS we combined homoyzogosity mapping with whole exome sequencing (WES) in a worldwide cohort of ~600 individuals with NS.

Results: In patient B891 with steroid resistant NS (SRNS) and FSGS, which presented at the age of 9 years, we detected a hemizygous mutation in the X-chromosomal gene TBC1D8B (c.233A>T; p.Thr789Ser). Thr789 is conserved since D. rerio. In patient A2563 who presented with steroid sensitive NS (SSNS) at the age of 7 years, and had minimal change disease on renal biopsy, we detected a hemizygous TBC1D8B mutation (c.190C>T; p.Arg64Cys). Arg64 is highly conserved since S. cerevisiae. Both TBC1D8B mutations are predicted to be disease causing by SIFT, Mutatser and PolyPhen2 programs. Both variants are not present hemizygously in the ExAC database. The affected amino acid residue is conserved through vertebrate orthologues and in 72% of 300 human GPCR sequences. The predicted protein change showed strong SIFT and PolyPhen-2 scores. In the ExAC Exome Database, the allele is not found in the nephrotic state and found occasionally in 60/632 individuals. Targeted sequencing of TBC1D8B in 599 additional families with calcium oxalate containing NL and/or NC identified 3 additional alleles (c.649T>C, p.C217R; c.697A>C, p.S233R; c.860C>T, p.S287F) in 4 additional families (0.8% of cohort).

Conclusions: We identified TBC1D8B mutations as novel monogenic cause of NS. As TBC1D8B is implicated in urine alkalinization, further study of the disease mechanisms may provide insight into novel therapeutic options for NL.

Funding: NIDDK Support, Other NIH Support - NIH DK086360, NIH T32-AR053461-04

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
826
**SA-PO574**

**A Rare Kidney Disease Family with CCDC114 Mutation and Cilia**

Xiangmei Chen, PLA General Hospital, Beijing, China.

**Background:** Ciliopathies is a group of diseases characterized by dysfunction of cilia and patients with ciliopathies have a variety of developmental and degenerative disorders.

**Methods:** We present the case of a 15-year-old child with dysplasia and multiple organ damage who was initially diagnosed as nephrotic syndrome. Her parents and sister are in good health. Physical examination shows normal blood pressure, edema of face and lower limbs, sensorineural deafness and hypoplasia. She also has dysplasia including congenital heart disease and duplex kidney. The patient also has intermittent cough. Laboratory investigation shows creatinine is 1.88 mg/dl; eGFR is 39.12 mL/min/1.73 m²; proteinuria is 3.42 g/24 h; albumin is 23.1 g/L; hemoglobin is 88 g/L; decreased thyroid hormone. The patient progressed to renal failure and received hemodialysis 10 months after renal biopsy. The patient’s clinical manifestations are consistent with ciliopathies, very similar to Alström syndrome. Cilia immunofluorescence of renal tissue showed a decrease number of cilia of the patient compared to normal kidney. Then WES shows a site mutation in CCDC114 (NM_144577.4, c.596C>T; p.Ala199Val) in patient. We found that CCDC114 located in centrosome and knock down CCDC114 could affect the occurrence of cilia in hRPE1 cells.

**Results:**

**Conclusions:** We found a decrease in the number of cilia in the kidney of patient with ciliopathies and identified CCDC114 as the main target gene by WES. We found that CCDC114 affected primary cilia formation in hRPE1 cells.

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

**SA-PO576**

**Whole Exome Sequencing Identifies Causative Mutations in 16% and Novel Candidate Genes in 24% of Individuals with a Diagnosis of CAKUT**

Dervla M. Connaughton,1 Annelie van der Ven,2 Hadas Itzeli,1 Shirlee Shiril,1 Nina Mann,1 Makiko Nakayama,1 Jing Chen,1 Asaf Vivante,1 Daw-ying Hwang,1 Eugen Widmeyer,1 Julian J. Schulz,1 Velibor Tasic,2 Shrikant M. Mane,1 Friedhelm Hildebrandt,1* Boston Children’s Hospital, Harvard Medical School, Boston, MA; 2University Children’s Hospital, Skopje, Macedonia (the former Yugoslav Republic of); 2Genetics, Yale University, New Haven, CT.

**Background:** Congenital anomalies of the kidney and urinary tract (CAKUT) cause 50% of chronic kidney disease in children. Several lines of evidence support the hypothesis that CAKUT has a monogenic origin: i) congenital nature, ii) monogenic multi-organ syndromes with CAKUT, iii) familial occurrence, iv) monogenic mouse models and v) the complex genetics underlying renal morphogenesis. About 40 monogenic causes of CAKUT are known so far, explaining ~17% of cases.

**Methods:** We applied whole exome sequencing (WES) to 135 individuals from 76 families with CAKUT. WES data were evaluated for mutations in known causes of CAKUT in humans (~40 genes), and novel candidate genes for syndromic (~200 genes) or murine CAKUT (~180 genes). In consanguineous or multiplex families, we also performed a search for novel recessive CAKUT genes (14/76) and trio analysis (24/76), respectively.

**Results:** In 9/76 (12%) families, a causative mutation in a known gene for isolated or syndromic CAKUT was identified that sufficiently explained the respective patients phenotype. In 3/76 (4%) of families, a mutation was identified in a gene causing a kidney disease that may represent a phenocopy of CAKUT (e.g. small kidneys). When evaluating candidate genes for human syndromic CAKUT, we detected deleterious mutations in 5/76 (7%) families with isolated CAKUT. In 1 family, mutations in a mouse candidate gene was identified. In 14/76 consanguineous and 24/76 non-consanguineous families we additionally applied a targeted search for homozygously mutated genes or trio analysis, respectively, and identified 12 potential novel candidate genes for CAKUT.

**Conclusions:** By WES, we detected causative mutations in 16% of cases with a diagnosis of CAKUT and identified 12 potential novel CAKUT genes. We show that syndromic and murine candidate genes are useful to identify genetic causes of isolated human CAKUT.

**Funding:** Other NIH Support - DK806306, NIH T32-AI053461-04

---

**SA-PO577**

**Noncystic Mendelian Diseases**

**Poster/Saturday**

**Noncystic Mendelian Diseases**

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

Underline represents presenting author.

827
SA-PO577

Precision in CAKUT: The Italian Study Group on the Genetics of Congenital Anomalies of the Kidney and Urinary Tract
Monica Bodria,1 Isabella Pisani,1 Claudio La scola,1 Davide Meneghesso,2 Francesca Taroni,1 Ilaria Luongo,1 Stefano Guarino,1 Milena Brugnara,2 Mario Giordano,2 Vinicio Guj,1 Pasquale Esposito,1 Pasquale Zamboli,1 Lucia Peruzzi,1 Giuseppe Masnata,1 Giovanni Conti,1 Domenico Santoro,1 Loreto Gesualdo,1 Ali G. Gharavi,2 Francesco Scolari,1 Simone Sanna-Cherchi,1 Gian Marco Ghiggeri,6 Azienda Ospedaliera G. Brozut, Cagliari, Italy; 2 Columbia University, New York, NY; 3 Fatebenefratelli Hospital, Milan, Italy; 4 University of Parma, Parma, Italy; 5 Fondazione IRCCS Policlinico “San Matteo”, Pavia, Italy; 6 University Hospital, Padua, Italy; 7 University of Padua, Italy, Padua, Italy; 8 University of Bari, Altamura, Italy; 9 University of Brescia, Montichiari (Brescia), Italy; 10 Nephrology and Dialysis Unit, Department of Pediatrics, Azienda Ospedaliero Universitaria Sant’Orsola-Malpighi, Bologna, Bologna, Italy; 11 Santobono Hospital, Naples, Naples, Italy; 12 Hospital Ospedaliero-Universitario “Luigi Vanvitelli”, Napoli, Italy; 13 Universitary Pediatric Clinic, Verona, Italy; 14 LOC Nefrologia Dialisi e Trapianto Pediatrico, Fondazione IRCCS Ca’ Granda Policlinico, Milano, Italy.

Group/Team: Precision In CAKUT Italian Study Group.

Background: Congenital anomalies of the kidneys and urinary tract (CACKUT) are a leading cause of end stage renal disease. Pathogenetic mechanisms behind CACKUT are mostly unknown. Point mutations and copy number variations (CNVs) account for 10-30% of the cases. Genetic tests are often not performed, thus limiting prognosis and management.

Methods: We present a multi-institutional Italian study group on CACKUT, composed of adult and pediatric nephrology and urology investigators. The group aims at recruiting and characterizing patients with CACKUT, a) blocks the characteristic and rare diagnosis with the focus on early intervention strategies. The remaining samples are undergoing DNA microarrays/WES.

Conclusions: We plan to enroll 5,000 patients. The deep and phenotypic characterization will allow precise anatomical classification of disease. Genetic data will be used to guide deep phenotyping.

SA-PO579

PRDM15 Mutations Cause Steroid-Resistant Nephrotic Syndrome with Microcephaly, Polydactyly, and Heart Defects
Sharia Ashraf,1 Denny Schanzel,2 Amelie van der Ven,1 ShaSha Shi,1 Svitlana Lovric,1 Neeven Soliman,1 Mohammed A. Jairajpur1, Jan Kadlec,2 Martin Zenker,3 Friedelmi Hildebrandt,1 Boston Childrens Hospital, Harvard Medical School, Boston, MA; 2 Cairo University, Cairo, Egypt; 3 INSERM, Grenoble, France; 4 Institute of Human Genetics, Magdeburg, Germany; 5 Jamia Millia Islamia University, New-Delhi, India.

Background: Steroid-resistant nephrotic syndrome (SRNS) causes 15% of chronic kidney disease in children and young adults. First insights into the pathogenesis of SRNS came from identification of <50 single-gene causes. PRDM proteins contain SET domain and multiple zinc fingers domains, and are involved in transcriptional regulation.

Methods: We performed whole exome sequencing (WES) to identify novel monogenic causes of SRNS in >1,000 individuals with SRNS.

Results: We identified 3 different recessive mutations in PRDM15 (PR domain containing 15) (p.M483K, E519K and C1173Y) in 6 unrelated families. Interestingly, 4 affected individuals with the C1173Y mutated allele exhibited SRNS (childhood-onset) with microcephaly, polydactyly, and heart defects, while the 2 mutations in the SET domain of PRDM15 only caused SRNS. PRDM15 C1173Y resides near the “knuckle” of the Cys-x-x-Cys sequence necessary to complex the zinc ion. We tested the stability of wild type (WT) protein versus two mutations (M483K and E519K) in the SET domain of PRDM15, using thermal stability assay by tryptophan absorption. We demonstrated that the M483K mutation leads to less stable than WT, while the E519K mutant was insoluble. Furthermore, we show that stable knockdown of PRDM15 results in decreased cell migration and severe proliferation defects in cultured human podocytes. WT, but not 3 mutant, constructs rescue the migration defects in podocytes, confirming a role in transcriptional control of the mutations that we identified in SRNS patients. By immunofluorescence studies, we find that PRDM15 colocalizes with fibrillin at nucleoli of human podocytes.

Conclusions: We have identified PRDM15 mutations as a novel cause of childhood-onset SRNS, with microcephaly, polydactyly and heart defects. Our findings may implicate a defect in a transcriptional program as a new cause of SRNS.

Funding: Other NIH Support - NIH DK076683 to F.H.

SA-PO580

Defects in All Components of the 6α-Biosynthesis Pathway Lead to Galloway-Mowat Syndrome
Geraldine Mollet,1 Bruno Collinet,2 Dominique Liger,2 Christelle Arrondel,1 Laurine Buscare,1 Gaelle Martin,1 Olivier Gribouval,1 Olivia Boyer,1 Daniela A. Braun,2 Anne-Claire Boschat,2 Sylvie Sanquer,1 Daniella Magen,2 Audrey Laurent,2 Friedelmi Hildebrandt,1 Herman Van tilberge,2 Corinne Antignac,1 Laboratory of Hereditary Kidney Diseases, Inserm UMR1163-Imagine Institute-Paris Descartes University, Paris, France; 2 Institut de Biologie Intégrative de la Cellule, Université Paris Sud CNRS UMR9198, Orsay, France; 3 Boston Children’s Hospital, Boston, MA; 4 Mass spectrometry Facility, Inserm U1163 Imagine Institute, Paris, France; 5 Metabolomic and proteomic Biochemistry Department-Necker Hospital, AP-HP, Paris, France; 6 Pediatric Nephrology Institute-Institut Rambam-University of Nice, Campus-University of Nice, Hafa, Nice; 7 Service de Néphrologie, Rhumatologie et Dermatologie pédiatriques, Hospices Civils de Lyon-Hôpital Femme-Mère-Enfant, Bron, France.

Background: The universal threonine/carbonoylamidomethane (6α) modification on RNAs, essential for translation initiation and translational efficiency, is catalyzed by two enzymes, YRDC and OSGBP, the last one being part of the highly conserved multiprotein complex KEOPS composed of 5 subunits (C14ORF142, LAGE3, OSGEP, TP53RK and YRDC) associating steroid-resistant nephrotic syndrome with microcephaly and neurological impairment. However, the role of the newly identified C14ORF142 (C14) subunit is still unclear.

Methods: To identify new genes of GMAM and better understand the role of C14, we performed whole exome sequencing, measured 6α modification by mass-spectrometry and performed western blot and qRT-PCR of KEOPS subunits in lymphoblastoid cell lines (LCLS) from GMAM patients.

Results: We identified compound heterozygous missense mutations in the YRDC/ SRNS in one patient with an extremely severe GMAM phenotype. Interestingly, primary fibroblasts from this patient present growth defects likely due to 6α deficiency. By contrast, we did neither observe any growth defects in C14-null fibroblasts, nor any change in the 6α level in C14-mutated LCLS. Nevertheless, we demonstrated that the C14 gene leads to a decreased expression level of the four other KEOPS subunits, likely through the shortening of the half-life of KEOPS subunits since without any effect on mRNA levels.

Conclusions: We identified mutations in an additional gene known to be involved in the pathogenesis of the 6α modification that confirms the crucial role of this modification in the pathogenesis of GMAM. The differences in the clinical phenotypes between YRDC and C14 patients can be explained by the different role of these proteins in 6α modification.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
modification, YRDC being directly involved in its biosynthesis, whereas C14 would stabilize the KEOPS complex to modulate its function(s).

Funding: Government Support - Non-U.S.

SA-PO581

Visualization of Force Dynamics and Actin Remodeling in ACTN4 Mutant Podocytes Subjected to Stretch

Di Feng1, Ava Benjamin,1 Jacob Notbohm,1 Minxian Wang,1 Ramaswamy Krishnan,1 Martin R. Pollak,1 Nephrology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA; 2University of Wisconsin-Madison, Madison, WI; 3Emergency Medicine, BIDMC/ Harvard Medical School, Boston, MA.

Background: Alpha-actinin-4 gene (ACTN4) mutations cause a rare form of familial focal segmental glomerulosclerosis (FSGS) and podocyte injury in humans. Our study aimed to better understand the mechanism by which mutant ACTN4 contributes to podocyte dysfunction by assessing the effect of the mutation on a podocyte’s response to transient stretch.

Methods: We used primary podocytes isolated from Actn4 K256E Knock in mutant mice (n=3) and WT littermates (n=3) as a cellular model. Measurements were performed in isolated single cells and data were pooled across multiple mice. We used traction force microscopy to quantify contractile forces exerted by podocytes on their underlying substrate in response to transient stretch. We used live cell imaging to examine the distribution of actin.

Results: Compared to WT, mutant ACTN4 podocytes bear more actin stress fibers bundles and exert greater contractility before stretch. After the first transient stretch, WT and mutant podocytes demonstrated similar reductions in their contractile forces. During the recovery period, WT podocytes demonstrated recovery of their contractile forces close to pre-stretch baseline values, whereas the majority of mutant podocytes showed impaired recovery. After a total of 3 transient stretches, WT podocytes on average recovered 79% of their baseline contractile forces, whereas the majority of mutant podocytes (10/15) recovered less than 50% of their baseline, with 7 failing entirely (completely losing their ability to generate contraction forces). Additionally, representative WT podocytes demonstrated cracks in their cytoskeletons after the first stretch that were subsequently repaired during the recovery period, whereas representative mutant podocytes whose contractile forces failed demonstrated cracks that persisted during the recovery period.

Conclusions: Our findings provide the first direct evidence of a mutant ACTN4 podocyte’s inability to maintain its structure and function in response to mechanical stress, suggesting a clearer path through which mutant ACTN4 leads to podocyte detachment and kidney injury.

Funding: NIDDK Support

SA-PO582

MicroRNA Content in Cells Is Globally Disrupted by the Nephrotic Syndrome-Related Point Mutation in XPO5

Iddo Z. Ben-Dov, Nephrology and Hypertension, Hadassah - Hebrew University Medical Center, Jerusalem, Israel.

Background: MicroRNA (miRNA) are small noncoding RNA that regulate gene expression. Mature miRNA are crucial for the development and homeostasis of podocytes. Maturation of miRNA entails a multistage process that involves several proteins. Recently, steroid-resistant nephrotic syndrome (SRNS) in a child was attributed to a point mutation in Exportin-5 (XPO5), a protein that exports miRNA precursors from the nucleus to the cytoplasm (Braun DA 2016). However, whether or not the mutation affects the miRNA-related function of Exportin-5 is not known. We hypothesized that the V552I mutation impedes miRNA maturation, and that the association with SRNS may be mediated by specific miRNA.

Methods: We transfected XPO5-knockout (XPO5-/-) HCT116 cells with plasmids encoding either wt XPO5 or XPO5[V552I] and compared global miRNA content with non-rescued XPO5-/- cells and parental cells via small RNA sequencing.

Results: miRNA quantification confirmed global depletion of mature miRNA in XPO5-/- compared to parental cells. Transfection experiments showed partial rescue of miRNA content with wt XPO5. Transfection of a plasmid encoding XPO5 harboring the V552I mutation did not rescue miRNA maturation (Figure). Conversely, mapping of small RNA reads to mRNA and tRNA was relatively higher in XPO5-/- cells and mutant XPO5-transfected XPO5-/- cells compared to parental and wt XPO5-transfected XPO5-/- cells.

Conclusions: Together with predictions of disrupting impact of the V552I mutation, our experiments show that the SRNS-related XPO5 mutation may cause global reduction of mature miRNA. Further experiments should pinpoint specific miRNA and miRNA targets responsible for the podocyte phenotype.

Funding: Government Support - Non-U.S.
SA-POS54

Rare GREB1L Mutations Contribute to the Genetic Heterogeneity of Congenital Kidney Malformations

Simone Sanna-Cherchi,1 Khanal,4 Rik Westland,1 Priya Krithivasan,2 Hila Milos Rasouly,3 Julia Ionta-Laza,2 David Fasel,3 Krzysztof Kurylik,4 Monica Bodira,1 Edgar A. Otto,1 Matt G. Sampson,2,4 C. Gilles,1 Adele Mitroitti,3 Loretto Gesualdo,3 Francesca Funti,2 Iria Pastore,2 Giovanni Piserchio,2 Marta Ferras,2 Marijan Saraga,2 Francesco Scolaro,2 Velibor Tasic,2 Gian Marco Ghiggeri,3 Anna Maternawa-Kurylik,2 David B. Goldstein,2 Nicholas Katzens,3 Erica Davis,2 Ali G. Gharavi,3 Boston Children’s Hospital, Boston, MA; 4Columbia University, New York, NY; 5Columbia University Medical Center, New York, NY; 6Duke University, Durham, NC; 7G. Gaslini Children Hospital, Genova, Italy; 8University of Brescia, Montichiari (Brescia), Italy; 9University of Bari, Altamura, Italy; 10University of Brescia, Brescia, Italy; 11University of Amsterdam, Amsterdam, Netherlands; 12Poznan University of Medical Sciences, Poznan, Poland; 13Duke University Medical Center, Durham, NC.

Background: Renal agenesis and hypoplasia (RHD) are a major cause of pediatric end-stage renal disease.

Methods: We conducted whole exome sequencing in 203 patients with RHD and identified diagnostic pathogenic mutations in 8/203 patients. In another 6 patients, we found non-recurrent novel loss-of-function (LOF) variants in genes associated with rare syndromes that include kidney defects (SETBP1, WNT3A), or in genes whose inactivation result in kidney malformations in the mouse (SLIT3, HSP4, T, SCTR).

Results: To define novel genetic drivers in the remaining cohort of 195 patients, we compared their LOF burden with 6,905 controls. We identified rare LOF variants in GREB1L (P=2.04x10^-4), a gene ubiquitously expressed in the developing mouse kidney. Expansion of our model with novel deleterious missense variants resulted in exome-wide significant association for exomes containing either 2 LOF (1 LOF and 1 missense) segregated in an autosomal dominant fashion and one predicted deleterious missense was de novo (joint value for burden, inheritance and de novo occurrence: P=1.0x10^-4).

In a replication cohort of 410 RHD cases, we identified 8 more qualifying LOF/missense variants in GREB1L. To directly test our genetic findings, we generated a grebl1 knockout mouse. Knockdown and CTRIPR:Cas9 deletion of grebl1 in zebrafish showed specific pronephric defects that could be rescued by introduction of wild-type human mRNA. Randomized testing of missense alleles by in vivo coletion showed that 4/4 alleles were exclusively in patients was unable to rescue the phenotype.

Conclusions: Taken together, our study provides new insight into the genetic landscape of renal malformations and identifies GREB1L as a novel susceptibility gene for RHD.

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

SA-POS58

The Novel, Non-Toxic Nonsense Suppressor Drug, ELX-02, Is Effective in Cystinosis

Emma J. Braszell,1 Lee Icke Chu,1 Iris Alroy,2 Idit Eshkar-Oren,1 Michal Shavit,1 Meytal Shohat,1 Pedro Huertas,1 Yojito Yamanaka,2 Paul R. Goodyer,2 Eloxx Pharmaceuticals, Behovot, Israel; 3McGill University, Montreal, QC, Canada; 4RI-MUHC, Montreal, AB, Canada.

Background: Cystinosis is caused by mutations in the cystinosin (CTNS) gene, encoding a lysosomal membrane transporter responsible for the efflux of cystine. Intralysosomal cystine accumulation drives progressive organ dysfunction in cystinosis.

In Quebec, about 50% of patients harbor a W138X nonsense mutation, causing a premature termination codon (PTC) in exon 7. PTCs cause nonsense-mediated decay (NMD) of mutant transcripts and inhibit protein translation. Aminoglycosides have generally well-tolerated in humans up to 5mg/kg. However, they are too toxic to be used for therapy. In contrast, the novel compound ELX-02 was safe and generally well-tolerated in patients with the phenotype.

Results: To test the efficacy of ELX-02, we treated human fibroblasts harboring the W138X mutation and examined CTNS expression and intracellular cysteine levels. Using zink finger technology, we generated an ELX-02 resistant mouse and replicated the in vivo experiments in mouse fibroblasts. Mice were then injected with ELX-02 (10mg/kg s/c x2/week for 22 days). Half-cysteine levels were assessed in kidneys and pharmacokinetics (PK) studied in plasma and kidney tissue.

Results: After treatment with ELX-02, CTNS mRNA transcript levels in CTNS<sup>W138X/ W138X</sup> fibroblasts increased to normal levels and intracellular cystine was reduced. These results suggest that ELX-02 reduces NMD of CTNS<sup>W138X</sup> transcript and allows production of functional CTNS protein. In addition, ELX-02 had a similar therapeutic effect on the Y226X mutation in mouse fibroblasts. In ELX-02 treated mice, pathologic half-life was extended to 85% of untreated levels. ELX-02 in plasma and kidneys had similar Cmax (15ug/ml at 15 min), AUC and elimination half-life (~30 min) following single and repeated administration. ELX-02 was more concentrated in kidney (Cmax 40ug/ml), with sustained levels of 15ug/g for > 8 hrs.

Conclusions: These results demonstrate read-through activity of ELX-02 on hCTNS W138X and mCTN Y226X mutations, producing sufficient CTNS protein for cystine efflux from lysosomes. Thus, ELX-02 may be an effective therapy for cystinosis caused by PTCs.

Funding: Commercial Support - Eloxx Pharmaceuticals, Private Foundation Support

SA-POS56

Identifying Modifier Genes of X-Linked Alport Syndrome Using a Novel Multi-Parent Mouse Model

Ron Korstanje,1 Daniel M. Gatti,2 Yuka Takemone,1 The Jackson Laboratory, Bar Harbor, ME.

Background: A major goal for precision medicine in genetic diseases is the identification of modifier genes as potential therapeutic targets. Using X-linked Alport Syndrome (XAS) as a model for heritable kidney diseases, we have developed a novel approach to identify modifier genes that modulate disease severity outcomes. To identify modifiers for XAS, we used a Col4α2 mutation into the genetically heterogenous Diversity Outbred (DO) mice and conducted high-resolution mapping for several renal phenotypes.

Methods: The DO mice are an ideal population for high-precision genetic mapping, containing 45 million SNPs originating from 8 founder strains. The diversity captured in the DO emulates the variation in the human genome. To introduce XAS into the DO population, we crossed female C57BL/6/COL4a2<sup>-/-</sup> mice with 100 unique male DO mice. From each mating we selected one COL4a2<sup>-/-</sup> male and one COL4a2<sup>-/-</sup> female F1 offspring to create a cohort of 200 mice. We measured albuminuria (ACR) at 6, 10, and 15 weeks, and glomerular function (GFR) at 14 weeks of age. We genotyped each animal, reconstructed haplotypes, and mapped loci associated with variation in ACR and GFR.

Results: There was large variation in GFR and ACR in our cohort. Similar to human XAS patients, males had increased severity with elevated ACR and reduced GFR relative to females. High-resolution linkage and association mapping revealed several loci as narrow as 1Mb harboring genes responsible for driving variation in ACR and GFR. The most significant GFR locus contains only 5 annotated genes, including a transcription factor. These genes form a microbicoid network related protein expression. Similarly, a locus for ACR contains a gene associated with actin filament formation. Both candidates suggest an affect on the structure and therefore the function of podocyte foot processes, critical for renal function.

Conclusions: Our study successfully identified several novel candidate genes implicated in modifying XAS disease severity outcomes. These candidates are prime therapeutic targets for XAS. This work demonstrates the power of high-resolution genetic mapping in the DO mice, an approach that can be applied to other forms for heritable renal diseases such as polycystic kidney disease.

Funding: Other NHI Support - NIH GM076468

SA-POS57

Clinical Overview and Long-Term Prognosis of Dent Disease and Lowe Syndrome in Japan

Ken-Ichi Muru,1 Yutaka Harita,2 Kiyonobu Ishizuka,1 Tomoo Yakubuchi,1 Naoto Kaneko,1 Shoichi Kanda,2 Atsushi Sato,2 Tsuyoshi Isosima,2 Takashi Igarashi,3 Motoshi Hattori,4 1Tokyo Women’s Medical University School of Medicine, Tokyo, Japan; 2Tokyo, Japan; 3Department of Pediatrics, University of Tokyo, Tokyo, Japan; 4National Center for Child Health and Development, Tokyo, Japan.

Background: Epidemiologic data of Dent disease (DD) and Lowe syndrome (LS) are lacking, and long-term prognosis of LS has not been surveyed. The aim of this study was to investigate the prevalence and long-term prognosis of patients with DD and LS in Japan.

Methods: Questionnaire was distributed to 1,814 departments of pediatrics, nephrology, endocrinology and internal medicine of major hospitals in Japan. Data of the patients who visited the hospitals in 3 years (between 2013 and 2015) were collected. This study was approved by the Ethics Committee of Tokyo Women’s Medical University (IRB No.3916) and was supported by Health and Welfare Labour Sciences Research Grants.

Results: The response rate was 49% and 83% in the primary and the secondary survey, respectively. Clinical and laboratory data obtained from 76 patients with DD and 67 patients with LS. A low response rate and small sample sizes did not allow estimation of patient numbers. The majority of patients with DD were diagnosed asymptptomatically by annual urinary screening test at median age of 3 years. Prominent low molecular weight proteinuria (LMWP), hypercalcemia and nephrocalcinosis were noted in 100%, 49% and 37% of patients, respectively. Only 3 (19%) out of 16 adult patients developed CKD stages 3 or 4 in their 20s and 30s. Genetic analyses were performed in 37% and mutations in the clcn5 and the ocrl genes were documented in 68% and 11%, respectively, the proportion of which was similar to the previous reports. Most patients with LS were diagnosed in infancy. All patients presented with prominent LMWP, cataract and mental retardation. Estimated GFR negatively correlated with age and indicated that most patients developed end stage renal disease in their 30s and 40s. OCRL mutations were documented in 23 (96%) out of 22 patients analyzed.

Conclusions: The prognosis of DD in Japan might be better than that in Europe and USA probably due to detection of individuals with milder phenotypes by annual urinary screening test. It might be suggested that the only required item for the diagnosis of DD is prominent LMWP in Japan. In addition, we described long-term renal prognosis of LS for the first time, which would contribute to treatment strategy and genetic counseling.

Funding: Government Support - Non-U.S.
SA-POS58

Genetic Findings in Adults with Sporadic Steroid-Resistant Nephrotic Syndrome

Aude Servais,1,2 Olivier Griveau,2 Olivia Boyer,2 Aurelie Hummel,1 Jacques Dantel,1 Marie-Joséphe Tête,3 Corinne Antignac,2,3
1Necker University Hospital, Paris, France; 2Inserm U1163, Imagine Institute, Paris Descartes University, Paris, France; 3Institut de Transplantation Urologie Néphrologie, Nantes, France.

Background: In recent years, proposals for genetic screening paradigms in Steroid-Resistant Nephrotic Syndrome (SRNS) preferentially addressed congenital, inflammatory, and familial onset and familial sporadic cases. SRNS/FSGS in adults are currently only tested for the NPHS2 nonpolar p.R229Q polymorphism. To uncover the distribution of disease-causing gene mutations in an adult sporadic FSGS/SRNS population, we used a NGS panel in a cohort of adult patients.

Methods: We selected adult patients (age at onset of proteinuria above 18 years), with non syndromic biopsy proven FSGS and/or SRNS, without known family history. We used strict clinical criteria including no response to glucocorticoids but also to cyclosporine and no relapse after renal transplantation. We applied a NGS panel covering 37 genes to 135 unrelated patients.

Results: Mean age at onset of proteinuria was 30.1 (18.1-84.0) years. Eighteen (13.3%) presented with mutation (15/135, 11.1%) or variant of unknown significance (VOUS) (3/135, 2.2%) in known monogenic SRNS genes and 14 (10.4%) with APOL1 high risk allele. We identified 11 novel mutations including mutations in PAI2, INK2, NPHS2, MYO1E, and CD2AP genes. Collagen mutations represented 38.8% of all mutations. Mean age at onset of proteinuria was lower in the group with mutations than in patients with no mutation or APOL1 risk variant (24.9±7.9 vs 30.9±17.0, p=0.01). Mutations in collagen genes were all found in patients younger than 30 years of age, whereas mutations in collagen genes were also identified in older patients until 50 years of age. Patients with mutations presented with lower eGFR at diagnosis (43.6±31.8 vs 87.4±7.4 years, p=0.01). Mean age at onset of proteinuria in patients with mutations in collagen genes than in patients with mutations in other genes (47.5±16.6 vs 26.6±4.6 years, p=0.01).

Conclusions: We identified a mutation or a VOUS in known monogenic SRNS genes in 13.3% of patients and APOL1 high risk allele in 10.4%. Collagen mutations causing Alport Disease were the most frequent identified mutations.

Funding: Government Support - Non-U.S.

SA-POS59

The Minor rs4293393 SNP Variant Is Associated with a Delayed Age of ESRD in Uromodulin Kidney Disease

Anthony J. Bleyer,1 Kendrah O. Kidd,2 Petry Vyletal,1 Jorge Reis Almeida,3 Joaquim T. Calado,3 Rosa J. Torres,6 Sofia C. Jorge,4 Catarina S. Silva,1 Eric G. Olinger,1 Olivier Devuyt,2 Stanislav Knoch,3½ First Faculty of Medicine, Institute of Inherited Metabolic Disorders, Charles University, Prague, Czech Republic; ½University of Zurich, Zurich, Switzerland; 3University of Lisbon, Portugal; 4Institute of Inherited Metabolic Disorders, Prague, Czech Republic; 5La Paz University Hospital, IdiPaz, Madrid, Spain; 6Vanderbilt University, Nashville, TN; ½Portuguese Society of Nephrology, Lisbon, Portugal; ¾Wake Forest School of Medicine, Winston-Salem, NC.

Background: Uromodulin kidney disease (UKD) is a form of autosomal dominant tubulo-interstitial kidney disease (ADTKD) caused by mutations in the UMOD gene in the proband. UKD is characterized by slowly progressive kidney failure. The minor variant of rs4293393 in the UMOD promoter is associated with 50% decreased uromodulin production. We hypothesized that if this minor variant is found in the mutated UMOD gene promoter in individuals with UKD, there will be decreased mutant UMOD production and a later ESRD onset.

Methods: Genotyping of the rs4293393 snp was performed in 365 individuals from 149 families. Association with the mutated UMOD gene was determined. Age of ESRD was determined.

Results: Hardy Weinberg equilibrium was not met, with only 8/149 (5%) families linked to the minor variant vs. 15% expected (p-value < 0.0001). The mean age of end stage renal disease (ESRD) for individuals linked to the minor variant was 59.5±11.1 (n=6) vs 45.3±10.5 years for individuals linked to the major variant (n=139) (p=0.008). No individual linked to the minor variant reached ESRD before age 45 as opposed to 71 individuals (51%) linked to the major variant (Figure 1).

Conclusions: The rs4293393 minor variant, previously linked to decreased uromodulin production has a significant protective effect on age of ESRD if it is found in the promoter of the mutant UMOD gene in individuals with UKD. The deviation from expected allele and genotype frequencies could be due to the preservation of kidney function such that families linked to the minor variant are not being diagnosed at the same rate as other UKD families. These findings identify a prognostic factor in age of ESRD in UKD and suggest that decreasing mutant uromodulin production will improve renal survival.

Funding: NIDDK Support

Figure 1: Association of CKD with rs4293393 linkage. The rs4293393 minor variant is C and the ancestral variant is T. CKD stages are based upon NKF KDOQI guidelines.

SA-POS91

Collagen IV Receptor Blockade as Add-On Therapy in Alport Syndrome

Diana Rubel,1 Rainer Girgenti, Gerhard A. Mueller, Olivier Gross. University Medicine Gottingen, Gottingen, Germany.

Background: Alport Syndrome (AS) is caused by a lack of misfolding of collagen IV alpha 3, 4 and 5 due to a mutation in one of these genes. Podocytes sense this abnormal glomerular basement membrane (GBM) by collagen receptors such as discoidin domain receptor 1 and Integrin α2. In our present study, we evaluated the nephrin-protective effect of knocking-out both receptors in AS (TripleKO) with and without standard ACE-inhibition (ACEi). We hypothesized that the loss of collagen-receptors could inhibit recognition of the altered GBM in AS and improve the renal phenotype. ACEi as the standard-label therapy delays renal failure until aldosterone escape. Therefore, it is important to evaluate new therapies on top of ACEi.

Methods: Here, we analyze the effect of ACEi and collagen receptor blockade as possible new therapy in wildtype (WT), mice with AS, TripleKO and ACEi treated mice. Modulation of action was characterized by real-time PCR, light and electron microscopy with immunohistochemical reactions.

Results: TripleKO mice showed a significant longer survival, less matrix accumulation and fibrosis compared to Alport mice. Additionally, the foot processes were preserved until later stages of disease and splitting of the GBM was considerably less. The reducing expression of ED-1 and fibrinogen in the glomerulus in WT. In contrast, the TripleKO mice showed a podocin expression which was comparable.
to WT. Nephrin expression was slightly reduced in TripleKO mice compared to WT, but significantly increased in ACEi treated mice. In Alport mice, the immunogold reactions revealed a podocin accumulation in the areas of podocyte effacement in an age-dependent manner. TripleKO mice showed the same ultrastructural changes, but at a later stage of disease. Nephrin aggregated in TripleKO mice in areas where footprocesses were still preserved.

Conclusions: ACEi and loss of collagen receptors both delay progression of AS in a similar manner, but have different ways of action. In contrast to ACEi therapy for example, podocin expression in TripleKO mice seemed to be maintained, but the protein was mislocated. This confirms a different mode of action resulting in a considerable add-on effect on delaying renal failure. Thus, these additive effects of collagen receptor blockade on top of ACEi should be in the focus of further studies.

Funding: Private Foundation Support

SA-PO592

Deleterious Impact of a Novel CFIH Splice Site Mutation in Individuals of Caucasian Ancestry

Poster/Saturday

Andrew S. Franzin,1 Rocio Coto,1 Anna Sanna-Cherchi,2 Valentina Giannini,2 G. Ghiggeri,2 Maria V. Cianfriglia,2 Piero Albonico,3 Nicola Cioni,3 Maik Grohmann,4 Maik Grohmann,4 Tom H. Lindner,5 Jan Halbritter,3

Bioskientzta, Ingelheim, Germany; 1University Clinic Leipzig, Leipzig, Germany.

Background: Atypical hemolytic uremic syndrome (aHUS) is a rare disease typically based upon uncontrolled activation of the alternative complement pathway (ACP). Clinical signs and symptoms comprise microangiopathic haemolytic anemia (MAHA), thrombocytopenia, and acute kidney failure (AKI). Mutations in ACP regulating genes such as C3, CFI, CFIH, and MCP/C1D4 are found in around 50% of patients.

Methods: A 27 year-old female without prior past medical history presented with nephrotic range proteinuria, petechial bleeding, and anuric AKI necessitating initiation of dialysis. Laboratory examination revealed MAHA with schistocytes but normal ADAMTS13 levels. Kidney biopsy showed glomerular thrombotic microangiopathy (TMA), which was treated with steroids, plasmapheresis, and eculizumab (induction/maintenance), leading to complete remission, as well as significant recovery of kidney function within 2 months. Targeted next generation sequencing for aHUS associated genes identified a paternally transmitted novel heterozygous mutation in the CFIH gene (c.1514+2A>G). CFIH encodes complement factor H, a key inhibitory protein of the ACP. The mutation is located in the obligatory splice acceptor site of intron 19. Sanger sequencing of patient cDNA indicated that as a consequence of the mutation, alternative splicing results in a deletion of the first 27 base pairs of exon 20. On the protein level, CFIH consists of 20 similar structural conserved Sushi domains, where each domain contains a pair of zinc finger motifs (p.Cys1048). As this cysteine is thought to be essential for proper protein folding, its loss may consequently result in a defective protein structure, impairing binding to C3.

Results: In summary, we detected a new CFIH splice site mutation in a patient with aHUS, which probably leads to an incorrect protein structure impairing inhibitory control of C3 and thereby ACP activity. Incomplete penetrance demonstrated by the clinically asymptomatic father underlines the necessity of an additional disease trigger.

Funding: Other U.S. Government Support

SA-PO594

A Bioinformatics Analysis of Gene Expression in Experimental Alport Syndrome Reveals an Fstl1 Signature in the Kidney

Saturday

Nicholas Maksimowski,1 Xuewen Song,2 Eun Hui Bae,3 York P. Pei,4 James W. Scholey.5

1University of Toronto, Toronto, ON, Canada; 2University Health Network and University of Toronto, Toronto, ON, Canada; 3Chonnam National University Hospital, Gwangju, Republic of Korea.

Background: Alport syndrome (AS) is a rare inherited form of chronic kidney disease characterized by progressive nephropathy and the development of end stage renal disease. It is caused by mutations in the Col4a3, Col4a4, and Col4a5 genes. The goal of my studies is to better understand the pathogenesis of AS in the kidney.

Methods: We performed studies using a well-characterized experimental murine model of AS. Global gene expression profiling of renal cortical mRNA samples was performed in male Col4a3-/- mice and Col4a3+/+ control mice at 4 and 7 weeks of age to identify early differentially expressed genes. We performed a cluster analysis and constructed a heat map on the microarray studies at 4 and 7 weeks of age. Finally, studies using HK2 cells were conducted to analyze inflammation and apoptosis related to a protein of interest and its cognate receptor.

Results: The microarray analysis revealed that only 5 genes were differentially expressed in the kidneys of male Col4a3-/- mice at 4 weeks of age compared to Col4a3+/+. Amongst these genes was Folliculin-related protein 1 (FSTL1). We used search tool for the retrieval of interacting genes/proteins to predict protein-protein interactions (PPIs) thereby identifying a functional protein association network for FSTL1. The network included 39 proteins. Cluster analysis of the cognate genes from the FSTL1 protein network showed upregulation of gene expression at 7 weeks of age. FSTL1 increased NFXB mediated luciferase activity, caspase 3 activation and PARP cleavage in HK2 cells. These effects were due, at least in part to TLR4 receptor activation.

Conclusions: Our microarray and bioinformatics analyses identified early upregulation of FSTL1 in the kidneys of Col4a3-/- mice. A FSTL1 gene signature, based on predicted PPIs, emerged in the kidneys by 7 weeks of age. FSTL1 elicited an inflammatory response and activated apoptosis in HK2 cells. These findings support the hypothesis that FSTL1 may be a novel determinant of kidney injury in mice with experimental AS.

Funding: Private Foundation Support

SA-PO595

Modelling Alport Syndrome in Zebrafish Richard W. Naylor, Saule N. Gasiunas, Rachel Lennon. University of Manchester, Manchester, United Kingdom.

Background: Alport syndrome is a hereditary renal disorder that manifests in early childhood with haematuria followed by proteinuria and ultimate progression to end stage renal disease. Genetic analysis has shown that patients with Alport syndrome carry mutations in genes encoding three isoforms of collagen type IV: COL4A3, COL4A4 and COL4A5. Type IV collagens are the most abundant collagens in basement membranes and exist as three different trimeric proteins, α1(IV)α2(IV), α3(IV)α5(IV) and α5(IV)α6(IV). In the glomerulus, podocytes deposit the α3(IV)α5(IV) trimer and the endothelium deposits the α1(IV)α2(IV) trimer. The fusion of these two extracellular matrices forms the glomerular basement membrane (GBM). In Alport syndrome, mutations in either COL4A3, COL4A4 and COL4A5 lead to depletion of the α3(IV)α5(IV) trimer in the three Caucasian cohorts (Western European: 301, Italian: 754, Turkish: 98), matched with healthy controls.
GBM. This loss of α3,α6coll(IV) initially creates a thinner GBM that at later stages of the disease acquires a 'basket-weave' appearance. Treatment of Alport syndrome is limited to angiotensin converting enzyme inhibitors but the mechanism of their action on the glomerulus has not been fully elucidated.

**Methods:** To improve our understanding of disease and treatment mechanisms we aimed to generate a zebrafish model of Alport syndrome. The zebrafish is a highly tractable system that has become a premier organism for disease modelling. Many of the cellular components of the glomerular filter are conserved between zebrafish and humans. We have used in situ hybridisation with RNA probes and immunofluorescence with collagen IV antibodies to observe if the molecular components of the glomerular filter are also conserved. In addition, we have used the CRISPR/Cas9 system to generate col4a5, col4a4 and col4a2 knockout mutant lines.

**Results:** We find zebrafish podocytes express col4a4, col4a4 and col4a5 and have also identified collagen type IV isoforms in the zebrafish GBM. We have also found phenotypic effects on the glomeruli of our knockout lines and have performed functional and ultrastructural analyses.

**Conclusions:** We have demonstrated expression of the α3,α6coll(IV) network in the zebrafish GBM and have created a new in vivo model for Alport syndrome. This model will allow the use of new approaches to investigate disease mechanisms in Alport syndrome and will facilitate high throughput compound screening for drug discovery.

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

SA-PO596

**Genetically Affected Individuals with UMOD and MUC1 Mutations Who Donate a Kidney Have Surprisingly Good Renal Outcomes**

Anthony J. Bleyer, Kendra O. Kidd, Peter J. Conlon, Peter J. Lavin, Claire Kennedy, AnaGreka, Stanislav Knoch, Beaumont Hospital, Dublin 9, Co Dublin, Ireland; 2Harvard Medical School, Boston, MA; 3Institute of Inherited Metabolic Disorders, Prague, Czech Republic; 4Beaumont Hospital, Dublin, Ireland; 5Wake Forest University School of Medicine, Winston-Salem, NC; 6Wake Forest School of Medicine, Winston-Salem, NC; 7Trinity Health Kidney Centre, Dublin, Ireland; 8Broad Institute, Cambridge, MA.

**Background:** Some individuals with UMOD and MUC1 mutations who were mildly affected donated kidneys prior to genotyping being available. The outcome of these individuals has not been studied.

**Methods:** We studied renal outcomes in 4 individuals with UMOD mutations and 3 individuals with MUC1 mutations.

**Results:** All donors donated to family members with the same mutation. One donor had a cerebral hemorrhage with donation immediately prior to death. The eGFR post-donation was lower seen in health donors, with a mean eGFR of 46.5±5.3 ml/min. However, kidney function remained stable, and no donors required renal replacement therapy at a mean follow up of 10.2±6.6 (range 3-18) years follow up. Likewise recipients have done well with all allografts functioning 12.9±9.6 (range 3-18) years post-transplant.

**Conclusions:** Some individuals with MUC1 or UMOD mutations are mildly affected, and their eGFR and that of their donors remain surprisingly stable in most instances after donation. However, at this time individuals with these mutations should not yet be considered as kidney donors until more data is available.

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

**Gene:** DHTKD1

**Donor Type:** DHTKD1

**Donor Age:** 42

**Recipient Age:** 56

**Cancer:** Other

**SA-PO597**

**Possible Link Between Aging Nephropathy and DHTKD1 in C57BL/6J Mice**

Nathan D. Susnik, Ron Korstanje, Laura Reinholdt, Nob Handke, Jan Hegermor, Christoph Wrede, Heike Bähr, Hermann G. Haller, Mario Schiffer, Roland Schmitt, 'Hannover Medical School, Hannover, Germany; 'The Jackson Laboratory, Bar Harbor, ME.

**Background:** During renal aging experiments, we found a spontaneous phenotype in a cohort of 18-22 month old C57BL/6J mice. Old mice developed pronounced glomerulosclerosis, amyloidosis, and renal dysfunction with proteinuria (GARD). Here, we tested the assumption that the GARD phenotype was due to a spontaneous mutation.

**Methods:** Whole exome sequencing data from a GARD mouse was compared to publicly available C57BL/6J reference sequence (GRCm38). C57BL/6J and C57BL/6JRJ mice purchased from different suppliers were sequenced for mutations in DHTKD1. Cellular localization of DHTKD1 was examined in murine and human kidneys and in renal cells. DHTKD1 expression was manipulated with Crispr-Cas9 and siRNA in cell lines and morpholinos in zebrafish.

**Results:** Whole exome sequencing revealed that GARD mice had a single nucleotide polymorphism leading to an amino acid substitution (A335T) in the thiamine-binding motif of dehydrogenase E1 and transketolase domain containing 1 (DHTKD1). All C57BL/6J mice in the GARD cohort were homozygous for the Dhtkd1 mutation (Dhtkd1<sup>A335T</sup>). A335T was expressed in podocytes, proximal tubules, and distal tubules. Contrary to previously reported data, knockout (KO) of DHTKD1 left mitochondrial morphology, genes associated with mitochondrial function, and ATP production unchanged. Flow cytometry however, revealed more MTOC in DHTKD1 KO cells. KO cells also had increased 2-aminoacidic and 2-oxoacidic acid, metabolites of lysine degradation. siRNA in human podocytes changed some mitochondria-associated genes, but made no difference in ATP production. Knockdown of Dhtkd1 in zebrafish larvae led to proteinuria and podocyte foot process effacement. While these changes indicate a functional role for DHTKD1 in renal maintenance, C57BL/6J Dhtkd1<sup>A335T</sup> mice aged at our own facilities did not develop GARD.

**Conclusions:** Overall, knockdown of DHTKD1 causes structural and functional changes in the GARD phenotype in both mice and zebrafish. The DHTKD1<sup>A335T</sup> mouse was not fully penetrant, suggesting that other variables like diet or housing are involved.

**Funding:** Other NIH Support - National Cancer Institute

**SA-PO598**

**A Novel Deletion in ACTN4 in a Patient with Renal FSGS and Concomitant TMA**

Johannes Muench, Ralph Wendt, Ria Schönan, Maik Grohmann, Joachim H. Beige, Thorsten Wiech, Tom H. Lindner, Carsten Bergmann, Jan Halbritter, BioScientia, Ingelheim, Germany; 2Department of Pathology, University Hospital Hamburg Eppendorf, Hamburg, Germany; 3Hospital St. Georg, Leipzig, Germany; 4Division of Nephrology, University Clinic Leipzig, Leipzig, Germany.

**Background:** Thrombotic microangiopathy (TMA) of the kidney leading to renal failure is associated with genetic susceptibility due to variants of genes encoding complement components in several causes of TMA. Recently, Challas et al (JASN 2015) reported two families with biopsy proven TMA who inherited mutations of INK2, a gene that is known to cause familial FSGS. As inactivated form 2 (INK2) is essential for podocyte cytoskeleton integrity by regulating the actin-polymerization and depolymerization processes, it is reasonable to assume, that genetically determined functional deficiency of further podocytic structural proteins might provoke renal TMA-phenotypes as well.

**Methods:** A 30-year old male patient presented with acute kidney failure and proteinuria (eGFR 11 ml/min, proteinuria 3563 mg/g creatinine). At the time of diagnosis, laboratory findings showed no signs of hemolytic-uremic or fish-eye phenotype. Whole-exome sequencing revealed advanced glomerulosclerosis and TMA in preglomerular arterioles and glomeruli. Genetic testing regarding mutations of known aHUS-genes showed no pathogenic variants but the risk polymorphisms MCP-H2 and CFHR1*8. However, a missense variant of the classical-three-base-deletion in exon 8 of ACTN4 was detected, leading to loss of lysine at amino acid residue 255 (c.763C>T, p.Lys255del). A therapeutic approach with eculizumab was unsuccessful as control biopsy after four months revealed progressive glomerular and tubulointerstitial scarring.

**Results:** ACTN4-mutations are known to cause autosomal dominant FSGS and most-disease-causing mutations are located within the protein's actin-binding domain. The pathogenicity of the ACTN4 mutation in our patient is assumable, as functional alterations upon amino acid substitution at the same position (c.763C>T, p.Lys255del) have been demonstrated previously (Feng et al, PLoS One 2015). However, ACTN4 mutations have not been associated with renal TMA yet, although this phenotype was already reported in other forms of familial FSGS (Benz et al, Pediatr Nephrol 2007). We therefore propose that pathogenic variants in ACTN4 may account for renal TMA, which adds to the clinical pleiotropy of mutated ACTN4. Hence, mutated ACTN4 should be considered in patients with renal TMA, especially in those with an eculizumab-resistant progress and unremarkable complement genetics.

**Funding:** Private Foundation Support

**SA-PO599**

**Comprehensive Analysis of the Renal and Systemic Phenotypes Associated with Familial Deficiency of Lecithin-Cholesterol Acyltransferase: A Case Series**

Carlos T. Sampayo, Bruno E. Balbo, Leonardo C. Sairava, Henriët N. A. Nakano, Andressa G. Amaral, Eliene Costa, Elieser H. Watanabe, Precil D. Neves, Ana P. Chacra, Raul Maranhao, Antonio A. Guerra, Ricardo M. Braga, Ruth M. Santo, Leonardo A. Testigrossa, Marlene A. Reis, Junior A. Silva, Henrique Carrascossi, Luiz F. Onuchic, 'Nephrology and Molecular Medicine, University of Sao Paulo, Sao Paulo, Brazil; 'Cardiopneumology, University of Sao Paulo, Sao Paulo, Brazil; 'Hematology, University of Sao Paulo, Sao Paulo, Brazil; 'Ophthalmology, University of Sao Paulo, Sao Paulo, Brazil; 'Pathology, University of Sao Paulo, Sao Paulo, Brazil; 'Pathology, Federal University of Triangulo Mineiro, Uberaba, Brazil; 'Piaui Municipal Service, San Francisco, Brazil; 'Araquara Municipal Service, Araquara, Brazil.

**Background:** Lecithin cholesterol acyltransferase (LCAT) is involved in cholesterol metabolism. Familial LCAT deficiency (FLD) is a recessive disease associated with systemic lipid deposition, often resulting in CKD and fish-eye opacities.

**Methods:** Retrospective study, comprising clinical, laboratory and molecular genetic analyses of FLD patients.

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

Underline represents presenting author.
SA-PO600

Clinical Characterization of Families with Mutations in the MUC-1 Gene

Anthony J. Blyer,1 Constantinios Deltas,2 Gregory Papagporiourou,3 Stanislav Kmochn,4 Kendrah O. Kidd,5 Seth L. Alper,6 Peter J. Lavrin,7 Daniel P. Gale,7 Peter J. Conlon,1 Peter C. Harris,1 Anna Greka,1 Beamont Hospital, Dublin, 9 Co Dublin, Ireland; 2Beth Israel Deaconess Medical Center, Boston, MA; 3Harvard Medical School, Boston, MA; 4Institute of Inherited NC; 5Trinity Health Kidney Centre, Dublin, Ireland

Background: Autosomal dominant tubulo-interstitial kidney disease (ADTKD) due to MUC1 mutations is caused most commonly by a single cytosine insertion within the variable number of tandem repeat (VNTR) region of the MUC1 gene. 30 families have been reported with this condition to date, with considerable variation in the observed age of onset of end stage renal disease (ESRD). We have reevaluated these clinical findings in a larger cohort of families.

Methods: MUC1 mutational analysis was carried out through an assay designed by a single cytosine insertion within the variable number of tandem repeat (VNTR) region of the MUC1 gene (Glu315). Comparisons were made between these and all other combinations (n = 28).

Results: Twenty males and 18 females were diagnosed with FLD at an age of 38 ± 14 yrs. Three genotypic mutations in LCAT were identified: p.R269H, p.T298I and p.1272F, corresponding to distinct disease clusters. All patients had HDL < 100mg/dL, ApoAI 40 ± 10mg/dL. Corneal opacities were seen in 36 cases; Scheimpflug densitometry revealed high corneal density in all 3 evaluated individuals. Anemia was present in 25 cases (Hb of 10.7 ± 2 g/dL) and hemolysis in 27. Increased resistance of red blood cells to osmotic stress was observed in all 5 evaluated patients. Estimated glomerular filtration rate (eGFR) displayed high intra- and interfamilial variability; 7 patients developed ESKD at an age of 38. ± 14 yrs. Protein/creatinine ratio was 0.54 ± 0.12 (p25-75: 0.12-1.77) in nondiabetic cases; 9 of 21 had hematuria. C3 was low in 1 patient while C4 was normal in all. Hypertension, present in most cases, was associated with age≥ 30 yrs and eGFR < 33mL/min/1.73m2 (OR 15.5). Coro...

Conclusions: The renal phenotypic variability suggests that environmental and/or genetic factors may modify CkD progression in FLD. Our findings suggest that, in addition to cholesterol deposition, TMA and C3 mesangial deposits may also contribute to renal injury, supporting a pathogenic role for activation of the alternative complement pathway.

Funding: Government Support - Non-U.S.

SA-PO601

Kidney Outcome in Primary Hyperoxaluria Type 3 Mary L. McIntosh,1 Peter C. Harris,2 Ramila A. Mehta,2 Julie B. Olson,3 Barbara M. Seide,4 Felicity T. Enders,4 David J. Sas,5 John C. Lieske,5 Dawn S. Milliner,6 Mayo Clinic, Rochester, MN; 7Mayo Clinic, Rochester, MN, Rochester, MN, Rochester, MN; Group/Team: Rare Kidney Stone Consortium.

Background: Primary hyperoxaluria type 3 (PH3) is caused by HOGA1 gene mutations. Little is known of the mechanism of hyperoxaluria, long term outcome, or genotype effects.

Methods: PH3 patients were identified (n=47) from the Rare Kidney Stone Consortium (RKSC) PH Registry and categorized by HOGA1 mutations. In addition to demographics and baseline laboratory data, eGFR and urinary oxalate (Uox) were compared at diagnosis (dx) and last followup (f/u). Comparisons between groups were by Chi-square test for categorical variables and Kruskal-Wallis test for continuous variables.

Results: Most frequent mutations were the splicing change p.Leu233_Gly234ins17, n=10 homozygotes (Leu233), and the infrared deletion p.Glu315del, n=9 homozygotes (Glu315). Comparisons were made between these and all other combinations (n = 28). Among PH3 overall, eGFR declined with age (r=−0.3, p < 0.0001). Among patients < 20 yrs of age, median eGFR at dx for Leu233 was 125.3 ml/min/1.73m2 vs. 115.7 in Glu315 and 83.9 in all others (p=0.057). There were no significant differences among genotype groups for age at dx or f/u yrs [median 4.5(1,11.7)]. There was a trend toward lower Uox and higher eGFR in the Leu233 group at dx and at f/u, though statistically significant only for Uox at f/u (p=0.02) and eGFR at dx (p=0.047). Urine HOG did not correlate with urine glycerine in PH3 overall (r=−0.3, p<0.12).

Conclusions: PH3 patients show decreasing eGFR over time. Lower Uox and higher eGFR trends were seen in Leu233 homozygotes, though patient numbers were small. HOGI suppression of GRHPR as a mechanism for the hyperoxaluria, predicted to elevate d-glycerate, is not supported by this data. Further study is needed to understand genotype effects and outcome of PH3.

Funding: NIDDK Support, Other NIH Support - NCATS, Private Foundation Support

SA-PO602

KEOPS Complex Dysfunction Causes Nephrotic Syndrome by Impairing Protein Biosynthesis and by Inducing ER Stress

Jia Rao,1 Geraldine Mollet,2 David Schapiro,3 Weiwen Tan,1 Jennifer Hu,6 Peter Deden,1 Herman Van tilbeurgh,2 Martin Zenker,4 Corinne Antinacig,5 Friedrich Hildebrandt,1 1Boston Children's Hospital, HMS, Boston, MA; 2Immunize Institute, Paris, France; 3Inserm U1163, Paris, France; M; 4Memorial Sloan-Kettering Cancer Center, New York, NY; 5Cambridge, MA; 6Mayo Clinic Hospital, Rochester, MN; 7University Hospital Magdeburg, Magdeburg, Germany; 8University Paris Sud CNRS UMR9198, Orsay, France.

Background: Steroid resistant nephrotic syndrome (SRNS), a disease of glomerular podocytes, is a frequent cause of end-stage renal disease in children and young adults. Identification of single-gene causes of SRNS has contributed to a better understanding of podocyte biology. In 32 unrelated families, we recently identified mutations in genes encoding the evolutionarily highly conserved KEOPS complex (LAGE3, OSGEP, TP53RK, and TPRKB) as novel monogenic cause of SRNS and microcythemia. The KEOPS complex catalyzes an essential posttranscriptional modification of tRNA. Methods: To characterize the pathogenesis of the four newly recognized human disease genes, we measured RNA modifications by mass-spectrometry, assessed protein biosynthesis in vitro, and performed immunoblotting of ER stress marker proteins.

Results: We show that shRNA knockdown of OSGEP or TPRKB in human podocytes reduced the cellular content of 6A, a specific posttranscriptional modification of RNA. Using a yeast system, we demonstrate that human mutations of OSGEP identified in patients with SRNS, alter the 6A-related catalytic activity of the encoded protein. We furthermore found that knockdown of OSGEP, TP53RK, or TPRKB inhibited de novo protein biosynthesis and activated the unfolded protein response in human podocytes, thus indicating the presence of ER stress. Knockdown of either of the three genes induced apoptosis in human podocytes, suggesting a central role in the pathogenesis of SRNS in patients with mutations in KEOPS complex genes.

Conclusions: Studying the pathogenesis of the four newly recognized monogenic causes of SRNS will generate evidence to support the altered function of the KEOPS complex results in podocyte damage by impairing the rate and the accuracy of protein biosynthesis, and perform immunoblotting of ER stress marker proteins.

Funding: NIDDK Support, Government Support - Non-U.S.
SA-PO603
Analysis of 24 Genes Reveals a Monogenic Cause in 11% of Cases with Steroid Resistant Nephrotic Syndrome at a Single Center Weiss Ten,1 Svjetlana Lovric,1 Shazia Ashraf,2 Jia Rao,1 David Schaprio,3 Merlin Arick,3 Shirlee Shril,1 Heon Yung Gee,3 Michelle A. Baum,2 Ghaleb H. Douk,1 Michael A. Ferguson,1 Nancy M. Rodig,1 Michael J. Somers,1 Deborah R. Stein,1 Asst. Vivian,2 Jillian K. Warkejo,2 Eugen Widmeier,1 Friedhelm Hildebrandt,1 1Boston Children’s Hospital, Boston, MA; 2Hanover Medical School, Hannover, Germany; 3University of Pittsburgh, Pittsburgh, PA.

Background: Steroid resistant nephrotic syndrome (SRNS) is the second most frequent cause of end stage renal disease (ESRD) among patients manifesting <25 years of age. We performed mutation analysis using a high-throughput PCR-based microfluidic technology in 24 single-gene causes of SRNS in a cohort of 72 families, who manifested with steroid resistant nephrotic syndrome before the age of 25 years.

Results: We identified an 18 month old who obtained DNA samples, pedigree information, and clinical information from 77 consecutive children with SRNS from 72 different families seen at Boston Children’s Hospital (BCH). Mutation analysis was completed by combining high-throughput multiplex PCR with next-generation exome sequencing. We analyzed the sequences of 18 recessive and 6 dominant genes of SRNS in all 72 families for disease causing variants.

Results: Results: We identified the disease causing mutation in 8 of 72 (11.1%) families. Mutations were detected in the 6 genes: NPHS1 (2/72), WT1 (2/72), and in NPHS2, MOYo1, TP53C9, and IN2. Median age of onset was 4.1 years in patients with a mutation (range 0.5-18.8), and 3.2 years in those where the causative mutation was detected (range 0.1-14.3). Dominant mutations in dominant genes presented with a median onset of 4.5 years (range 2.4-14.3). Mutations in recessive genes presented with a median onset of 0.5 years (range 0.1-3.2).

Conclusion: Our molecular genetic diagnostic study identified the underlying monogenic cause of steroid-resistant nephrotic syndrome in ~11% of patients with SRNS using a cost effective technique. We delineated some of the therapeutic, diagnostic, or prognostic implications. Our study confirms that genetic testing is indicated in pediatric patients with SRNS.

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

SA-PO604
Clinical and Molecular Analysis of 17 Families with a Heterozygous Mutation in COL4A3 or COL4A4 Jeroen Deegens,1 Jeroen Schoots,1 Jack F. Wetzels,1 Dorien Lugtenberg,1 Jeroen Van den Berg,2 Jia Rao,1 Eugen Widmeier,1 Friedhelm Hildebrandt,1 1Boston Children’s Hospital, Boston, MA; 2Hanover Medical School, Hannover, Germany; 3University of Pittsburgh, Pittsburgh, PA.

Background: Heterozygous mutations in COL4A3 and COL4A4 (COL4A3/4) have been described as a cause of Alport syndrome and benign familial hematuria. Recently, these mutations were associated with focal segmental glomerulosclerosis (FSGS) and renal function deterioration as well. The aims of this study are 1) further delineation of the phenotypic spectrum of heterozygous COL4A3/4 variants, and 2) to investigate whether these mutations in NPHS2 (R229Q / R138Q) and NEPH3 (V353M) modify the phenotypic expression of COL4A3/4 mutations.

Methods: Patients with a heterozygous mutation in COL4A3/4, detected by diagnostic exome sequencing, were included. All exome gene panel variants were reviewed. COL4A3/4 and FSGS were evaluated.

Results: Of 72 patients analyzed because of a familial glomerular disease, a heterozygous mutation in COL4A3/4 was found in 17 (24%). All patients had microscopic hematuria at clinical presentation and 14 had (micro)albuminuria, including two patients with nephrotic range proteinuria (1.7 and 6.2 g/24h). Median age at presentation was 43 years (range 4-45). Renal biopsy in ten index patients showed FSGS (n=3), TBMN (n=1) and (rare) membrane thickening and lamellation of tubular basal membranes. Known responsible genes are COL4A3/4 (COL4A3/4) have also been associated. Despite a recent genome-based diagnosis, the clinical characteristics and diagnostic criteria of various ADTKD subgroups remain to be defined.

Conclusion: Our molecular genetic diagnostic study identified the underlying monogenic cause of steroid-resistant nephrotic syndrome in ~11% of patients with SRNS using a cost effective technique. We delineated some of the therapeutic, diagnostic, or prognostic implications. Our study confirms that genetic testing is indicated in pediatric patients with SRNS.

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

SA-PO606
Clinical Gout Separates ADTKD-MUC1 from ADTKD-UMOD in a Large International Registry Eric G. Olinger,1 Kendra O. Kidd,1 Anna Greka,2 Sven Moller,3 Anthony J. Bleyer,4 Olivier Devuyst,5 1Harvard Medical School, Boston, MA; 2Institute of Inherited Metabolic Disorders, Prague, Czech Republic; 3University of Zurich, Zurich, Switzerland; 4Wake Forest School of Medicine, Winston-Salem, NC.

Background: Autosomal dominant tubulointerstitial kidney diseases (ADTKD) comprise a group of rare disorders characterized by progressive CKD with interstitial fibrosis and tubular atrophy. ADTKD is genetically heterogeneous: mutations in UMOD are mainly involved but MUC1, HNF1B and REN have also been associated. Despite a recent genome-based diagnosis, the clinical characteristics and diagnostic criteria of various ADTKD subgroups remain to be defined.

Methods: In an international effort, 463 families diagnosed with ADTKD were included in a comprehensive registry. Index cases were screened for UMOD mutations, followed by MUC1, HNF1B and REN mutations in UMOD-negative families.

Results: We detected mutations in UMOD in 181 families (39.1%). Among the UMOD-negative families, 20.3% screened positive for MUC1, 12.5% positive for HNF1B and 1.8% positive for REN mutations. 107 mutations were detected in UMOD, all missense except 7 small indels, with 90% clustering in exon 3 and 56% involving cysteine residues. All MUC1 families displayed cytosine insertion in the VNTR region. Point mutations, small indels and large genomic rearrangements were reported in HNF1B. Clinical gout was more prevalent in ADTKD-UMOD cases compared to ADTKD-MUC1 (58% vs. 17% of cases respectively, p<0.001, OR 3.66) and was more frequent at onset (29.0±12.7 vs. 43.3±14.2 years; p<0.0001). A family history (FH) of CKD and gout was reported in 66% of ADTKD-UMOD cases contrasting with a predominant FH of isolated CKD in 84% of ADTKD-MUC1. FH of CKD with gout separates ADTKD-UMOD from ADTKD-MUC1 (p<0.0001; PPV: 9.8%).

Conclusions: Mutations in UMOD and MUC1 are the leading genetic causes for ADTKD. Personal or familial history of clinical gout and early age of gout onset are specifically associated with ADTKD-UMOD inside this group of disorders. This international registry will help to identify modifying genes and biomarkers in ADTKD subgroups and to test future interventions.

SA-PO607
Identification of a New Mutation Mapping in the Renin Mature Protein Associated with Autosomal Dominant Tubulo-Interstitial Kidney Disease Celine Schaefer,1 Claudia Izzii,2 Gianfranco Savoldi,2 Elena Pasqualotto,1 Gianluca Caridi,1 Antonio Amoroso,2 Luca Rampoldi,1 Francesco Scolati,1 San Raffaele Scientific Institute, MILAN, Italy; 2Montichiari Hospital, ASST, Montichiari (Brescia), Italy; 3Gaissini Institute, Genova, Italy; 4University of Torino, Torino, Italy.

Background: Autosomal dominant tubulo-interstitial kidney diseases (ADTKD) is a renal disorder characterised by interstitial fibrosis, tubular atrophy and dilation, and thickened tubulointerstitial and lamellation of tubular basal membranes. Known responsible genes are ADTKD-UMOD (uromodulin), MUC1 (mucin 1), HNF1B (HNF1beta), REN (renin) and SEC61A1 (Sec 61 translocon alpha 1 subunit). ADTKD-REN is usually characterised by early onset, anaemia during childhood, hyperkalaemia and mild hypotension. All ADTKD mutations in renin so far reported are located in the leader peptide of the protein (aa 2-23; exon 1), affecting its co-translational insertion in the endoplasmic reticulum (ER).

Methods: Whole exome sequencing was performed on 3 sibs (affected and healthy) of a pedigree with suspected ADTKD of unknown origin that tested negative for

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

835
UMOD, HNF1B and REN (exon 1). A variant was found in REN (exon 10) and confirmed by Sanger sequencing. The frequency of such variants is determined by expression in cell culture and population genetic studies (ExAC, gnomAD). Interestingly this variant maps in mature renin and is predicted to be damaging (Polyphen, SIFT, SDM). Functional studies in HEK293 and AT20 cell lines showed that L381P renin is fully retained in the ER and not secreted into the culture medium. This likely due to abnormal protein folding. The retention ER stress is due to the interaction of mutant protein with wild type renin does not interfere with wild type renin trafficking and secretion.

**Conclusions:** These results suggest that the spectrum of REN mutations associated with renal disease is broader than previously thought in patients complaining of proteinuria. ADTKD diagnosis should not be limited to exon 1. Interestingly, the possible mechanism of pathogenesis associated with the P381L mutation, i.e. ER stress and reduced secretion, is likely to be similar to the one proposed for already described mutations in the leader peptide.

**SA-PO608**

Diet-Dependent Development of CKD in a Mouse Model of Cystinuria

**Type 1 Lauren E. Woodard,1,2 Rick C. Welch,1 Ruth A. Veach,1 Thomas M. Beckerman,1 Feng Sha,1 Talat Alp Ikizler,1 Jay A. Tischfeld,3 Amirik Sahota,2 Matthew H. Wilson,1,4 Veterans Affairs, Tennessee Valley Healthcare System, Nashville, TN; 2Vanderbilt University Medical Center: Nashville, TN; 3Medicine, Division of Nephrology, Vanderbilt University Medical Center, Nashville, TN; 4Genetics, Rutgers University, Piscataway, NJ.

**Background:** Cystinuria type I results from mutation of SLC3A1 and is a disorder of renal amino acid transport, resulting in recurrent nephrolithiasis and significant morbidity. It is one of the most common autosomal recessive genetic disorders in humans with an incidence in the United States of 1 in 15000. Using two diets, we compared the rate of stone and chronic kidney disease development in Slc3a1 knockout mice.

**Methods:** In a mouse model of cystinuria type I, mice lacking the gene had increased basic amino acids in their urine and developed cystine stones. Mice were supplied with either a normal or breeder chow diet and allowed to age for approximately one year. Both male and female mice were included in the study. Result showed that the Slc3a1 knockout mice that were aged on a breeder containing higher levels of cystine had more severe chronic kidney disease as indicated by both elevated BUN and serum creatinine. Additionally, we observed lower cystine levels in the liver and glutathione (GSH) levels in the liver.

**Results:** When placed on a normal diet, aged Slc3a1 knockout mice had an elevated blood urea nitrogen (BUN) and normal serum creatinine. Slc3a1 knockout mice that were aged on a breeder diet containing higher levels of cystine had more severe chronic kidney disease as indicated by both elevated BUN and serum creatinine. Histologic analysis also revealed a greater degree of kidney and bladder injury in aged mice maintained on a breeder diet than in those maintained on a normal diet. Additionally, we observed lower cystine levels in the blood of knockout mice. The availability of cystine, which forms cystine when two molecules are joined together, is a major determinant of the regulation of GSH synthesis. We found that glutathione levels in the liver were reduced in Slc3a1 knockout mice.

**Conclusions:** These results suggest that diet can modulate the severity of kidney disease that developed over time in an animal model of cystinuria and may have implications for the potential to modulate disease severity in cystinuric patients. Additionally, we observed lower cystine levels in the blood of knockout mice. The availability of cystine, which forms cystine when two molecules are joined together, is a major determinant of the regulation of GSH synthesis. We found that glutathione levels in the liver were reduced in Slc3a1 knockout mice.

**SA-PO609**

Macrophage Enzyme Chitotriosidase Reflects Long-Term Cystine Accumulation in Cystinosis

Mohamed A. Elmonem,1,2 Koenaan Veys,3 Maria Van dyck,4 Mirian C. Janssens,5 Elisabeth A. Cornillissen,1 Elena N. Levchenko,1 Radboud University Medical Centre, Nijmegen, Netherlands; 2Laboratory of Pediatric nephrology, University Hospital Leuven, KU Leuven, Leuven, Belgium; 3University Hospitals Leuven, Leuven, Belgium; 4Department of Developmental Biology and Chemical Pathology, Faculty of Medicine, Cairo University, Cairo, Egypt; 5Radboudumc university Medical centre, Nijmegen, Netherlands.

**Background:** Cystinosis is an autosomal recessive lysosomal storage disorder characterized by early renal damage. Strict compliance to the cystine depleting agent cysteamine is necessary for more efficient treatment. Leucocyte cystine is the current therapeutic monitor. Although highly specific, its use is hindered by many technical difficulties and its availability in only few laboratories. Recent evidence suggests that inflammatory cells play a major role in the pathogenesis of cystinosis and its rapid progression to ESRD. Macrophage activation markers, such as chitotriosidase and several cytokines have been linked to disease severity and response to cysteamine therapy in cross-sectional studies. Previous studies aimed to assess the level of HNF-1β in control and patients with potential therapeutic monitors in a large cohort of cystinosis patients.

**Methods:** Fifty four patients (19 children and 35 adults) were recruited from the cystinosis clinics in Leuven (Belgium), Nijmegen (Netherlands) and Traunstein (Germany). Patients were followed-up for two years during which, clinical and laboratory data were regularly collected from hospital records. Every three months, plasma samples were obtained to analyze chitotriosidase and other cytokines. These markers were correlated with leucocyte cystine concentration and with other parameters of renal disease such as proteinuria and GFR. The results of such variables and correlation were expressed by expression in cell culture.

**Results:** Patients cystinosis showed large variation in compliance/response to cysteamine therapy. Average leucocyte cystine concentrations over two years ranged from 0.65 to 5.8 mmol ½ cystine/mg protein. During the first year of the study, plasma cytokine activities ranged from 2 to 834 mmol/ml plasma/h in cystinosis patients (reference range <55 mmol/ml plasma/h). Chitotriosidase activities correlated with individual cystine measurements (r=0.432, P<0.002). More importantly, the correlation was stronger with the average cystine values (r=0.582, P<0.001).

**Conclusion:** The chitotriosidase activity correlates with long-term cystine concentrations and can be used for the therapeutic monitoring of cysteamine therapy in nephropathic cystinosis.

**Funding:** Commercial Support - Raptor pharmaceuticals
be expanded to other rare diseases, accelerating mutational analysis for therapeutic interventions.

Funding: Commercial Support - IBM

SA-PO612
Pharmacologic Chaperone Responsiveness in Canadian Patients with Fabry Disease Michael L. West,1 Daniel G. Bichet,2 Sandra Simr,3 Dalhousie University, Halifax, NS, Canada; 1University of Montreal, Montreal, QC, Canada; 2Vancouver General Hospital, Vancouver, AB, Canada. Group/Team: Canadian Fabry Disease Initiative Research Group.

Background: Fabry disease (FD) is an X-linked lysosomal storage disease due to deficiency of the enzyme α-galactosidase. This results in premature death from renal failure, hypertrophic cardiomyopathy and strokes. Treatment with intravenous enzyme replacement therapy (ERT) is expensive and not curative. Pharmacologic chaperone therapy is considered in these patients with liver involvement, increases residual enzyme activity by stabilizing the molecule and delivering more enzyme to the lysosome. Recent data suggests that some patients on ERT may derive additional benefit from PCT. We report the prevalence of chaperone responsiveness in Canadian Fabry disease patients as a guide to planning future therapy.

Methods: The Canadian Fabry Disease Initiative (CFDI) is a registry of 466 FD patients followed for up to 10 years. All known GLA gene mutations in CFDI patients were evaluated using a published library of chaperone responsive mutations based on a good laboratory practice-validated HEK cell assay (Benjamin et al Genetics in Medicine 2017;19:430-8).

Results: The majority of Canadian patients with FD are enrolled in the CFDI with ascertainment of 92%. Over 95% have been genotyped. We evaluated 404 FD patients with 143 males, 261 females, mean age 45.0±17.8 (sd), range 8-86 years. ERT use under Canadian Fabry Treatment Guidelines was 50%. Chaperone responsiveness mutations (n=257) were detected at 50% (p=0.001, 95.6%; half were receiving ERT. Non-responsive mutations (n=67) were found in 318 patients (78.7%); missense 53%, deletion/insertion 26%, stop codon 13%, duplication 3%, intronic 3%, frame shift 2%. Patients harboring chaperone responsive mutations had classic FD phenotype in 72.1%, vs. non-variant (P<0.05) where 23% had RTA.

Conclusions: Oral PCT could be currently used in about one fifth of the Canadian FD population. Only half of those patients meet the current Canadian FD treatment guidelines for ERT suggesting that introduction of chaperone therapy would potentially only offer a change of treatment in a maximum of 40% (10%) FD patients in Canada. These data will help plan future therapy.

Funding: Commercial Support - Amicus, Shire

SA-PO613
We Propose a Single Heterozygous Mutation in ATP6V0A4 as a Novel Genetic Cause of Fabry Disease Takayasu Mori,1 Motoko Chiga,1 Takuya Fujimaru,1 Shintaro Tatemitsu,2 Daniel G. Bichet,1 and Hiroshi Mandai1

Background: We recently reported the development of a comprehensive diagnostic panel using next-generation sequencing (NGS) for 166 genes responsible for inherited kidney diseases. Over 95% have been genotyped. We evaluated 404 FD patients with 143 males, 261 females, mean age 45.0±17.8 (sd), range 8-86 years. ERT use under Canadian Fabry Treatment Guidelines was 50%. Chaperone responsiveness mutations (n=257) were detected at 50% (p=0.001, 95.6%; half were receiving ERT. Non-responsive mutations (n=67) were found in 318 patients (78.7%); missense 53%, deletion/insertion 26%, stop codon 13%, duplication 3%, intronic 3%, frame shift 2%. Patients harboring chaperone responsive mutations had classic FD phenotype in 72.1%, vs. non-variant (P<0.05) where 23% had RTA.

Conclusions: Oral PCT could be currently used in about one fifth of the Canadian FD population. Only half of those patients meet the current Canadian FD treatment guidelines for ERT suggesting that introduction of chaperone therapy would potentially only offer a change of treatment in a maximum of 40% (10%) FD patients in Canada. These data will help plan future therapy.

Funding: Commercial Support - Amicus, Shire

SA-PO614
Whole Exome Sequencing Frequently Detects a Monogenic Cause in Early Onset Nephrolithiasis and Nephrocalcinosis Anchana Daga,1 Amar J. Majmudar,2 Jennifer A. Lawson,3 Shirlee Shril,4 Daniela A. Braun,4 Michelle A. Baum,1 Friedhelm Hildebrand,2 1Boston Children Hospital, Boston, MA; 2Boston Children’s Hospital, Somerville, MA; 3Boston Children’s Hospital, Boston, MA; 4Boston Children’s Hospital, Boston, MA; 5University of Connecticut School of Medicine, Farmington, CT; 6Nephrology, Boston Children’s Hospital, Boston, MA.

Background: The incidence of Nephrolithiasis (NL) continues to rise. We previously detected a monogenic cause of NL in 20% of patients manifesting before the age of 25 years, and recently confirmed this high rate of monogenic causation (17%) in a pediatric cohort of patients by using a gene panel sequencing approach containing 30 known NL genes. We here employ whole exome sequencing (WES) rather than panel sequencing to identify monogenic causes of NL and/or nephrocalcinosis (NC).

Methods: Patients who had a history or renal ultrasound finding of at least one renal stone (NL) or NC before age 25 years were enrolled between 1/2014 to 12/2015. WES was performed on 51 families (65 affected individuals), and evaluated for causative mutations in 30 NL/NC genes. Deletiousness of mutations was evaluated by pathogenicity prediction scores, evolutionary conservation, and prior reporting status of mutations.

Results: 63% were males, and the median age at presentation was 6 years (Range: 1 mo – 24 years). Of the 65 individuals, 32 had isolated NL, 22 had isolated NC, and 11 had both NL and NC. We detected a causative mutation in 15 out of 51 (29.4%) families. We detected a mutation in 7 recessive genes (AGXT, ATP6V1B1, CLDN16, CLDN19, GRB10, SLC3A1, SLC12A1), in 1 dominant gene (SLC34A1), and in 1 gene (SLC34A1) with both recessive and dominant inheritance. 7 of the 19 different mutations were not previously described as disease causing. Median age of onset was significantly lower in patients in whom we detected a monogenic cause of NL/NC (3 yrs) vs. those without mutation detection (7 yrs) (p < 0.05). In one family we detected a causative mutation in a new gene (CPNS) that encodes a heat shock protein. Chaperone responsive mutations associated monogenic traits. In several factors that correlated with higher detection rate were younger age of onset of NL/NC (58%), presence of multiple affected in a family (41%), and presence of consanguinity (75%). In 9 of 15 families the genetic diagnosis led to specific implications for future clinical management and prevention of stone recurrence.

Conclusions: Thus, we established WES as an efficient approach towards a molecular genetic diagnosis in individuals with NL/NC who manifest before 25 years. Specific genetic diagnosis holds potential for personalization of the treatment plan.

SA-PO615
Mutational Burden in Monogenic Glomerular Kidney Disease Genes in Adult CKD Patients Jennifer A. Lawson,1 Shirlee Shril,2 Daniela A. Braun,1 Michelle A. Baum,1 Friedhelm Hildebrand,2 1Boston Children Hospital, Boston, MA; 2Boston Children’s Hospital, Somerville, MA.

Background: Monogenic kidney diseases often show severe manifestations in childhood (recessive) or mid-age (dominant traits). Conversely, moderate chronic kidney disease (CKD) in adults is often regarded a complex disease with a genetic predisposition. The contribution of mutations in monogenic kidney disease genes in adult CKD patients and the combined effects of rare variants and common susceptibility alleles are understudied.

Methods: 341 participants of the German Chronic Kidney Disease study (inclusion criteria CKD stages G1-G3 or A3 with biopsy-proven primary glomerular disease) underwent next-generation gene panel sequencing (Illumina MiSeq) of 37 glomerulopathy-associated monogenic traits. Read alignment and variant calling followed GATK best practices and incorporated consensus calling. Variants were annotated using VEP/SNPeff and filtered using GEMINI based on frequency, predicted impact and clinical relevance to determine putative deleterious outcomes.

Results: At present, data are available for 202 patients. Definite pathogenic mutations were identified for 12 patients (median age 44 yr, eGFR 49 ml/min/1.73m2, UACR 357 mg/g, 67% FSGS) in genes with dominant inheritance mode (4 in COL4A5, 2 in PAX2, and 1 each in GLA, INF2 and WT1) and 3 compound heterozygous variants in NPHS2. In addition, 21 individuals carried plausible pathogenic variants (in ACTN4, ANLN, ARHGAP24, COL4A5, CRB2, GLA, LMxb1, PAX2, TRPC6, TCTC2B and WT1). Within the next weeks, sequencing and evaluation of atypical presentations and extra-renal manifestations as well as integration with common susceptibility alleles from GWAS will be completed.

Conclusions: About 5% of adult patients selected for CKD stages G1-G3 or A3 and with presumed primary glomerular etiology carry pathogenic mutations in monogenic glomerular disease genes. Another 10% carry plausible pathogenic variants. Evaluating rare mutations together with common CKD susceptibility variants may provide further insights into their combined impact and contribution to atypical presentations and a mild disease course.
SA-PO616

The Comprehensive Gene Screening for Congenital, Infantile, and Steroid Resistant Nephrotic Syndrome in Japan

Keita Nakashi,
Kandai Nozu,
Junya Fujimura,
Shogo Minamikawa,
Yoko Shimaya,
Koichi Nakasui,
Kazumoto Iijima,
Dept. of Pediatrics, Kobe Univ. Graduate School of Medicine, Kobe, Japan;
Graduate School of Medicine, University of the Ryukyus, Nishihara-cho, Japan;
Kobe University, Kobe, Japan;
Kobe University Graduate School of Medicine, Kobe, Japan;
None, Kobe, Japan;
Wakayama Medical University, Wakayama City, Japan.

Background: Cases with congenital nephrotic syndrome (CNS), infantile nephrotic syndrome (INS) or steroid-resistant nephrotic syndrome (SRNS) frequently progress to end stage renal disease (ESRD). It has been reported that about thirty percent of CNS/INS/SRNS patients possessed single causative gene variants in podocyte related genes that were detected by next generation sequencing. It has been revealed CNS/INS/SRNS patients with gene defects show severe renal prognosis; however, those patients seldom show recurrence of nephrotic syndrome after kidney transplantation. Thus, we established a gene screening system for CNS/INS/SRNS patients in their early stages, to suggest their clinical courses.

Methods: The gene screening system by targeted sequencing for 45 podocyte related genes that have been reported as causative genes for CNS/INS/SRNS was established. Newly diagnosed patients as CNS/INS/SRNS were recruited between January in 2016 and May in 2017.

Results: In total, 84 patients from 42 hospitals in Japan were screened. We detected causative genes in 25 patients (30%). The most frequent gene was WT1 (4 patients), and other genes were LAMB2 (3 patients), ADCK4, TRPC6, LMX1B, INF2, NUP107 (2 patients each), and so on. None of our cases possessed NPHS2 gene variants, which is the most common causative gene in European countries. Seven out of 25 patients progressed to ESRD, and only one patient who had TRPC6 variant had kidney transplantation and showed no recurrence of nephrotic syndrome. The cost of gene screening for one sample was about 250,000 (USD).

Conclusions: We have established a comprehensive gene screening system for CNS/INS/SRNS cases in their early disease stages in Japan and detected a single causative gene in 30% of our cohort. The variation of causative genes in Japan was different from those in other countries. The screening results will be used in deciding treatment and thereby help to improve the quality of life for patients.

SA-PO617

Quantifying Mendelian Genetic Disease in the Pediatric Renal Clinic

Yadvahan Upendran,
Fiona Mackie,
Rebecca A. Spicer,
Shah Kim,
Sean E. Kennedy,
Hugh J. Mccarthy,
Sydney Children’s Hospital, Randwick, NSW, Australia;
University of New South Wales, Sydney, NSW, Australia.

Background: With the advent of new sequencing technology, gene tests are more readily available to the nephrologist and increasingly cost effective. Planning is required to provide the same level of counseling for those now undergoing testing in the renal clinic compared to the clinical genetic clinic. The aim of this study was to determine the prevalence of disease with a likely genetic aetiology within the pediatric renal clinic.

Methods: An algorithm was configured to determine those with a possible Mendelian genetic aetiology to disease who could be offered gene testing. A retrospective review was then undertaken of new referrals to the renal clinic at a tertiary children’s hospital from 2012-2015 to determine the number of patients who would have then required genetic counseling.

Results: The algorithm identified risk as Inherited Glomerular (including steroid resistant or congenital nephrotic syndrome and Alport’s syndrome); Tubular or Metabolic disorders; Complement mediated disorders, Nephrocalcinosis/Sclerosis; Cystic Kidney Disease; Syndromic Congenital Anomalies of Kidney and Urinary Tract (CAKUT); other including familial not otherwise specified. Simple CAKUT was excluded due to low rate of identifiable genetic aetiology. In the total cohort, the mean age at presentation was 5.25 years and male to female ratio was 1.52. 173/751 (23%) patients so far analysed have showed no recurrence of nephrotic syndrome. The cost of gene screening for one sample was about 250,000 (USD).

Conclusions: The significant enrichment of pathway gene sets across SLE and its co-morbidities suggest that these diseases may share an underlying molecular architecture. Further analysis of these data may be able to guide treatment decisions when SLE is complicated by co-morbidities, or delineate gene expression signatures that could prompt focused screening of patients with SLE for relevant co-morbidities.

Funding: Government Support - Non-U.S.

SA-PO618

Integrative Analysis of Genome-Wide Transcriptome Data Sets Reveals Shared Biology Between Lupus and its Co-Morbidities

Thomas Oates,
Alan D. Salama.
University College London, London, United Kingdom.

Background: The autoimmune disease Systemic Lupus Erythematosus (SLE) is frequently complicated by co-morbidities such as cardiovascular disease and stroke. The biology of these disease associations are largely unknown but increased understanding may result from transcriptomic analysis of SLE and its co-morbidities.

Methods: 7 major co-morbidities of SLE were identified for analysis: chronic kidney disease, stroke, cardiovascular disease, osteoporosis, lung cancer, Hodgkin lymphoma, and viral infections. Transcriptomic datasets for these diseases available via the Gene Expression Omnibus were screened and those with over 30 subjects in a case-control design were retained for analysis. Previously described methods were used to explore SLE and the chosen co-morbidities at gene, pathway and disease level (PMID: 27842596). The methods used are statistically robust to the multiple-test corrections required in genome-wide experiments and the combination of results from several independent tests.

Results: 36 microarray datasets passed the filter criteria above. These contained expression data from 4,776 individuals (3,320 cases, 1,456 controls). Differentially expressed genes (DEGs) between cases and controls were calculated for each dataset and combined for all datasets per disease (see Figure row A). Next, enrichment of the DEGs per disease was examined in multiple reference pathways including the Kyoto Encyclopedia of Genes and Genomes (KEGG) (Figure row B). Combining P-values across the 8 studied diseases (Figure row C) delineated pathways that retained statistical significance for dysregulation in SLE and all co-morbidities (Figure Heatmap & blue text).

Conclusions: The deleted in malignant brain tumor 1 (DMBT1) gene is prone to copy number variation (CNV) that alters the number of bacteria-binding domains in 2 distinct gene regions (CNV1 and CNV2). DMBT1’s role in urinary tract functions (UTI) has not been previously evaluated.

Methods: RIVUR study children with UTI and vesicoureteral reflux treated with antibiotics vs. placebo were studied. Copy number estimates for CNV1 and CNV2 were determined using a paralogue ratio test (PRT). Experimental UTI was induced by transurethral inoculation of uraporphogenic E. coli (UPEC) into Dmbt1<sup>−/−</sup> vs wild-type mice. DMBT1-UPEC aggregation was evaluated by evaluating differential GEP expressing UPEC aggregation in the bottom of wells coated with DMBT versus control.

Results: DNA samples from 314 Caucasian children (159 in antibiotic prophylaxis group and 155 in the placebo group) were typed for DMBT1 CNV1 and CNV2. No higher copy number of CNV2 (but not CNV1) was associated with fewer infections (p<007), particularly in the prophylaxis group (Figure). Compared to wild type mice, Dmbt1<sup>−/−</sup> mice had 5-fold higher bladder bacterial burdens (cfu/bladder) at 6 hrs following following inoculation. DMBT1-UPEC inoculum and a 2.4-fold higher UPEC bladder burden at 6 hrs following a high (10<sup>4</sup> UPEC) inoculant; p values were 0.04 and 0.01 respectively. Kidney UPEC burdens were not different between Dmbt1<sup>−/−</sup> and wild-type mice. Additionally, DMBT1 protein, but not control resulted in bacterial clumping in our bacterial agglutination assay. Conclusion: Our results indicate that kidney with low copy number of DMBT1 CNV2 would benefit from antibiotic prophylaxis. Increased murine bladder bacterial burdens in Dmbt1<sup>−/−</sup> mice compared to wild type and increased UPEC agglutination with DMBT demonstrates it’s functional relevance in the innate immune defense against UTI.

Funding: NIDDK Support.
SA-PO620

Congenic Substitution to Uncover the Genetic Pathway of Hypertensive Renal Injury

Peter A. Doris,1 Michael C. Braun,1 John Hicks,1 Isba Dhande.3
1TCI/BCM, Houston, TX; 2UNIVERSITY OF TEXAS HOUSTON, Houston, TX; 3University of Texas Health Science Center at Houston, Houston, TX.

Background: The SHR-A3 line of the spontaneously hypertensive rat experiences progressive renal injury (RI). Susceptibility arises from natural genetic variation and contrasts with injury resistant SHR-B2. These two lines are 87% genetically identical. SHR-A3 has higher blood pressure (BP) than SHR-B2. We have mapped a locus responsible to an SMR block on chr17. Here we assess whether a congenic line (CL) in which this block is transferred from SHR-B2 into SHR-A3 experiences different levels of BP and RI than SHR-A3. The SHR-A3 and SHR-B2 genomes are most divergent in the immunoglobulin heavy chain (IgH). We created a CL substituting the SHR-B2 IgH locus into SHR-A3 and assessed the effect on BP and RI. Finally we have created a bicongenic (2CL) line containing both these SHR-B2 loci within the SHR-A3 background.

Methods: CLs were created by backcrossing using genetic markers to identify those regions of the genome at which SHR-A3 and SHR-B2 differ. Blood pressure was measured by telemetry. Renal injury was assessed histologically in paraffin-embedded tissue stained with Periodic acid-Schiffs stain.

Results: Congenic substitution of the chr17 locus was associated with a reduction in blood pressure to a level that was significantly below SHR-A3, but not different from SHR-B2. At 40wks of age, glomerular injury (GI) was indistinguishable in this CL from SHR-B2. Tubulointerstitial injury (TI) in the CL was intermediate, but significantly below SHR-A3. Congenic substitution of the IgH locus from SHR-B2 into the SHR-A3 background had no effect on BP. At 40wks, this CL also had GI indistinguishable from SHR-B2 and TI intermediate between SHR-A3 and SHR-B2. In the 2CL, GI and TI were both reduced to the SHR-B2 level.

Conclusions: RI in SHR-A3 appears to result from at least two genetic loci. One is an 8Mbase block on chromosome 17 that results in higher blood pressure in SHR-A3 than SHR-B2. The other is the immunoglobulin heavy chain, indicating that genetic variation in germ-line antibody sequences may contribute to the pathogenesis of renal injury in this model. The combined effect of these loci eliminates histologically assessed RI, resulting in animals that are 99.5% genetically identical to SHR-A3, but resistant to renal injury.

Funding: NIDDD Support, Private Foundation Support

SA-PO621

COLA3 Gene Variants Exacerbate Diabetic Kidney Disease: Genetic Investigation from Nine MODY Families

Yiting Wang,1 Junlin Zhang,2 Fang Liu.3 1Division of Nephrology, West China Hospital of Sichuan University, Chengdu, China; 2West China Hospital of Sichuan University, Chengdu, China.

Background: Despite the advances in the identification of genetic factors of diabetic kidney disease (DKD), much of the heritability for the clinical heterogeneity of DKD remains unexplained. In the study, DKD of nine probands who were suspected maturity-onset diabetes of the young (MODY) were reviewed and analyzed with Gene Ontology enrichment. The variants which have been reported to be associated with DKD, or MAF>0.05 and predicted to be pathogenic by software in susceptibility genes of DKD were selected.

Results: HNF1B-MODY, CEL-MODY, PAX4-MODY, and WFS1-MODY were identified among nine families. There were 174 selected variants of 25 susceptibility genes among all participants, quantity of selected variants in genes related to DKD were identified more in offspring, moreover, pathogenic variants in COLA3 genes were only identified in four probands but their MODY parents. Combined with analysis of gene function and Protein-Protein interaction network, we speculated the cumulative effect of susceptibility genes on the severity of DKD and identified the potential pathogenesis of COLA3 gene variants in aggravating the progression of DKD.

Conclusions: Pathogenic variants of COLA3 gene and cumulative effect of susceptibility genes exacerbate DKD.

Funding: Government Support - Non-U.S.

SA-PO632

Collagen VI Associates with Basal Membrane Defects in Alport Syndrome

Michael J. Randles,1 Franziska Lausecker,3 Paul K. Potter,2 Sara Falcone,2 Hani Suleiman,1 Jeffrey H. Miner,7 Rachel Lennon.7 1University of Manchester, Manchester, United Kingdom; 2Medical Research Council, Harwell, United Kingdom; 3Washington University, Saint Louis, MO; 4Washington University School of Medicine, Saint Louis, MO.

Background: Alport Syndrome is caused by genetic defects in COL4A3, COL4A4 or COL4A5, leading to inadequate assembly of the type IV collagen α3, α4, α5 network in basement membranes. In the glomerulus this causes irregularities in glomerular basement membrane (GBM) width and a characteristic basket weave appearance. We aimed to build our basic understanding about the glomerular extracellular matrix (ECM) in Alport syndrome and performed global analysis of composition and ultrastructural imaging in the both the Col4a3−/− and Col4a5−/− Alport mouse models.

Methods: Cellular and ECM fractions from wild type and Alport glomeruli at 6-8 and 16-18 weeks of age were analysed by mass spectrometry (MS) based proteomics. Imaging included serial block face-scanning electron microscopy (SBF-SEM) and stochastic optical reconstruction microscopy (STORM).

Results: MS analysis revealed moderate changes in the composition of glomerular ECM at 6-8 weeks, even prior to the onset of glomerular barrier dysfunction. These changes included complete absence of type IV collagen α3, α4, α5 in both mouse models and an upregulation of type IV collagen α1, α2, α6 and the interstitial type VI collagen. At 16-18 weeks more dramatic changes were detected including elevated type IV collagen α1, α2, fibronectin, type I collagen, laminin α2 and fibrinogen chains. Global and pathway analysis of cellular fractions indicated changes in actin regulating proteins at 6 weeks and mitochondrial dysfunction at 16 weeks. SBFSEM demonstrated thickened and irregular GBM with evidence of invading podocyte protrusions. Interestingly, STORM localised type VI collagen to GBM defects in Alport mice whereas collagen VI was absent from wild type controls.

Conclusions: Our data demonstrate that Alport syndrome progresses with distinct early changes in ECM followed by more profound ECM accumulation, disruption and a marked increase in type VI collagen in the GBM. Enhanced understanding about the pathways that control matrix deposition in glomerular disease may ultimately inform targeted strategies to correct or repair glomerular barrier dysfunction.

Funding: Government Support - Non-U.S.

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

Underline represents presenting author.
SA-PO625
Impact of High-Risk APOL1 Variants in Kidney Disease in South America
Cristian Riella,1 Tobias A. Siemens,2 Rodrigo P. Campos,3 Thyago P. Moraes,4 David J. Friedman,5 Miguel C. Riella,5 Martin R. Pollak.2
1Beth Israel Deaconess Medical Center, Boston, MA; 2Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA; 3Hospital Universitario Evangélico de Curitiba, Curitiba, Brazil; 4Pontaica Universidade Católica do Parana, Curitiba, Brazil; 5Nephrology, Federal University of Alagoas, Maceio, Brazil.

Background: The presence of apolipoprotein L-1 (APOL1) mutations is associated with increased risk of end-stage renal disease (ESRD) in African Americans. This effect has not been investigated in South Americans of African descent. In this study we analyzed APOL1 variants in dialysis patients and healthy controls with African descent in Brazil.

Methods: Inclusion criteria: dialysis patients 18 years of age or older who reportedly had African ancestry, first degree relatives were selected as controls. Exclusion criteria: individuals below the age of 18, history of obstructive uropathy, polycystic kidney disease, and known SLE or other vasculitic etiologies. After informed consent was obtained, clinical data along with blood samples for DNA extraction were collected. Genotyping was performed with a TaqMan RT-PCR assay for the wild type allele G0, and G1 and G2 risk alleles.

Results: 440 individuals were included in the study (271 patients and 169 controls). The frequency of high risk variants (G1,G2) was higher in dialysis patients than controls: one variant frequency was 17.7%(48) vs. 10.6%(18); two variants 12.2%(33) vs. 1.2%(2), respectively. In a multivariable logistic regression model, the presence of one risk variant was associated with a 4-fold increase in risk of ESRD (OR=3.95, p<0.002, CI=1.19-13.12), while carriers of two risk variants had a 21-fold increase in risk of ESRD (OR=21.66, p<0.001, 95% CI=4.13-113.51). After adjusting for comorbidities and other variables, patients with two risk alleles started dialysis 7.5 years earlier (Coef=7.5365, p=0.007) in a multivariable linear regression model. The analyses were adjusted for gender, comorbidity, smoking status, income and education level.

Conclusions: APOL1 mutations are a significant risk factor for the development of ESRD in South American individuals of African descent. The presence of two APOL1 risk alleles conferred up to 21-fold higher risk of ESRD and was associated with younger age at the start of dialysis.

SA-PO624
APOL1 Nephropathy Risk Variants and Incident Cardiovascular Disease Events in Community-Dwelling Black Adults
Orlando M. Gutierrez, Marguerite Irvin,1 Ninad S. Chaudhuri,3 Mary Cushman,4 Neil A. Zakai,5 Sophie Limou,6 Nathalie Pamar,6 Alex Reiner,6 Rakhil Naik,6 Michele Sale,6 Georgia W. Nelson,6 Monika M. Safford,6 Hyacinth I. Hacini,6 Suzanne E. Judd,6 Jeffrey B. Kopp,6 Cheryl A. Winkler.7 Aflac Cancer and Blood Disorder Center, of Children’s Healthcare of Atlanta, Atlanta, GA; 2Johns Hopkins, Baltimore, MD; 3NCI, NIH, Frederick National Laboratory, Frederick, MD; 4NIDDK, NIH, Bethesda, MD; 5NIH, Leidos Biomedical Research Inc, Nantes, France; 6Oregon Health and Science University, Portland, OR; 7NCH/Frederick/FNLC, Frederick, MD; 8UAB, Birmingham, AL; 9UAB School of Medicine, Birmingham, AL; 10University of Alabama at Birmingham, Birmingham, AL; 11University of Vermont, Colchester, VT; 12University of Virginia, Charlottesville, VA; 13Weil Cornell Medicine, New York, NY; 14University of Washington, Seattle, WA.

Background: APOL1 nephropathy risk variants are strongly associated with chronic kidney disease progression in Black adults, but associations with incident cardiovascular disease (CVD) are uncertain.

Methods: We examined associations of APOL1 risk variants with incident coronary heart disease (CHD,n=235), stroke (n=331), and a combined CVD end point (n=500) in 10,605 Black participants of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. Main analyses compared those with APOL1 high-risk nephropathy genotypes (2 risk variants) to APOL1 low-risk genotypes (0/1 risk variant) in Cox models adjusted for CVD risk factors and ancestry principle components.

Results: APOL1 high-risk participants were younger and more likely to have albuminuria than APOL1 low-risk participants. The risk of incident stroke, CHD or the composite CVD endpoint did not significantly differ between APOL1 genotype in multivariable models. However, the association of APOL1 genotype with the composite CVD outcome differed by diabetes status (P=0.01). In those without diabetes, high-risk genotypes were associated with higher risk of incident composite CVD than low-risk genotypes in fully adjusted models [table]. This association appeared to be driven by incident stroke risk. In contrast, the APOL1 high-risk genotype was associated with a trend towards lower risk of CVD in diabetics.

Conclusions: APOL1 high-risk genotypes are associated with higher incidence of CVD in individuals without diabetes, whereas the association appeared to be opposite among individuals with diabetes.

Funding: NIDDK Support, Other NIH Support - NINDS

SA-PO625
Clinician Attitudes Toward Use of APOL1 Genetic Testing in Clinical Practice
Ebele Umeokejie, Wylie Burke,2 Kerri L. Cavanaugh,3 Stephanie M. Fullerton,4 James G. Wilson,5 Bessie A. Young.6 Nephrology, Vanderbilt University Medical Center, Vanderbilt Center for Kidney Disease, Nashville, TN; 2Biophysics & Bioinformatics, University of Washington, Seattle, WA; 3Physiology & Biophysics, Medicine, University of Mississippi Medical Center, Jackson, MS; 6Nephrology, University of Washington, VA Puget Sound Health Care System, Kidney Research Institute, Seattle, WA.

Background: Apolipoprotein L1 (APOL1) high-risk variants are common among African Americans (AA) and are associated with a 7-10 fold higher risk of non-diabetic endstage renal disease (ESRD). However, there are gaps in knowledge regarding the clinical implication of APOL1 variants in patients with associated effects on risk in combination with co-morbidities or environmental exposures are not fully established. The objective of this study is to describe clinicians’ views of APOL1 genetic testing in clinical practice.

Methods: As part of an ongoing study of stakeholder views regarding APOL1 genetic testing in AA, we conducted key informant interviews with primary care (N=13) and nephrology (N=14) clinicians in Seattle WA, Nashville TN, and Jackson MS. Interviews assessed clinicians’ views about the use of APOL1 genetic testing in clinical care.

Results: Clinicians were recruited from different practice settings (63% in Academic centers; 26% in private practice; and 11% in the VA and other settings), and 78% of them provide care to a significant proportion of AA patients (a 25%). Dominant themes included possible increased monitoring and motivation of patients with risk factors (e.g. hypertension, family history) vs. possible over or under treatment, increased cost, stigmatization and increased psychological stress. Exemplar quotes: “In terms of getting people to change their lifestyles, for some people, having this risk might help that. It might just freak them out. I don’t really know. I think those are all – I think we’re in an uncharted territory clinically actually.” “We want to make sure we’re not drawing the data and not jumping to conclusions about when to apply something that may still be in the phase of further interpretation in the science.”

Conclusions: Our results suggest that clinicians hold uncertain views on the use of APOL1 testing to guide clinical practice. Further research is needed to determine the impact of testing on clinical outcomes especially in patients with ESRD risk factors.

Funding: Other NIH Support - NIH / National Human Genome Research Institute (NHGRI): 1R01HG00779-01A

SA-PO626
Nephrologists Treating C3 Glomerulopathy Patients Report Highest Clinical Utility by Using Gene Sequencing to Confirm a Diagnosis of C3G in Departure from C3G Consensus Report
Heino Stromness, Maehoon Diagnostics, Oakland, CA.

Background: C3 glomerulopathy (C3G) is a recent naming of a group of diseases and applies to MPGN Type II and III as well as C3 Glomerulonephritis [2]. In 2013, a C3 glomerulopathy consensus report was published with testing guidelines [1, 3]. We were curious about the degree to which physicians followed these guidelines and their impressions of the tests recommended in that report.

Methods: An anonymous survey titled “C3 glomerulopathy testing: A questionnaire for nephrologists” was sent via email to approximately 4,000 nephrologists.

Results: The C3 glomerulopathy consensus report recommended all suspected C3G patients receive testing for C3 Levels, C4 Levels, C3 Nephritic Factor, CFH Level, Serum paraprotein detection and screening for a CFHR5 mutation. Of the physicians who completed the first detailed section of the survey, 97% reported ordering C3 Levels, 93% had ordered C4 Levels, 69% had ordered CFH Levels and 76% had ordered C3 Nephritic Factor testing. For the self-identified experts, there were five tests seen as having “High Utility in C3G.” Those tests were C3 Level (67%), C4 Level (67%), CFH Nephritic Factor (67%), C4 Nephritic Factor (67%), CFHR5 mutation screen (83%).

Conclusions: The clinical value of gene sequencing (CFH, CFI, CD46, C3, FBG, DGKE, CFHR5), C3 Nephritic Factor and CFH antibody testing appears greater than the consensus report indicated. The importance of serum paraprotein detection (Serum Protein Electrophoresis, or SPEP) and the CFHR5 mutation screen may need to be further demonstrated to the field. Additionally, in a search for performing laboratories, we could not find a test which explicitly targeted the CFHR5 duplication referenced in the consensus report and so physician may not actually be screening for that specific mutation.

Funding: Clinical Revenue Support
SA-PO627
Attitudes towards Biosample Collection and Genetic Testing in a Racially Diverse CKD Population in Cleveland, OH
Jessica N. Cooke Bailey,1 Dana C. Crawford,1 Julie A. Pencak,1 Marlene Schachere,1 William S. Bush,1 John R. Sedor,2 John F. O’Toole,1 1Case Western Reserve University, Cleveland, OH; 2Case Western Reserve University, Cleveland, OH; 3MetroHealth Medical Center, Cleveland, OH.

Background: The NIH All of Us Research Program (AURP) is an ambitious national effort to longitudinally collect health data and biospecimens from a million Americans for storage, processing, and analysis in a government-funded data repository. Previous studies have suggested minority populations would be reluctant to share personal data and samples with the Federal government. We tested this premise in a population of chronic kidney disease (CKD) patients in Cleveland, OH.

Methods: Patients in a CKD clinic were approached prior to standard of care visit, asked to complete a structured 5 question bioethics and IRB-approved survey, and to provide blood sample for future genetic analysis.

Results: Most (86%) patients in the genetic study took the survey; 50% African American, 54% female, average age 61.5. Responses from 111 individuals indicate the majorization of inclinations in the AURP and were willing to send biosamples to a national repository and share de-identified data, but <50% of respondents were willing to install a phone app to track personal data. Most wanted results returned and 96% of those who did wanted personal (health or genetic) data returned; 41% wanted at least summary data about the PMI-CP cohort, 4% only summary data about the overall group, 76% at least personal health data, and 4% only personal health data. Genetic data was priority; 89% wanted at least personal genetic data while 19% wanted only personal genetic data. 10% did not want any results returned. We found no significant difference between responses when using African American and White individuals.

Conclusions: Attitudes of CKD patients in a diverse health care environment towards the AURP are varied but, in contrast to published data, did not differ across self-reported race (African Americans and Whites) in this sample. Willingness to participate in some aspect of a AURP-like project was high. Of those agreeing to the survey, almost all wanted return of genetic results. Given this demand, efficient processes should be developed to provide subjects with appropriate education and context for results return. Other chronic disease populations and healthy subjects need to be studied to determine if health status, race or ethnicity modifies willingness to join the AURP.

SA-PO628
Renal Biopsy Findings Precede Clinical Evidence of Renal Disease in Female Patients with Fabry Disease
Lucas A. Moura,1 Maria Eugenia Caranzani,2 Hugo Abensur,3 Valeria Veloso,3 Simone M. Lima,3 Marlene A. Reis,6 Nayze L. Aldeman,1 David G. Warnock,4 Agnes B. Fogo,5 1FEDERAL UNIVERSITY OF PIAUÍ, TERESINA, Brazil; 2Federal University of Sao Paulo, Sao Paulo, Brazil; 3Hospital do Rip de Hiripertensao, Sao Paulo, Brazil; 4UBAB, Birmingham, AL; 5Vanderbilt University Medical Center, Nashville, TN; 6Universidade do Estado de Sao Paulo, Sao Paulo, Brazil; 3hospital Universidade Federal de Goias, Goiania, Brazil; 4Medical Affairs, Saofo Genzyme, Sao Paulo, Brazil; 2Federal University of Triângulo Mineiro - UFTM, Uberaba, Brazil.

Background: Fabry nephropathy results from mutations in the GLA gene causing a deficiency in alpha-galactosidase and the accumulation of glycosphingolipids in kidney cells, proteurinaria and progressive loss of kidney function. The aim of this study was to describe renal biopsy findings in a Brazilian cohort of Fabry patients according to the ISCGFN Fabry renal pathology scoring system and correlate these findings to clinical and laboratory data.

Methods: Kidney biopsies, indicated based upon a family screening program, were retrieved from patient medical records.

Results: A total of 27 (14 male and 13 female) kidney biopsies from Fabry patients were analyzed. None of the patients had previously initiated enzyme replacement therapy. Males and females were the same age (34.7±10.8 vs. 36.8±18.4 y) and predominantly in CKD stage 1 (95%) and 2 (2%). Proteurinaria was significantly more pronounced in males compared to females (p<0.05). Renal biopsies in female patients showed histological alterations, particularly podocyte inclusions, even with proteinuria less than 200mg/24h and GFR greater than 60 ml/min/1.73 m2. There was no difference males vs females in vacuolization or inclusions in podocytes. Two of these patients had better preserved renal function than males, but still histological lesions, mainly podocyte inclusions, even though renal function was nearly normal. Renal histologic findings may be important factors to be considered when making therapeutic decisions for patients with Fabry disease.

Conclusions: Males with Fabry disease, even in early stage of CKD, showed substantially more interstitial fibrosis and inflammation than females. Females had better preserved renal function than males, but still histological lesions, mainly podocyte inclusions, even though renal function was nearly normal. Renal histologic findings may be important factors to be considered when making therapeutic decisions for patients with Fabry disease.

SA-PO629
Fabry Disease Prevalence in Kidney Transplant Patients: A Multicenter Study

Background: Higher prevalence of Fabry disease was reported in specific patient populations. To the best of our knowledge, a formal prevalence study was not conducted in kidney transplant (TX) recipients. We aimed to investigate the prevalence of Fabry disease in transplant recipients.

Methods: We performed a multicenter cross-sectional study in transplant centers. We also screened dialysis (D) patients to have comparative data. All adult patients were screened regardless of primary disease. Blood was collected for the measurement of alpha-galactosidase enzyme activity in males and for the screening of genetic mutations in females. Additionally, a genetic screening was performed in males with low alpha-galactosidase enzyme activity.

Results: We screened 2206 TX and 1442 D patients for a total of 3648 cases (mean age 48,9±15,7; 63,1%male). Data regarding study population are shown in Table 1. In the whole population, a total of 12 unique mutation were detected in 23 patients (0,63%) (15 with TX, 8 with D).

Conclusions: Our results have important implication regarding TX activity. First, in countries where living donation is common, donors are generally relatives of the patients. Therefore in those cases, screening for the genetic diseases that can lead to kidney failure is important. Second, recurrence can be prevented with timely initiation of enzyme replacement therapy and patients might have better survival.

SA-PO630
Fabry’s Disease within Dialysis Patients in Madeira Island: An Unexpected Surprise
Maria M. Pestana, José M. Durães, Ana F. Gomes da silva, Miguel Gonçalves, Pedro M. Vieira, Luis Resende, Jose N. Guimaraes Rosa, José Teixeira, Gil Silva. Nephrology, Hospital Central do Funchal, Funchal, Portugal.

Background: Fabry’s Anderson disease (FAD) is a rare disorder that is highly undiagnosed worldwide. This entity is caused by alpha-galactosidase A (GLA) mutations. FAD, being a rare cause of end-stage renal disease (ESRD), accounts for less than 0.02% of all causes. The prevalence of FAD in Portugal is expected to be 1 in 5,000. Considering Madeira Island’s (MI) population of about 250,000, one would not ponder more than one case, but little is known about FAD. Nevertheless, preliminary studies taking course point out to an increased genetic pool.

Methods: Screening of FAD is being performed among dialysis patients in MI. Alpha galactosidase A (AGAL) activity is obtained by a blood spot test. Male patients with decreased AGAL activity are tested for genetic mutations. Female patients are tested for genetic mutations regardless of AGAL activity. The diagnosis is confirmed by the presence of the mutations in the GLA gene. These patients also have lyso-Gb3 measurements. The pathogenicity is determined according to Annual Clinical Meeting Genetics (ACMG).

Results: Among 72 patients tested, we found 4 different mutations in 4 different families, all with distinctive pathogenicity. Following studies in those families revealed 10 additional cases and we are still testing other members. Two of these families have

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
a previously described pathogenic mutation, c.937G>T (p.Asp313Thr) in family 1 with 2 affected females and the c.1707C>T (p.Met590Leu) in family 2 with 1 affected male and 5 affected females. Family 3 has a c.352C>T (p.Arg118Cys) mutation labelled as pathogenic although with conflicting reports in several studies. Curiously, we discovered a novel mutation in family 4 never reported before, referring to exon 4 of GLA gene, c.580A>G (p.Thr194Ala). Further evaluations of clinical findings suggest this mutation to be pathogenic.

Conclusions: Testing in dialysis patients and other members of identified families in MI will probably result in higher prevalence of FAD. These results are clearly above what is usually expected from published literature. For example, the 17q21 deletion further prompt investigation is required. Additional evaluation of affected patients will help understand the pathogenic implications.

Funding: Commercial Support - Shire

SA-PO631

A Potential Novel Mutation of CYP24A1 Leading to Hypercalcemia and Hyperparathyroidism

Pace Romney, Robert H. Yenchek, Josephine Abraham, 1Salt Lake City, UT; 2University of Utah, Holladay, UT; 3University of Utah Medical Center, Salt Lake City, UT.

Background: Mutations of CYP24A1 can lead to a deficiency of vitamin D 24-hydroxylase and can lead to hypercalcemia due to dysregulation of vitamin D 1,25-OH2. New mutations are continuing to be discovered.

Methods: A 29 year old man with history of prior nephrolithiasis sustained a traumatic pelvic fracture and he was incidentally discovered to have CT findings consistent with severe bilateral medullary nephrocalcinosis, hypercalcemia, and elevated creatinine. The patient was started on empiric low dose calcitriol to control his hypercalcemia. He had 24 hour urine collections done and was found to have hypercalcemia. Parathyroid hormone was low, vitamin D 25-OH and vitamin D 1,25-OH levels were both within normal limits. Given his long history of nephrocalcinosis and nephrolithiasis at a young age, a genetic mutation of CYP24A1 was suspected and so he was started on empiric low dose calcitriol to control the hypercalcemia. He subsequently underwent genetic sequencing for nephrocalcinosis. The results of the genetic test were positive for three mutations; heterozygous for a c.626del (p.Pro21Arg) in CYP24A1, homozygous for c.1219T>A in CYP24A1, and heterozygous for c.374G>C (p.Thr125Arg) in GD2.

Results: Heterozygous mutation for CYP24A1 is reported as a recessive mutation for idiopathic infantile hyperparathyroidism. The heterozygous mutation of SLCA29 was felt not to fit his clinical picture. The homozygous mutation of CYP24A1 has not been previously reported in literature and modeling predicted this mutation to have probable deleterious effects. Since starting fluconazole, the patient’s calcium level has normalized.

Results: Idiopathic hyperparathyroidism is often caused by genetic mutations of CYP24A1 which encodes for the enzyme 24-hydroxylase. This enzyme converts 1,25-(OH)2D to 1. With a deficiency of this enzyme, various phenotypes of hypercalcemia and nephrocalcinosis have been described. This patient has been found to have a newly discovered mutation of the CYP24A1 gene which is suspected to be causing hypercalcemia and nephrocalcinosis.

SA-PO632


Background: Genomic Disorders (GDs) are caused by pathogenic deletions or duplications of large genomic regions of the genome. GDs are associated with many multiorgan developmental disorders and are enriched in children with chronic kidney disease (CKD), associating with poorer neurocognitive scores.

Methods: We studied the prevalence of GDs in adults with all-cause CKD enrolled in the Chronic Renal Insufficiency Cohort (CRIC, N= 3,375) and in the Columbia University CKD cohort (CU-CKD, N= 1,146) and compared them to 21,498 population controls. All samples were genotyped on Illumina microarrays and screened for deletions and duplications using ChromeShots software. The CRIC cohort, while diagnosis data were not available in CRIC. Analysis of available baseline clinical data in carriers) despite normal BMI, as well as hypomagnesemia (7/9 carriers).

Conclusions: Diodependent effects. Since starting fluconazole, the patient’s calcium level has normalized. Further evaluations of clinical findings suggest this mutation to be pathogenic.

Funding: NIDDK Support

SA-PO633

Plasma Biomarkers and Renal Outcome in African Americans with High-Risk APOL1 Variants and Reserved Renal Function

Girish N. Nadkarni, 1Kinsuk Chauhan, 1Divya A. Verghese, 1Chirag R. Parikh, 2Ron Don, 1Carol Horowitz, 2Erwin P. Bottinger, 2Steven G. Coca. 1Icahn School of Medicine at Mount Sinai, New York, NY; 2Yale University and VAMC, New Haven, CT.

Background: Variants in Apolipoprotein L1 (APOL1) gene are associated with end stage renal disease (ESRD) to African Americans (AAs). However, risk stratification in AAs with high risk APOL1 genotype (G1/G1; G2/G2 or G1/G2) is poor. We assessed the association between plasma biomarkers and renal outcomes in AAs with high-risk APOL1 genotype.

Methods: We genotyped AA Biome Biobank participants for high-risk APOL1 genotype. We measured soluble tumor necrosis factor receptor 1/2 (sTNFR1/2) and kidney injury molecule-1 (KIM1) in plasma specimens via MesoScale Discovery multiplex assay and determined their association with a composite renal outcome of ESRD or 40% sustained decline in eGFR. We assessed improvement in area under curve (AUC) with addition of biomarkers from a baseline model using kidney failure risk equation (KFRE) with age, sex and eGFR.

Results: Among 498 APOL1 high-risk participants, median age was 56 years, 68% were female and baseline eGFR was 83 ml/min. 80 (16%) experienced the composite renal outcome over median of 6.9 years. After adjusting for age, sex and baseline eGFR, stTNFR1, stTNFR2, and KIM1 were independently associated with the renal outcome when expressed continuously or in tertiles, and in sensitivity analyses adjusting for baseline proteinuria in those with available measurements (n=209). (Table) AUC improved from 0.66 to 0.72 for KFRE model to 0.78 with a biomarker-enhanced model. The event rate for participants with all 3 biomarkers in the top tertile was 40%, compared to 7% and 19% with 0 or 1 biomarker elevated, respectively (p < 0.001).

Conclusions: stTNFR2 and KIM1 are independently associated with renal outcome in AAs with high-risk APOL1 genotype and improve risk discrimination. These markers can be valuable for risk stratification in AAs with APOL1 high risk.

Funding: NIDDK Support

SA-PO634

African and European Ancestry Proportions Are Associated with GFR Measures in Over 270,000 Participants from the Million Veterans Program (MVP) Digna R. Velez Edwards, 1Ayush Giri, 1Eric S. Tortorenso, 1Jacklyn N. Hellwege, 1CSaba P. Kovess, 1Christopher J. O'Connell, 2Todd L. Edwards, 2Adriana Hugg 4Boston Veterans Administration, Boston, MA; 1University of Tennessee Health Science Center, Memphis, TN; 4Yale University and VAMC, New Haven, CT; 5University of Tennessee Health Science Center, Memphis, TN; 3Yale University Medical Center, Nashville, TN; 4Vanderbilt University, Nashville, TN; 1VA TVHS, Nashville, TN; 1Group/Team: On behalf of VA Million Veteran Program.

Background: Current methods estimate glomerular filtration rate (eGFR) using a creatinine based equation. Because African Americans have higher muscle mass and creatinine generation, current eGFR equations incorporate a dichotomous indicator for race (black/not black). It is unclear if this measure appropriately accounts for eGFR variability due to genetic ancestry.

Methods: To determine whether ancestry proportions influence eGFR, we evaluated associations between genetically inferred proportions of ancestry relative to 5 reference populations (GIBR, PEL, YRI, CHB, and LWK) and eGFR in 56,237 self-reported blacks and 216,528 self-reported whites from the MVP. Traits were modeled using linear regression against each ancestry proportion variable adjusted for important covariates to report estimates per 10% increase for a given inferred ancestry percentage in whites and blacks separately.

Results: In self-reported blacks, every 10% increase in GBR ancestry was associated with 1.1 unit increase in eGFR levels (p-value = 5 x 10^-10), while 10% increase in African ancestry was inversely associated with eGFR (beta = -1.1; p-value = 1 x 10^-76). The virtually identical magnitude of effect estimates is consistent with the known two-way European/African admixture observed in blacks from the United States. Interestingly, despite the small contribution of Native American (estimated using Plink's (10)) admixture to this group, PEL ancestry was positively associated with eGFR (beta= 2.16; p-value = 1.2 x 10^-10); with the largest effect estimates observed in non-diabetic blacks. Neither CHB nor LWK ancestry was associated with eGFR in blacks (beta = -0.05). In whites, the PEL ancestry was positively associated with eGFR (beta = 0.63; p-value = 2.5 x 10^-10), while both African ancestry proportions were inversely associated (YRI beta = -0.86, p-value = 8 x 10^-30; LWK beta = -3.10, p-value = 8x10^-20).

Conclusions: Overall, Yoruban ancestry strongly associates with decreased eGFR in both whites and blacks, after accounting for dichotomous race in the eGFR equation. Since
eGFR is a strong predictor of end stage renal disease, our results suggest incorporating ancestry proportion information into eGFR calculations may provide a better predictor for future disease risk.

**Funding:** Veterans Affairs Support

**SA-PO635**

Sparantan Pharmacokinetics and Pharmacodynamics as the Basis of Dose Selection for Primary Focal Segmental Glomerular Sclerosis (FSGS)

**Methods:** The DUET trial determined the sparantan-induced changes in urine protein/creatinine ratio (Up/C), (baseline to Week 8) in patients assigned to 200 (n=13), 400 (n=21), or 800 (n=30) mg/day. The relationship between sparantan dose or area under the curve (AUC), and change in Up/C was assessed. PK/PD analyses were based on actual doses received, accounting for dose reductions resulting in PK/PD sample sizes of 17, 23, and 22 for 200, 400, and 800 mg/day, respectively.

**Results:** Due to small sample sizes, antiproteinemic effects across sparantan doses were not statistically distinguishable; however, likelihood of a patient having drug exposures resulting in a decrease in Up/C was greater for the 800 mg dose. For the three dose groups, the percentages of patients with a decrease in Up/C were 76%, 74%, and 91%, respectively, as shown in the Figure. Of the 30 patients assigned to the 800 mg dose, 18% experienced hypotension. In general, sparantan was safe and well tolerated with no clinically significant changes in vital signs or major clinically significant abnormalities in laboratory tests.

**Conclusions:** Initial daily dosing at 400 mg, followed by escalation to 800 mg for those that tolerate 400 mg, increases the likelihood of antiproteinemic effect while maximizing safety. Both the therapeutic effect vs dose or AUC and AUC distribution analyses each led to the same conclusion.

**Funding:** Commercial Support - Retrophin Inc.
vs. 1310 hr mg/ml), and T1/2 was shorter in HD subjects (64.2 hrs vs. 87.9 hrs). HD was associated with minimal alterations in KBP-5074 plasma concentrations and outflow dialysate concentrations of KBP-5074 were undetectable, indicating negligible clearance of KBP-5074 via HD. Plasma aldosterone and serum potassium values were generally comparable between HD and non-HD subjects. Hemodialysis had a negligible effect on plasma concentrations of KBP-5074. These data support further evaluation of KBP-5074.

**Conclusions:** KBP-5074 at a dose of 0.5 mg was safe and well tolerated in all study subjects. Plasma exposures of KBP-5074 in HD subjects were significantly lower than in non-HD subjects. Hemodialysis had a negligible effect on KBP-5074.

**Funding:** Commercial Support - KBP Biosciences

**SA-PO640**

The Effect of Tacrolimus Exposure on CYP3A5 and P-gp Expression in a Model of Human Proximal Tubule Cells for Studying the Role of Pharmacogenetic Variation in Renal Drug Metabolism and Toxicity

**Noel Knopf,** Yasaman Ramazani, Elena N. Levtechenko, Dirk R. Kuyper.

**Background:** Tacrolimus (Tac) constitutes the mainstay of immunosuppressive therapy and is metabolized through the interplay between CYP3A enzymes and the P-gp transporter (ABCB1). Clinical and fundamental studies have demonstrated the importance of genetic variation for the expression of corresponding proteins in relation to drug metabolism and toxicity. The effect of Tac on their expression in renal cells with a variable pharmacogenetic background common in the general population is unknown.

**Methods:** Human immortalized proximal tubule cells (PTC) with 4 combinations of genetic variants for CYP3A5 (rs776746) and ABCB1 (rs1045642) were selected. Tac exposure during experiments was based on WST-1 assay and in vivo data on tissue levels in allograft recipients, i.e. vehicle, 50 ng/ml and 300 ng/ml for 24 and 72 hrs. Quantitative and functional expression was assessed by RT-PCR, WB, midazolam (MDZ) hydroxylation (for CYP3A5) and calcein efflux (for P-gp).

**Results:** Only very high Tac concentrations (45,000ng/ml) resulted in cell death. Baseline mRNA, protein and functional expression of CYP3A5 was higher in ciPTC with the *f1 versus *5.3* allele. Increasing Tac conc. within the range of tissue levels had no effect on CYP3A5 mRNA or protein expression but resulted in decreasing 1’OH MDZ hydroxylation (p<0.001). Quantitative expression of ABCB1 mRNA and P-gp was similar between variants of ABCB1 3435C>T, but calcein-AM efflux was higher in TT vs. CC/CT (delta fluorescence: 45.3% vs. 27.1%, p= 0.001). Tac conc. did not affect quantitative ABCB1/P-gp expression but resulted in decreasing calcein efflux (p=0.001) in both variants.

**Conclusions:** Tacrolimus exposure associated with in vivo tissue levels are not lethal and have no direct effect on the regulation of gene/protein expression for CYP3A5 and P-gp in PTC with a variable pharmacogenetic background. However, these concentrations do result in decreasing functional expression of both actors involved in Tac metabolism on top of the differences associated with the genetic background. The potential nephrotoxic effect ascribed to Tac might therefore be the result of basic variation in functional expression due to underlying genotype for CYP3A5 or ABCI, and/or in combination with the inhibitory effect of tacrolimus on the enzyme and pump function.

**SA-PO641**

Age Influences on Tacrolimus Pharmacokinetics Post-Transplantation

**Katiehong Tran,** Kris Attwood, L. Rose C. Venuta.

**Background:** Minimal data is available describing the influence of age on tacrolimus (TAC) pharmacokinetics (PK) in African American (AA) and Caucasian (C) renal transplant recipients (RTR) in spite of increased renal transplantation in the elderly. This sub-study investigated the impact of age on TAC PK in stable AA and C RTR.

**Methods:** The 12-hour PK study of TAC was investigated in 35 AA and 32 C RTR receiving enteric coated MPA and tacrolimus. Cumulative adverse effects (AE) were assessed including gastrointestinal, neurologic and aesthetic manifestations. Patents were categorized by age as follows: Young: <21 & > 40 years. Middle Age: >40 & 60 years, and Elderly: >60 years. Apparent clearance (CL), BMI normalized CL (CL(BMI)), Area Under the Concentration-time curve 0-12h (AUC12), dose-normalized AUC12 (AUC*), 12 hour troughs (C12h) and dose normalized C12h (C12hDose) with CAE were determined and analyzed with univariate ANOVA.

**Results:** Table summarizes the results. All groups were within the therapeutic AUC12 guide of 120-200 hr mg/ml for TAC. The elderly received the lowest TAC dose and achieved comparable, therapeutic C12h troughs and AUC12 to other groups. The elderly had a higher dose normalized trough and AUC* with slower CL and more C AE compared to younger patients.

**Conclusions:** These findings suggest that TAC dosing regimens need be individualized based upon adult ages and time post transplant. Further investigations into age-related changes in TAC exposure and relation to clinical responses (i.e. adverse effects) remain important for safe and efficacious immunosuppression.

**Funding:** NIDDK Support, Commercial Support - ASTELLAS

**SA-PO642**

Antibiotics: A Novel Factor Associated with Tacrolimus Trough Variability in Kidney Transplantation

**John R. Lee,** Yuanyu Zheng, Michael P. Wagner, Darshana Dadhania, Thangamani Muthukumar, Manikkam Suthanthiran.

**Background:** We previously reported a relationship of the gut microbiota to tacrolimus dosing requirements. Based upon this data, we hypothesized that antibiotics, which are known to alter the gut microbiota, is associated with tacrolimus trough variability.

**Methods:** We performed a retrospective chart review of subjects who received a kidney transplantation at our institution from 2012 to 2013. We divided the population into subjects who received antibiotics during the first month of transplantation (Abx Group, N=60) and subjects who did not (No Abx Group, N=169) (Fig A). We evaluated whether antibiotics increase tacrolimus trough levels and tacrolimus trough level over dosing (C/D) in the Abx Group and whether antibiotics increase tacrolimus trough variability as measured by standard deviation (SD) and coefficient of variation (CV) between post op days 31 to 45.

**Results:** In the Abx Group, 48 subjects had a tacrolimus trough level measured prior to antibiotic administration and these subjects had increased tacrolimus trough levels and increased tacrolimus C/D, 7 and 15 days after antibiotic administration (Fig 2B, 2C). Subgroup analysis of type of antibiotics suggested increasing C/D after 7 days after antibiotic administration in penicillin type antibiotics and clindamycin type antibiotics (P=0.08, 0.09, respectively). Tacrolimus trough variability as measured by SD and CV between post op days 31 to 45 was significantly different between the Abx Group and the No Abx Group (SD median 2.6 vs 1.6, P=0.03; CV median 0.29 vs. 0.18, P=0.02, Wilcoxon rank sum test) (Fig 3).

**Conclusions:** Our identification of antibiotics’ association with tacrolimus trough variability highlights the need to measure tacrolimus trough levels after antibiotic administration.

**Funding:** Other NIH Support - NIAID K23 AI 124464
SA-PO643

Inpatient Tacrolimus Variability Has Similar Outcomes on Kidney Allograft Function between UK Transplant Centers Ryan Ghiha. NHS Greater Glasgow and Clyde, Glasgow, United Kingdom. Group/Team: UK Transplant Audit Collaborative.

Background: Tacrolimus based immunosuppression regimes are the mainstay of treatment for transplant patients in the United Kingdom. High inpatient variability (IVP) of tacrolimus levels has been associated with poorer kidney allograft function. A retrospective study looked at the effects of high IVP on eGFR in five transplant centers across the UK (Glasgow, Oxford, King’s London, Liverpool, Manchester).

Methods: Data was collected from patients who received a kidney transplant between 2009 and 2014 in one of the UK centers. Tacrolimus trough levels were recorded at two time points - 6-12 months post transplant (T1) and most recent 12 months (T2). Exclusion criteria included patients that received dual-organ transplants or if death or graft loss occurred within two years of transplantation, or if their immunosuppression regimes included modified release tacrolimus. For each transplant center, patients that fell into the highest and lowest IVP quartiles were identified and their MDRD eGFR were compared using a Mann-Whitney U-test. The results are in table1.

Results: Three of the comparisons between the high and low variability groups had a U-value lower than the critical value suggesting a significant difference in MDRD eGFR. In all other groups the median eGFR was lower in the high IVP group however this was not found to be statistically significant.

Conclusions: The results suggest a correlation between high IVP and worse allograft function, as determined by eGFR, throughout the UK transplant centers. However the small patient cohort in each center limits analysis. Further analysis will be performed merging the data from all centers which to the best of our knowledge will be the largest study looking at IVP with over 1000 patients.

Table 1: eGFR comparison between patients with high and low tacrolimus variability in UK transplant centers

<table>
<thead>
<tr>
<th>Group</th>
<th>Glasgow</th>
<th>Oxford</th>
<th>Liverpool</th>
<th>Manchester</th>
<th>King’s London</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>48</td>
<td>54</td>
<td>63.5</td>
<td>49</td>
<td>38.5</td>
</tr>
<tr>
<td></td>
<td>(49.7)</td>
<td>(56.4)</td>
<td>(48.55)</td>
<td>(38.56)</td>
<td>(48.73)</td>
</tr>
<tr>
<td>T2</td>
<td>46</td>
<td>50</td>
<td>48.5</td>
<td>48.5</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>(34.56)</td>
<td>(35.55)</td>
<td>(36.52)</td>
<td>(39.53)</td>
<td>(43.42)</td>
</tr>
</tbody>
</table>

SA-PO644

Drug Dosing During AKI Michael E. Brier,1 George Aronoff,1 Adam E. Gaweda,1 DuVita, Inc., Naples, FL; 2University of Louisville, Louisville, KY.

Background: When renal function is rapidly changing during acute kidney injury (AKI), estimating the proper dosage for drugs that are renally eliminated becomes difficult. We tested the hypothesis that estimating the creatinine production rate (CPR) combined with measured serum creatinine (Scr) allows us to determine the level of renal function as the estimated glomerular filtration rate (eGFR) to guide drug dosing.

Methods: Baseline creatinine production was determined by rearranging the CKD-EPI equation and solving for creatinine generation using the principle that at steady-state the rate of elimination = rate of production. We calculated creatinine production over a 24-hour period.

Results: When renal function is rapidly changing during AKI, dosing adjustments using CPR and Scr can help in determining drug dosage adjustments. CKD-EPI shows that CPR is decreased in the population as baseline Scr increases.

<table>
<thead>
<tr>
<th>Baseline Scr</th>
<th>White/Male</th>
<th>White/Female</th>
<th>Black/Male</th>
<th>Black/Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>17</td>
<td>25</td>
<td>54</td>
<td>27</td>
</tr>
<tr>
<td>2.0</td>
<td>30</td>
<td>21</td>
<td>39</td>
<td>24</td>
</tr>
<tr>
<td>3.0</td>
<td>24</td>
<td>26</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>4.0</td>
<td>20</td>
<td>23</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>5.0</td>
<td>17</td>
<td>12</td>
<td>20</td>
<td>14</td>
</tr>
</tbody>
</table>

SA-PO645

Proteinuric Renal Disease Alters the Biodistribution of Antisense Oligonucleotides Allowing Reduction in Dose for Kidney Targets Anna Granqvist,1 Lena William-Olsson,1 Barbro Basta,2 Thomas Bjell, Patrik Anderson,2 Magnus Soderberg,2 Mark J. Anderton,2 Christine Ahlström,1 Innovative Medicines & Early Development Cardiovascular & Metabolic Disease, AstraZeneca R&D, Gothenburg, Sweden; 2Drug Safety & Metabolism, AstraZeneca R&D, Gothenburg, Sweden; 3Ionis Pharmaceuticals, Carlsbad, CA.

Background: An increasing number of oligonucleotide therapeutics are used in clinical trials today. Antisense oligonucleotides (ASOs) are predominantly taken up by the liver and kidneys, which makes them a desirable modality for the treatment of renal disease. However, there is a concern regarding potential clinical safety risks such as thrombocytopenia, injection site reactions and renal/liver toxicity at higher doses. The biodistribution of ASOs to different tissues is assisted by plasma protein binding that delays urinary excretion and it was therefore hypothesized that distribution of ASOs with phosphorothioate backbone is altered in proteinuric renal disease.

Methods: We investigated the tissue exposure and distribution of a phosphorothioate cET gapper ASO in the obese diabetic BTBR ob/ob mouse. This is a suitable model as it mimics key features of human diabetic nephropathy, including progressive proteinuria and glomerulopathy. Mice were subcutaneously administered weekly doses of 3, 10, 30 or 100 mg/kg ASO in saline and followed for 2-12 weeks.

Results: In all animals tissue exposure and significant knock down of the target gene in kidney was achieved (between 45-75% decreased expression, p<0.001). In the diabetic BTBR ob/ob mice a shift in the distribution of ASO towards the kidney was observed in comparison to healthy mice, leading to a lower exposure in liver. Similar exposure and knock down in the kidney was achieved in the diseased animals with a 30 mg/kg dose compared with a 100 mg/kg dose in healthy animals. There were no nephrotoxic effects of the ASO treatment (determined by biomarker analysis and histology).

Conclusions: These results suggest that in a model of proteinuric renal disease similar level of kidney mRNA knockdown is observed at lower ASO dose levels compared to healthy mice. If such observations translate to patients with kidney disease, this may reduce the risk of toxicities in other organs and tissues.

SA-PO646

Targeted C4 Inhibition by Affinity Purified Immunoglobulins Elena Volokhina,1 Thea J. Van der velden,2 Marloes Michels,1 Nicole Van De Kar,1 Marcin Okrój,1 Bert Van den heuvel,3 Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; 4UMC St. Radboud Nijmegen, Nijmegen, Netherlands; 5Medical University Gdansk, Gdansk, Poland.

Background: Immunoglobulins (Igs) can activate complement when bound to their antigens. Moreover, they may inhibit complement activation and in clinical practice intravenous Igs are widely used to treat immunodeficiencies as well as inflammatory conditions. Complement inhibitory properties of Igs are poorly understood, which limits their use for targeted complement modulation in renal disorders. In this study we describe immunoglobulin preparations with specific complement inhibiting properties.

Methods: Igs from healthy donors were purified using Protein L or Protein A/G affinity chromatography. Classical (CP) and alternative pathway (AP) activation was assessed using hemolytic assays. Activation of C1q, C4b, C3b and C5b-9 in CP was assessed by ELISA. Purified fractions were analyzed by SDS-PAGE and silver staining.

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

Underline represents presenting author.

845
Effect of the Microbiota-Derived Uremic Toxin Indoxyl Sulfate on FMO Expression and TMAO Formation: A Pilot Study

**Background:** Cardiovascular disease (CVD) is the leading cause of death in kidney disease. Microbiota-derived uremic toxins likely contribute to CVD progression and may be modifiable risk factors. The microbiota-derived uremic toxins indoxyl sulfate and trimethylamine-N-oxide (TMAO) are associated with poor CVD outcomes. Indoxyl sulfate activates the aryl hydrocarbon receptor (AhR) transcription factor, which partially regulates flavin-containing monooxygenase (FMO) expression. FMOs are an important class of hepatic enzymes that oxidize trimethylamine to TMAO. We hypothesize that induction of AhR by indoxyl sulfate induces FMO expression and activity, thereby increasing TMAO formation. The aim of this pilot study was to assess the effect of indoxyl sulfate on the expression and activity of FMO.

**Methods:** Primary cultures of human hepatocytes (n=1 donor) were pre-treated with 0.1 µM indoxyl sulfate for 24 hours. FMOs were induced with endotoxin (vehicle control), rifampin (induction control), PCB-77 (AhR agonist) and indoxyl sulfate (1, 25, 100 and 250 µM) for 72 hours. All experiments were run in duplicate. Hepatocytes were then incubated for 3 hours with trimethylamine and formation rate of TMAO was used as an indicator of hepatic FMO activity. TMAO was measured via LC-MS. Gene expression was determined by RT-qPCR using specific Taqman® probes and master mix. All data was analyzed using one-way ANOVA.

**Results:** FMO3 mRNA expression increased by 2.4-fold, 2.1-fold, 2.9-fold and 5.1-fold compared to vehicle control with indoxyl sulfate 1, 25, 100 and 250 µM, respectively (p<0.0055). CYPIA2 mRNA expression increased by 2.7-fold, 1.6-fold, 9.6-fold and 254-fold compared to vehicle control with indoxyl sulfate 1, 25, 100 and 250 µM, respectively (p<0.0003). AhR mRNA expression was not significantly changed compared to control. Indoxyl sulfate 1, 25, 100 and 250 µM increased TMAO formation by 1.2-fold, 1.6-fold, 1.0-fold, and 3-fold compared to vehicle control, respectively (p<0.0049).

**Conclusions:** These results suggest that indoxyl sulfate induces FMO3 mRNA expression and activity, leading to increased FMO-mediated TMAO formation. This novel metabolic interaction may contribute to dramatically increased systemic exposure of TMAO and CVD progression in kidney disease patients.

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

---

Genetics of Serum Urate Concentrations and Gout in a High-Risk Population, Patients with CKD

**Background:** Gout is the most common inflammatory arthritis in many countries with a strong genetic component. Individuals with chronic kidney disease (CKD) represent a high-risk population for gout. Genetic risk factors for gout and their interactions with clinical factors in CKD are understudied.

**Methods:** Association studies of serum urate and gout were performed in 4941 CKD patients (1217 with gout) in the German Chronic Kidney Disease Study. Effect sizes of 26 known serum urate-associated SNPs from population-based studies were examined. Interactions of urate-associated variants with serum urate-altering medications and clinical characteristics of gout were evaluated.

**Results:** Genotype-wise significant associations (p<0.05) with serum urate and gout were identified for the known loci SLC2A9 and ABCG2, encoding urate transporters. Effects of known SNPs were similar in magnitude in CKD patients and population-based studies (Figure 1). Gene-medication interactions implicated interactions (e.g. ABCG2 rs2231142 and loop diuretics) but were not significant when accounting for multiple testing. Effects of ABCG2 rs2231142 on serum urate were higher in those with lower eGFR, consistent with the transporters role in urate excretion. Associations with gout in specific joints were strongest for SLC2A9 rs12498742 in elbows and wrists, and ABCG2 rs2230591 in C7/C1/2 intervertebral joints.

**Conclusions:** Known genetic variants in SLC2A9 and ABCG2 were associated with serum urate and gout in a CKD cohort with effect sizes similar to population-based studies. Studying pharmacogenomic interactions is challenging in the setting of polypharmacy in CKD. Patients with impaired kidney function was conducted to determine the effect of apabatolone on plasma proteins associated with CVD complications in CKD.

**Funding:** Commercial Support - Astra Zeneca, Grünenthal, Private Foundation Support, Government Support - Non-U.S.

---

**SA-PO646**

**SA-PO649**

**SA-PO650**

**SA-PO650**

**SA-PO650**

---

**SA-PO647**

Targeting Stat3 Activity Blocks Muscle Wasting in CKD

**Background:** Muscle wasting with morbidity and mortality is common in patients with chronic kidney disease (CKD) but there are no regularly effective treatments. We found there is activation of a p-Stat3/CIBP/myostatin signaling pathway in muscles of patients or mice with CKD and inhibition of myostatin or p-Stat3 blocked muscle loss in mice. We also found that C188-9, a small-molecule inhibitor of Stat3 increases muscle mass and improves muscle function despite CKD. To extend these results, we examined optimal dosing, frequency and route of administration of C188-9 in rats with CKD.

**Methods:** CKD (subtotal nephrectomy) was created in male Sprague-Dawley rats. C188-9 was administered by gavage feeding or i.p. injection; plasma levels of C188-9 were measured by LC/MS.

**Results:** For pharmacokinetics, we administered C188-9 (doses 0.1, 10, 30, 100 mg/kg) once to 2 groups of rats: A sham-operated, control rats; and B rats with CKD, pair fed with control rats. Plasma was collected at 0.25, 0.5, 1, 2, 4, and 8 hours following i.p. injection. We found that plasma C188-9 concentrations in mg/ml were similar in CKD vs. control rats at different doses: 10 (CKD, 2.5 vs control, 2.4); 30 (8.4 vs. 8.3) and 100 mg/kg, (13 vs. 9.8). Time to maximal C188-9 blood level was 1h after subcutaneous and CKD rats. 4) In CKD rats, the C188-9 half-life was greater vs. results in control rats. 5) At 3 days after C188-9 dosing, we measured C188-9 in muscle lysates; levels of C188-9 in muscle were similar in sham and CKD rats. 6) Notably, C188-9 suppressed muscle p-Stat3 levels in CKD rats vs. controls (no C188-9) and the p-Stat3 levels were inversely correlated with the C188-9 in muscle. 7) C188-9 was tolerated in CKD rats even at 100 mg C188-9/kg/day for 7 days.

**Conclusions:** 1) The optimal C188-9 dose is 30mg/kg which blocks p-Stat3 effectively in muscle of rats with CKD and it has a half-life similar to that of 100 mg/kg. 2) The C188-9 half-life, C188-9 could be dosed every 4 hrs to CKD rats. 3) C188-9 has a potential for developing oral dosing as results with gavage feeding were similar to those of i.p. injection. 4) The drug remains in muscles, inhibiting p-Stat3 effectively. 5) C188-9 exhibits minimal short-term toxicity. Thus, C188-9 has a potential for combating muscle wasting in patients with CKD.

**Funding:** NIDDK Support, Commercial Support - Atara Biotherapeutics, Private Foundation Support

---

Apabatolone (RVX-208) Impacts Key Markers and Pathways Associated with CKD in Patients with Severe Renal Impairment

**Background:** Chronic kidney disease (CKD) is associated with a progressive loss of renal function and a high risk of cardiovascular disease (CVD). Apabatolone is an orally active BET protein inhibitor that decreased major adverse cardiac events (MACE) in CKD patients in phase 2 clinical trials. Thus, a phase 1, open-label, parallel group study of patients with impaired kidney function was conducted to determine the effect of apabatolone on plasma proteins associated with CVD complications in CKD.

**Methods:** 8 subjects with stage 4 CKD not on dialysis (mean eGFR=20 ml/min/1.73m²) and 8 matched controls (mean eGFR=78.5 ml/min/1.73m²) received a single 1mg loading dose of apabatolone. Plasma was collected over 48h for PK analysis and at 12h post dose for proteomics analysis using the SOMAscan® platform (1305 proteins). Data

---

**Figure 1:** Effect size comparison of SNPs on serum urate in population-based studies (X) vs. CKD patients (Y) for urate (panel A) and gout (panel B, log odds ratio).

**SA-PO647**

**SA-PO649**

**SA-PO650**

**SA-PO650**
were analysed with Ingenium® Pathway Analysis (IPA®) to identify pathways regulated by apabetalone.

Results: PK parameters were similar in CKD patients and controls. Plasma proteomics in CKD patients showed that after 12h apabetalone altered levels of 261 proteins by 10-58% (p<0.05), versus baseline. 257/261 proteins were downregulated, consistent with inhibition of BET sensitive genes. IPA® revealed a robust effect of apabetalone on pathways involved in immunity and inflammation, acute phase response, diabetes, endothelial dysfunction, vascular calcification, fibrosis, and hypertension. Apabetalone also reduced circulating CKD and CVD markers, including IL-6, TNF-α, IL-1, ICAM-1, VCAM-1, CRP, PAI-1, selectin, E-selectin, MMP-3, MMP-10, fibrinectin and SPP1 (p<0.05).

Conclusions: In stage 4 CKD patients, apabetalone rapidly downregulates plasma markers and molecular pathways linked to renal disease and CVD complications. The long term impact of apabetalone is currently being studied in a subpopulation with impaired kidney function of the phase 3 BETomMACE CVD outcomes trial.

SA-PO651

Personalized Levetiracetam Dosing for Patients Undergoing Continuous Venovenous Hemofiltration - Francois1, Chet2, Nishant3; 1Ottawa Hospital Research Institute, Ottawa, ON, Canada; 2China Medical University Hospital, Taichung, Taiwan; 3China Medical University, Taichung, Taiwan.

Background: Drug disposition can be severely altered in patients with chronic kidney disease (CKD) due to the multitude of physiological changes that occur. Cytochrome P450s and membrane transporters are major contributors to overall drug disposition, and have been extensively studied in rodent models of CKD. Induction of CKD in rat models by 5/6 nephrectomy or dietary treatment with adenine has shown decreased expression of CYPs such as CYP3A2 and CYP2C11. CKD mouse models using 3/4 nephrectomy clinically ill patients receiving levetiracetam aims to understand the (1) methodology of conducting a appropriate CRRT study to characterize PK, (2) potential barriers that exist with an observational CRRT study, and (3) derivation of individualized dosing recommendations.

Methods: Five patients receiving oral or intravenous levetiracetam and continuous venovenous hemofiltration (CVVH) in a neurocritical care unit were sampled to investigate the need for dosing adjustments. Pre-filter, post-filter, and ultrafiltrate samples were taken before dosing, after the completion of a 15 minute infusion, and at 4-5 additional time points respectively. Plasma concentrations were determined using a validated HPLC-UV bioanalytical method. Blood and effluent flow rates and laboratory parameters were also collected at the time of sampling. Non-compartmental analysis was conducted using Phoenix WinNonlin® 7.1 (Pharsight Corporation).

Results: The average sieving coefficient of ultraltrafiltrate concentrations to pre-filter plasma concentrations was 0.90 ± 0.1 and the average volume of distribution was 52.7 ± 7.6 liters. Three out of the five patients experienced concentrations outside the reported therapeutic range (12-46 mg/L) of levetiracetam. Average total drug clearance for patients taking 750 mg, 1000 mg, and 2000 mg were 3.10, 5.14, and 3.46 L/hr respectively, indicating that differences in clearance can be attributed to differences in ultrafiltration flow rates.

Conclusions: Preset ultrafiltrate rates were different amongst patients and need to be taken into consideration when determining appropriate doses. With higher ultrafiltrate rates will have increased drug clearance and therefore will require higher doses in order to match exposures seen in patients with normal renal function. Therefore, individualized dosing recommendations should be based on CRRT flow parameters and drug specific sieving coefficients. Funded: Private Foundation Support.

SA-PO652

Effect of CKD on Expression of Cyp3a11, Cyp2e37, Cyp2d22, and Oatp1b2 in C57BL/6 Mice - Urquhart1,2, Thibodeau1,2, ON, Canada; 1School of Pharmacy, University of Maryland, Baltimore, Maryland, MD; 2University of Maryland, Baltimore, MD; 1University of Maryland Medical Center, Baltimore, MD.

Background: Few clinical data exist on the effect of continuous renal replacement therapy (CRRT) on drug pharmacokinetics (PK). Appropriately designed PK studies could potentially optimize dosing recommendations in patients undergoing CRRT. Few CRRT studies in critically ill patients receiving levetiracetam aims to understand the (1) methodology of conducting a appropriate CRRT study to characterize PK, (2) potential barriers that exist with an observational CRRT study, and (3) derivation of individualized dosing recommendations.

Methods: Five patients receiving oral or intravenous levetiracetam and continuous venovenous hemofiltration (CVVH) in a neurocritical care unit were sampled to investigate the need for dosing adjustments. Pre-filter, post-filter, and ultrafiltrate samples were taken before dosing, after the completion of a 15 minute infusion, and at 4-5 additional time points respectively. Plasma concentrations were determined using a validated HPLC-UV bioanalytical method. Blood and effluent flow rates and laboratory parameters were also collected at the time of sampling. Non-compartmental analysis was conducted using Phoenix WinNonlin® 7.1 (Pharsight Corporation).

Results: The average sieving coefficient of ultrafiltrate concentrations to pre-filter plasma concentrations was 0.90 ± 0.1 and the average volume of distribution was 52.7 ± 7.6 liters. Three out of the five patients experienced concentrations outside the reported therapeutic range (12-46 mg/L) of levetiracetam. Average total drug clearance for patients taking 750 mg, 1000 mg, and 2000 mg were 3.10, 5.14, and 3.46 L/hr respectively, indicating that differences in clearance can be attributed to differences in ultrafiltration flow rates.

Conclusions: Preset ultrafiltrate rates were different amongst patients and need to be taken into consideration when determining appropriate doses. With higher ultrafiltrate rates will have increased drug clearance and therefore will require higher doses in order to match exposures seen in patients with normal renal function. Therefore, individualized dosing recommendations should be based on CRRT flow parameters and drug specific sieving coefficients. Funded: Private Foundation Support.
Conclusions: Ferric pyrophosphate citrate (Triferic®) iron is bioavailable via peritoneal dialysis. The adverse effects were mild to moderate in severity and appeared to be dose dependent. Iron absorbed from PDF to the systemic circulation was rapidly cleared with a time course similar to IV FPC. FPC added to PDF may be an effective and simple iron replacement therapy for PD patients.

Funding: Commercial Support - Rockwell Medical Inc.

SA-PO655

Parathyroid Hormone Contributes to the Down-Regulation of Cytocrome P450 3A through the cAMP/P13K/Akt Signaling Pathway in Secondary Hyperparathyroidism

Hiroshi Watanabe,1 Ryuuet Sugimoto,1 Masafumi Fukagawa,2 Toru Maruyama,1 Department of Biopharmaceutics, School of Pharmacy, Kumamoto University, Kumamoto, Japan; 2 Tokai University School of Medicine, Isehara, Japan

Background: Although it is reported that humoral factors, such as urmic toxins, may contribute to the change of extra-renal drug clearance observed in CKD, the details have not been clarified. We investigated the role of parathyroid hormone (PTH) in the change of extra-renal clearance.

Methods: Secondary hyperparathyroidism (SHPT) model rats were created by feeding a high phosphorus diet to the 5/6 renal nephrectomy rats. In vitro experiments were performed using rat primary hepatocytes and Caco-2 cells. Results: In rats with SHPT, hepatic and intestinal expression of CYP3A was down-regulated. Pharmacokinetic study using midazolam, a probe of CYP3A metabolism, showed that area under the curve (AUC) after oral administration increased about 8 times in the SHPT group compared to the sham group. These changes were suppressed by the administration of cinacalcet, a calcimimetic PTH suppressor, suggesting PTH contributes to the down-regulation of CYP3A. Using rat primary hepatocytes and Caco-2 cells, PTH (1-34) treatment decreased the expression of CYP3A proteins. The data supported the results obtained from SHPT rats. In Caco-2 cells, PTH (1-34) down-regulated mRNA expression of CYP3A but inactive PTH derivative (13-34) did not, suggesting that the action of PTH (1-34) occurs via PTH receptor. In addition, 8-BrcAMP significantly reduced mRNA expression of CYP3A. Inhibitors of P13K, NF-kB, PKC and PKA reversed the PTH-induced CYP3A down-regulation.

Conclusions: PTH down-regulates hepatic and intestinal CYP3A expression through a cAMP/P13K/Akt pathways, following the elevation of intracellular cAMP via PTH receptor. Such effects of PTH can be prevented by a calcimimetic treatment.

SA-PO656

Time for an Ex)Change: Treatment of Acute Cardiac Glycoside Intoxication with Extracorporeal Fab-Glycoside Removal in the Setting of Oliguria or Anuria: Experience from Two Cases Treated with TPE

Michael S. Balzer, Klaus Stahl, Susanne V. Fleig, Sascha David, Hermann G. Heller, Hannover Medical School, Hannover, Germany

Background: Anti-cardiac glycoside-antibody-fragments (Fab) (46kDa) are the only approved treatment for severe digitoxin intoxication. Simplified binding of the Fab to the glycoside inhibits its therapeutic effects and facilitates its renal excretion. Therefore, sustaining effectiveness of this detoxification strategy requires a certain glomerular filtration rate. It becomes obvious that in acute kidney injury (AKI) or chronic kidney disease (CKD) scenarios this elimination efficacy might be negatively affected. Removal of the Fab-glycoside complex by conventional hemodialysis is not efficient.

Methods: We here report 1 case of a patient with oliguric AKI and 1 case of an anuric patient with CKD stage 5D, both with symptomatic digitoxin intoxication. Treatment with Fab was complemented by subsequent elimination of the Fab-glycoside complex using either therapeutic plasma exchange (TPE) alone or a combination of TPE and high cut-off (HCO) dialysis. Digitoxin serum levels prior to, during and after the different treatment regimens are presented in Figure 1 and include a kinetic time course during TPE for the anuric patient.

Results: Conclusions: TPE appeared to be much more efficient in reducing digitoxin serum levels than HCO dialysis. This was most likely due to the high extent of plasma protein binding of digitoxin. As demonstrated by these 2 cases, we suggest to consider extracorporeal Fab-glycoside removal to prevent rebound toxicity following Fab treatment in severe cardiac glycoside intoxication in oliguric or anuric patients. While it has still to be demonstrated that HCO dialysis is efficient in digitoxin intoxication, TPE might be the preferred treatment modality in digitoxin intoxication.

SA-PO657

Mortality after Continuous Renal Replacement Therapy (CRRT) in Maintenance Hemodialysis Patients: A Scoring System of Short-Term Mortality Risk after CRRT

Toma Hamada, Masahide Mizobuchi, Yasuto Shikida, Takanori Shibata, Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

Background: Critically ill patients, suffering from serious diseases such as acute heart failure, acute kidney injury, septic shock, and so on, often require continuous renal replacement therapy (CRRT). Little is known about the outcome of CRRT in maintenance hemodialysis (MHD) patients, and what clinical parameters are risk factors of short-term mortality after CRRT. The objective was to investigate whether MHD patients are at high risk of the short term mortality after CRRT and to determine a scoring system relating to the mortality.

Methods: In this study, 308 patients who required CRRT in our facility from April 2013 to March 2015 were retrospectively analyzed. We excluded patients who were indicated HD within 7 days before CRRT, transferred to other hospital, and lost to follow. Patients were stratified by two groups, MHD group and Non-MHD (control) group. Analyses were performed using JMP.

Results: Two hundred fifty eight patients are included in the study. Sixty five % of them were male, mean age was 71 years. Cumulative incidence of death for MHD group versus control group was 60.4 % versus 46.0 % at 30 days (p=0.09), respectively. Kaplan-Meier analysis revealed that MHD group (log-rank test: p=0.02), intubated patients (log-rank test: p < 0.0001) had significant lower cumulative survival rate at 30 days after CRRT. Logistic regression analysis revealed that MHD patients were likely to die within 30 days after CRRT but did not reach statistically significance (unadjusted odds ratio 1.79; 95 % CI 0.92 – 3.54). After adjustment for elderly (age over 65 years), catecholamine administration, intubation, and MHD, MHD was an independent risk factor for 30-days mortality after CRRT (adjusted odds ratio 2.75; 95 % CI 1.31 – 5.94; p = 0.0067). We formulated a scoring system. The scoring system, MEIC score, was derived as follows: (MHDx5) x(Elderly(Age>65 y)x3)+Intubated(x7)+(Catecholamine)x5). The area under the ROC curve was 0.73 for the MEIC score.

Conclusions: These results suggested that MHD, intubation, elderly, catecholamine administration were independent risk factors of 30-days mortality after CRRT. The MEIC score could be a useful scoring system for the short-term mortality.
Impact of Early Initiation of Continuous Renal Replacement Therapy in Critically Ill Patients with AKI

Methods: We performed a retrospective analysis of all patients receiving CRRT in our ICU between January 7, 2007, to Oct 31, 2015. CRRT was classified into two groups: CRRT (Continuous renal replacement therapy) widely used in ICU because of slower solute clearance and removal of fluid (better hemodynamic tolerance). However the optimal timing for initiation of CRRT in critically ill patients with AKI remains controversial. The purpose of this study is to investigate the outcomes of patients who received CRRT without any of these indications (Non-classic) with patients with one or more of these indications (Classic).

Results: In conclusion, initiating CRRT in critically ill patients with AKI should not be delayed until fulfillment of classic indications.

Females Receive Continuous Dialysis Modalities Less Often Than Their Male ICU Counterparts

Background: Acute kidney injury (AKI) carries significant mortality with rates as high as 50-70% reported in the Intensive Care Unit (ICU). Standard clinical parameters for hemodialysis (HD) in AKI include azotemia, hyperkalemia, acidosis, and volume overload. Continuous renal replacement therapy (CRRT) is used in hemodynamically unstable patients or those with massive volume overload requiring prolonged ultrafiltration. Initiation of CRRT involves dedicated ICU nurses and is generally more expensive than HD. Race and initiation of dialysis has been evaluated though data remains conflicted. Gender also influences delivery of care as some studies suggest that males with AKI receiving CRRT have a significantly increased risk of death compared to females. Other factors including race and SES did not significantly affect the decision to start CRRT versus HD.

Methods: We used a clinical database “Clinical Looking Glass” (CLG) to retrospectively analyze 1,519 patients in the ICU between 2012-2015. AKI was defined as creatinine ≥3.0 mg/dL with pre-admission creatinine < 2.0 mg/dL. Endpoints included: CRRT, HD, Palliative Care or no intervention. Variables evaluated included age, gender, SES, race, ethnicity, payer, primary diagnosis, and laboratory parameters before RRT initiation, and the type of ICU. We did bivariate analyses examining demographic and clinical variables with treatment assignment. We then built a logistic regression model to test our hypothesis.

Results: A total of 370 subjects (24.4%) received CRRT, 307 (20.2%) received HD, 268 (17.7%) received HD and CRRT, and 570 (37.9%) received no intervention. In the cohort, 46.7% were female, 32.8% were black and 18.3% were white; with a mean age of 63 years. Our logistic regression model included 408 subjects and showed a significant association between gender and type of RRT received, with females having a significantly lower odds of receiving RRT(odds ratio: 0.58, CI(0.37-0.89), as compared to HD, after adjusting for other variables. Other variables significantly associated with use of CRRT were vasopressor use, lower pH, lower creatinine, type of ICU, and hospital location.

Conclusions: Female patients were less likely to receive CRRT than males. Other factors including race and SES did not significantly affect the decision to start CRRT versus HD.

Thrombocytopenia among Critically Ill Patients Receiving CRRT in the Medical ICU: Is it AKI or CRRT?

Background: Thrombocytopenia is commonly used in patients requiring RRT who are hemodynamically unstable in the ICU for both patients with AKI and ESRD. However, these populations are different in multiple aspects. There are various patient and treatment-related factors that are proposed to be contributing to thrombocytopenia. Furthermore, thrombocytopenia has been linked to increased mortality among patients receiving CRRT. We hypothesized that the rates of thrombocytopenia will be higher among patients with AKI in comparison with ESRD patients given their severe inflammatory state, new exposure to extracorporeal membranes from the electronic medical chart. We included patients in medical ICUs and excluded patients in surgical and cardiovascular ICUs. We identified ESRD patients using ICD 9 and 10 codes. New thrombocytopenia was defined as a 50% drop in platelets count after CRRT initiation. We performed a chi-square test to compare rates of decline in platelets among ESRD and AKI patients. A P-value of 0.05 was considered to be statistically significant. Data analysis was done using STATA 14.0. We provide a standard CVH prescription with regional citrate anticoagulation for all patients in our ICUs.

Results: We identified a total of 673 unique patients who received CRRT in medical ICUs. A total of 94 patients (13.9%) had a diagnosis of ESRD. 54.4% were males. Median (IQR) age was 60 years (51-68). The rate of new thrombocytopenia after CRRT initiation was 55.4%. Median platelet count prior to CRRT was 107 and median lowest platelet count after CRRT initiation was 45. The incidence of drop of platelets amongst patients with ESRD was 53.8% vs. 55.6% amongst those without ESRD (P=0.7)

Conclusions: Both ESRD patients and AKI patients requiring CRRT are at significant risk of developing thrombocytopenia. The risk is not different between the two patient populations and is possibly influenced by CRRT treatment-related factors in the setting of critical illness.

Propofol Induced CRRT Failure

Methods: Case report A 42 year old African American male with newly diagnosed stage 4 Hodgkin’s lymphoma was admitted to the intensive care unit with septic shock and respiratory failure that developed after receiving the first cycle of chemotherapy. Sedation was provided with propofol infusion at a rate of 5 mcg/kg/min. He developed acute renal failure and was started on continuous renal replacement therapy (CRRT). Local circuit anticoagulation was not used due to severe thrombocytopenia and liver disease. CRRT was interrupted 48 hours after initiation due to failure to clot. This was associated with a yellow discoloration of the blood in the dialyzer tubing. The serum triglyceride (TG) level was elevated at 1,552 mg/dL (reference range 30-149 mg/dL). Propofol was discontinued and follow up serum TG decreased to less than 500 mg/dL. CRRT was successfully restarted within 48 hours of stopping propofol infusion.

Conclusions: Critically ill patients receiving propofol sedation are at risk of developing hypertriglyceridemia. Elevated triglyceride (TG) levels can promote a procoagulant state, potentially inducing cartridge clotting. CRRT cartridge failure due to hypertriglyceridemia was previously described in association with TPN infusion. Our case illustrates the importance of frequent monitoring of triglyceride levels with prolonged propofol use.

A Mystery Case of Blood Leak Alarm Triggering

Methods: A 68 year-old male with end stage renal disease on hemodialysis admission was admitted to the hospital after presenting with weakness and fatigue. He was previously scheduled to have outpatient coronary artery bypass grafting due to severe coronary artery disease. Patient was found to have aortic valve infective endocarditis and urgent aortic valve replacement along with coronary artery bypass grafting. His postoperative course was complicated by hypotension, resulting in acute kidney injury. Blood gas returned negative. Hemoglobin remained stable. Hemodialysis was attempted twice using different 2008K Fresenius dialyzer instruments with adequate tolerance. On post-operative day 10, BLD interrupted dialysis as the dialyzer effluent became red in color. Work up for hemolysis returned negative. Hemoglobinol remained stable. Hemodialysis was attempted twice using different 2008K Fresenius dialyzer instruments and the BLD alarm interrupted dialysis on each occasion. We bypassed the BLD alarms by testing the dialysate fluid for blood leuk cell count for 15 minutes and by continuously resetting the alarm. Review of administered medications revealed that the patient received 5 mg of hydroxocobalamin (Vitamin B12A) intravenously on the day preceding the first blood leak alarm for vasoplegia syndrome. Rifampin was included in the patient’s antibiotic regimen for infective endocarditis and led to the presence of reddish discoloration of bodily fluids. Rifampin was discontinued but did not resolve the issue. The BLD no longer alarmed two days following discontinuation of hydroxocobalamin. Rifampin was restarted without any additional blood leak alarms.

849

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: This case highlights the importance of recognizing other etiologies of BLD alarms, especially when mechanical issues and hemolysis have been ruled out. It is important to recognize hydroxocobalamin as a cause for BLD false alarms. Fleishman issued a black box warning several months after our case.

SA-PO665
Single-Pass Albumin Dialysis with Continuous Renal Replacement Therapy in Patients with Liver Failure
Vimal Chaudhry,1 Darcy K. Weidemann,2 Nathan T. Beins,3 Uttam Garg,3 Rebecca M. Greene,1 Brooke English,1 Marita Thompson.1 1Children’s Mercy Hospital, Kansas City, MO; 2Children’s Mercy Hospital, Kansas City, MO; 3Children’s Mercy Hospitals and Clinics, Kansas City, MO; 4None, Kansas City, MO; 5University of Missouri Kansas City, Children’s Mercy Hospital, Kansas City, MO.

Background: Multiple organ dysfunction syndrome is not uncommon in critically ill children. While many of these children receive CRRT for management of AKI, there is no standard approach available for managing liver failure in which several metabolites that are highly protein bound accumulate, and thus are not cleared with conventional CRRT. Molecular Adsorbent Recycling System (MARS) has been successfully used in these situations, but is unavailable in most centers. Modification of CRRT with Single-Pass Albumin Dialysis (SPAD) has been reported previously.

Methods: We report our experience in four children who were treated with SPAD-CRRT. All patients received CRRT (CVVHDF) with a clearance of 2 L/hr/1.73 m2. For SPAD, 400 mL of 25% albumin was added to the 5 L dialysate (PrismaSol®) bag to give final albumin concentration of 1.85%. Serum bilirubin was used as a surrogate marker of efficacy of SPAD. Serum and dialysate bilirubin concentrations were monitored to calculate the mass bilirubin removal.

Results: The findings are briefly summarized in the Table.

Conclusions: Our experience shows >10-fold increase in bilirubin clearance with SPAD-CRRT. While SPAD-CRRT is effective in decreasing serum bilirubin and other toxins, its impact on removal of nutrients and medications is currently unknown. Further studies are needed to see if SPAD-CRRT can improve patient outcomes.

SA-PO664
Concurrent Hemoperfusion and Hemodialysis in Patients with Acute Pesticide Intoxication
Hyo-Wook Gil, Soon-Chung-Hyang University Cheonan Hospital, Cheonan, Chungcheongnam-do, Republic of Korea.

Background: Water soluble and insoluble chemicals in the pesticide formulation may be eliminated more effectively in time if hemodiagnosis (HD) and hemoperfusion (HP) are performed concurrently. This study is aimed at evaluating the efficacy of concurrent HP and HD in patients with acute pesticide intoxication.

Methods: Between January 2011 and December 2012, we used HP and HD concurrently (HPD group, 347 cases), and then during the next 2 years (January 2013 to December 2014), we used concurrent HP and HD (HDP group, 383 cases). We compared the clinical outcomes between the 2 groups. For HP, we used an Absroba 300C HP membrane and for HD, we used a Polyflux 170H HD dialyzer (Baxter).

Results: The mortality was higher in the HPD group than in the HDP group: (48.1% vs. 20.9%) for the overall mortality and (81.8% vs. 57.9%) for the paraprot (bipyrindol) mortality (p < 0.001). In multiple logistic analyses, age (p = 0.013), ingested volume (p < 0.001) and HD (p = 0.014) were significant risk factors for mortality in the paraquat intoxicated group.

Conclusions: Concurrent HP and HD would be an effective and safe treatment for patients with acute pesticide intoxication, in particular, paraquat intoxication.

Funding: Government Support - Non-U.S.
hour urine volume was heavily weighted in best predicting the change in Kru (Figure 1). Increase or decrease of pre-dialysis serum creatinine poorly predicted the change in Kru.

**Conclusions:** While other factors were included in the model, change in 24 hour urine volume was most important in the correlation with kidney function urea clearance change in patients undergoing in-center HD. Pre-dialysis serum creatinine poorly correlated with change in Kru. Extrapolating these findings to AKI-D patients, formal urine collection and clearance calculation is the best method of gauging renal recovery, but serial measure of timed urine volume may be a convenient and appropriate way for weekly, frequent monitoring.

**Funding:** Commercial Support - NxStage Medical

---

**SA-PO667**

**Calculation of Weekly Standard Kt/V by Urea Mass Removed During Hemodialysis Results in a Simple Equation J. Ken Leyboldt, Edward F. Vonesh. San Clemente, CA.**

**Background:** Accurate calculation of weekly urea standard Kt/V (stdKt/V) during hemodialysis (HD) requires first calculating sequentially single-pool and equilibrated Kt/V (Daugirdas et al, Kidney Int 2010), but this approach can be intimidating to clinicians. We explored whether an alternative approach to calculating stdKt/V based on urea mass removed would lead to a simple equation with approximately equivalent accuracy for both conventional and more frequent HD.

**Methods:** Theoretical consideration of urea mass balance during HD treatments derived the following equation for stdKt/V, namely stdKt/V = N × (URR + UFV/V)/(1 - N * t/1080) where N is number of treatments per week, URR is urea reduction ratio per treatment, UFV is ultrafiltration volume per treatment, V is post-dialysis urea distribution volume and t is treatment time in minutes. The URR requires correction for post-dialysis rebound (Tattersall et al, Kidney Int 1996). The numerator of this equation represents the fractional urea mass removed from V and the denominator corrects for intradialytic urea generation. We compared the accuracy of this novel equation for calculating stdKt/V with the conventional approach (Daugirdas et al, Kidney Int 2010) by simulations using a two-compartment model of urea kinetics. Model simulations were performed for patients with V of 20-50 L, weekly UFV of 0-14 L, treatment times of 2-8 hours, 5 different dialyzers, urea clearances; this generated 350 different treatment conditions for HD performed 3, 4, 5 and 6 times per week.

**Results:** Results are tabulated as the absolute value of differences between approximation equations and the numerically simulated stdKt/V.

**Conclusions:** The urea mass removed and Daugirdas et al equations compute values of stdKt/V that are clinically equivalent. This work provides a novel, simple equation for calculating stdKt/V during HD and strengthens the theoretical understanding of stdKt/V.

**Funding:** National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (AG021172); National Center for Advancing Translational Sciences (NCATS) (UL1 TR001866)

**SD = standard deviation; IQR = interquartile range**

---

**SA-PO668**

**Volume of Urea Cleared as a Therapy Dosing Guide for More Frequent Hemodialysis J. Ken Leyboldt, Allan J. Collins. Chronic Disease Research Group, Minneapolis, MN; None, San Clemente, CA.**

**Background:** Prescribing more frequent hemodialysis (HD) based on conventional thrice weekly HD therapy normalized to a weekly dose is challenging. Urea kinetic modeling based on the normalized urea distribution volume (V) has been shown to be superior for smaller and female patients. Alternatively, prescribing the volume of urea cleared (Kt) to patient body surface area (BSA) has been recently been shown to be promising (Maduell et al, Kidney Int 2016; Sridharan et al, Am J Kidney Dis 2017). Prescribing more frequent HD (5 or 6 times-per-week) to BSA has not been adequately explored.

**Methods:** We compared the use of Kt to the nearest L required to achieve a minimal dose of therapy based on BSA as defined by Lowrie et al (Kidney Int 2005) with that recommended by KDOQI Clinical Practice Guideline for Hemodialysis Adequacy Update based on patient V, i.e. weekly stdKt/V=2.1 (NKF, Am J Kidney Dis 2015). Estimates of Kt were calculated for conventional, thrice weekly HD (treatment time=240 min) and 5 and 6 times-per-week HD (treatment times=180 min). Results were compared for patients with different anthropometric estimates of total body water (Vw). BSA was assumed proportional to V to the power of 0.7, and residual kidney function was assumed negligible.

**Results:** Modeled Kt (L) for the therapies are tabulated. As during conventional thrice weekly HD, minimal Kt for more frequent HD based on BSA is higher for patients with Vw at or above: Vw and lower for patients with large Vw than based on weekly stdKt/V=2.1. Simple Kt prescriptions for 5 times-a-week HD based on the principles from Lowrie et al in L are equal to 20+0.4×(Vw-35). For 6 times-a-week HD, Kt prescriptions in L are equal to 16+0.3×(Vw-35). Such prescriptions require careful consideration of dialyzer type, blood flow rate, and dialysate flow rate (or total dialysate volume).

**Conclusions:** Prescribing more frequent HD based on BSA as extrapolated from Lowrie et al suggests the minimal dose of Kt is higher for small patients and lower for large patients than based on a weekly stdKt/V=2.1. Other aspects of dialysis adequacy require additional consideration.

**Funding:** Commercial Support - NxStage Medical

**Modeled Kt (L) versus Patient Vw (L)**

<table>
<thead>
<tr>
<th>Patient Vw (L)</th>
<th>3 Times-per-week HD</th>
<th>4 Times-per-week HD</th>
<th>5 Times-per-week HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowrie et al</td>
<td>KDOQI</td>
<td>Lowrie et al</td>
<td>KDOQI</td>
</tr>
<tr>
<td>25</td>
<td>36</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>35</td>
<td>43</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>55</td>
<td>54</td>
<td>34</td>
<td>26</td>
</tr>
<tr>
<td>75</td>
<td>55</td>
<td>74</td>
<td>31</td>
</tr>
<tr>
<td>95</td>
<td>55</td>
<td>74</td>
<td>31</td>
</tr>
</tbody>
</table>

SD = standard deviation; IQR = interquartile range

---

**SA-PO669**

**The Cost of Dialysis in Canada: A Contemporary Cost Minimization Analysis Thomas W. Ferguson, Sandi M. Dumanski, Alain Beaudry, Navdeep Tangri, Claudio Rigatto, Paul Komenda. Winnipeg, MB; Winnipeg, MB, Canada; University of Manitoba, Winnipeg, MB, Canada.**

**Background:** Over 5,000 patients experience renal failure in Canada every year. Most of these patients will be unable to secure a transplant and will require life-saving hemodialysis or peritoneal dialysis. These therapies are expensive and require a substantial investment from the Canadian public health care system, with over 1.8 billion dollars spent annually. In this study, we aimed to describe the costs of dialysis modalities, including facility hemodialysis, home peritoneal dialysis (PD), and home hemodialysis (HHI) (both for conventional home hemodialysis and with the NxStage System One).

**Methods:** We determined costs from the perspective of the Canadian public health payer; namely, human resource expenses, medical and surgical supplies, dialysis-related drugs, equipment, utilities, and capital costs. Cost estimates were sourced from hospital statements of operations, product suppliers, established utility rates, and activity-based dialysis workload estimates. Human resource time estimates are based on a review of literature, yielding mean direct and indirect resource consumption. Beyond a model-defined threshold of treatment duration, home-based renal replacement therapy is less expensive than facility-based hemodialysis. When treatment and quality of life outcomes are similar between both treatments, these therapies should be recommended in patients who are capable of self-care. Ease of administering home modality should also be considered in its relation to patient uptake rates. Assisted home dialysis programs should be evaluated in more complex cases.

**Funding:** Commercial Support - NxStage Medical Inc.

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

851
SA-PO670
Technique Failure in a Multicenter Canadian Home Hemodialysis Cohort
Robert P. Pauly,1 Iram Usman,1 Rhonda J. Rosychuk,1 Frances D. Reintjes,2 Malika Muneer,3 Christopher T. Chan,3 Michael A. Copland,1 Robert M. Lindsay,1 Jennifer M. MacRae,2 Gihad E. Nesallah,3 Andreas Pierratos,4 Deborah Lynn Zimmerman,1 Paul Komenda,5 University of Alberta, Edmonton, AB, Canada; 6 Alberta Health Services, Edmonton, AB, Canada; 7 Toronto General Hospital, Toronto, ON, Canada; 8 University of British Columbia, Vancouver, BC, Canada; 9 London Health Sciences Centre, London, ON, Canada; 4 University of Calgary, Calgary, AB, Canada; 10 The University of Western Ontario, Toronto, ON, Canada; 5 London Health Sciences Centre, London, ON, Canada; 6 University of Ottawa, Ottawa, ON, Canada; 11 University of Manitoba, Winnipeg, MB, Canada.

Background: Increasing uptake of home hemodialysis (HD) has led to interest in characteristics that predict mortality. Recent reports of practice pattern variability led us to hypothesize there are patient- and center-specific factors that influence outcomes in home HD.

Methods: We assembled a retrospective cohort of incident home HD patients from 7 centers in Canada from 2000 to 2010 to evaluate case-mix and process characteristics on technique failure and mortality. Care characteristics included intervals of follow up/blood work/vascular access monitoring, nursing and physician models of care, patient-to-nurse ratio, and presence/absence of routine home visits and technique audits among others.

Results: The cohort consisted of 579 patients. Mean age was 49.9±14.1 years, 74% were Caucasian, with a median dialysis vintage of 1.9 years (IQR 0.6, 5.2); 68% used an AVF or AVG. Mean duration of dialysis 31.2±12.6 hrs/wk. Unadjusted 1 and 2 year technique survival (censored for death and transplantation) and overall survival was 90% and 83%, and 94% and 86%, respectively. Treating center was a strong predictor of adverse outcomes (Table). With baseline adjustment for center effect, few patient-specific variables remained significant predictors of either study outcome; we did not identify significant program-specific characteristics of care processes to explain the center effect.

Conclusions: The home HD treating center has a significant impact on technique failure and patient mortality. We did not identify specific components of programmatic care to explain this observation. The relationship between process of care and patient outcomes is critical and requires further investigation.

Funding: Private Foundation Support

SA-PO671
Predictors of Care Gaps in the Home Dialysis Virtual Ward
Annie-Claire Nadeau-Fredette,1 Karthik K. Tennankore,2 Joanne M. Bargman,1 Michael A. Copland,1 Deborah Lynn Zimmerman,2 Matthew J. Oliver,1 Nikki A. Shah,1 Simon N. Finkle,1 Robert P. Pauly,4 Jeffrey Perl,3 Christopher T. Chan,3 Dalhousie University, Hammonds Plains, NS, Canada; 1 The Ottawa Hospital, Ottawa, ON, Canada; 2 Hospital Maisonneuve-Rosemont, Montreal, QC, Canada; 3 University of Alberta, Edmonton, AB, Canada; 4 Sunnybrook Health Sciences Center, Toronto, ON, Canada; 5 University of British Columbia, Vancouver, BC, Canada; 6 Dalhousie/Nova Scotia Health, Halifax, NS, Canada; 7 St. Michael’s Hospital, Toronto, ON, Canada; 8 University of Toronto, Toronto, ON, Canada; 9 Sunnybrook Health Sciences Center, Toronto, ON, Canada; 10 The Ottawa Hospital, Ottawa, ON, Canada; 11 University of Toronto, Toronto, ON, Canada; 12 University of Manitoba, Winnipeg, MB, Canada.

Background: Despite the benefits of home dialysis, home dialysis patients are prone to medical complications, especially at time of a transition/change in care. The home dialysis virtual ward (HDVW) initiative aimed to describe gaps in care following these transition periods.

Methods: The HDVW is a multicenter Canadian study conducted between January 2014 and December 2015. Patients admitted to the HDVW experienced a transition event defined as one of: (1) transition from peritoneal dialysis (PD) or home hemodialysis (HHD) training to autonomous home dialysis (2) a discharge from hospitalization, (3) receipt of a medical/radiological procedure and (4) treatment with antibiotics. HDVW admission consisted of a maximum of 14 days of follow-up using repeated clinician-led telephone interviews. Gaps of care were identified when a change of management was required in any of these 3 domains: dialysis prescription, medication and follow-up care. Predictors of the care gaps were assessed in an adjusted ordinal logistic regression.

Results: Ninety HHD and 103 PD patients were included. Overall, 245 care gaps were identified in 135 patients. (Figure 1) Higher age > 65 years (odds ratio [OR] 2.92, 95% confidence interval [CI] 1.15-7.42, p=0.02) and female (OR 1.73, 95% CI 1.18-2.52, p=0.005) were associated with an increased risk in care gaps while medical procedure as a cause for HDVW admission (OR 0.22, 95% CI 0.09-0.54, p=0.001) or antibiotic-treatment (OR 0.35, 95% CI 0.14-0.87, p=0.03) had lower risk of care gaps compared to post hospital discharge HDVW admissions.

Conclusions: Gaps in care are frequent in the home dialysis population particularly following hospital discharge. Efforts should be directed toward improvement of transitional care especially among older individuals.

Funding: Private Foundation Support

SA-PO672
A Single Center Cross-Sectional Study of Health Literacy Levels in Pre-Dialysis, Home Dialysis, and In-Center Hemodialysis Patients
Fabrice Mac-Way,1 Yannick Bégin,1 Mathieu Rousseau-Gagnon,2 Mohsen Agharazi,3 CHUQ-HDQ, Quebec City, AB, Canada; 4 CHUQ-Hôtel-Dieu-de-Québec, Lac-Beauparlant, QC, Canada; 5 None, Quebec, QC, Canada; 6 Université Laval, Quebec, QC, Canada.

Background: Health literacy is the ability to obtain, understand and use healthcare information to make appropriate health decisions. Recent studies have suggested that chronic kidney disease (CKD) patients may have low levels of health literacy. We aimed to evaluate and compare the health literacy levels in pre-dialysis and dialysis patients.

Methods: This is a cross-sectional single-center study conducted at CHU de Québec-Laval University. Adult patients attending pre-dialysis clinic, and ongoing home hemodialysis, peritoneal dialysis and in-center HD completed a French Canadian version of the Health Literacy Questionnaire (HLQ), a validated questionnaire. Cronbach’s Alpha analysis was used. The HLQ measures nine specific domains of health literacy: feeling understood and supported (D1), having sufficient information (D2), actively managing health (D3), social support (D4), appraising information (D5), engaging with health providers (D6), navigating the health care system (D7), finding good information (D8) and understanding information (D9). Each domain is composed of 4 to 6 questions.

Results: A total of 353 patients (152 pre-dialysis, 157 in-center hemodialysis, 38 peritoneal dialysis (PD) and 16 home hemodialysis (HHD)) completed the HLQ. There was a high level of agreement within each domain’s questions with a Cronbach’s Alpha of at least 0.75. Patients on HHD and PD were more likely to feel understood and supported (D1 p<0.001). HHD patients were more likely to understand and appraise health information (D5 and D9 p<0.001). There was a nonsignificant tendency for them to feel like they had sufficient information (D2 p=0.06), that they could actively manage their health (D3 p=0.07) and that they had a good social support (D4 p=0.09). However, we did not find any difference between the CKD groups regarding the ability to actively engage with healthcare providers (D6), to navigate through the healthcare system (D7) or to find good health information (D8).

Conclusions: This study reports for the first time detailed health literacy levels in pre-dialysis, home dialysis and in-center hemodialysis patients. Our findings will be useful in implementing strategies that take into account these nine domains of health literacy in order to improve CKD patient outcomes and quality of life.
SA-PO673
Nephrologist/Patient Conversations About Renal Replacement
Meg Wise,1 Dorian R. Schatell,2 Betty Cheung,3 Micah R. Chan.1
1Medical Education Institute, Madison, WI; 2University of Wisconsin, Madison, WI; 3University of Wisconsin-Madison, Madison, WI.

Background: Patient-centered, valued-based decision-making is the gold standard for choosing complex medical treatments.

Methods: We conducted a mixed-method conversation study to understand how nephrologists and patients communicate about renal replacement therapy (RRT), with 8 nephrologists from 3 clinics and 61 of their patients with eGFR <25. Analysis of verbatim transcripts of audio-recorded clinic visits assessed word ratios and discussion of RRT options. Surveys collected demographics and RRT preferences.

Results: Nephrologists reported rapport with patients and worked to delay dialysis. RRT was the most uncomfortable part of the conversation for both nephrologists and patients: clinicians spoke ~3.25 times more in the whole visit, but ~8 times more about RRT, suggesting that patients shut down. In-center hemodialysis (HD), peritoneal dialysis (PD), and transplant (despite non-eligibility) were most often discussed; home HD was hardly discussed. Nephrologists’ used scripted didactic (teaching) versus dialogic (two-way) communication about RRT, perhaps overwhelming patients. Nephrologists may have inadvertently discouraged PD by emphasizing a need for a care partner (vs. optional), a sterile home (vs. just the dialysis room), and extensive training (vs. easy to learn). Home vs. center-borne infections, or that the “professionals” administering HD are largely technicians were not cited. Nephrologists did not talk about end-of-life or address patients’ emotional or existential concerns. They did not directly elicit patients’ values or tailor information/giving to those values even when patients inserted them. All but one nephrologist said they would use tools to help communicate more easily with their patients about RRT options.

Conclusions: A patient-centered values-based dialysis decision aid might serve as an ice-breaker, include the patients’ values into the RRT conversation, and increase patients’ participation in the RRT conversation and preferences for home dialysis.

Funding: Commercial Support - Amgen, Inc.

Participant Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>39.4±17.84</td>
</tr>
<tr>
<td>Training (total hours)</td>
<td>7.1±10</td>
</tr>
<tr>
<td># of patients</td>
<td>8</td>
</tr>
<tr>
<td>eGFR (mean ± SD)</td>
<td>30.67±4.08</td>
</tr>
<tr>
<td>Age range (SDX range)</td>
<td>66.1±12.78-25.94</td>
</tr>
<tr>
<td>Female</td>
<td>36%</td>
</tr>
<tr>
<td>College degree</td>
<td>40% (55%)</td>
</tr>
</tbody>
</table>

SA-PO674
Higher Likelihood of Home Hemodialysis Training Graduation in Patients Using Nx2me Connected Health Technology
Eric D. Wenthondal,1,2 Allan J. Collins.1,2 NxStage Medical, Inc., Victoria, MN; University of Minnesota, Minneapolis, MN.

Background: In the United States, approximately 1 in 6 patients who initiate home hemodialysis (HDH) training fail to complete training. Strategies that increase the likelihood of training graduation would permit more patients to dialyze at home and improve the economics of home dialysis programs. Digital tools that are introduced during HDH training and that “go home” may accelerate development of patient understanding about HDH equipment and procedures. We assessed whether introduction of the Nx2me iPad app during HDH training was associated with higher likelihood of training graduation.

Methods: We ascertainment HDH patients that initiated use of Nx2me during the first 2 weeks of HDH training with the NxStage System One. For each Nx2me user who was prescribed q treatments per week and had accumulated t training days with the System One at first use of Nx2me, we identified potential controls who were prescribed q treatments per week and had accumulated at least t training days (without use of Nx2me), and we randomly selected 3. We followed Nx2me users and their respective matched controls from t days after training initiation until either HDH training graduation or training dropout. We used Cox regression to model incidence of training graduation, with stratification by matched cluster and adjustment for age, race, sex, vascular access modality, and center-level costs of training activity and success (number of trainees during the past 12 months, probability of graduation among trainees, and mean duration of training among graduates).

Results: We identified 94 Nx2me users. The mean number of days between HDH training initiation and Nx2me introduction was 7.2. In Nx2me users (matched controls, but without adjustment), the cumulative incidence of training graduation was 5.3% (5.5%) after 1 week of follow-up, 23.1% (18.0%) after 2 weeks, 46.9% (34.9%) after 3 weeks, 71.6% (49.8%) after 4 weeks, 88.0% (66.0%) after 6 weeks, and 93.6% (71.9%) after 8 weeks. The adjusted hazard ratio of training graduation for Nx2me users versus matched controls was 1.52 (95% confidence interval, 1.02-2.92).

Conclusions: Introduction of the Nx2me iPad app during the first 2 weeks of HDH training is associated with significantly higher likelihood of training graduation, even after adjustment for center-level performance metrics.

SA-PO675
Effects of a System-Wide Application of a Comprehensive Pre-Dialysis Education Program on Home Dialysis Therapies
Colin A. Hinkamp,2 Emma R. Sega1, Teri B. Martinez,3 Michelle Thomas,1 Shahab Bozorgmehri,2 Tezcan Ozrazgat-baslanti,1 Ashutosh Shukla.1 1Dialysis Clinic, Inc., Gainesville, FL; 2None, Newberry, FL; 3University of Florida, Gainesville, FL.

Background: The efficacy of comprehensive pre-dialysis education (CPE) with respect to its ability to improve home dialysis (HoD) choice and utilization, across the unsolicited, spectrum of prevalent US advanced CKD patients has not been examined.

Methods: We present a retrospective analysis of the first 20 months of our CPE program to show the impact of implementing a new CPE program across the entire spectrum of CKD, in a university CKD population with respect to its impact on HoD choice and utilization. Details of our CPE protocol has been prior published.

Results: Over the first 20 months, 200 patients were referred for CPE, of which 32% (n=63) patients chose not to participate in the awareness effort. Of the 137 patients enrolled, the majority (91%) chose to participate in only one session of CPE whereas 8% and 1% attended 2 and 3 sessions, respectively. At the end of the CPE, 72% chose HoD (69% peritoneal dialysis (PD) and 3% home HD (HHD)) whereas 11% chose in-center HD (HID) with 17% remaining undecided. Over the 20 months of follow-up, 25% needed initiation of renal replacement therapy therapies. Amongst these, 73% were initiated on HoD. Univariate and multivariate analyses showed that age, gender, race, insurance status, marital status, smoking status, body mass index and comorbidity status (Diabetes/ CHF), had no impact on the individual choice of HoD. The institution of CPE program led to an overall 66% (p trend=0.001) increase in utilization of HoD over the first 20 months with HoD representing 72% of all prevalent dialysis subjects.

Conclusions: The results validate that institution of CPE program leads to increase in HoD choice and utilization. We further show that benefits of CPE are not limited to only those with socio-economic privilege.

SA-PO676
Feasibility and Effectiveness of an Online Portal for Delivery of Care to Home Dialysis Patients
Karthik K. Tennankore,1 James Kiberd,1 Kenneth A. West,1 Christopher T. Chan,3 Steven D. Sorko.3 Dalhousie University, Halifax, NS, Canada; 2Toronto General Hospital, Toronto, ON, Canada.

Background: Home dialysis has a number of advantages over in-center hemodialysis. However, there is the potential for improvement in patient communication and experience. The purpose of this study was to determine if an online portal improved patient experience and quality of life (QoL) for home dialysis patients.

Methods: We conducted a pilot interventional study of home dialysis patients. Consecutive patients were enrolled over a four-month period and asked to join the portal via email. The portal (RelayHealth®) consisted of an online messaging platform that permitted asynchronous communication between patients and home dialysis staff. The Consumer Quality Index (CQI, a tool to measure patient experience) and EQ-5D QoL index were recorded at baseline, six and 12 months after enrollment. Satisfaction with the portal was evaluated at the end of follow-up using a Likert scale.

Results: 63 patients were approached, 41 patients consented to participate and 27 (66%) joined the online portal. Mean age was 57.1±1.9 years and 48% were female. Most messages exchanged were for health-related issues. Sixteen and 10 patients completed follow-up at six and 12 months, respectively. Patients had a positive experience with their care at baseline, however, there was no improvement in mean CQI during follow-up. EQ-5D QoL index were recorded at baseline, six and 12 months after enrollment. Satisfaction with the portal was evaluated at the end of follow-up using a Likert scale.

Conclusions: While feasible, we found no significant improvement in patient experience or QoL after using the portal. Participants were generally satisfied with the portal and it did improve some aspects of their dialysis care.

Figure 1. Patient Portal Mean Messaging Frequency (Patients/Staff)

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
583
SA-PO677
Quality of Life in Caregivers Compared with Dialysis Recipients: The CO-ACTIVE Substudy of the ACTIVE Dialysis Trial
Nicholas A. Gray,1 Vlado Perkovic,2 Daqing Hong,3 Robert Min,3 Karthik Bargman,4 Michael A. Copland,5 Joanne J. Tennankore,6 Nicholas A. Gray,7 Vlado Perkovic,2 Li Zuo,3 Meg J. Jardine,4 Peking University People’s Hospital, Beijing, China; 2Newtown, NSW, Australia; 3Sichuan Provincial People’s Hospital, CHENDU, China; 4Sunshine Coast University Hospital, Birtinya, NSW, Australia; 5The George Institute for Global Health, UNSW, Newtown, NSW, Australia; 6The George Institute for Global Health, UNSW Sydney, Newtown, NSW, Australia; 7The George Institute for Global Health, Sydney, NSW, Australia; 8University of Sydney, Sydney, NSW, Australia. Group/Team: ACTIVE Dialysis Steering Committee.

Background: The support of people living with chronic illness may be dependent on voluntary caregivers whose well-being is critical for patient management.

Methods: A subgroup of participants in the ACTIVE Dialysis study and their nominated caregivers completed quality of life (QOL) questionnaires including the EQ5D, SF-36 physical composite score (PCS) and mental composite score (MCS) as well as the Personal Wellbeing Index. Data was collected at baseline (prior randomization to standard or extended hour dialysis) and every quarter until study end at 12 months. Baseline caregiver QOL was compared with dialysis patient QOL using paired t test for continuous variables, while predictors of baseline caregiver QOL were determined using multivariable regression.

Results: There were 54 patient and caregiver pairs, predominantly from China. Caregivers had a mean (SD) age of 53.4 (11.3) years and 56% were female. Most (89%) were married or lived with a partner and 24% were in paid employment. Half were educated to secondary school and 33% to university level. Caregivers mostly cared for their spouse/partner (67%) or child (11%), while 20% reported admission to hospital in the preceding year. At baseline, caregivers had a better physical but similar mental QOL compared with dialysis patients (PCS: 46.9±7 vs 40.4±10.2, P=0.001; MCS: 47.8±9.7 vs 49.6±12.0, P=0.84). Chinese SF-36 population norms are 77.5 for PCS and 73.6 for MCS. EQ5D for caregivers was 0.9 (0.2) compared with 0.8 (0.2) for dialysis patients (P=0.054). The Chinese EQ5D norm is 0.92. Personal Wellbeing Index was 43.7±15.5 for caregivers (Chinese norm 60-70). Higher SF-36 scores among caregivers was predicted by university education but not age, gender or daily hours spent caring.

Conclusions: Caregivers have a higher physical QOL and equivalent mental QOL to dialysis patients but poorer physical QOL, mental QOL and personal wellbeing than the general Chinese population. University education predicts better QOL and may be a surrogate for current financial resources or other socioeconomic factors. (NCT00649298)

Funding: Private Foundation Support

SA-PO678
Patient Satisfaction with a Home Dialysis Virtual Ward
Yu-K. K. Tannennkore,1 Annie-Claude Nadeau-Fredette,2 Joanne M. Bargman,3 Michael A. Copland,3 Simon N. Finkle,4 Matthew J. Oliver,5 Robert P. Pauly,6 Jeffery Perly,7 Nikhil A. Shah,8 Deborah Lynn Zimmerman,9 Christopher T. Chan,10 Dalhouse/Nova Scotia Health, Halifax, NS, Canada; 11Hospital Maisonneuve-Rosemont, Montreal, QC, Canada; 12None, Edmonton, AB, Canada; 13St. Michael’s Hospital, Toronto, ON, Canada; 14Sunnybrook Health Sciences Center, Toronto, ON, Canada; 15Toronto General Hospital, Toronto, ON, Canada; 16University of British Columbia, Vancouver, BC, Canada.

Background: The home dialysis virtual ward (HDVW) initiative aimed to address gaps in care after periods of patient transition. The purpose of this study was to assess patient satisfaction with the HDVW.

Methods: The HDVW was a multicenter Canadian trial of home dialysis patients conducted from January 2014-December 2015. The intervention consisted of 5-6 clinician-led telephone interviews over 14 days using a standardized questionnaire to identify and address gaps in care (including medication discrepancies and dialysis prescription changes). The intervention occurred after four care transition events: graduation from home dialysis training, discharge from hospital, following a medical procedure and after treatment with antibiotics. Satisfaction with the HDVW including perceived impact on several care domains was assessed following the intervention using a visual analogue scale (VAS; 1 not satisfied to 10 completely satisfied).

Results: Fifty-five percent (106/193) of patients completed satisfaction surveys and most transitioned to the HDVW after completion of home dialysis training (65%). The mean age of responders was 55±15 years and 51% were female. 58% of patients were performing peritoneal dialysis and most patients (87%) were independent in performing their dialysis. Overall, patients were satisfied with the HDVW (median VAS 8, IQR 2). Patients perceived that the HDVW had a positive impact on their overall health, understanding of medications and access to a nephrologist. In contrast, patients perceived a neutral impact on their chance of needing readmission or travel for dialysis care (Figure 1).

Conclusions: Patients enrolled in the HDVW were highly satisfied with their care. This intervention may be valuable in supporting home dialysis patients during care transition.

Funding: Commercial Support - Baxter: Investigator Initiated High Dose Hemodialysis Grant

SA-PO679
Use of an NxStage Machine at Home for Vegetative, Disabled, and Home Bound Dialysis Patients: A Preliminary Result of a Unique Experience
Bassam O. Bernheid,1 Fredric Calaud,2 Musa Ahmed,2 Bienmelyn L. Hernandez,2 1Al Ain Life, Abu Dhabi, United Arab Emirates; 2The Heart Medical Center, Al Ain-Abu Dhabi, United Arab Emirates.

Background: Home hemodialysis (HHD) was intended to treat active, autonomous, and relatively, healthy dialysis patients. The number of dialysis patients, who are vegetative, debilitated, bed and home bound is steadily increasing, creating a major burden on the health care system. We are presenting our new and unique experience of treating these highly co-morbid and disabled dialysis patients, with nursing assisted home hemodialysis (NAHHD). The purpose of this modality is to decrease risks, financial, and emotional burdens, of the patients, their families, and of the health care providers.

Methods: Hemodialysis patients who were fulfilling the National Insurance Company criteria for HHD were accepted in the NAHHD program. These criteria include mainly bed and home bound patients. NxStage System One is used to deliver the hemodialysis at home. Duration of session, weekly number of session and volume of fluid are calculated by dose calculator given by NxStage Company, with a target standardized KT/V of 2.

Results: Nineteen dialysis patients on NxStage machine at home or in a long term care facility were included in this preliminary study. 7(36.8%) males and 12 (63.2%) females. Median age 73 year (42-88). Median duration on NAHHD was 3 months (2-8). Etiology of end stage renal disease was DM 13 (68.5%), HTN 5 (26.5%), and familial nephropathy 1(5%). Indications of NAHHD were: vegetative status 1, bed and home bound 7, and 1 HIV case. Vascular access: AVF 8 (42%), AVG 1(5%), and tunneled catheter 10(53%). Average dialysate volume was 25 L. Number of session per week was 4, and average duration of session 3.10 hours. Pre-dialysis BP 131.2±9.3, post dialysis BP 136.6±36.7/ 64.4±5 (p<.005). The average of the standardized KT/V was 1.94. There was a positive impact of the NAHHD on the patients’ quality of life, as measured by time of recovery of 13.75 minutes, average sleeping of 6 hours, and satisfaction of 7.5/10.

Conclusions: NAHHD by using NxStage machine is a very promising modality for treating vegetative, debilitated, bed and home bound dialysis patients, providing a good quality of care, managing the sufferance of the patients, and of their families, and decreasing the risks and the cost of special transportation.

SA-PO680
Correlation between Changes in Body Mass Index and Mortality in Patients Undergoing Long Intermittent Hemodialysis without Dietary Restriction
Manabu Hishida,1 Takahiro Imaizumi,2 Sawako Kato,3 Toshiro Nishiyama,4 Hiroshi Kaneda,5 Shoichi Maruyama,6 1Nagoya University Graduate School of Medicine, Nagoya, Japan; 2Nephrology, kamome clinic, Yokohama, Japan; 3Nephrology, kamome clinic, Kitabarakai, Japan.

Background: Poor nutritional status is a known mortality risk in chronic kidney disease (CKD) patients. Patients undergoing long intermittent hemodialysis (LIH) without dietary restriction are generally well nourished. We aimed to study whether body mass index (BMI) in patients undergoing this therapy is maintained better and longer than those in conventional hemodialysis (CH), and to understand the association between BMI changes and mortality.

Methods: We examined patients undergoing LIH without dietary restriction with at least one-month dialysis vintage at Kamome Hitachi Clinic (KHC) between January 2002 and April 2016. BMI was calculated based on dry weight. Longitudinal BMI changes were monitored in these patients, and compared to those in CH patients, obtained from previous reports. Using the Cox proportional hazard model, we evaluated mortality risk associated with decrease in BMI.

Results: We enrolled 195 patients, with a mean observation period of 5.7 ± 3.7 years. The baseline BMI at the onset of LIH without dietary restriction was 23.36 ± 3.81. The
mean BMI increased for 3 years after initiation of this therapy, similar to the pattern in CH patients. However, BMI in this study population remained stable longer than that in CH patients. BMI in 52/195 patients decreased from the third to 12th month after initiation of this therapy. The hazard ratio (HR) of mortality was 3.004 (95% confidence interval (CI): 1.415-6.374).

Conclusions: We showed that patients undergoing LIH without dietary restriction maintain BMI for a longer period. Additionally, we found that decreased BMI was associated with an increased mortality risk, suggesting that preserving a good nutritional status in these patients contributes to a better prognosis. In conclusion, although further studies are needed, non restricted dietary therapy in LIH maintains good nutritional status and lowers mortality risk in CKD patients.

Methods: We assessed the conversion rate from 6 to 7 times a week, the prevalence of absences from hemodialysis treatments (no shows), the hospitalization rate and the actuarial survival curve of 160 private-insured patients (98M-62F; mean age at dialysis initiation 53.8 ± 13.2 years, range 8-92) receiving in-center short daily hemodialysis treatments (6-7 times/week; lasting 118±18.7 min, range 90-180; ultrapure dialysate and single-use highflux dialyzer). To accommodate all patient needs, our hemodialysis schedule encircles five 2-hour duration shifts on weekdays, 3 shifts on Saturdays and 2 shifts on Sundays. From June 2007 to May 2017, 24 out of 160 (55%) of our cumulative short daily hemodialysis patients extended their schedule from 6 to 7 treatments per week, 9 (6%) chose Saturdays as their regular day-off, and the remained 127 (79%) have occasionally dialysed on Saturdays to replace most of the missed treatment occurring in their original schedule. Over the 10-year study period, the average missed treatment rate was 1.47% or 4.5 days per patient-year and the hospitalization rate was 0.4 admissions per patient-year. In parallel, the 5-year cumulative patient survival rates were 98%, 92%, 82%, 69% and 60% at 12, 24, 36, 48 and 60 mo, respectively. Sunday dialysis additional costs have been offset by favoring low missed treatment rate and very low hospitalization rate.

Conclusions: Historically all but a few dialysis centers have provided treatments and care for patients Monday to Saturday, leading to concerns of higher mortality over weekends. To sustain a short daily hemodialysis program and to overcome its compliance and economic challenges, our dialysis center has successfully established a regular seven days a week schedule.

SA-PO683
Quasi-Frequent Dialysis Affects Hospitalization for Cardiovascular Disease in ESRD Patients with Severe Heart Failure
Masataka Banshandani, Hideki Kawanishi, Misaki Moriiishi, Sadanori Shintaku, Shinichiro Tsuichiyi, Tsusha General Hospital, Hiroshima, Japan.

Background: Previous reports indicated that frequent hemodialysis (FHD) maintained cardiac function. However, no reports have evaluated the impact of quasi-FHD (q-FHD) on hospitalization for cardiovascular diseases (CVDs) and cardiac function in end-stage renal disease (ESRD) patients with severe heart failure.

Methods: This is a retrospective observational study that evaluated hospitalizations for the period from 1 year before to 1 year after q-FHD initiation (≥4 times a week) and ejection fraction (EF) by using echocardiography in ESRD patients with severe heart failure (New York Heart Association Functional Classification III or IV) at a single center hospital in Hiroshima 2005 and 2014.

Results: Of 1,955 hemodialysis (HD) patients, 60 (3.1%; 42 men, mean age, 65.4 years; mean dialysis vintage, 80.0 months) started q-FHD (mean, 4.3 ± 0.7 times a week) and 52 continuously received q-FHD (4.6 ± 0.8 times a week) 1 year later. The 1-year mortality rate after q-FHD initiation was 13.3%. The mean EF decreased from 61.8% at dialysis initiation to 50.6% at q-FHD initiation (P < 0.001) but did not change 1 year later (49.4%; P = 0.7). All-cause hospitalization rates (per person-year) were similar between before and after q-FHD initiation (1.79 [102 hospitalizations] vs 2.07 [115 hospitalizations]; P = 0.2). On the other hand, the emergency hospitalization rate for CVDs significantly decreased from 0.73 to 0.37 after q-FHD initiation (P = 0.002). However, the emergency hospitalization rates for infectious diseases, including vascular access-related infection, were similar before and after q-FHD initiation (0.12 vs 0.11 person-years).

Conclusions: The hospitalization rate for CVDs significantly decreased after the q-FHD initiation in the ESRD patients with severe heart failure. Moreover, q-FHD maintained cardiac function in these patients. Further multicenter studies are needed to evaluate these findings.

SA-PO684
Change in Ultrafiltration Volume in Incremental Hemodialysis
Inkyong Hug, Yoshitsugu Obi, Elani Streja, Connie Rhee, Csaba P. Kovesdy, Kamyar Kalantar-Zadeh,1 UC Irvine, Orange, CA; 2University of Tennessee Health Science Center, Memphis, TN.

Background: Incremental hemodialysis (IH) is a strategy of the gradual increase from twice-weekly to thrice-weekly HD in incident ESRD patients. While it is expected that augmentation of dialysis frequency leads to improvement in patients' health status, there are scarce data about changes in ultrafiltration in such patients.

Methods: We retrospectively examined 569 HD patients who underwent incremental HD between 2007 and 2013. We compared the ultrafiltration volume (UFV) per session and weekly interdialytic weight gain (IDWG) before and after the transition (i.e., <140 [27%], 140-<160 [42%], and ≥160 mmHg [31%]).

Results: The mean UFV decreased from 2.8 ± 1.8, 3.5 ± 2.3, and 4.6 ± 3.0 L at 1M, 2M, 3M, respectively; p = 0.001 [Figure]. The hospitalization rate for CVDs significantly decreased after the q-FHD initiation in the ESRD patients with severe heart failure. Moreover, q-FHD maintained cardiac function in these patients. Further multicenter studies are needed to evaluate these findings.

SA-PO681
Change in Blood Pressure and Body Weight in Incremental Hemodialysis Patients Inkyong Hug1, Yoshitsugu Obi, Elani Streja, Melissa Soooh, Connie Rhee,2 Csaba P. Kovesdy,3 Kamyar Kalantar-Zadeh.1 1UC Irvine, Orange, CA; 2University of Tennessee Health Science Center, Memphis, TN.

Background: Fluid status is expected to improve by increasing hemodialysis (HD) frequency from twice-weekly to thrice-weekly (i.e., incremental HD), but there are scarce data about how much improvement in blood pressure that can be achieved in such patients.

Methods: We retrospectively examined 569 HD patients who transitioned from twice-weekly to thrice-weekly HD within 3 months (M). We compared the pre-dialysis systolic blood pressure (SBP) and post-dialysis body weight (BW) before and after the transition (i.e., <3M to 3M). Data at <1M served as the reference and SBP was categorized into three groups (i.e., >140 [27%], 140-<160 [42%], and ≥160 mmHg [31%]).

Results: The meansSD age of the cohort was 66±14 years and included 46% women. SBP was increased up to 1M. Patients with the highest baseline SBP showed the greatest improvement in SBP after transition (-7.6±1.3, -10.4±1.9, and -11.9±1.8 mmHg at 1M, 2M, 3M, respectively; p=0.001). Decreasing trends in post-dialysis BW after transition was consistently observed across the three groups, but was greater in higher baseline SBP patients (-0.7±1.8, -1.0±2.7, and -1.2±3.0 kg at 1M, 2M, 3M, respectively; p=0.001 [Figure].

Conclusions: The transition from twice-weekly to thrice-weekly frequency resulted in an improvement in pre-dialysis blood pressure control especially in patients with higher baseline SBP, which coincided with decreasing trends in post-HD body weight.

Funding: NIDDK Support

SA-PO682
Seven Days a Week Dialysis Service to Achieve an Effective In-Center Short Daily Hemodialysis Program Pedro Pascoal, Adolfo Simon, Kelia Xavier, Vilber Bello, Juliane Laur, Isteno Pascoal. Centro Brasileiro de Nefrologia & Dialise, Brasilia, Brazil.

Background: In-center hemodialysis programs usually operate Monday through Saturday, encompassing two conventional thrice-weekly schedules: Mon-Wed-Fri or Tues-Thur-Sat. On Sundays, in the midst of the long 72-hour Fri-Mon or Sat-Tue interval, dialysis centers are regularly closed and patient care relies on emergency rooms. After setting up a 6 days a week in-center short daily hemodialysis program, we started to provide dialysis treatments also on Sundays. We have now examined the 10-year impact of the seven-day availability on patient schedule and compliance as well as on hospitalization and survival.

Results: From June 2007 to May 2017, 24 out of 160 (15%) of our cumulative short daily hemodialysis patients extended their schedule from 6 to 7 treatments per week, 9 (6%) chose Saturdays as their regular day-off, and the remained 127 (79%) have occasionally dialysed on Saturdays to replace the majority of the missed treatment occurring in their original schedule. Over the 10-year study period, the average missed treatment rate was 1.47% or 4.5 days per patient-year and the hospitalization rate was 0.4 admissions per patient-year. In parallel, the 5-year cumulative patient survival rates were 98%, 92%, 82%, 69% and 60% at 12, 24, 36, 48 and 60 mo, respectively. Sunday dialysis additional costs have been offset by favoring low missed treatment rate and very low hospitalization rate.

Conclusions: Historically all but a few dialysis centers have provided treatments and care for patients Monday to Saturday, leading to concerns of higher mortality over weekends. To sustain a short daily hemodialysis program and to overcome its compliance and economic challenges, our dialysis center has successfully established a regular seven days a week schedule.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO685

Calcium (Ca) and Phosphate (P) Balance in Short Daily Hemodialysis (SDHD) with the NxStage System One Cycler (NSO): Comparison with Standard Bicarbonate Dialysis (BHD)  
Chiara Carla Maria Brunati,1 Roberto Corciulo,1 Francesca Gervasi,1 Costanza Casati,2 Simone Corciulo,2 Loreto Gesualdo,1 Giacomo Colussi,1 ASST Niguarda, Milano, Italy; 2University of Foggia, Foggia, Italy; 3Azienda Ospedaliera Policlinico Bari, Bari, Italy; 4University of Bari, Altamura, Italy; 5University of Milan Bicocca, Milano, Italy.

Background: SDHD with NSO has gained popularity as home HD prescription. Short HD sessions, as in use with NSO, might not allow adequate removal of P, which benefits from time to optimize removal.

Methods: We compared single run and weekly balances of P and Ca, and changes in plasma levels, in 25 pts treated with NSO in 2 centers with different prescription: 14 pts (Milan) were prescribed 6 runs/week (dialyse 22.7±3.8L/session, run time 154±22min/run), 11 pts (Bari) 4 or 5 runs/wk (mean 4.8±0.48, dialyse 24.1±3.5, time 194±24). Data were compared to those in 14 pts treated with BHD (3/week, 4 hours, dialyse 500±450 ml/hour).

Results: Are shown in table 1.

Conclusions: Despite lower P removal per run in NSO, weekly removal was equal (Bari) or higher (Milan) than in BHD. More frequent NSO runs (6) are more efficient than less frequent runs (4/5). Plasma P decrease was quantitatively similar in NSO and BHD, despite lower run duration. P removal was directly correlated with pre-HD plasma levels in both NSO and BHD. Plasma Ca level increased less in NSO than in BHD, yet PTH fell along the run, Ca balance was correlated to basal Ca levels and net UF; at observed UF, it was negative at plasma Ca<8.5mg/dL. Our data show that SDHD with NSO, despite lower run time and dialyse volume, allows similar P removal as compared to BHD; plasma Ca changes and balance do not substantially differ in NSO and BHD.

Table 1. P and Ca

<table>
<thead>
<tr>
<th>Parameter (start [mg/dL])</th>
<th>NSO-Milan</th>
<th>NSO-Bari</th>
<th>BHD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Ca (mg/dL)</td>
<td>6.3±0.6</td>
<td>6.5±0.6</td>
<td>6.5±0.6</td>
<td>0.32</td>
</tr>
<tr>
<td>Net removal (mg/session)</td>
<td>-0.1±0.2</td>
<td>-0.2±0.2</td>
<td>-0.2±0.2</td>
<td>0.024</td>
</tr>
<tr>
<td>Weekly Ca (mg/week)</td>
<td>-2.8±0.5</td>
<td>-2.9±0.5</td>
<td>-2.9±0.5</td>
<td>0.262</td>
</tr>
<tr>
<td>Total P (mg/dL)</td>
<td>5.5±2.4</td>
<td>5.6±2.4</td>
<td>5.6±2.4</td>
<td>0.76</td>
</tr>
<tr>
<td>Net removal (mg/session)</td>
<td>0.6±0.2</td>
<td>0.7±0.2</td>
<td>0.7±0.2</td>
<td>0.022</td>
</tr>
<tr>
<td>Weekly P (mg/week)</td>
<td>2.8±0.3</td>
<td>3.0±0.3</td>
<td>3.0±0.3</td>
<td>0.0077</td>
</tr>
</tbody>
</table>

Vs start: *p<0.0001, **p<0.006; †vs NSO-Milan and Bari; ‡vs NSO-Milan

SA-PO686

Cardiovascular Assessment in Patients on NxStage System One (NxO) Chiara Carla Maria Brunati,1 Francesca Gervasi,1 Costanza Casati,2 Giacomo Colussi,1 ASST Niguarda, Milano, Italy; 2University of Milan Bicocca, Milano, Italy.

Background: Left ventricular hypertrophy (LVH) is an independent risk factor for mortality in patients on conventional hemodialysis (HD). According to the Frequent Haemodialysis Network daily trial, increased frequency of conventional in-centre HD is associated with a reduction in antihypertensive therapy, extracellular fluid (ECW) and left ventricular mass. Little data exists with the non-conventional daily dialysis system, NxO.

Methods: From May 2011 to December 2016, we enrolled 12 patients (median age 49±13 yr, from 25yr-66yr) on a NxO home program, follow up of 22 months (variation 3 to 6months, 6runs a week, QD 22±4L, duration of session 144±25min SiToV 2,4±0.2). Treatment effects of volume parameters were evaluated monthly in all patients in the interdialytic period, according to BIA parameters (BIA impedance frquency) including the proBNP levels. In 6 patients with 12 months of follow up, an echocardiography was also performed in order to evaluate the cardiac mass and compare with data at baseline. We compared BIA evaluation, measurements of the cava diameter and of the presence of lung comets in NxO patients, a total 134 tests, with those of 30 patients on traditional HDB treatment who were evaluated directly post session, as mentioned above.

Results: We observed a reduction of mean blood pressure (from 97±17 to 81±5mmHg) and this even despite a reduction in antihypertensive drug units (median – 2UD from 0 to – 1.5UD). In 7 patients with 12 months of follow up, a significant reduction in cardiac mass index was recorded (184±44 g/m2 to 120±35 g/m2 p=0.05). The BIA evaluation evidences an overhydration state in only 10% of measurements. In comparison with normohydrate HBBD patients, no difference in ECW/TBW values were recorded. NxO patients had higher levels of ICW/TBW values, indicating a more physiological distribution of volume as reflected by lower levels of proBNP.

Conclusions: According to our results, daily HD sessions using NxO improves certain cardiovascular parameters. Although no reduction in extra-cellular volume was seen, we can hypothesize excellent volume control due to the interdialytic measurements.

SA-PO687

Successful Home Hemodialysis in a Patient with an LVD (Left Ventricular Assist Device) Shubha Ananthakrishnan,1 Munir Jamjoom,2 1UC Davis, Sacramento, CA; 2Cardiology, UCSF, San Francisco, CA.

Background: LVADs for end-stage heart failure are on the rise as the bridge to transplantation, including the increasing number of patients on home dialysis. Clinical and logistic challenges faced by patients with an LVAD, who dialyze at a dialysis center. Here we describe successful home hemodialysis by a patient with an LVAD, awaiting a combined heart-kidney transplant.

Case Report: The patient is a 39 yr old African American male, with ESKD due to FSGS, formerly on peritoneal dialysis for 6 years, who started home hemodialysis in 2015. He also has a h/o non-ischemic cardiomyopathy with EF around 18%. Given cardiac status and pulmonary hypertension, a decision was made to implant a HeartMate II® LVAD in March 2016 as a bridge to transplant, with a flow of 5L/min, speed 2400 RPM, pulsatility of 7. The patient continued on home hemodialysis after the LVAD insertion, caring for the LVAD equipment, drive line dressing changes, as well as performing home hemodialysis without a partner. Home hemodialysis was performed using the NxStage® platform, Qb 400 mL/min, Flow Fraction 35%, 1K. 3CA baths, 5mmHg, 23min/run), 11±5mmHg) and this even despite a reduction in antihypertensive drug units (median of – 2UD from 0 to – 1.5UD). In 7 patients with 12 months of follow up, a significant reduction in cardiac mass index was recorded (184±44 g/m2 to 120±35 g/m2 p=0.05). The BIA evaluation evidences an overhydration state in only 10% of measurements. In comparison with normohydrate HBBD patients, no difference in ECW/TBW values were recorded. NxO patients had higher levels of ICW/TBW values, indicating a more physiological distribution of volume as reflected by lower levels of proBNP.

Conclusions: According to our results, daily HD sessions using NxO improves certain cardiovascular parameters. Although no reduction in extra-cellular volume was seen, we can hypothesize excellent volume control due to the interdialytic measurements.

Table 1. P and Ca

<table>
<thead>
<tr>
<th>Parameter (start [mg/dL])</th>
<th>NSO-Milan</th>
<th>NSO-Bari</th>
<th>BHD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Ca (mg/dL)</td>
<td>6.3±0.6</td>
<td>6.5±0.6</td>
<td>6.5±0.6</td>
<td>0.32</td>
</tr>
<tr>
<td>Net removal (mg/session)</td>
<td>-0.1±0.2</td>
<td>-0.2±0.2</td>
<td>-0.2±0.2</td>
<td>0.024</td>
</tr>
<tr>
<td>Weekly Ca (mg/week)</td>
<td>-2.8±0.5</td>
<td>-2.9±0.5</td>
<td>-2.9±0.5</td>
<td>0.262</td>
</tr>
<tr>
<td>Total P (mg/dL)</td>
<td>5.5±2.4</td>
<td>5.6±2.4</td>
<td>5.6±2.4</td>
<td>0.76</td>
</tr>
<tr>
<td>Net removal (mg/session)</td>
<td>0.6±0.2</td>
<td>0.7±0.2</td>
<td>0.7±0.2</td>
<td>0.022</td>
</tr>
<tr>
<td>Weekly P (mg/week)</td>
<td>2.8±0.3</td>
<td>3.0±0.3</td>
<td>3.0±0.3</td>
<td>0.0077</td>
</tr>
</tbody>
</table>

Vs start: *p<0.0001, **p<0.006; †vs NSO-Milan and Bari; ‡vs NSO-Milan

SA-PO688

Case Report: Patient with a Total Artificial Heart Maintained on Outpatient Dialysis While Listed for Combined Organ Transplant: A Single Center Experience  
Ramy M. Hanna,2 Huma S. Hasnain,3 Mohammad Kamgar,1 Raffi R. Minasian,1 James Wilson,1 1Manhattan Beach, CA; 2UCAL Health, Rolling Hills Estates, CA; 3UCLA Nephrology, Los Angeles, CA.

Background: Advanced mechanical circulatory support is increasingly being used with more sophisticated devices that can deliver pulsatile rather than continuous flow. These devices are more portable as well, allowing patients to await cardiac transplantation in an outpatient setting. It is known that patients with renal failure are at increased risk for developing worsening acute kidney injury during implantation of a ventricular assist device (VAD) or more advanced modalities like a total artificial heart (TAH).

Methods: Dealing with patients who have an implanted TAH who develop renal failure has been a challenge with the majority of such patients having to await a combined cardiac and renal transplant prior to transition to outpatient care. Protocols do exist for VAD implanted patients to be transitioned to outpatient dialysis care, but there are no reported cases of TAH patients with ESRD being successfully transitioned to outpatient dialysis care.

Results: In this report, we identify a patient with a TAH and ESRD transitioned successfully to outpatient Hemodialysis (HD) and maintained for more than two years, though he did not survive to transplant.

Conclusions: It is hoped that this report will raise awareness of this possibility, and assist in the development of protocols for similar patients to be successfully transitioned to outpatient dialysis care.
Funding: Commercial Support - Fresenius Medical Care

SA-PO699

In Vitro Mas Cell Degranulation Assay to Assess Hemodialysis Sorbent Cartridges

Stephen Merchant,4 Mark Costanzo,4 Claudia Mullon,4 Mayuri Thakuria,4 Amparo L. Figueroa,1 Robert J. Kossmann,2 ´Fresenius, Boston, MA; 2Fresenius Medical Care North America, Waltham, MA; 3Fresenius Medical Care, North America, Waltham, MA; 4Fresenius Medical Care, Oklahoma City, OK.

Background: Hemodialysis (HD) sorbent cartridges aimed at dialysate regeneration contain urease to hydrolyze urea into bicarbonate and ammonium. Urease may come from sources that can cause allergic reactions. Here, we compared in vitro, two sorbents in their propensity to cause allergic reaction.

Methods: In vitro mast cell degranulation method was used to examine dialysate samples from an FDA cleared sorbent cartridge (REDFY) and a new cartridge (PAK). Both sorbent cartridges were primed with typical hemodialysis dialysate and recirculated for 30 minutes. Samples for analysis were taken from the recirculated dialysate in the reservoir at 10, 20, and 30 minutes. Diluted (50 µl) concanavalin A (Con A) standards in complete RPMI plus IL-3 medium (positive controls), culture medium (negative control), or sorbent cartridge effluent test articles were added to 200 µl of culturing medium containing ~0.3 million MC/9 cells, in duplicate. Cells were incubated for 24 hours at 37°C under 5% CO₂. Histamine levels in each cell culture supernatant sample were determined using Histamine ELISA Cell Culture Kit. To evaluate the responsiveness of the method, various concentrations of Con A were used as positive controls.

Results: There was no significant difference (p=NS) in the histamine concentrations between the both the PAK and REDFY sorbent dialysates vs. negative control at 10, 20, and 30 minutes. At Con A concentration of 0.1 – 0.8 µg/ml, positive correlation was observed with histamine release, r=0.95, p<0.001. At con A concentration of 0.1 – 0.8 µg/ml, the mean histamine release was between 17.6±9.42 ng/ml. On the other hand, the negative control had a mean histamine release of 17.86 ng/ml.

Conclusions: In this proof of concept study, we report the first ever in vitro histamine release testing of sorbent cartridge dialysates incubated in the presence of mast cells. The findings demonstrate that the histamine release from the dialysate generated by the PAK sorbent is not significantly different to that of the negative control culture medium and the dialysate generated by the REDFY sorbent.

Funding: Commercial Support - Fresenius Medical Care

SA-PO690

Natural History of Thyroid Functional Disease in Peritoneal Dialysis

Jean-christophe Szegel,1 Carlos Cardozo,2 Myriam Pastural, Maurice Laville,2 ´AURAL, LYON, France; 2Université de Lyon, Pierre-Bénite, France.

Background: Thyroid functional disease (TFD) is frequent in chronic kidney disease. The main reported abnormalities are hypercalcemia, especially in its subclinical pattern (SCH), and low circulating triiodothyronine (low T3 syndrome). Recent data has established a link between TFD and mortality in stage V CKD, however, little is known about the natural evolution of TFD in end stage renal disease patients, especially treated with peritoneal dialysis.

Methods: We studied a cohort of 114 incident peritoneal dialysis patients (mean follow up, 23 +/- 19 months; mean: 59.6%, diabetes: 25%, 61.7%(±16.6 years) old) tested for thyroid function on a quarterly basis. ThS above the highest normal lab value (4.2 mIU/L) defined TSH, in untreated patients.

Results: At baseline, 96 patients were euthyroid, 17 (14.9%) displayed a SCH and only one a low T3 condition (0.8%). Low T3 corrected in less than three months. The SCH was corrected in all but two SCH patients along an average period of 9 +/- 7.7 months. A late recurrence was observed in one patient. Multivariate analysis didn’t suspect any predictive variable associated with baseline SCH (age, sex, diabetes, hemodialysis before PD, cardiac-renal syndrome, nutrition status, inflammation status) while two previous stories of thyroiditis and one exposition to amiodarone were found in three patients with persistent/recurrent SCH. Eight patients (8.3%) with normal thyroid status at baseline subsequently evolved to SCH (4) or low T3 syndrome (4) after a mean follow up of 6.2±5.9 and 7.1±6.9 months, respectively. Diabetes (SCH, p=0.02) and albumin level (SCH, p=0.043) were the only factors associated with the occurrence of a thyroid disturbance in baseline euthyroid patients. Of interest, low T3 was always transient and disappeared spontaneously while SCH became a constant disorder in all but one patient (75%). No patient developed overt hypothyroidism over the follow-up.

Conclusions: SCH is highly prevalent in patients starting PD but disappeared within the first year in the absence of previous thyroid disease. Its significance could be different when occurring in initially euthyroid individuals. Low T3 syndrome is less common and seems to be a transient condition associated with albumin variations.

SA-PO691

Dialysis Modality in PD Patients Undergoing Laparoscopic Surgery

Janis Cho,4 Jennifer L. Waller,5 Mufaddal F. Kheda,2 Stephanie L. Baer,2 Rhonda E. Colombo,1 Lu Huber,2 John J. White,4 Troy J. Plumb,1 Stanley Nahamana,1,4 ´Augusta VA Medical Center, Augusta, GA; 2Avera Medical Group Nephrology, Sioux Falls, SD; 3Medical College of Georgia at Augusta University; 4University of Nebraska Medical Center, Omaha, NE; 5Augusta University, Augusta, GA.

Background: Historically, PD patients requiring abdominal surgery required a change to hemodialysis (HD). Laparoscopic surgical procedures have been performed on patients undergoing PD. Therefore, we queried the USRDS.

Methods: Incident PD patients from 2004 – 2011 (n=56,192) who underwent PD were studied. Groups included: no interruption of PdPD; planned temporary (PT) HD then back to PD(PH-PD); permanent switch (PS) to HD; urgent temporary (UT) HD then back to PD(PH-PD), or urgent(U) HD with PS to HD(PH-HD-PD). Demographics and outcomes were determined. The relative risk (RR) of complications versus no interruption of PD (P) up to 3 months post-op were estimated.

Results: 7298 PD patients had LPS, 45% women, 74% White, with mean±SD age 55.3±5 years, and time on dialysis of 16.6±1.9 months. Outcomes and group comparisons are shown in the table. Continuing PD was the most common form of dialysis in PD patients undergoing LPS, had the lowest complication rate, and may represent the lowest-risk cohort for LPS. Planned switches to HD were better than urgent switches, and were likely applied to higher risk patients. Urgent switches that returned to PD had the highest complication rates for peritonitis, bacteremia, and wound infection, and may indicate cohorts of patients developing complications with or during LPS.

Conclusions: Continuing PD during laparoscopic surgery is common and appears safe. The need for urgent HD is uncommon, but if PD is resumed, it is associated with a high risk of post-op complications. Risk stratification may help predict whether to switch dialysis modality in PD patients prior to LPS.

Funding: Commercial Support - Baxter

Comparison of Two Different Neutral Peritoneal Dialysis Fluids in Japan, Bicarbonate/Lactate-Buffered Fluid versus Lactate-Buffered Fluid

Yutaka Tanno, Nanako Matsuo, Ichiro Okihido, Keisuke Yokoyama, Takashi Yoko. Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan.

Background: Recently, new neutral peritoneal dialysis fluid (PDF) containing bicarbonate 25mEq/L and lactate 10mEq/L (Bic/Lac PDF), instead of lactate 40mEq/L contained neutral fluid (Lac PDF), was available in Japan. Bic/Lac PDF is expected to achieve better biocompatibility and to compensate overcorrection of metabolic acidosis by reducing total alkaline buffer. However, there are few reports comparing Bic/Lac PDF and neutral Lac PDF. Therefore, we conducted a prospective study to clarify the effect of Bic/Lac PDF on clinical status including acid-base disturbance.

Methods: Sixty-three stable PD patients were included (60±12 y/o, male 76%, PD duration 43.6±30.2 months). All PDF contained 40mEq/L of lactate before changing to Bic/Lac PDF, and the daily volume of PDF was not changed until the end of the examination period. The patient’s existing medications were not changed during the study period. The patients’ data (bicarbonate, pH, ionized calcium, carbon dioxide and Lactate levels) were obtained before and 3 months after the induction of Bic/Lac PDF. We also investigated the change in effluent drain volume, D/P creatinine ratio from the 4-hour peritoneal equilibration test and residual renal function.

Results: After switching PDF, bicarbonate and carbon dioxide were decreased significantly (26.5±2.8 vs. 24.4±2.6 mEq/L; P=0.01, 46.6±4.3 vs. 43.2±5.8 mmol/L; P=0.01, respectively). Patients treated with low dose PDF (3.3±0.5 L/day) demonstrated insufficient correction of metabolic acidosis (bicarbonate 24.0±2.7 vs. 21.9±3.8 mEq/L, P=0.01) as compared with middle dose PDF (5.6±0.6 L/day), bicarbonate 26.7±2.2 vs. 23.9±2.0 mEq/L; P=0.01) and high dose PDF (7.5±1.0 L/day), bicarbonate 29.7±2.5 vs. 28.6±1.6 mEq/L; P=0.01). Whereas, other parameters did not change significantly between before and after induction of Bic/Lac PDF.

Conclusions: The new Bic/Lac PDF is effective for overcorrection of metabolic acidosis in PD patients, although it must be carefully managed in such a patient who is treated with low dose PDF.

Funding: Commercial Support - Baxter
**SA-PO693**

**Association of Gender with the Utilization of Peritoneal Dialysis**

*Saavannah Vogel,1 Brad C. Astor,1 Sana Waheed,1 1University of Wisconsin, Madison, WI; 2University of Wisconsin - Madison, Madison, WI.*

**Background:** Peritoneal dialysis (PD) is undertaught in the United States compared to other countries. We analyzed data from the USRDS and US census to assess the association between gender and initial dialysis modality to determine whether gender might impact PD utilization. We also investigated gender-specific associations of age, race/ethnicity, median household income and employment status on the incidence of PD.

**Methods:** We estimated the proportion of USRDS patients utilizing PD as their initial modality between 2000-2014, adjusting estimates to the mean value of all covariates (age, race, ethnicity, cause of ESRD, comorbidities, incidence year, income and employment status) and compared these estimates for women and men.

**Results:** 108,022 patients (45% women) initiated PD and 1,375,825 patients (44% women) initiated hemodialysis during this time period. Women were more likely than men (OR: 1.16, 95% CI 1.15-1.18) to initiate PD as their initial dialysis modality. Women were more likely than men to initiate PD for age <67. However, this relationship was reversed for those ≥68 years [Fig. 1]. Other factors influencing the likelihood of being on PD included black race (OR: 0.56), median household income (OR for each $10k higher: 1.03), and being employed (OR: 2.49) [Table 1].

**Conclusions:** Our results indicate that in the US the were more likely than men to utilize PD as their initial modality, but this association varies with age. This study emphasizes the role gender may play in medical decision making and highlights the need to further investigate the factors that influence patients of each gender to choose PD.

**Table 1. Gender, race, income and employment influence the likelihood on being on PD.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>White/Nat</td>
<td>1.16</td>
<td>(1.15,1.18)</td>
</tr>
<tr>
<td>Black/Whit</td>
<td>0.56</td>
<td>(0.53,0.57)</td>
</tr>
<tr>
<td>Each $10k higher in median household income</td>
<td>1.03</td>
<td>(1.02,1.04)</td>
</tr>
<tr>
<td>Post or high school employment</td>
<td>2.49</td>
<td>(2.40,2.55)</td>
</tr>
</tbody>
</table>

**Figure 1. More likely to initiate PD at age 67.**

**SA-PO694**

**Engaging Stakeholders in Protocol Development for Qualitative Research**

*Lalita Subramanian,1 Rosalind H. Kirk,2 Rachel Perlman,2 Therese T. Adamowski,3 Margie D. Mccall,4 Erica E. Perry,4 Kathy A. Restovic,5 Lisa M. Fitzpatrick,5 Nicole E. Bryant,5 Rachel Tocco,5 Kimberly Fox,5 James A. Slount,5 Jeffrey Perl,5 Ronald L. Pisoni,5 1Arbor Research Collaborative for Health, Ann Arbor, MI; 2Independent Qualitative Research Consultant, Edinburgh, United Kingdom; 3University of Michigan Health Center, Ann Arbor, MI; 4Greenfield Health Systems, Detroit, MI; 5Stakeholder Group, Arbor Research Collaborative for Health, Ann Arbor, MI; 6McLaren Northern Michigan, Harbor Springs, MI; 7National Kidney Foundation-Michigan, Ypsilanti, MI; 8Baxter Healthcare Corporation, Deerfield, IL; 9St. Michael’s Hospital, Toronto, ON, Canada.*

**Background:** Remote management (RM) involves various technologies designed to remotely monitor and manage a range of health conditions in order to alert healthcare professionals (HCPs) of any changes that might need follow-up. In this study, patients, social workers, nurses and nephrologists, together with researchers, developed interview and focus group guides for qualitative data collection on factors important to different stakeholders in considering RM technology for patients on peritoneal dialysis (PD).

**Methods:** Researchers introduced concepts and shared information on current RM technology for PD before proceeding with four brainstorming sessions with the stakeholder group on positives and negatives of RM for patients, care partners and HCPs in turn. Interviews of five HCP teams in the United Kingdom, United States and Canada using or transitioning to RM use for PD care provided insight on current technology.

**Concepts derived from all these sessions were categorized and mapped to domains in the COM-B framework (Figure 1).**

**Results:** Literature, stakeholder and RM user perspectives, and a theoretical framework to explore the role of RM in modifying behavioral factors influencing PD and RM use informed the semi-structured interview and focus group guides for collecting data from patients, care partners and HCPs, as well as the study protocol.

**Conclusions:** This stakeholder-engaged process will increase the relevance of questions to participants and improve the quality of data collected, without the limitations of researchers’ pre-conceived views on RM. Data from this study will provide deeper understanding of factors relating to skill, access and motivation in PD and RM use which will inform HCPs and technology developers leading to improved care for patients.

**Funding:** Commercial Support - Baxter Healthcare Corporation

**SA-PO695**

**Ribonucleases Defend the Peritoneum from Invading Pathogens During Chronic Peritoneal Dialysis**

*Neha Dhingra,1 Hanna H. Cortado,2 Sudipti Gupta,2 Birong Li,1 Ashley R. Jackson,1 Ariel Cohen,1 Christina B. Ching,2 John D. Spencer,1 Rose M. Ayoob,1 Brian Becknell,1 1Nephrology, Nationwide Children’s Hospital, Columbus, OH; 2Urology, Nationwide Childrens Hospital, Columbus, OH.*

**Background:** Peritonitis is a rare but serious complication in ESRD patients undergoing peritoneal dialysis (PD). Improvements in standardized dialysis (PD) have reduced but not eliminated the incidence of peritonitis, which remains the leading cause of PD failure and change in dialysis modality. The RNase A superfamily encodes cationic antimicrobial peptides (AMPs) with broad spectrum activity against pathogens implicated in peritonitis in the PD population. Here, we evaluated the expression of these AMPs in the baseline PD effluents of pediatric ESRD patients undergoing chronic PD, in the absence of peritonitis.

**Methods:** PD effluent was collected from seven pediatric patients undergoing chronic PD prior to starting nightly dialysis. We also collected ascites fluid from patients with acute kidney injury undergoing paracentesis or acute PD. RNases were analyzed by immunocytochemistry, qRT-PCR Western blotting, and ELISA. RNase localization within omentum was analyzed by immunofluorescence microscopy. RNase bacterial activity was evaluated by incubation with Staphylococcus epidermidis, followed by plating and colony enumeration.

**Results:** Viable cells recovered from PD effluent expressed RNase3, RNase6, and RNase7 mRNA and protein. These AMPs are present in cell-free supernatants from PD effluent, and RNase7 levels are the most abundant. Immunocytochemistry identifies RNase3+ eosinophils, RNase6+ macrophages, and RNase7+ mesothelial cells as sources of these AMPs. These RNases are distributed similarly in omentum, and RNase7 expression is detected in immortalized mesothelial cells. Functionally, recombinant peptides derived from RNase 3, 6, and 7 exhibit potent bacterial activity toward S. epidermidis.

**Conclusions:** Multiple AMPs in the RNase A superfamily are present in peritoneal fluid of patients with ESRD undergoing PD. These AMPs have distinct cellular sources and exhibit antimicrobial activity toward S. epidermidis. The omentum is a source of multiple AMPs producing cells, among with potential utility in the practice of omentectomy at PD catheter insertion. Strategies aimed at preserving or enhancing RNase levels and antimicrobial activity may comprise a feasible approach to peritonitis prevention and treatment.

**SA-PO696**

**Activation of mTORC1 Disrupted LDL Receptor Pathway: A Potential New Mechanism for the Progression of Peritoneal Fibrosis by High-Glucose PDS**

*Liu Jing,1 Institute of Nephrology, Affiliated Drum Tower Hospital, Medical School of Nanjing University, Nanjing, China., Nanjing, China.*

**Background:** High-glucose peritoneal dialysis solution (PDS) play important roles in the peritoneal fibrosis. Recent studies demonstrated that high glucose could promote the intracellular accumulation of cholesterol via low density lipoprotein receptor (LDLR) in peritoneal mesothelial cell (PMC), which induce the expression of extracellular

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

Underline represents presenting author.
Changsha, China; 2The third Xiangya Hospital of Central South University, Changsha, China

Peritoneal Dialysis - II

Vesicles (EVs) in the Treatment of Experimental Peritoneal Dialysis

Comparison of Mesenchymal Stem Cells (MSCs) and Extracellular Vesicles (EVs) in the Treatment of Experimental Peritoneal Dialysis

Background:

Besides the low molecular weight (LMW) solutes, macromolecule transport is also an important part of peritoneal dialysis (PD). Peritoneal clearances of β2-microglobulin, albumin, fibrinogen, and α1-antitrypsin were registered. Patients were distributed by 3 groups of bPPL (group 1: <4.5 gr/day, group 2: 4.5-9.0 gr/day, and group 3: >9.0 gr/day) and clinical data were recorded at baseline. Number and timing of peritonitis episodes were collected for the last 9 years. bPPL, serum hemoglobin (Hb) and albumin (alb) and other relevant analytic data were recorded. The aim of the study was to investigate whether baseline PPL (bPPL) was a risk factor of peritonitis in PD patients.

Methods:

We retrospectively studied all incident PD patients in our center during the last 9 years. bPPL, serum hemoglobin (Hb) and albumin (alb) and other relevant analytic and clinical data were recorded at baseline. Number and timing of peritonitis episodes were registered. Patients were divided by 3 groups of bPPL (group 1: <4.5 gr/day, group 2: 4.5-9.0 gr/day, and group 3: >9.0 gr/day) in order to compare their peritonitis risk.

Results:

bPPL was lower than Kt/V POL (p<0.0001), Kt/V was higher than CCr POL (p<0.0045) and nPCR was higher than nPCR POL (p=0.0001). We observed a strong positive correlations between total protein level and Kt/V (r=0.69, p<0.05), CCr (r=0.56, p<0.05), Kt/V POL (r=0.55, p<0.05) as well as between blood urea level and nPCR calculated classically (r=0.77, p<0.05) and with POL formula (r=0.69, p<0.05). Phosphatemia was negatively correlated with Kt/V (r=-0.51, p<0.05), Kt/V POL (r=-0.62, p=0.03), CCR (r=-0.61, p=0.05) and CCr POL (r=-0.65, p=0.05).

Conclusions:

POL software seems to be a better tool in assessing PD patients’ nutritional status than Randerson formula, because it takes into account dialysate and urine protein loss. Kt/V POL, but not Kt/V values, positively correlated with total protein level. Phosphatemia and urea concentration were strong predictors of adequacy and surveillance in PD patients.

SA-PO700


Background:

Peritoneal protein losses (PPL) are an inevitable process on peritoneal dialysis (PD). Few studies have supported a positive correlation between PPL and infections or general morbidity and mortality. The aim of this study was to investigate whether baseline PPL (bPPL) was a risk factor of peritonitis in PD patients.

Methods:

We retrospectively studied all incident PD patients in our center during the last 9 years. bPPL, serum hemoglobin (Hb) and albumin (alb) and other relevant analytic and clinical data were recorded at baseline. Number and timing of peritonitis episodes were registered. Patients were divided by 3 groups of bPPL (group 1: <4.5 gr/day, group 2: 4.5-9.0 gr/day, and group 3: >9.0 gr/day) in order to compare their peritonitis risk.

Results:

104 patients were included, 54% male, median age: 57 years, median follow-up: 29 months. Group 3 patients had lower baseline Alb and alb (p=0.03 and p=0.02). Higher bPPL patients had a greater chance of having at least one peritonitis (group 3 vs group 1: 10% vs 4%. p=0.02) and removal of the PD catheter by PD related infection was higher (group 3:374%, group 2:247%, group 1:199%, p=0.01). bPPL was shown to be an independent predictor after adjustment for age, sex, and diabetes (p=0.02).

Time until the first peritonitis was shorter in higher bPPL groups (p=0.02) and, after adjustment for covariates, group 3 maintained a significant higher risk of peritonitis over group 1 (HR 2.38, p=0.04). bPPL and age significantly increased the absolute number of peritonitis episodes.

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

Underline represents presenting author.
Effect of Peritoneal Dialysis on Cardiac Functional Parameters in Patients with Congestive Heart Failure

**Methods:** We enrolled 18 pts (mean age 80.3 years) in PD. Inclusion criteria were NYHA stage IV and dialysis clearance <8 ml/min/1.73 m². Higher cardiac function was assessed by echocardiographic (CE) examination in an effort to identify markers to distinguish population that might benefit from early PD application.

**Results:** Mean time on the method was 10.1 (6-12) months. We observed body weight decrease (p=0.0083), improved eGFR (p=0.026), decrease of bilirubin levels (p=0.0475), subclinical increase of diuretics, as well as elevation of hospitalizations due to CHF decompensation & remarkable improvement of NYHA class. Significant reductions of LA and LV (p<0.05) were noted in every patient. The rest of the parameters remained unaffected. LVFVE showed equivocal changes. One pts died on the 8th month of therapy due to sudden death.

**Conclusions:** All pts demonstrated clinical improvement of their living status, as a result of the gradual & continuous removal of excess fluid. Therefore, dramatically diminishing hospitalizations, due to cardiac events, & restoring pts autonomy. Furthermore, there was an improvement of left cardiac function. However, markers of right cardiac function did not change, probably due to technical or individualised causes. For the same reasons interpretation of LVFVE changes is ambiguous & cannot be used as an objective marker to identify this population. The results of this prospective, but small scale, study encouraged the application of PD in selected pts with CHF.

Glucose Metabolism as Part of Metabolic Syndrome in Non-Diabetic PD Patients: Results from PD-CRAFT

**Methods:** We enrolled 18 pts (mean age 80.3 years) in PD. Inclusion criteria were NYHA stage IV and dialysis clearance <8 ml/min/1.73 m². Higher cardiac function was assessed by echocardiographic (CE) examination in an effort to identify markers to distinguish population that might benefit from early PD application.

**Results:** Mean time on the method was 10.1 (6-12) months. We observed body weight decrease (p=0.0083), improved eGFR (p=0.026), decrease of bilirubin levels (p=0.0475), subclinical increase of diuretics, as well as elevation of hospitalizations due to CHF decompensation & remarkable improvement of NYHA class. Significant reductions of LA and LV (p<0.05) were noted in every patient. The rest of the parameters remained unaffected. LVFVE showed equivocal changes. One pts died on the 8th month of therapy due to sudden death.

**Conclusions:** All pts demonstrated clinical improvement of their living status, as a result of the gradual & continuous removal of excess fluid. Therefore, dramatically diminishing hospitalizations, due to cardiac events, & restoring pts autonomy. Furthermore, there was an improvement of left cardiac function. However, markers of right cardiac function did not change, probably due to technical or individualised causes. For the same reasons interpretation of LVFVE changes is ambiguous & cannot be used as an objective marker to identify this population. The results of this prospective, but small scale, study encouraged the application of PD in selected pts with CHF.

Conclusions:

- Higher βPPL were able to independently predict risk for peritonitis, reflecting its impact on the morbidity of PD patients. The association between higher βPPL with lower basal serum alb and hb may highlights the hypothesis that βPPL can be a marker of severity of PD possibly being related to a malnutrition and pro-inflammatory state. It would be useful to explore these effects prospectively and understand the underlying mechanisms in future. This could include a better characterization of the type of protein loss and its quantification of immunoglobulins, which could theoretically explain the higher infectious risk.

**SA-PO703**

Determinants of Carnitine and Acetylcarnitine in Peritoneal Dialysis Patients

**Methods:** We enrolled 18 pts (mean age 80.3 years) in PD. Inclusion criteria were NYHA stage IV and dialysis clearance <8 ml/min/1.73 m². Higher cardiac function was assessed by echocardiographic (CE) examination in an effort to identify markers to distinguish population that might benefit from early PD application.

**Results:** Mean time on the method was 10.1 (6-12) months. We observed body weight decrease (p=0.0083), improved eGFR (p=0.026), decrease of bilirubin levels (p=0.0475), subclinical increase of diuretics, as well as elevation of hospitalizations due to CHF decompensation & remarkable improvement of NYHA class. Significant reductions of LA and LV (p<0.05) were noted in every patient. The rest of the parameters remained unaffected. LVFVE showed equivocal changes. One pts died on the 8th month of therapy due to sudden death.

**Conclusions:** All pts demonstrated clinical improvement of their living status, as a result of the gradual & continuous removal of excess fluid. Therefore, dramatically diminishing hospitalizations, due to cardiac events, & restoring pts autonomy. Furthermore, there was an improvement of left cardiac function. However, markers of right cardiac function did not change, probably due to technical or individualised causes. For the same reasons interpretation of LVFVE changes is ambiguous & cannot be used as an objective marker to identify this population. The results of this prospective, but small scale, study encouraged the application of PD in selected pts with CHF.

Conclusions:

- Higher βPPL were able to independently predict risk for peritonitis, reflecting its impact on the morbidity of PD patients. The association between higher βPPL with lower basal serum alb and hb may highlights the hypothesis that βPPL can be a marker of severity of PD possibly being related to a malnutrition and pro-inflammatory state. It would be useful to explore these effects prospectively and understand the underlying mechanisms in future. This could include a better characterization of the type of protein loss and its quantification of immunoglobulins, which could theoretically explain the higher infectious risk.

**SA-PO703**

Determinants of Carnitine and Acetylcarnitine in Peritoneal Dialysis Patients

**Methods:** We enrolled 18 pts (mean age 80.3 years) in PD. Inclusion criteria were NYHA stage IV and dialysis clearance <8 ml/min/1.73 m². Higher cardiac function was assessed by echocardiographic (CE) examination in an effort to identify markers to distinguish population that might benefit from early PD application.

**Results:** Mean time on the method was 10.1 (6-12) months. We observed body weight decrease (p=0.0083), improved eGFR (p=0.026), decrease of bilirubin levels (p=0.0475), subclinical increase of diuretics, as well as elevation of hospitalizations due to CHF decompensation & remarkable improvement of NYHA class. Significant reductions of LA and LV (p<0.05) were noted in every patient. The rest of the parameters remained unaffected. LVFVE showed equivocal changes. One pts died on the 8th month of therapy due to sudden death.

**Conclusions:** All pts demonstrated clinical improvement of their living status, as a result of the gradual & continuous removal of excess fluid. Therefore, dramatically diminishing hospitalizations, due to cardiac events, & restoring pts autonomy. Furthermore, there was an improvement of left cardiac function. However, markers of right cardiac function did not change, probably due to technical or individualised causes. For the same reasons interpretation of LVFVE changes is ambiguous & cannot be used as an objective marker to identify this population. The results of this prospective, but small scale, study encouraged the application of PD in selected pts with CHF.

Conclusions:

- Higher βPPL were able to independently predict risk for peritonitis, reflecting its impact on the morbidity of PD patients. The association between higher βPPL with lower basal serum alb and hb may highlights the hypothesis that βPPL can be a marker of severity of PD possibly being related to a malnutrition and pro-inflammatory state. It would be useful to explore these effects prospectively and understand the underlying mechanisms in future. This could include a better characterization of the type of protein loss and its quantification of immunoglobulins, which could theoretically explain the higher infectious risk.

**SA-PO703**

Determinants of Carnitine and Acetylcarnitine in Peritoneal Dialysis Patients

**Methods:** We enrolled 18 pts (mean age 80.3 years) in PD. Inclusion criteria were NYHA stage IV and dialysis clearance <8 ml/min/1.73 m². Higher cardiac function was assessed by echocardiographic (CE) examination in an effort to identify markers to distinguish population that might benefit from early PD application.

**Results:** Mean time on the method was 10.1 (6-12) months. We observed body weight decrease (p=0.0083), improved eGFR (p=0.026), decrease of bilirubin levels (p=0.0475), subclinical increase of diuretics, as well as elevation of hospitalizations due to CHF decompensation & remarkable improvement of NYHA class. Significant reductions of LA and LV (p<0.05) were noted in every patient. The rest of the parameters remained unaffected. LVFVE showed equivocal changes. One pts died on the 8th month of therapy due to sudden death.

**Conclusions:** All pts demonstrated clinical improvement of their living status, as a result of the gradual & continuous removal of excess fluid. Therefore, dramatically diminishing hospitalizations, due to cardiac events, & restoring pts autonomy. Furthermore, there was an improvement of left cardiac function. However, markers of right cardiac function did not change, probably due to technical or individualised causes. For the same reasons interpretation of LVFVE changes is ambiguous & cannot be used as an objective marker to identify this population. The results of this prospective, but small scale, study encouraged the application of PD in selected pts with CHF.

Conclusions:

- Higher βPPL were able to independently predict risk for peritonitis, reflecting its impact on the morbidity of PD patients. The association between higher βPPL with lower basal serum alb and hb may highlights the hypothesis that βPPL can be a marker of severity of PD possibly being related to a malnutrition and pro-inflammatory state. It would be useful to explore these effects prospectively and understand the underlying mechanisms in future. This could include a better characterization of the type of protein loss and its quantification of immunoglobulins, which could theoretically explain the higher infectious risk.

**SA-PO703**

Determinants of Carnitine and Acetylcarnitine in Peritoneal Dialysis Patients

**Methods:** We enrolled 18 pts (mean age 80.3 years) in PD. Inclusion criteria were NYHA stage IV and dialysis clearance <8 ml/min/1.73 m². Higher cardiac function was assessed by echocardiographic (CE) examination in an effort to identify markers to distinguish population that might benefit from early PD application.

**Results:** Mean time on the method was 10.1 (6-12) months. We observed body weight decrease (p=0.0083), improved eGFR (p=0.026), decrease of bilirubin levels (p=0.0475), subclinical increase of diuretics, as well as elevation of hospitalizations due to CHF decompensation & remarkable improvement of NYHA class. Significant reductions of LA and LV (p<0.05) were noted in every patient. The rest of the parameters remained unaffected. LVFVE showed equivocal changes. One pts died on the 8th month of therapy due to sudden death.

**Conclusions:** All pts demonstrated clinical improvement of their living status, as a result of the gradual & continuous removal of excess fluid. Therefore, dramatically diminishing hospitalizations, due to cardiac events, & restoring pts autonomy. Furthermore, there was an improvement of left cardiac function. However, markers of right cardiac function did not change, probably due to technical or individualised causes. For the same reasons interpretation of LVFVE changes is ambiguous & cannot be used as an objective marker to identify this population. The results of this prospective, but small scale, study encouraged the application of PD in selected pts with CHF.

Conclusions:

- Higher βPPL were able to independently predict risk for peritonitis, reflecting its impact on the morbidity of PD patients. The association between higher βPPL with lower basal serum alb and hb may highlights the hypothesis that βPPL can be a marker of severity of PD possibly being related to a malnutrition and pro-inflammatory state. It would be useful to explore these effects prospectively and understand the underlying mechanisms in future. This could include a better characterization of the type of protein loss and its quantification of immunoglobulins, which could theoretically explain the higher infectious risk.
the right side. In this study, we compared left-side and right-side insertions of peritoneal catheter by surgical technique.

Methods: We retrospectively compared the right approach for PDC insertion by open surgical technique with the left approach. From June 2013 to September 2016, 69 of the catheters were successfully inserted Rt. side and 79 of catheters were inserted Lt. side. Primary outcome was catheter survival. Secondary outcome were peritonitis free survival and exit site infection free survival.

Results: The mean(±SD) age of patients was 63 ± 12 years, the ratio of male to female is 42.6% vs. 57.4%. Of all patients, 55.1% have diabetes and 70.7% have hypertension. The repositioning operation due to malposition was 2 of 66(3%) in Rt. side insertion(RSI) and 3 of 76(3.8%) in Lt. side insertion(LSI)(p=0.03). Exit infection was 6 of 66(9.1%) in RSI and 4 of 76(5.1%) in LSI(p=0.513). Peritonitis was 15 of 66(22.7%) in RSI and 13 of 76(16.5%) in LSI(p=0.401). The catheter survival was not statistically significant for RSI compared to LSI(p=0.126). Catheter survival(Fig.1) and exit site infection free survival were not different between two group(p=0.432). However, peritonitis free survival of RSI was significantly higher than LSI(p=0.020)(Fig.2).

Conclusions: When the peritoneal dialysis catheter was inserted by open surgical technique, catheter survival was not inferior to the left side insertion on the right side insertion. In addition, peritonitis free survival showed statistically superior results in the right side insertion.

SA-PO706
The Choice of Urgent-Start Peritoneal Dialysis versus Hemodialysis through a Tunneled Central Venous Catheter: A Single Center Experience in the United States

Delin Wang, Eric S. Kerns, Jonah Licht, Susie L. Hu. Division of Kidney Disease and Hypertension, Brown University, Providence, RI.

Background: Peritoneal dialysis (PD) has been underutilized for patients with unplanned need for initiation of renal replacement therapy compared to hemodialysis (HD) through a tunneled central venous catheter (CVC) in the United States.

Methods: We examined outcomes related to urgent start PD versus HD (with a tunneled CVC) in a retrospective cohort of 47 adults who required urgent dialysis initiation from January 2015 to December 2016. Those who are unstable with critical illness were excluded. In addition to baseline demographics and comorbidities, we compared dialysis access related complications and total number of procedures required related to dialysis modality selection. Comparisons were performed using t-test for linear variables, and chi-square test for categorical variables.

Results: 28 patients had tunneled CVC placed for HD and 19 patients had PD catheter placed. Mean follow-up was 60 months for HD patients and 46 months for PD patients. The PD group was significantly younger, with less heart failure, more hypertension, and higher pre-dialysis serum creatinine (Table). 75% of patients who underwent HD with a tunneled CVC versus 47% who performed urgent start PD had any access related procedures.

Conclusions: The complication rate related to dialysis modality choice between urgent start PD and HD with a tunneled CVC is similar. There was a trend towards fewer procedures required for urgent start PD and should be more commonly considered for those requiring dialysis urgently.

Comparisons between urgent start PD and HD

<table>
<thead>
<tr>
<th></th>
<th>HD</th>
<th>PD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60 ± 15</td>
<td>48 ± 17</td>
<td>0.007</td>
</tr>
<tr>
<td>Follow-up duration (months)</td>
<td>40</td>
<td>46</td>
<td>0.65</td>
</tr>
<tr>
<td>Pretx (ug/dl)</td>
<td>4.2 ± 0.9</td>
<td>4.2 ± 0.7</td>
<td>0.05</td>
</tr>
<tr>
<td>ESRD (n/total)</td>
<td>0/6</td>
<td>2/4</td>
<td>0.04</td>
</tr>
<tr>
<td>HEM (g/dl)</td>
<td>97.4 ± 4.7</td>
<td>98.1 ± 4.7</td>
<td>0.35</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>8.4 ± 3.2</td>
<td>17.0 ± 6.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Crea x urea davice (%)</td>
<td>79</td>
<td>89</td>
<td>0.08</td>
</tr>
<tr>
<td>Creatinine x body gals (%)</td>
<td>3.95</td>
<td>3.95</td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>25</td>
<td>98</td>
<td>0.01</td>
</tr>
<tr>
<td>Dementia (mild) (%)</td>
<td>51</td>
<td>54</td>
<td>0.51</td>
</tr>
<tr>
<td>Access-related events (%)</td>
<td>57</td>
<td>17</td>
<td>0.05</td>
</tr>
</tbody>
</table>

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

861
SA-P0709

Non-Infectious Peritoneal Dialysis Exit Site Rash: Unusual Case Report and Review of Literature

Srilakshmi Ravula,1 Mohammed M. Siddiqui,1 Omar Rabadi,1 Manisha Singh,2 ‘Little Rock, AR; 1University of Arkansas For Medical Sciences, Little Rock, AR; 2University of Arkansas Medical Center, Little Rock, AR; 3University of Arkansas for Medical Sciences, Little Rock, AR.

Background: Peritonitis is one of the leading causes of morbidity in patients on peritoneal dialysis(PD). Exit site infection(ESI) can cause six-fold increase in the risk of peritonitis. Exit site infection is characterized by purulent drainage, erythema, pain and swelling at PD catheter site. On review of literature case reports of non-infectious exit site rash are found to be rare, hence we are reporting this case of PD exit site non-infectious rash. The patient was finally diagnosed as granuloma gluteal adiponectin.

Methods: A 74-year-old white man with ESRD from diabetics with CCPD(continuous cycling) assisted PD presented with localized area of redness, itching and serous drainage around PD catheter site measuring 1x1cm. The lesion was noticed few weeks ago that progressively worsened. He denied trauma to catheter site, pain, fever or cloudy effluent. He was compliant with exit site care instructions and was using mupirocin ointment as part of catheter care regimen, denied changes in medications or povidone iodine use. On exam, abdomen was soft and no purulent drainage was expressed from exit site. PD fluid cell count ruled out peritonitis. Exit site cultures were obtained & keflex was started. On follow up exam, it was noted that areas of skin desquamation had gotten worse with increased itching. Dermatology was consulted and shave skin biopsy was done. Histopathological findings were consistent with spongotic dermatitis with eosinophils, diagnosis of granuloma gluteal adiponectin was made. Topical zinc oxide was prescribed in addition to continuing topical antibiotic therapy. Patient had significant improvement in one week. As discussed, erythema with pain and purulent discharge are hallmarks of ESI. There have been very few case reports published reviewing non-infectious PD site dermatitis.

Results: Conclusions: ESI is a differential for catheter site erythema, pain and discharge. Empiric treatment with antibiotics is warranted. Prompt dermatological assessment and skin biopsy should be considered if there is no resolution of symptoms.

Review of Case Reports

<table>
<thead>
<tr>
<th>Authors et al</th>
<th>Agent Identified</th>
<th>Description of Rash</th>
<th>Management</th>
<th>Literature References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5-ASA</td>
<td>Purulent dermatitis</td>
<td>Topical AZA + topical corticosteroids</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Mupirocin ointment</td>
<td>Itch, serous drainage</td>
<td>None</td>
<td>2</td>
</tr>
</tbody>
</table>

SA-P0710

Metformin Ameliorates the Phenotype Transition of Peritoneal Mesothelial Cells and Peritoneal Fibrosis via a Modulation of Oxidative Stress

Dak-Hex Kang1, Hyun-Jung Kang1, Eun-sun Ryu1, Dal-ah Kim,2 ’Ewha Womans University College of Medicine, Seoul, Republic of Korea; 1Ewha Womans University Medical Center, Seoul, seoul, Republic of Korea; 2Ewha Womans University School of Medicine, Seoul, Republic of Korea; 3Ewha Womans University, Seoul, Republic of Korea.

Background: Phenotype transition of peritoneum is an early mechanism of peritoneal fibrosis. Metformin, 5'-adenosine monophosphate-activated protein kinase (AMPK) activator, has recently received a new attention due to its preventive effect on organ fibrosis. Recent studies revealed that inhibiting epithelial mesenchymal transition (EMT) is a possible means to combat peritoneal fibrosis.

Methods: EMT was evaluated by morphological changes of human peritoneal mesothelial cells (HPMCs) and the expressions of E-cadherin and α-SMA by real time PCR, WB and IHC. ROS generation was assessed byDCF-DA staining, NOX activity, NOX mRNA expressions, and MitoSOX® staining. Activation of Smad2/3, MAPK, GSK-3β phosphorylation, nuclear translocation of β-catenin and snail expression were assessed. The effect of AMPK gene silencing or AMPK inhibitor on peritoneal EMT was assessed. The effect of AMPK gene silencing or AMPK inhibitor on peritoneal EMT was assessed. The effect of AMPK gene silencing or AMPK inhibitor on peritoneal EMT was assessed. The effect of AMPK gene silencing or AMPK inhibitor on peritoneal EMT was assessed. The effect of AMPK gene silencing or AMPK inhibitor on peritoneal EMT was assessed.

Results: TGFβ1 (1 ng/mL)-induced EMT in HPMC was ameliorated by metformin. Metformin (1 ng/mL) alleviated NOX- and mitochondria-mediated ROS production with an increase in superoxide dismutase (SOD) activity and SOD2 expression. Metformin inhibited the activation of Smad2/3 and MAPK, GSK-3β phosphorylation, with an increase in superoxide dismutase (SOD) activity and SOD2 expression. Metformin (1 ng/mL) alleviated NOX- and mitochondria-mediated ROS production with an increase in superoxide dismutase (SOD) activity and SOD2 expression. Metformin (1 ng/mL) alleviated NOX- and mitochondria-mediated ROS production with an increase in superoxide dismutase (SOD) activity and SOD2 expression. Metformin (1 ng/mL) alleviated NOX- and mitochondria-mediated ROS production with an increase in superoxide dismutase (SOD) activity and SOD2 expression. Metformin (1 ng/mL) alleviated NOX- and mitochondria-mediated ROS production with an increase in superoxide dismutase (SOD) activity and SOD2 expression. Metformin (1 ng/mL) alleviated NOX- and mitochondria-mediated ROS production with an increase in superoxide dismutase (SOD) activity and SOD2 expression.

Conclusions: A modulation of AMPK in peritoneum can be a novel tool to prevent peritoneal fibrosis by providing a favorable oxidant/anti-oxidant milieu in peritoneal cavity and ameliorating phenotype transition of peritoneal mesothelial cells.

SA-P0711

Novel Score to Predict the Risk of Loss of Technique at 3 Months in Patients with Peritonitis Associated with Peritoneal Dialysis

Monica C. Jimenez cornejo,1 Daniel Murillo brambila,2 Jonathan Chavez,2 Karina Renorite,1 Gabriela J. Abundis Mora,1 Ricardo Rubio,1 Hernandez阿古 runnable,2 Guillermo Garcia-Garcia.1 ’Hospital Civil De Guadalajara, University of Guadalajara, Guadalajara, Mexico; 1EMSS, Zapopan, Mexico.

Background: CKD is a major public health problem in Mexico, the incidence of CKD in Mexico 2017 reached 377 patients per million, the most frequent modality of RRT is PD. Peritonitis is the most frequent cause of technique failure.

Methods: A descriptive, prospective study of 116 PD patients with peritonitis, we determined by multivariate analyzes the risk factors associated with loss of peritoneal technique at 3 months of onset of peritonitis. Data are shown in numbers, percentage, mean, standard deviation, chi square, according the magnitude of the OR we develop a numeric scale, a ROC curve was done to determinate the AUC of the best cut-off point to predict loss of peritoneal technique at 3 months of onset of peritonitis.

Results: A total of 116 PD patients, the peritonitis were recorded, fifty-two (45%) of them resulted in technique failure. Factors independently associated with increased risk were: diarrhea (OR =3.0, 95% CI 0.023), >1000 white cells in PD fluid (OR =1.98, 95% CI), turbid PD fluid (OR = 0.032), time in PD (OR=6.1-0.04) and first episode of peritonitis (OR 4, 95% CI 0.06). Severity score was set as low risk (≤3 points) and high risk (≥4 points). The incidence of technique failure in the first 3 months occurs more often in high-risk patients (OR 7.2 I95% 1.2 to 3.3, OR <0.001), the AUROC was 0.686, sensitivity 70% and specificity 32%.

Conclusions: In patients with peritonitis associated with PD, a simple score including clinical characteristics and laboratory data is available on admission may predict the risk of technique failure in the next 3 months; this finding may assist clinician to ensure a close follow-up of the patient at high-risk and anticipate possible outcomes.

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

FAQ: Your question here.
Protein Kinase C Isosforms Alpha and Beta Are Differentially Regulated in Glucose-Mediated In Vivo and In Vitro Peritoneal Dialysis

**Background:** Damage to the peritoneal membrane (PM) during peritoneal dialysis (PD) comprises inflammatory, neoangiogenic and fibrotic processes. In a PD mouse model, we have previously demonstrated glucose-mediated pro-inflammatory, pro-fibrotic and pro-angiogenic properties of protein kinase C (PKC)-alpha, which is the dominant mesothelial PKC isoform. Preliminary data suggest regulation of PKC-α by PKC-beta at the PM. The specific role of PKC-beta and especially its main source in omentum, mesothelial cells and macrophages of WT animals. For in vitro PD, both immortalized mouse peritoneal mesothelial cells (MPMC) and primary mouse peritoneal macrophages were stimulated with different glucose concentrations and studied for cytokine and PKC expression.

**Results:** In comparison to WT mice, PKC-beta KO mice undergoing PD demonstrated a stronger fibrotic and angiogenic phenotype with higher peritoneal TGF-beta production, large fibrotic areas and increased peritoneal VEGF and CD31 expression. PKC-beta deficiency in vivo increased peritoneal IL-6, TNF-alpha, MCP-1 and MIP-2 by 2.5 fold, which exhibited a PM inflammatory response, which was not seen in the JAK1/2i group. In contrast to MMPI, which is regulated by high glucose. After LPS stimulation PKC-beta KO peritoneal macrophages demonstrated increased production of pro-inflammatory cytokines IL-6, TNF-alpha and IL-18, IL-10 compared to WT cells.

**Conclusion:** PKC-beta, the dominant mesothelial PKC isoform in peritoneal macrophages, is up-regulated and exerts peritoneal anti-inflammatory effects during PD through regulation of the dominant mesothelial PKC isoform PKC-alpha. PKC-beta deficient animals present a macrophage phenotype in response to in vivo PD.

**SA-P0715**

**Effect of TGF-B1 on GDF-5-induced Phenotype Transition of Mesothelial Cells via Modulation of the NLRP3 Inflammasome**

**Background:** Phenotype transition of mesothelial cells(MC) such as epithelial-to-mesenchymal transition(EMT) is known as an early mechanism of peritoneal fibrosis in peritoneal dialysis(PD). Nod-like receptor 3(NLRP3) inflammasome is comprised of the NLRP3, the adaptor ASC and procaspase-1, which promotes the maturation of IL-1β and IL-18. Toxicity-sensitive enhancer binding protein(TonEBP) is a transcriptional enhancer that enables cellular adaptation to hypertonic stress by promoting expression of specific genes. The aim of this study is to investigate whether Tgfβ1 is involved in EMT due to its role in regulating MC phenotype transition via modulation of NLRP3 inflammasome in peritoneal MCs isolated from omentum and dialysate effluents from patients on PD.

**Methods:** The expressions of TGFβ1 and components of NLRP3 inflammasome, nuclear translocation of TGFβ1 and nlrp3 were evaluated by western blotting. E-cadherin protein expression was confirmed by immunofluorescence assay. E-cadherin gene silencing on EMT was examined using siRNA technique. MCs were also isolated from overnight dwell dialyses from 9 clinically stable PD patients (MC-DE) to assess the expression of Tgfβ1 and NLRP3 inflammasome, and to clarify the association with the markers of EMT.

**Results:** TGFβ1 enhanced TGFβ1-mediated nuclear translocation of MC, which was followed by an altered expression of epithelial and mesenchymal cell markers. TGFβ1 also activated the expression of NLRP3 inflammasome, which was increased when the TGFβ1 dose was increased. E-cadherin protein expression was confirmed by immunofluorescence assay. E-cadherin gene silencing on EMT was examined using siRNA technique. MCs were also isolated from overnight dwell dialyses from 9 clinically stable PD patients (MC-DE) to assess the expression of TGFβ1 and NLRP3 inflammasome, and to clarify the association with the markers of EMT.

**Conclusion:** This data suggest Tgfβ1 plays a role in peritoneal EMT via modulation of the NLRP3 inflammasome. E-cadherin expression was confirmed by immunofluorescence assay. E-cadherin gene silencing on EMT was examined using siRNA technique. MCs were also isolated from overnight dwell dialyses from 9 clinically stable PD patients (MC-DE) to assess the expression of TGFβ1 and NLRP3 inflammasome, and to clarify the association with the markers of EMT.
Lithium-Mediated Protection of Mesothelial Cells during Peritoneal Dialysis

Rebecca Herzog,1,2 Katarzyna Bialas,3 Christoph Aufricht,4 Klaus Kratchowill1,5,6,7
1Pediatric Nephrology, Medical University of Vienna, Vienna, Austria; 2Christian Doppler Laboratory of Molecular Stress Research, Zytoprotec, Vienna, Austria; 3Research, Zytoprotec, Vienna, Austria.

Background: Peritoneal mesothelial cells (MC) are harmed by peritoneal dialysis fluids (PDF), at least in part caused by inadequate cellular stress responses. In immortalized MC, we have shown that addition of lithium chloride (LiCl) restored heat shock protein expression. Lithium salts could therefore be a promising group of molecules to be used as cytoprotective additives to PDF. Here, we analyzed the protective potential of LiCl in human primary MC (HPMC) on the gene and protein expression level in a multi-omics approach and in vivo in a chronic mouse model of PD.

Methods: HPMC of 5 individual donors were exposed to PDF (Extraneal, Baxter) without or with 2.5 or 10mM LiCl 30 min and allowed to recover for 4 or 16 h. Cell death was analyzed by LDH-release. mRNA levels were analyzed by gene expression microarrays and significantly altered biological processes were identified using the PANTHER database. Changes of the proteome were analyzed with a 2D difference gel electrophoresis (DIGE) based approach. C57/B6 mice (n=32) were treated with PDF without or with 5mM LiCl for four weeks via an implanted catheter. The peritoneal lavage of the mice was selected based on the propensity score matching by age, sex, and diabetes mellitus.

Results: PDF-induced cell injury was associated with significantly differential expression of 601 genes compared to control. Six biological pathways (oxidative stress response, VEGF signaling, PDGF signaling, angiogenesis, CCKR signaling, GNRHR pathway) were significantly overrepresented. Added LiCl led to significantly decreased cell death and significantly altered the expression of 1003 genes, of which 62 showed an abolishment of the PDF-effects. These genes are regarded as markers of LiCl-mediated cytoprotection. In vivo LiCl lead to a decrease of PDF-induced peritoneal membrane thickening and increased Treg/IL-17 ratio of the effluent cells.

Conclusions: The cytoprotective effects of added LiCl, combined with the modulation of the cellular stress response, fibrosis and inflammation suggests a therapeutic potential of this intervention. Future studies including pharmacokinetics following once daily exposure to LiCl added to Extraneal are needed to further translate these findings into the clinical setting of PD.

Funding: Commercial Support - Zytoprotec GmbH

Impact of Liver Cirrhosis on the Outcome of Peritoneal Dialysis

Young Lee Jung,1 Jae Yoon Park,2 Hyunjin Ryu,1 Yaeirim Kim,1 Jae shin Choi,1 Dong Ki Kim,1 Chun Soo Lim,1 Yon Su Kim,1 Kook-Hwan Oh,1 Seung Seok Han,1,2 Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea; 1Dongguk University Ilsan Hospital, Gyeonggido, Republic of Korea; 1Seoul National University Boramae Medical Center, Seoul, Republic of Korea.

Background: Peritoneal dialysis(PD) is popular treatment modality for ESRD. However, its application to liver cirrhosis(LC) and subsequent outcomes have not been thoroughly evaluated yet.

Methods: We retrospectively reviewed 1,366 patients(418 yrs old) who started PD at Seoul National University Hospital between January 2000 and December 2015. Radiologic evaluation was applied to define LC at the time of PD initiation. 33 patients were assigned to LC, and their outcomes were compared with non-LC(n=357), which was selected based on the propensity score matching by age, sex, and diabetes mellitus. Primary outcome was the technical failure;secondary outcomes were peritonitis, exit site infection, and all-cause mortality.

Results: Patients were followed for a mean duration of 42.9±35.8 months. During this period, 6 patients with LC encountered technical failures, but this rate was not different from that of non-LC(Figure 1). This difference did not alter despite adjusting several covariates, such as comorbidities and lab findings. When evaluating infection, common causes for peritonitis and exit site infection were E.coli(5.8%) and S.aureus(19.3%); these rates were not different from those of non-LC. Overall mortality were similar between LC and non-LC. All of these outcomes were not dependent on severity of LC, which was quantitatively determined by Child-Pugh and MELD score. LC with hepatocellular carcinoma(n=6) did not have inferior outcomes including mortality to counterpart group without carcinoma.

Conclusions: The presence of LC and its severity did not affect subsequent outcomes in patients starting PD. Based on the fact that trials with randomization of dialysis modality are not feasible, the present observational results may provide reassurance to the LC starting PD.

Staphylococcal Peritonitis in Chronic Peritoneal Dialysis Patients: A Seven-Year Review

Tiago J. Carvalho, Patricia Q. Branco, Ana Rita M. Martins, Domingos S. Machado, Maria augusta C. Gaspar. Nephrology, Santa Cruz Hospital, Carnaxide, Portugal.

Background: Staphylococcal peritonitis (SP) is a serious complication of chronic peritoneal dialysis (CPD). The aim of this study was to examine the frequency, predictors and clinical outcomes of SP.

Methods: We reviewed all consecutive cases of SP in a CPD unit from 2010 to 2016. The mean number of patients treated per year was 87±14. There were 300 episodes of peritonitis, of which 109 (36.3%) were SP, affecting 59 patients, aged 52±15 years. Peritonitis rates varied from a minimum of 0.32 to a maximum of 0.52 episodes/patient/year. The unit’s empirical antibiotic protocol was intraperitoneal cefazolin and ceftriaxone.

Results: Among SP affected patients, 30 had one episode, 17 had two episodes and 12 had three or more. There were 63 cases (57.8%) of coagulase-negative SP and 46 (42.2%) of Staphylococcus aureus peritonitis, 4 of which were methicillin-resistant. Caucasians had a higher risk of S. aureus peritonitis (Odds Ratio (OR) 22.71, 95% Confidence Interval (CI) 5.06-101.85, p<0.001). Overall primary response to treatment was 75.2%.

Figure 1. Technical failure-free survival curves between LC and non-LC patients
When compared to coagulase-negative SP, S. aureus peritonitis was associated with a higher risk of catheter substitution/removal (OR: 11.3, 95% CI 2.93-43.57, p < 0.001). Cox regression model revealed that age, diabetes mellitus and previous site exit infection (Hazard Ratio (HR) 2.81, 95% CI 1.08-7.29, p = 0.033). There was also a trend towards increased hospitalization (OR 2.27, 95% CI 0.95-5.43, p = 0.066). There were no differences in relapse rate (34.8% vs 33.3%) or time to transfer to hemodialysis (0.02% vs 0.07%). No deaths occurred. Other factors associated with a higher risk of catheter substitution/removal were previous site exit infection (OR 6.68, 95% CI 1.57-28.48, p = 0.010) and relapse or repeat episode (OR 11.30, 95% CI 2.93-43.57, p < 0.001). Patients who died or dropped out were decreasing. All other factors associated with a higher risk of catheter substitution/removal were not statistically significant (p > 0.05).

Conclusions: In order to make a decision, four key predictors from this study may potentially help to identify patients at risk of treatment failure. Establishment of the severity of PD-related peritonitis patients may offer opportunities to improve treatment outcomes.

Funding: Government Support - Non-U.S. Factors Predicted Treatment Failure among PD-Related Peritonitis by Multivariable Logistic Regression Analysis

### SA-P0720

**Alanyl-Glutamine in Peritoneal Dialysis Fluids Restores Cytotoxic Effects of Endothelial Cells**

**Background:** Peritoneal vascular changes manifested as vasculopathy and increased angiogenesis causing an increased risk of catheter substitution/removal in patients undergoing peritoneal dialysis (PD). Hyperglycemic conditions created during PD fluid (PDF) exposure are similar to those responsible for cardiovascular pathomechanisms relevant in diabetic retinopathy and nephropathy. This study focused on characterizing endothelial cell (EC) injury and response responses after exposure to PDF with/without cytotoxic intervention with alanyl-glutamine dipeptide (AlaGln).

**Methods:** Human umbilical vein ECs (HUVECs) exposed to PDF were subjected to a combined proteomic and bioinformatics approach using 2D-DIGE and fluorescent cymography. Cellular injury was associated with a molecular landscape of a set of enriched biological processes that characterize PDF cytotoxicity and counteracting cellular repair processes. These include "glycocalcic process", "cell redox homeostasis", "RNA metabolic process", "protein folding", "regulation of cell death", and "actin cytoskeleton reorganization".

**Results:** Supplemention of PDF with AlaGln preserved EC viability and restored control levels of proteins in PDF perturbed processes, especially enhancing protein folding capacity and stress responses. The direct comparison revealed 55 differentially abundant spots of which 58.2% were restored with AlaGln. In support to the findings in our model, cross-comparison with transcriptomic data obtained from human endothelial cells showed that 40% of the differential expressed genes in response to PDF exposure were differentially expressed in a similar manner.

**Conclusions:** This combined proteomics and bioinformatics approach shows that PDF harms endothelial cells and leads to drastic changes of the cellular process landscape. Cell damage and proteome changes were effectively counteracted by AlaGln. In summary, this study elucidates potential mechanisms by which AlaGln exerts cytoprotective effects in endothelial cells, offering therapeutic targets to reduce side effects of PD.

### SA-P0721

**Peritonitis and Predictors of Treatment Failure in Peritoneal Dialysis Patients: An Experience of 902 Consecutive Episodes in Thailand**

**Background:** Peritonitis among peritoneal dialysis patients is an important cause of morbidity and mortality. A multicenter, retrospective observational study was conducted in Thailand. The incidence of peritonitis and its risk factors were assessed in four time-points: at the time of initiation of PD (T1) and after 3 (T2), 6 (T3) and 12 months (T4) of PD. Collected 230 samples were analyzed using LC-ESI-MS/MS and MS-GC-MS/MS. Qualitative and quantitative differences in the accumulation of the individual proteins and metabolites were determined.

**Results:** One hundred forty-two ANOVA significant differential molecules were identified in plasma and PF samples when time T1 and T4 were compared. For example increased accumulation of CD59 glycoprotein, proliferation-inducing protein 33, insulin-like growth factor-binding protein 4 and 6 were revealed in PE of T4 diabetic samples compared to their T1. The same proteins did not differ T1 and T4 PF samples if derived from non-diabetes. One of the most interesting result concerned monocytic antigen CD14 and lipopolysaccharide-binding protein. Both proteins differentiated T1 and T4 plasma and PF samples obtained from non-diabetes and diabetes but in completely different way. The abundance of CD14 antigen was increased in PF of T4 non-diabetic patients (fold change 3.4, p = 0.004) compared to their T1 and in plasma of diabetics (fold change 2.4; p = 0.02). In turn, accumulation of CD14 was 3.4 times lower in PF of T4 diabetic (p = 0.02) and 3.2 times lower (p = 0.005) in T4 plasma of non-diabetes.

**Conclusions:** Obtained data indicate that PD duration is strongly associated with alterations in proteomic and metabolomic profiles of plasma and PD. Patients starting PDs differed considerably in abundance of many molecules compared to the same patients 1 year after PD initiation. However large differences in accumulation of proteins between diabetes and non-diabetes may suggest that in these patients molecular mechanisms related to these variations are different. Especially interesting are differences concerning CD14, a key pattern recognition receptor of the innate immune system.

### SA-P0723

**Peritoneal Dialysis in Sichuan Province of China—Report from the Chinese National Renal Data System**

**Background:** The Chinese National Renal Data System (CNRDS) was established in 2010 to collect data from patients undergoing Peritoneal Dialysis in renal department of China. In this study, we aimed to study the patients of Sichuan province in the registry and analysis total characteristics and treatment effect and to examine whether or not the based clinical statistics effected the outcome of peritoneal dialysis, exploring the risk factors for peritoneal dialysis patients.

**Methods:** This study included 2654 patients undergoing peritoneal dialysis between January 2010 and December 2016. All data were conducted statistical analysis using SPSS 23.

**Results:** Primary glomerular disease, secondary glomerular disease and hereditary nephritis were the first three causes (Figure 2). From 2010 to 2016, the number of patients on the rise, while patients who died or dropped out were decreasing. All CI, confidence interval; Methicillin-resistant Staphylococcus aureus, OR, odds ratio
drugs including Erythropoietin, antihypertensive drugs, iron, calcium agents, phosphorus lowering medicine and Vitamin D were beneficial for patients technical survival (P<0.05). In which the percentage of using erythropoietin, iron and antihypertensive agents were higher than other drugs. There was no significant association between based clinical variable and outcome of patients, except that ALB had a beneficial effect (P<0.05) for technical survival.

Conclusions: Our registry results, representing the first largest report of PD in the Southwest of China, indicate that peritoneal dialysis patients are increasing, which will require more and more medical cost to improve their outcome.

Figure 1 Prevalence of peritoneal dialysis patients.

Figure 2 Cause of end-stage renal disease of peritoneal dialysis patients

SA-PO724

Optimal Dwell Time for Maximal Small Solute Clearances in Peritoneal Dialysis Patients Suchai Sritippayawan, Division of Nephrology, Internal Medicine, Siriraj Hospital, Bangkok, Thailand.

Background: The adequacy of peritoneal dialysis was assessed by urea and creatinine clearances which depend on daily dialysate volume and dwell time. The objective of this study was to identify the optimal dwell time producing maximal small solute clearances in peritoneal dialysis patients.

Methods: Prospective cohort study was performed in chronic peritoneal dialysis patients at Siriraj hospital. We compared small solute clearances at 9 dwell time periods (0, 5, 10, 15, 20, 30, 40, 50 and 60 minutes). Weekly KT/V urea and weekly nCr were obtained to identify the optimal dwell time which produced maximal small solute clearances. We also compared rate of glucose absorption, ultrafiltration and other small solute removals such as sodium, potassium, calcium, phosphorus and uric acid at each dwell time period.

Results: Twenty-two peritoneal dialysis patients were enrolled. The 20 minutes of dwell time had maximal weekly KT/V urea (5.01; p < 0.001), weekly nCr (104.95 ± 17.35 ml/min/m²; p 0.018) and potassium removal (78.17 mmol/day; p 0.002). Maximal sodium removal was observed at 0 minutes (394.56 mmol/day; p 0.005). There were no significant difference of glucose absorption, ultrafiltration rate and other small solute removals with 0, 5, 10, 15 and 20 minutes of dwell time periods. Small solute clearances, ultrafiltration and solute removals were not associated with the peritoneal membrane transport types.

Conclusions: 20-minutes dwell time had the highest weekly KT/V urea and weekly nCr in chronic peritoneal dialysis patients. Small solute clearances were not associated with peritoneal membrane transport types in each short dwell time period.

Funding: Government Support - Non-U.S.

SA-PO725

Use of Composite Endpoint to Improve Feasibility of Clinical Trials in Peritoneal Dialysis Christoph Aufrecht1, Harald Hерker2, Klaus Kratochwill2, Andreas Vychytil2.1Pediatric Nephropathy and Gastroenterology, Medical University of Vienna, Vienna, Austria; 2Christian Doppler Laboratory for Molecular Stress Research in Peritoneal Dialysis, Medical University of Vienna, Vienna, Austria; 3Emergency Medicine, Medical University Vienna, Vienna, Austria; 4Medicine III, Nephrology and Dialysis, Medical University Vienna, Vienna, Austria.

Background: Peritoneal dialysis (PD) is frequently complicated by peritoneal membrane damage and/or peritonitis. Currently used PD fluids likely contribute to pathological mechanisms responsible for these complications. Low feasibility to recruit PD populations for adequately powered trials may impair clinical development of improved PD fluids. In trials in which more than one endpoint is thought to be affected by the treatment, the use of composite endpoint can be recommended. Here, we test the effect of introducing clinically relevant composite PD outcomes on clinical trial design in PD.

Methods: The composite outcome “Major Adverse Peritoneal Events (MAPE)” was designed based on incidence rates of 3 individual endpoints obtained from published clinical trials: ultrafiltration (component 1), peritoneal transport characteristics (2), and peritonitis rate (3). Taking into account that some patients could experience more than one event, several degrees of overlaps of events were investigated. Sample size calculations were carried out using a chi-square test for a parallel group design in binary composite endpoint MAPE with two-sided significance level of 5% to achieve power of 80%.

Results: Based on previously reported clinical trials, event rates of 33% were assumed for each individual component (1,2,3) for the control group. In a scenario with reduction of adverse events rates by 25%, adequately powered studies would need a sample size of more than 1000 patients to test effects on ultrafiltration, peritoneal transport characteristics or peritonitis rate, when studied individually. Combining 2 of these outcome variables reduces the required sample by approximately half, whereas the composite outcome MAPE may reduce the needed sample size to 256 patients.

Conclusions: Introduction of the composite outcome MAPE, covering 3 major PD outcomes, increases power of future clinical trials in PD, thereby improving feasibility. This results in the need for significantly lower sample sizes for assessing clinically relevant effects on PD-related complications.

SA-PO726

Peritoneal Dialysis as a Treatment for Diuretic Resistant, Refractory Heart Failure in Patients with CKD: A Single Centre Experience Amar M. Mahdi1, Madhavan S. Menon, Helen P. Capper, Dwawarak K. Satchitanandana, Simon J. Davies2.1University Hospital North Midlands, Stafford, United Kingdom; 2University Hospital North Midlands, Stafford, United Kingdom.

Background: To assess the role and feasibility of peritoneal dialysis (PD) on clinical outcomes in patients with diuretic resistant refractory heart failure (HF) and Chronic Kidney Disease (CKD).

Methods: Retrospective data and case-note review of 20 patients with HF and CKD started on PD for fluid management. Setting: UK PD unit with an established assisted APD programme. The period of the study was between November 2010 and January 2017. Patients with eGFR <15ml/min were only included if believed to have decline in eGFR as a result of compromising heart failure (cardio-renal syndrome).

Results: Mean age was 72±9 years, 18 (90%) aged 65 year or older, 85% male. Mean eGFR at PD initiation were 12.1±4.7 and 6 (30%) patient had eGFR of <15 ml/min at start at treatment. The aetiology of heart failure was ischaemic in 17 patients (85%). All patients had NYHA class III or IV, and diuretic resistance. Recent estimated ejection fraction (EF) before starting PD was available in 15 patients (EF 10%-60%), 46.6%: EF<35%, 33.3%: EF 35-45% and 20%: EF >45%. All PD catheters were inserted using Seldinger technique and had a patency rate of 95%. The median duration of PD was 9.35 months (IQR 3.41-16.08). During the study period 14 patients (70%) died, 50% (6 patients) died within the first year, and overall the median survival was 14.8 months (IQR 4.81-24.89). Among those who has lasted on PD for at least 12 months the mean number of hospital visits (days per year) for HF or PD related issues in the year before starting PD (52.4±27.8) was significantly higher than the year after starting PD (6.86±5.87) p<0.007. The median eGFR has shown a rise by 0.95 ml/min/month over the first 3 months and a decline by 0.83 ml/min/month at 6 months.

Conclusions: Peritoneal dialysis could serve as a feasible therapeutic intervention to reduce hospital admissions in fluid management in heart failure patients where symptom control with conventional medical treatment becomes a challenge.

SA-PO727

Carbamylated Albumin Predicts Mortality in Peritoneal Dialysis (PD) Patients Yang Li,1 Dongyang Liu,2 Lanping Jiang,1 Jie Liu,1 Zijuan Zhou,1 Huyan Wang,1 Ying Wang,1 Xuemei Li,1 Pei Hu,2 Sahir Mahdi,1 Limeng Chen,1 Department of Nephrology, Chinese Academy of Medical Sciences, Peking Union Medical College Hospital, Beijing, China; 2Clinical Pharmacology Research Center, Chinese Academy of Medical Sciences, Peking Union Medical College Hospital, Beijing, China; 3Renal Division, Massachusetts General Hospital, Boston, MA.

Background: Carbamylation is a posttranslational protein modification mediated by cyanate, the dissociation product of urea, which increases in patients with kidney dysfunction. Recently, carbamylated albumin (C-Alb) was reported to be independently associated with mortality in maintenance hemodialysis patients, but its value in peritoneal dialysis populations has not been studied yet. We employed high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) to measure C-Alb levels and analyze its association with mortality in PD patients.

Methods: We collected serum samples from 114 maintenance adult PD patients at a single university medical center between July 2010 and January 2011, following them until December 2016 (mean length of follow up was 39.6 ± 25.6 months). C-Alb levels were natural log-transformed, and then divided into two groups (high and low levels) according to the cut-off value with highest Youden Index in ROC curve for death. Multifactor Cox regression models were used to analyze the association between C-Alb and death.

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

Underline represents presenting author.
**SA-PO728**

Higher Serum Magnesium Is Associated with Lower Abdominal Aortic Calcification Burden in Peritoneal Dialysis (PD) Patients

**Methods:** 95 stable PD patients were studied (52 men), with a mean age of 62±15 years and a median dialysis vintage of 43 (IQR:28-71) months. The AAC was evaluated with Leena Kauppi (LK) score (range 0-24) on plain lateral abdominal radiographs. Patients were divided in a Low calcification score (CS) group (LK score 0-4) and a High CS group (LK score 5-24), each comprising 38 (40%) and 57 (60%) patients, respectively. Univariate and multivariate regression analysis were used to determine factors associated with a High CS.

**Results:** Mean CS in the whole group was 6.9±5.6. Patients with a High CS (10.4±7) were older, had a higher prevalence of diabetes (38.6 vs. 17.6; p=0.04) and peripheral vascular disease (PVD) (29.8 vs. 10.5; p=0.02), higher pulse pressure (PP) (57±14 vs. 51±15 mmHg; p=0.037) and malnutrition inflammation score (MIS) (5.12±3.1 vs. 3.8±2.7; p=0.039, lower serum magnesium (sMg) levels (2.12±0.36 vs. 2.37±0.54; p=0.008) and less use of cinacalcet (19.3 vs. 39.5%; p=0.03). In a multivariate analysis, every 1mg/dl increase in sMg was associated with 74% lower odds of having a High CS (Table). MIS also emerged as a significant predictor of a high CS (Table 1). sMg was significantly (r=0.31; p=0.002) correlated with dialysate Mg concentration (0.50±0.25 mmol/L).

**Conclusions:** Our data indicate that sustaining higher sMg levels, as by using higher Mg dialysate concentration, and correcting the malnutrition and inflammation complex syndrome may potentially lower the AAC burden and, thus, improve cardiovascular risk in PD patients.

**Funding:** Clinical Revenue Support

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UNIVARIATE</strong> (n=78)</td>
</tr>
<tr>
<td>Age (17 yr)</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>PVD</td>
</tr>
<tr>
<td>MIS (17 yr)</td>
</tr>
<tr>
<td>sMg (mg/dl)</td>
</tr>
<tr>
<td>Cr (mg/dl)</td>
</tr>
</tbody>
</table>

**SA-PO729**

The Influence of Alanly-Glutamine on the Peritoneal Peritoneum in a Chronic Model of Peritoneal Dialysis

**Methods:** We retrospectively investigated 78 patients who had performed PD over 10 years. We analyzed the characteristics of patients, the episodes of PD peritonitis, the change of laboratory findings between the beginning of PD and 10 years after PD, and peritonitis survival.

**Results:** The mean duration of PD was 152 ± 26.6 months. The mean age at which dialysis began was 46 ± 12 years. The mean number of peritonitis episodes was 0.228 times/patient/year. The mean time from the beginning of PD to first episode of PD peritonitis was 57 ± 5.1 months. Patient survival was 100% at 10 years, 63.7% at 15 years, 45.2% at 20 years, and the leading cause of death was infection (16.7%), followed by cardiovascular disease (3.8%). There were no changes of level of serum albumin, TG, LDL, HDL, and CRP between basal and 10 year follow-up result. Nutritional status,

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
immunization markers, and chronic kidney disease-mineral bone disease were well maintained compared with overall PD population.

Conclusions: In the long-term PD patients, the mean age at which dialysis began was younger and the mean time to occur first peritonitis was longer, compared with the previous reported studies. It means long-term PD patients had attack of PD peritonitis less and late and maintained good nutritional status and serum calcium and phosphorus balance for long time. We should pay more attention to maintain good nutritional status and low incidence of PD peritonitis for maintenance of long-term PD.

SA-PO732

Background: Elevated intraperitoneal pressure (IPP) in peritoneal dialysis patients (PD) is linked to alterations in peritoneal transport. IPP is commonly measured at the start of volume infusion and a maximum IPP of 18 mmHg has been recommended which corresponds to 1400 ml/m² of volume infusion. Nevertheless, there may be an adaptation of the peritoneal cavity that could cause IPP to decrease during peritoneal dwell time. Our aim was to study the hypothesis of peritoneal cavity adaptation, and analyze the relationship between IPP and dialysis infusion and drainage volumes.

Methods: We determined IPP in 17 patients in the PD program at our center by measuring the fluid column of solution in the drainage tube at the beginning and end of the peritoneal equilibration test (PET). No patient presented peritonitis or abdominal complications within 4 weeks prior to measurement. Demographic, anthropometric and PET data were collected.

Results: Out of the 17 patients studied, 12 were men (70.6%); 2 were on CAPD (70.6%) and 5 on ADP (29.4%); mean age 61.8±17.8 years, mean body mass index (BMI) was 29.0±5.48 kg/m², mean body surface area was 1.82±0.23 m², median time in PD was 499 days (IQR 142-880.5). The mean IPP was 14.7±4.34 cmH2O at infusion and 15±4.64 cmH2O at drainage. Mean ultrafiltration was 516.12±265.9 ml, with a mean weekly Kt/V of 2.0±0.5. We observed a decrease in IPP/volume of 7.97±3.68 cmH2O/ml (p=0.019) at drainage compared to the initial infusion value. IPP/infrastruction volume ratio (at both infusion and drainage) showed strong correlation with volume/BSA ratio (at infusion; r=0.624, p=0.007 and at drainage; r=0.703, p=0.002). There was a significant correlation between infused volume/initial IPP and final IPP, so that the final IPP= 21.14 - [0.041x (Infused Volume/initial IPP)] (r= 0.578, p=0.015). There was a correlation between final IPP/BSA and infusion volume so that Volume Infused = 2355.201- [52.727 * (final IPP/BSA)] (r=0.630, p=0.007).

Conclusions: The lower IPP/volume ratio at drainage confirms the adaptation of the abdominal cavity during dwell time, rendering it more important to measure IPP at the end of the exchange. We have determined an equation to predict the final IPP at drainage by measuring the infused volume on infusion volume and BSA. In addition, IPP showed stronger correlation to BSA than to weight.

SA-PO733
Changes in Dialysis Prescription Affect the Time of Course Transport in Peritoneal Dialysis Irene Brenna,1,2 Emma H. Elphick,1,2 Mark Lambie,1,2 Simon J. Davies,1,2 Kelee University, Stoke on Trent, United Kingdom; 1University Hospital of North Midlands, Stoke-on-Trent, United Kingdom.

Background: Long term peritoneal dialysis (PD) is associated with increased peritoneal solute transport rate (PSTR), which correlates with hard outcomes. Whether different clinical approaches affect PSTR rate of increase is unclear.

Methods: We conducted a retrospective longitudinal analysis, collecting data from 01/01/1990 to 31/12/2016 from PETs routinely performed twice a year in all PD patients at the Royal Stoke University Hospital. Using a linear mixed model approach, 3889 PETs from 865 patients were analysed, follow-up being up to 12.7 years, median 1.6. We used a random intercept/slope model to fit to assess whether the exposure to different clinical practice patterns (PD type, average glucose exposure, long dwell strategy) had an effect on the PSTR rate of increase, adjusting for patients' demographics, comorbidities, residual renal function (RRF) and peritonitis episodes.

Results: Predicted PSTR at PD start was 0.723, average increase 0.012 per year. Average glucose exposure affected PSTR absolute value, but not its rate of increase. The use of icodextrin was associated with higher PSTR at PD start (+ 0.055, 95%CI 0.040-0.070) and slower increase over time (0.005 per year, p=0.002). A dry long dwell resulted in lower PSTR at PD start (+0.090, 0.049-0.141, p=0.007), but faster increase (0.029 per year, p=0.0001). The pattern of PSTR changed with starting-period too (p=0.001), the starting PSTR being lower in 1990-95 (0.723) and rising until 2005-2010 (0.824), and lowering starting values were associated with greater increases over time. The change with starting-period was only partially explained by changes in practice pattern.

Conclusions: Both the initial PSTR and the subsequent change over time are associated with different PD prescription strategies.

SA-PO734
Are We Worried about Early Complications in Urgent-Start Peritoneal Dialysis? Jiri Vlasak. Dialysis center, Fresenius Medical Care, Sokolov, Czech Republic.

Background: Urgent-start peritoneal dialysis is defined as initiation of peritoneal dialysis (PD) in patients with newly diagnosed end-stage renal disease (ESRD) who are not yet on dialysis and who require dialysis initiation less than two weeks after PD catheter placement, but do not require urgent hemodialysis. Theoretically, an increase in the incidence of peritoneal leaks could be assumed.

Methods: Since 2011 in our dialysis center eighty-nine patients have started peritoneal dialysis (PD) with laparoscopically introduced PD catheter. Fifteen of them had initiated urgent-start PD and peritoneal dialysis treatment was initiated with lower volumes of exchange. Seventy-four of them started with PD conventional (routinely 3-4 weeks after PD catheter placement). We compared retrospectively these groups focusing on early complications - infections, leaks and catheter migration, both following catheter insertion and subsequent PD weeks.

Results: Urgent-start patients were more likely to be referred late, some of them were under the control of a nephrologist, but they experienced unexpected impairment of renal function. We did not record leaks in either group and only three patients from conventional started PD had early catheter migration. There were no infectious complications in either group.

Conclusions: Urgent-start peritoneal dialysis appears to be as safe as conventional (planned) peritoneal dialysis.

SA-PO735

Background: Thousands of patients under chronic peritoneal dialysis (PD) every day but it has been remarkably difficult to establish experimental models of chronic PD in uremic animals. Such models are needed for tests of new dialysis fluids, new medications and techniques in order to further improve treatment of patients with PD. For that purpose, we have developed a new system for chronic automated PD (APD) in uremic rats.

Methods: Rats were made uremic using the nephrotoxin orellanine, a mushroom toxin known to induce uremia through selective destruction of the tubular epithelial cells with no other effects on other organs acutely or chronically, as previously investigated by us both in patients and animal models. The uremic rats and a control group of saline treated rats subsequently underwent APD for three weeks in an automated PD system; one additional control set of rats did not undergo dialysis (n=8 in each group). Each day 70 ml of dialysis fluid (0.7% Gambro) was introduced in the APD-system. At the end of the experiment, dialysate, serum and peritoneal tissue were collected for further analysis.

Results: APD worked equally well in both groups of rats. Peritoneal dialysis per se induced elevated expression levels of the growth factors TGF-ß and VEGF in the peritoneal fluid and tissue compared to rats that did not undergo APD. Orellanine treatment did not affect the rats negatively part from the induced uremia. Anuric rats did well on dialysis and continued to grow, albeit at slower pace compared to healthy rats with normal kidney function.

Conclusions: This study shows that it is possible to maintain uremic rats for at least three weeks in peritoneal dialysis. The elevated levels of levels of TGF-ß and VEGF in the peritoneal fluid and tissues were found to be due to APD itself, and uremia did not affect these biomarkers significantly. The use of orellanine to induce uremia in rats is an effective option without the side effects commonly seen in surgical models of uremia. We believe that the APD model shown here is a new, effective and reliable model for the testing of new dialysis fluids or new therapeutic targets in uremic animals. We hope this will improve dialysis treatment of patients in the future.

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

SA-PO736
Sclerosing Encapsulating Peritonitis Developing Two Years after Peritoneal Dialysis Cessation Rhyan Maditz, Beaumont Health - Royal Oak, Royal Oak, MI.

Background: Sclerosing encapsulating peritonitis (SIP) is a rare chronic inflammatory condition of the peritoneum believed to result from recurrent low grade peritonitis. The condition occurs when loops of bowel are encased within the peritoneal cavity by a membrane, leading to intestinal obstruction. Long peritoneal dialysis (PD) duration, acetate-buffered or hypertonic solutions and recurrent episodes of peritonitis might contribute to the development of SIP.

Methods: 46 yo male with PMHS of ESRD secondary to FSGS and located sclerosing peritonitis presented with fatigue of one-week duration. He was previously on PD for years but switched to HD two years prior to presentation because he was unable to achieve adequate clearance. He passed two HD sessions prior to arrival due to fatigue. CT performed on admission revealed a large amount of complicated/complex ascites, thickening of the peritoneum and nonspecific colitis and enteritis. Soon after admission, the patient became altered, hypotensive, and was transferred to the medical intensive care unit. Patient was anorexic; dialysis was stopped due to inability to tolerate oral intake. PEG tube insertion was determined to be too risky given his comorbidities and a dobbioff tube was inserted. Methylprednisolone 500 mg daily for three days was trialed, which did not lead to clinical improvement. Further immunosuppression with Imuran/calcinurin

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
868
SA-PO737

Trehalose Ameliorates Peritoneal Fibrosis through the Induction of Autophagy and the Downregulation of Snail Protein in Peritoneal Mesothelial Cells

Eleftheria-Kleio Ploumis,1 Akinori Hara,2 Yasunori Iwata,3 Mio Shimizu,1 Kengo Furuchi,4 Takashi Wada.1,2 Division of Nephrology, Kanazawa University Hospital, Kanazawa, Japan; 2Department of Nephrology and Laboratory Medicine, Kanazawa University, Kanazawa, Japan.

Background: Peritoneal fibrosis is a severe complication of peritoneal dialysis, but there are few effective therapies to treat it and/or provide for it. Trehalose is a non-reducing disaccharide and can be an osmolyte of peritoneal dialysis solution. Recent studies reveal new biological effects of trehalose as an autophagy inducer and it can be considered to be a potential candidate of therapeutic reagents for some diseases. But there are few reports about therapeutic effects of trehalose on fibrotic diseases. We therefore examined if trehalose has anti-fibrotic effects on the peritoneum.

Methods: Peritoneal fibrosis was induced by intraperitoneal injection of chloral hydrate-glucosate (CG) 3% trehalose or vehicle (normal saline) was administered by intraperitoneal injection to mice every other day. For in vitro study, we isolated primary mouse peritoneal mesothelial cells to investigate the ability of trehalose to attenuate the profibrotic responses.

Results: CG-induced increases in peritoneal thickness, type I procollagen mRNA expression and hydroxyproline content were significantly attenuated in trehalose-treated mice (n=4–9). In addition, CG challenges induced a marked peritoneal accumulation of α-smooth muscle actin (αSMA)+ fibroblasts that was significantly reduced by trehalose. To test whether or not trehalose stimulates autophagy, dual immunostainings of peritoneal sections were performed using anti-Wilms’ tumor 1 (WT1) antibody and anti-αSMA antibody. The number of WT1+αSMA dual positive cells in the peritoneum after CG challenges was significantly suppressed by trehalose (n=4). In mesothelial cells, trehalose attenuates the increase of αSMA and type I procollagen mRNA expression induced by TGF-β1, through the induction of autophagy and the downregulation of Snail protein.

Conclusions: Our results suggest that trehalose might be a novel therapeutic reagent for peritoneal fibrosis through the induction of autophagy and the downregulation of Snail protein in peritoneal mesothelial cells.

SA-PO739

Immunophenotypic Abnormalities of Uremic Patients Undergoing Peritoneal Dialysis

Maria Molina,1 Claudia Yuste,2 Enrique Morales,3 Manuel Praga.4 Nephrology Department, Hospital Universitario 12 de Octubre, Madrid, Spain.

Background: Chronic kidney disease (CKD) is usually associated with various immunological abnormalities. However, there is a scarcely data regarding the impact of peritoneal dialysis (PD) on these abnormalities.

Methods: We presented a descriptive transversal study analysing lymphocyte absolute numbers and subpopulations (CD3+, CD4+, CD8+, CD56+, CD19+, and CD16+ CD5+) in patients undergoing PD. Those patients were compared with a similar cohort of haemodialysis (HD) patients.

Results: Nineteen PD patients were studied (mean time on PD 7.6 ± 6.57 [3-20] months; age 48.8 ± 18.7 [22,80] years, 57.9% women, 10% diabetics, mean weekly KTV 2.52 ± 0.22 [2.22,2.82]). For PD, patients identified the fibroblasts originated from peritoneal mesothelial cells, dual immunostainings of peritoneal sections were performed using anti-Wilms’ tumor 1 (WT1) antibody and anti-αSMA antibody. The number of WT1+αSMA dual positive cells in the peritoneum after CG challenges was significantly suppressed by trehalose (n=4). In mesothelial cells, trehalose attenuates the increase of αSMA and type I procollagen mRNA expression induced by TGF-β1, through the induction of autophagy and the downregulation of Snail protein.

Conclusions: Our results suggest that trehalose might be a novel therapeutic reagent for peritoneal fibrosis through the induction of autophagy and the downregulation of Snail protein in peritoneal mesothelial cells.

SA-PO740

Urgent-Start Peritoneal Dialysis in the Outpatient Setting in an Underserved Urban Area

Andres Serrano, Melby Philip. Mount Sinai Hospital, Chicago, IL.

Background: Despite an increase in End-Stage Renal Disease (ESRD) incident cases selecting Peritoneal Dialysis (PD), the proportion of patients on PD remains below historical levels achieved in the 80s. There is an increased interest in urgent-start PD, as a way of increasing the number of patients on PD, and decreasing the number of patients initiating hemodialysis (HD) through a central venous catheter. However, implementing these programs could be challenging in a community hospital with scarce resources. Also, there is a great level of concern regarding complications at the moment dialysis is initiated. We are presenting our experience with a group of patients who had urgent-start PD.

Methods: Results: During a period of 8 years, a total of 81 patients initiated PD. Forty-three patients (53%) had an indication for urgent dialysis initiation, and they either decided in advance for PD or after education regarding RRT then decided for PD. The patients undergoing urgent start PD catheter placement and they initiated PD training as outpatient. Two patients started PD immediately in the hospital after the catheter was placed because of emergent dialysis needs and no HD access. In terms of complications, there were 2 mechanical complications (1 percutaneous leakage, 1 poor catheter flow) and 1 PD related peritonitis, which resolved with PD treatment as outpatient. The patients who started PD had a successful outcome.
Conclusions: Our experience shows that urgent-start PD is a safe alternative to initiate renal replacement therapy avoiding the use of long term central venous catheters. We also demonstrated that urgent-start PD can be done successfully in the outpatient setting.

SA-PO741
Peritoneal Dialysis Modalities Portend Distinct Decongestive Properties
Abhilash Koratala, Olanrewaju A. Olayo, Amir Kazory, University of Florida, Gainesville, FL.

Background: Previous studies have established the adverse impact of lingering fluid overload on the outcomes of patients with ESRD treated with peritoneal dialysis (PD). There is mounting evidence that decongestion, if not associated with significant sodium removal, does not improve the outcomes in specific subsets of patients such as those with heart failure. We sought to explore available evidence on the ability of the two main modalities of PD (i.e. continuous ambulatory PD [CAPD] and automated PD [APD]) with regard to sodium removal.

Methods: Articles cited in PubMed database from January 2000 to March 2017 using key words “peritoneal diab.”, “sodium removal”, and “ultrafiltration” were searched. Articles evaluating sodium extraction and ultrafiltration (UF) were reviewed. Clinical trials on comparative impacts of CAPD and APD were selected. Relevant data including urine volume, UF volume, and sodium removal were extracted and compared. Using Pearson product-moment correlation, the degree of linear dependence between sodium removal and UF was determined.

Results: A total of 76 citations were reviewed and 7 studies with 654 participants were included. The mean age was 55.7 years and 55.9% were men. The mean PD sodium removal was 142±44 and 87±23 mmol/day for CAPD and APD respectively (p=0.006). There was no difference between urine sodium excretion between the two groups (42±25 and 39±21 mmol/day for CAPD and APD respectively, p=0.42). The mean UF volume was 1133±331 and 931±210 mmol/day for CAPD and APD (p=0.09). There was a strong correlation observed between PD sodium removal and UF volume for CAPD (r=0.99, p<0.00) while it was only modest for APD (r=0.6, p=0.15).

Conclusions: Currently available evidence suggests that fluid removal is comparable for CAPD and APD. However, CAPD is associated with significantly greater sodium extraction compared to APD, with strong correlation between UF volume and the amount of sodium removal. Therefore, it is conceivable that CAPD would be advantageous in clinical settings such as heart failure where sodium removal per se is of utmost importance. Future prospective studies are needed to explore whether the advantageous sodium extraction by CAPD would translate into improved outcomes in these patients.

SA-PO742
Intradialytic Blood Pressure Stability during Hemodialysis with a Novel Hemodialysis Device
Luis Alvarez, Paul Chen,4, Sarah S. Prichard,4 Advisor, Outset Medical Inc, San Jose, CA; 3Nephrology, Palo Alto Medical Foundation, Palo Alto, CA; 4Outset Medical Inc, San Jose, CA; 4Outset Medical, San Jose, CA.

Background: Intradialytic hypertension (IDH) is a common event. The literature suggests that up to 20% of dialysis patients have IDH that requires intervention, over 70% of patients have a decrease of systolic BP (SBP) of 20mmHg and up to 27% have a decrease of 40mmHg. Patients with frequent IDH have worse outcomes. The Tablo™ Hemodialysis System is a novel technology designed to be simple for both patients and staff to use, which enables self-care hemodialysis in a variety of clinical settings. This study reports on the intradialytic BP of patients dialyzed using Tablo.

Methods: 2012 dialysis treatments using Tablo were assessed in the outpatient setting at 10 dialysis units. Tablo automatically takes and records BP at preset intervals during dialysis as prescribed by the physician and transmits them wirelessly in real time. The percent of patients with a change in SBP of 20 mmHg or 40 mmHg, a change in mean arterial pressure of 10 mmHg, or a SBP < 90mmHg (with a diastolic BP of <60) were calculated. UF and pre/post weights were also collected.

Results: Results are shown in Table 1

Conclusions: Patients dialyzed with Tablo have less IDH compared to that reported in the literature. For the reason this difference may relate to differences in the patient populations or unique features of Tablo. This important clinical observation needs further study to determine if the use of Tablo could favorably influence outcomes.

Funding: Commercial Support - Outset Medical Inc

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60</td>
<td>203</td>
</tr>
<tr>
<td>Δ SBP &gt; 20 mmHg</td>
<td>&lt;60%</td>
</tr>
<tr>
<td>Δ SBP &gt; 40 mmHg</td>
<td>&lt;60%</td>
</tr>
<tr>
<td>Δ MAP &gt; 30 mmHg</td>
<td>&lt;60%</td>
</tr>
<tr>
<td>&lt; 90% SBP &amp; &lt; 60% DBP</td>
<td>15% (6.5%)</td>
</tr>
<tr>
<td>Postdialysis weight</td>
<td>50.2 ± 20.8 (21.6 ± 14.2 kg)</td>
</tr>
<tr>
<td>Pre-weight</td>
<td>78.5 ± 20.4 (42.1 ± 9.5 kg)</td>
</tr>
<tr>
<td>Average Ultrafiltration</td>
<td>248 ± 100 mL (60 ± 20 mL/hr)</td>
</tr>
<tr>
<td>Avg UF rate</td>
<td>8.7 ± 3 mL/hr (1.85 ± 0.6 mL/hr)</td>
</tr>
</tbody>
</table>

SA-PO743
Achieving Dry Weight, Intradialytic Hypotension, and Outcomes in Patients Undergoing Hemodialysis
Salim Bou Slaiby, Nabil Zeineddine, Staten island university hospital, Staten Island, NY.

Background: Patients with end stage renal disease (ESRD) are known to have high rate of hospitalizations and increased mortality compared to the general population. These morbidity or be related to a set of complications that occur during hemodialysis (HD) sessions, such as hypotensive episodes. On the other hand, reaching the dry weight (DW) during a HD session was also linked to improved outcomes.

Methods: This is a retrospective study with patients recruited in a dialysis center in Staten Island, NY; 36 HD sessions per patient in 3 months duration, with the rate of hypotensive episodes (as defined by KDOQI), and whether a DW was achieved or not, will be collected. Hospitalization rate and complications (cardiovascular and fistula-related) will be recorded for the following 12 months.

Results: 49 patients with a mean age of 60.42 (±14.6) years and their 1729 HD session were analyzed so far. They were 50% males and 50% females. Results didn’t show any significant difference in hospitalization or complications in patients who had more episodes of hypotension (p=0.25), however a statistically significant difference was found between patients who achieved DW and those who didn’t in terms of having a clotted arteriovenous (AV) access (p=0.048). There was a statistically significant negative correlation between hypotension and achieving DW (R²= 0.136; p= 0.022). Also female gender was strongly associated with more hypotensive episodes on one hand, and failure to achieve DW during HD sessions on the other hand (p=0.0001 for both differences).

Conclusions: The results seen so far didn’t appreciate any significant effect of hypotension or achieving DW during HD sessions on morbidity and complications in the following year except for a slightly significant difference in having a clotted AV access seen more in patients who achieved their DW; this might be secondary to a more aggressive ultrafiltration for attaining the target weight. The strong negative correlation between achieving DW and hypotensive episodes indicates that the main reason for not achieving DW is hypotension. On the other hand, females were more prone for intradialytic complications such as hypotension and failure to achieve DW. A larger population is needed for a better analysis and to further investigate any relation between intradialytic complications and morbidity and mortality in patients with ESRD.

SA-PO744
Displacer-Enhanced Dialytic Removal of Protein-Bound Uremic Toxins during Hemodialysis
Karla B. Cano Escobar,1 Xia Tao,1 Israel Campos,4 Vaibhav Maheshwari,2 Jillian Brown,4 Garry J. Handelman,1 Stephan Thijssen,2 Peter Kotanko,2 BEATRIZ E. CORNEJO MEDELLIN,1 Magdalena Madero,1 1INCIC, Mexico, Mexico; 2Renal Research Institute, New York, NY; 3Renal Research Institute, New York, NY; 4University of Massachusetts, Lowell, MA

Background: Hemodialysis(HD) has limited efficiency on protein-bound uremic toxins(PBUTs) removal due to their high albumin binding. Binding competitors to PBUTs ("displacers") such as ibuprofen(IBF) can increase the free concentration of PBUTs. We sought to explore available evidence on the ability of the two main displacers - IBF and Sodium Tripolyphosphate (STPP) to enhance the dialytic removal of PBUTs. In this work, we evaluated the ability of these displacers to enhance PBUT removal during HD in Chronic HD patients using STPP and IBF as displacers.

Methods: 220 hemodialysis sessions were studied during a mid-week HD on their standard prescriptions(Q 300 mL/min;Q 500 mL/min). IBF(800 mg) was infused at a constant rate into the arterial line, from 20 to 40 minutes into the treatment. Dialysate levels of IS, pCS, IBF, tryptophan(TRP) were measured by HPLC. Concentration data were normalized to the respective patient mean levels, which are reported as means±SD and were compared before, during and after IBF infusion.

Results: Seventeen patients were included(10 females, mean age 36±11 years;HD vintage 24 (3-111) months). IBF infusion was well tolerated. Mean of relative levels in the dialysate outlet before, during and after IBF infusion were 0.67±0.23,1.42±0.14, and 0.61±0.19 for IS, 0.63±0.24,1.42±0.15, and 0.66±0.19 for pCS, respectively; indicating a marked increase of dialytic PBUT removal during IBF infusion. Creatinine and urea, non-protein bound control solutes, continued to decline during the IBF infusion, while TRP, a moderately protein bound molecule, increased non-significantly(Fig.1).

Conclusions: This first-in-man study shows that IBF as a displacer during HD significantly enhanced the dialytic removal of PBUTs. These results should stimulate the search for safe and effective molecules that may be used as displacers during HD
SA-PO745
Assessment of the Impact of Fluid Removal Rate on Central Arterial Waveform Analysis Michael E. Brier,1 Alfred A. Jacobs,2 George Aronoff.1
1DaVita, Inc., Naples, FL; 2University of Louisville, Louisville, KY

Background: Rapid fluid removal during dialysis is associated with poor cardiac outcomes when rates exceed 10 ml/h/kg. We tested the hypothesis that measuring central arterial pressure and waveform analysis including measures of vascular stiffness would help identity those patients at risk.

Methods: Nineteen subjects at the University of Louisville were enrolled in a prospective study measuring central blood pressure and waveform analysis using the SphygmoCor device. Subjects were studied following informed consent on the first and last dialysis treatment of the same week. Measurements were obtained prior to dialysis and at 30 minute intervals. Measurement data were summarized using regression analysis and the resulting slope and intercept were tested against fluid removal rate. We compared central arterial pressures (systolic, diastolic, mean, augmentation), augmentation index, and reflection magnitude. All analyses were performed in SPSS using linear regression.

Results: Subject predialysis weight ranged from 53 to 167 kg. Four subjects were female. Fluid removal rates ranged from 4.1 to 30.8 ml/h/kg and were significantly related to predialysis weight (p<0.003). The results of the analysis comparing fluid removal rate to measured parameters are shown in the following table.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Regression Estimate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central systolic pressure</td>
<td>-0.52</td>
<td>0.132</td>
</tr>
<tr>
<td>Central diastolic pressure</td>
<td>0.46</td>
<td>0.002</td>
</tr>
<tr>
<td>Central pulse pressure</td>
<td>0.00</td>
<td>0.113</td>
</tr>
<tr>
<td>Augmentation pressure</td>
<td>-0.85</td>
<td>0.227</td>
</tr>
<tr>
<td>Augmentation index</td>
<td>-0.92</td>
<td>0.009</td>
</tr>
<tr>
<td>Reflection magnitude</td>
<td>-0.08</td>
<td>0.112</td>
</tr>
</tbody>
</table>

Conclusions: Comparison of central pressures and vascular stiffness with fluid removal rate demonstrated a significant relationship between central diastolic pressure and central mean pressure. The relationship demonstrated an increase in these measures for those subjects with the greatest fluid removal rate which may be a contributing factor in the observed morbidity and mortality of these patients. This observation is confounded by predialysis weight where the largest fluid removal rates were associated with the smallest patients. Three measures of vascular stiff were not found to be related to fluid removal rates.

SA-PO746
Routine Hemodialysis Does Not Result in Optimal Plasma Magnesium Concentrations Niki H. Leenders,2 Tiny Hoenstra,2 Frans J. van Ittersum,2 Joost Hoenderop,1 Marc G. Vervloet.1 1Radboud university medical center, Nijmegen, Netherlands; 2VU University Medical Center, Amsterdam, Netherlands.

Background: Lower plasma magnesium (Mg) concentrations have been associated with a higher overall and cardiovascular mortality in hemodialysis patients. The optimal level of plasma Mg in hemodialysis patients appears to be above the reference range for the healthy population (typically 0.70–1.00 mmol/L). Plasma Mg is not routinely measured after hemodialysis. Aim of this study was to determine the effect of standard hemodialysis treatment on plasma Mg.

Methods: Plasma Mg was measured in duplicate before (Mgpre) and after (Mgpost) 6 consecutive dialysis sessions in 34 patients on a regular 3 times weekly hemodialysis schedule with a standard 0.50 mmol/L dialysate magnesium concentration.

Results: Mean Mgpre was 0.88 mmol/L (SD 0.14), 76% of patients had a mean Mgpre below 1.00 and the coefficient of intra-individual biological variation was 5.6%. Post-dialysis, mean Mg was decreased to 0.78 (SD 0.06, p<0.001). Univariate linear regression showed that mean Mgpre and Mgpost in an individual were positively correlated (r=0.001) and the regression line indicated that Mg was stable during dialysis at a Mgpre of 0.73, decreased at a Mgpre above 0.73 and increased at a Mgpre below 0.73. In an analysis with linear mixed models a 0.10 mmol/L higher Mgpre was associated with a 0.03 mmol/L higher Mgpost (95%-CI 0.024-0.037, p<0.001). If added to the model, baseline factors including gender, age, serum albumin, height and weight; and dialysis characteristics including vascular access type, dialysis duration, ultrafiltration volume, blood flow and dialysis efficiency did not change this association.

Conclusions: In the majority of the hemodialysis patients Mgpre was suboptimal. Routine hemodialysis further decreases magnesium in the majority of patients. Current dialysate magnesium concentrations may be too low.

Funding: Private Foundation Support

SA-PO747
Enhanced Phosphate Clearance of Dialyzers by Membrane Inner Surface Structure Optimization Tiancheng Xu1,2 Chunyao Zhang3, Xingya Wang4, Changjun Mu1,3 WEGO blood purification products Co., Ltd, Weihai, China; 2Wego Blood Purification Products Co., Ltd, Weihai, China.

Background: Elevated phosphate levels increased morbidity and mortality among dialysis patients, so the control of serum phosphate concentration is a considerable clinical approach. To enhance the phosphate clearance of dialyzers, hemodialysis membranes with different properties of inner surface structure have been specially developed and researched.

Methods: Firstly, SEM, dextran retention method (DRM), SurPASS and liquid-liquid displacement porometry (LLDP) were used to characterize the zeta potential, mean flow pore diameter of membranes respectively in MF13 and F6HPS dialyzers. In addition, a case-control study including 105 chronic kidney diseases patients (55 males, 50 females, mean age 56 years) enrolled at two hospitals in China who had been undergone stable hemodialysis for at least three months was conducted in 2016. Polysulphone dialyzers (Fresenius F6HPS or Wgo MF13) were applied to each hemodialysis treatment. Finally, the SPSS PASW (statistical package of social science) Statistics v18.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the patient data.

Results: When pH=7.0 (close to the blood pH of the hemodialysis patient), the membrane inner surface zeta potential of MF13 (-17.1 mV) was smaller than that of F6HPS (-15.0 mV), but the mean flow pore diameter of membrane of MF13 (28.3 nm) was much larger than that of F6HPS (22.2 nm). A thinner inner surface and higher inner surface porosity were obtained in the membrane of MF13. According to the tortuous capillary pore diffusion model, the increase of kM above 0.73. In an analysis with baseline factors including gender, age, serum albumin, height and weight; and dialysis characteristics including vascular access type, dialysis duration, ultrafiltration volume, blood flow and dialysis efficiency did not change this association.

Conclusions: The mean flow pore diameter, surface thickness and porosity are the determinant factors of phosphate clearance when the other characteristics of membrane inner surface structure were same, such as membrane surface materials and surface zeta potential.

Funding: Other NIH Support - China Association for Medical Devices Industry (CAMDI)

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Phosphate clearance</th>
<th>Phosphate diffusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-HD</td>
<td>N</td>
<td>55</td>
</tr>
<tr>
<td>Post-HD</td>
<td>32</td>
<td>53</td>
</tr>
<tr>
<td>Mean</td>
<td>52</td>
<td>51</td>
</tr>
<tr>
<td>SD</td>
<td>16.5</td>
<td>19.0</td>
</tr>
<tr>
<td>Reference</td>
<td>25.4</td>
<td>12.4</td>
</tr>
<tr>
<td>P-value</td>
<td>0.005</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-P0748

Study of Lung Ultrasound as a Sensitive Tool for Evaluating Fluid Status in Chronic Hemodialysis Patients

Hala S. Elwakil1, U of Alexandria - Faculty of Medicine, Alexandria, Egypt. Group/Team: Hemodialysis lung comets group.

Background: Control of fluid status is an important constituent of adequate and efficient hemodialysis treatment. Dry weight is usually assessed clinically, and several methods have been developed to assess the hydration status in chronic hemodialysis patients. Ultrasonographic lung comets evaluates extravascular lung water while the diameter of inferior vena cava (IVC) estimates central venous pressure, so ultrasound is considered as a useful tool to evaluate the hydration status of hemodialysis patients. The present study was designed to use lung ultrasound to assess lung congestion before and after a dialysis session in correlation to clinical signs and symptoms and the achieved dry weight as well as IVC diameter in hemodialysis patients.

Methods: The present study included 25 patients on maintenance hemodialysis in Alexandria University Hospitals. All the patients were suboptimal to thorough history taking with special concern on grade of dyspnea and ultrafiltration volume, as well as clinical examination for signs of hypervolemia. Radiological examination including ultrasound lung comets score and diameter of hepatic portion of inferior vena cava (IVC) before and after dialysis session.

Results: The mean lung comets score before dialysis was 54.72±28.47 and decreased significantly after dialysis to 28.52±19.68 (p=0.000). There was a significant positive correlation between ultrafiltration volume and the absolute change of lung comets score (p=0.003) while there was no significant correlation between the ultrafiltration volume and the absolute change of IVC diameter (p=0.219). There was a significant correlation between lung comets score and grade of dyspnea before and after dialysis (p=0.037, 0.001 respectively). Furthermore lung comets were found in asymptomatic patients as well as after dialysis. There was a significant positive correlation between the grade of lung comets and IVC diameter both before and after dialysis (p=0.004, 0.003 respectively).

Conclusions: Ultrasound lung comets score is a sensitive marker of lung congestion and even may precede the development of symptoms of lung congestion in hemodialysis patients. Moreover, lung comets score is highly correlated with ultrafiltration volume, thus, it could be used as a good marker for achieving dry weight in hemodialysis patients with normal severity over IVC diameter assessment.

Funding: Government Support - Non-U.S.

SA-P0749

Diary of Sodium Intake and Clinical Outcomes in Hemodialysis Patients

Antonio R. Morales1, Carlos Alberto López lozano2, Sandra L. Báez López1, Anel V. Barbárin vázquez1, Javier Soto-Vargas2, Jorge fernando Totpe reyes2. Clinical Nutrition, University of Guadalajara, Guadalajara, Mexico; 2Regional General Hospital 46, Mexican Institute of Social Security, Guadalajara, Mexico, Guadalajara, Mexico.

Background: Dietary sodium is thought to play a major role in the pathogenesis of hypertension, hypervolemia and mortality in hemodialysis patients. The evidence supporting daily dietary sodium intake of 2 g on hemodialysis is not strong. Our objective was to assess the relation between sodium intake and interdialytic weight gain, hyper and hypotension in hemodialysis sessions, and hospitalizations.

Methods: We included 70 patients receiving thrice-weekly hemodialysis treatment in this prospective observational study. The median follow up was 32.4 months (IQR 28.4-34.3). Available data included demographics, laboratory and clinical measures and details of the dialysis prescription. We examined the dietary sodium intake in a hemodialysis and inter dialytic day with 2-day diary-assisted recalls.

Results: There was a male predominance (62.9%). The mean age was 45 years (IQR 29-60). The median sodium intake in a hemodialysis day was 1144.5 mg (IQR 576.0-1905.5) and in no HD day of 1499.5 mg (IQR 877-2098.2). The dry weight assessed by impedance was 60.0 kg (IQR 50.4-66.5) and the post HD weight was 62.5 kg (IQR 52.0-68.4), with a median ultrafiltration of 2.5 liters (IQR 2.0-3.5), only 24 (34.3%) of the patients were in theirs dry weight. 40 (57%) patients were hypertensive previous to the first session, 2-day diet diary-assisted recalls. There was a weak correlation between sodium intake on HD day and no HD day, with the average correlation coefficient (R2) of 0.362 and 0.261, p = 0.002 and 0.041 respectively, but no with the sodium intake before and after session. There were an inverse association between the amount of sodium intake and hospitalizations (p=0.026). There were no association between sodium intake and the difference of actual weight and dry weight, or the development of hypotension or hypertension.

Conclusions: We find an inverse association between the amount of sodium intake and the number of hospitalizations; however there were no association with interdialytic weight gain, hypertension or hypotension in this cohort of HD patients.

SA-P0750

Increasing Erythropoietin-Stimulating Agent (ESA) Administration in Hospitalized ESRD Patients

Benjamin Griffin1, Elizabeth Flenigan, Cara A. Chao, Diana J. Jalal, John M. Carson. 1Memorial Health System, Colorado Springs, CO; 2None, Aurora, CO; 3University of Colorado, Aurora, CO; 4University of Colorado Denver Health Science Center, Aurora, CO; 5University of Colorado School of Medicine, Aurora, CO.

Background: Anemia is a common complication in patients with ESRD due to decreased production of erythropoietin in the diseased kidneys. ESAs have been developed to combat anemia in ESRD, and now are widely used to maintain hemoglobin levels in the range of 10–11 g/dL. ESAs can cause side effects in ESRD patients who are hospitalized at greater risk to develop anemia than their outpatient counterparts. Despite this, ESA use rates in the hospital for patients with ESRD patients are exceedingly low. Our magnitude assessment shows that only 30% of patients received their ESA while an inpatient at UCH.

Methods: Given the known harms associated with anemia in the ESRD population, the high rates of anemia following hospitalization, and the low use of ESAs in the inpatient setting, we set out in this QI project to increase inpatient ESA administration from 30% to 60%. Our intervention was to implement a standardized ESA dosing protocol for all ESRD patients based on their outpatient dose and inpatient hemoglobin values (Figure 1). Hold parameters included blood pressure > 180/100, and active myocardial infarct (MI), stroke, or thrombosis. The hemodialysis template was also modified to prompt the provider to include ESA administration information.

Results: Since implementation of the ESA administration interventions in April 2017, 92 ESRD patients have been hospitalized a total of 138 times. During these hospitalizations, the rate of ESA administration, defined as receiving one or more doses of an ESA as an inpatient, was 70%. The rates of thrombosis, cardiac events, and strokes has remained constant since implementation. Hemoglobin values at 3 months from discharge are being collected, but are not yet available for the majority of our patients.

Conclusions: The implementation of an ESA dosing algorithm results in higher rates of inpatient ESA administration without an increase in complications.

Funding: Government Support - Non-U.S.

SA-P0751

Comparison of Stroke Volume Measurements during Hemodialysis Using Bioimpedance Cardiography and Echocardiography

Michael J. Germain, Jyovani W. Joubert, Brian H. Nathanson, Yossi Chait, Nathan W. Levin. 1Kidney Care and Transplant Services of New England, Agawam, MA; 2None, New York, NY; 3OptiStatim, LLC, Longmeadow, MA; 4Renal and Transplant Assoc of New England, Hampden, MA; 5University of Massachusetts, Amherst, MA.

Background: Inadequate fluid management during hemodialysis (HD) has serious morbidity and mortality consequences. Intradialytic fluid management is typically guided by blood pressure, an indirect measure of hemodynamics status. Direct measurements of hemodynamic parameters may improve cardiovascular outcomes by providing empirical bases for intervention. We compare stroke volume (SV) measurements using a non-invasive, regional biopedance cardiography device (NiCaS) with Doppler echocardiography (Echo) in an HD setting.

Methods: Stroke volumes were simultaneously measured using the devices in 17 patients receiving maintenance HD. Measurements were made during two weekly HD treatments, and twice within each HD treatment during the first and last hour, for a total of 64 SV measurements. Agreement between devices was assessed using linear regression, Pearson’s correlation coefficient, a Bland Altman plot, and 4-Quadrant plot each adjusted for repeated measures within patients.

Results: Echo and NiCaS SV mean and 95% CIs were 58.0 (50.1, 65.8) and 56.7 (49.4, 64.0) ml respectively. NiCaS SV correlated strongly with Echo SV during the first and last hours of treatments (r = 0.93, p<0.001 and r = 0.92, p<0.001, respectively). Linear regression of NiCaS on Echo showed a slope of 0.97, 95% CI (0.91, 1.02) which did not differ from 1, p = 0.20. A Bland-Altman plot and 4-Quadrant plot (Figure, left) demonstrated excellent agreement between devices. Mean arterial pressure (MAP) changes during first and last hours of treatments did not correlate with SV changes during the same periods (Figure, right).

Conclusions: NiCaS SV measurements correlate with and are similar to Echo SV measurements. Thus, noninvasive NiCaS technology may be a practical method for measuring SV during HD.

Funding: Commercial Support - New NI Medical
SA-PO752

Characteristics of ESRD Patients Admitted for Inpatient Dialysis and Its Contribution to Cost of Care
Madhuri Ramakrishnan,1 Siva sagar Taduru,1 Reem Mustafa.1 1University of Missouri Kansas City; Kansas City, MO; 2Nephrology, Kansas University Medical Center, Kansas City, KS.

Background: The United States Renal Data System (USRDS) 2010 report shows that Medicare spent $29 billion, or almost 6% of its annual budget in 2009, on patients with end stage renal disease (ESRD). This covers a variety of expenditure, including hospital admissions. These admissions can be for complications that require emergent dialysis. We aim to present data on admissions of patients with ESRD for complications including hyperkalemia, acidosis and pulmonary edema requiring inpatient dialysis.

Methods: We identified ESRD patients who were admitted with indications of emergent dialysis, and with a length of stay (LOS) < 2 days, and therefore had conceivably no further indication for continued admission. We searched the National Inpatient Sample (NIS) from 2008 – 2014 using International Classification of Diseases Clinical Modification (ICD-9-CM) codes to identify patients with ESRD on long-term dialysis, who were admitted with a primary diagnosis of hyperkalemia, acidosis, or pulmonary edema. We then identified those patients who received dialysis while inpatient, and those whose LOS was < 2 days. We describe categorical variables as proportions and continuous variables as means.

Results: We identified total of 30,918 admissions between 2008 – 2014 for patients with ESRD, who were admitted with indications for emergent dialysis, and had a LOS < 2 days. These represented 1.03% of all-cause admissions in ESRD patients. The patients’ mean age was 52.0 ± 15.6 years and 54% were males. Of these patients, 32.2% were Caucasians, 31.5% African-Americans, and 25.8% Hispanics. Hyperkalemia was the primary indication in 92% of cases, pulmonary edema in 12.3%, ESRD in 8%, and acidosis in only 0.5% of cases. 63.6% patients were insured by Medicare, 18.8% by Medicaid, 9.1% by private insurance, and 5.8% were uninsured. 55.9% of these admissions were seen in urban teaching hospitals. The mean total charges were $13,141 ± 9,522 per admission, which amounts to a mean annual charge of $58,041,920.

Conclusions: Our study reports on admissions of ESRD patients with indications for emergent dialysis. We hypothesize that a proportion of which could represent preventable admissions, incurring higher costs than outpatient dialysis. Further studies are needed to identify factors associated with such admissions, and form strategies to prevent them.

SA-PO753

A Twelve Month Retrospective Analysis of Corrected Serum Calcium (CSC) and Parathyroid Hormone (iPTH) in Patients Hemodialyzed with Citrate Acidified Dialysate (CD) Compared to Acetate Acidified Dialysate (AD)
Linda E. Fasciocchi,1 Ludmila Anderson,1 Paul Balter,2 Alice Topping,2 Claudy Mullon,1 Robert J. Kossmann.1 1Veterans Affairs Support

Background: Citrate, when compared to acetate, has been shown to increase the stability of red blood cells and to increase the amount of Calcium (Ca) absorbed by the gastrointestinal tract. Citrate, when administered intravenously as part of the dialysate, sequesters calcium and diverts it away from the extracellular space, thus reducing the risk of hypocalcemia. The objective of this database analysis was to assess potential changes in corrected serum calcium, parathyroid hormone, and other dialysis related parameters.

Methods: We collected data on 30 HD patients with 3 mos. of AD treatment data (baseline [BL]) followed by 12 mos. of CD treatment data analyzed. Mean pre-HD CSC and iPTH laboratory values for AD and CD treatment periods were compared by quarters (Q1-Q4) and overall. Subanalyses were carried out by iPTH ranges (<130, 130-600, >600 pg/ml) during BL.

Results: Non-significant changes in CSC were observed after the CD conversion. Increases in iPTH during Q1 leveled off during Q2-Q4, with the exception of the BL iPTH > 600 pg/ml group where a steady iPTH decrease occurred (BL: 1,095.4 vs. Q4: 905.1 pg/ml, p<0.001) (Table). From BL to Q4, the proportion of patients treated with CaPB by 12 mos. of CD treatment data were analyzed. Mean pre-HD CSC and iPTH laboratory values for AD and CD treatment periods were compared by quarters (Q1-Q4) and overall.

Conclusions: No changes in CSC, and clinically modest changes in iPTH, followed the conversion from AD to CD. Variability was observed according to the BL iPTH range.

SA-PO754

Control of Uremic Solute Levels in Smaller Pediatric Hemodialysis Patients
Frank J. O'Brien,1 Enrica Fung,1 Natalie Plummer,1 Timothy W. Meyer,1 Paul R. Brakeman,2 Scott M. Sutherland,3 Tammy L. Sirich,3 1Stanford University/VAMC Nephrology, Palo Alto, AL; 2UCSF, San Francisco, CA; 3Stanford University, Palo Alto, CA.

Background: Current guidelines for hemodialysis (HD) in pediatric patients are adapted from those for adults, and dialysis is prescribed proportional to urea’s distribution volume to achieve a target Kt/V. Dosing HD proportional to volume in smaller patients, however, has been questioned. Uremic waste solutes may be produced in proportion to metabolic rate, may be more nearly proportional to body surface area (BSA) than volume. As body size decreases, the ratio of BSA to volume increases. Plasma levels of uremic solutes may thus remain higher in smaller patients when dialysis is prescribed proportional to volume. We tested this hypothesis by measuring plasma levels of pseudouridine (PU), a uremic waste solute whose generation is proportional to BSA, in pediatric dialysis patients.

Methods: PU and urea nitrogen (UN) were measured in plasma and dialysate obtained at the midweek session in 19 pediatric patients with BSA from 0.64 to 1.88 m² receiving thrice weekly HD.

Results: The dialytic clearance (Kₜ/V) of PU was proportional to that of UN (Kₜ/V, R² = 0.83±0.06, R² = 0.95, p<0.001). As expected, the generation of PU assessed by PU recovery in the dialysate was proportional to BSA (189±45 µmol/day/m², R² = 0.70, p <0.001). The Kₜ/V was well maintained averaging 1.5±0.24 and did not vary over the range of BSA values. As shown in the figure, however, the pre-treatment plasma PU level was significantly higher in the patients with lower BSA (p <0.05).

Conclusions: Dosing HD by volume may leave uremic solutes at higher levels in smaller pediatric patients. Further studies are needed to determine whether prescription of HD based on BSA provides clinical benefit.

Funding: Veterans Affairs Support
symptoms associated with dialysis were assessed at baseline using the Kidney Disease Quality of Life-36 (KDQOL-36) survey. Follow-up surveys were completed at 12 months and differences from baseline were assessed using paired t-testing.

Results: Thirty-six patients were enrolled in ICNHD during the study period (69% male, mean age 54). Mean time on dialysis prior to enrollment was 31 months and mean Charlson Comorbidity Index score was 2.19 (range 0-4). Twenty-four patients (67%) were included in final analyses. Table 1 shows changes in the domains of the KDOQOL-36. Significant improvements were seen in the “Effects of Kidney Disease” and “Mental Health Composite” domains (increase of 17% and 16%, respectively). Analyses yet to be conducted include an assessment of individual symptoms, as well as a sub-analysis using baseline KDOQOL-36 scores to divide the cohort into tertiles.

Conclusions: In-centre nocturnal hemodialysis results in improved HRQoL. Previous studies have shown that patients with the lowest HRQoL at baseline derive the most benefit from home hemodialysis; further analyses will examine whether the same is true for ICNHD. Further studies are needed to determine whether improved HRQoL with ICNHD is associated with improved patient survival.

Table 1: Change in Health-Related Quality of Life

<table>
<thead>
<tr>
<th>Domain</th>
<th>Baseline Mean (SD)</th>
<th>12-Month Follow-up Mean (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms/Problem</td>
<td>7.3 (1.13)</td>
<td>7.7 (1.26)</td>
<td>0.00</td>
</tr>
<tr>
<td>Effects of Kidney Disease</td>
<td>6.0 (2.21)</td>
<td>6.6 (2.23)</td>
<td>0.046</td>
</tr>
<tr>
<td>Basic of Kidney Disease</td>
<td>29.1 (7.52)</td>
<td>31.4 (25.1)</td>
<td>0.35</td>
</tr>
<tr>
<td>Physical Health Composite</td>
<td>34.7 (1.31)</td>
<td>36.4 (1.37)</td>
<td>0.24</td>
</tr>
<tr>
<td>Mental Health Composite</td>
<td>45.6 (12.1)</td>
<td>51.0 (11.5)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Table 1: Mean and standard deviations for each of the 5 domains of the KDOQOL-36. Each domain scored on a scale of 1 to 100, with higher values representing superior HRQoL.

SA-PO756

Using Intradialytic Blood Pressure Slopes to Assess Extracellular Volume in Hemodialysis Patients

Peter N. Van Buren,1 Hao Liu,1 Mark T. Sonderman,1 Shani Shasiri1

1Internal Medicine, Nephrology, UT Southwestern Medical Center, Dallas, TX; 2UT Southwestern, Dallas, TX.

Background: Extracellular volume (ECV) overload increases mortality risk in hemodialysis (HD) patients, but there is no standardized clinical method to assess ECV in them. We evaluated the association between slopes of multiple intradialytic blood pressure (BP) measurements with bioimpedance spectroscopy (BIS)-determined measurements of ECV overload as a novel method to assess ECV using routine clinical data.

Methods: We measured systolic BP every 30 minutes in a mid-week HD treatment. Using multifrequency BIS, we measured pre and post HD extracellular water (ECW), total body water (TBW), ECW/TBW and ECW/weight. Using Pearson correlation and mixed linear regression we compared associations between post-HD ECV overload with total body water (TBW), ECW/TBW and ECW/weight. Using BIS based measurements of ECV overload in hypertensive HD patients. The slope of BP was calculated with pre-HD (r=-0.2,p=0.3), post-HD (r=0.2,p=0.1), or delta SBP (r=-0.2, p=0.09). This significant association persisted after controlling for age, gender, and ultrafiltration rate (β=-1.9, p=0.001) and was stronger than associations with slope and other ECV metrics. ECV/weight had a stronger association with intradialytic BP slope than with pre-HD (r=-0.2, p=0.3), post-HD (r=-0.2, p=0.1), or delta SBP (r=-0.2, p=0.09).

Conclusions: There is a significant correlation between intradialytic BP slopes and BIS based measurements of ECV overload in hypertensive HD patients. The slope of multiple intradialytic BP measurements better assesses ECV than pre, post or delta SBP. Determining intradialytic blood pressure slope is an innovative way to objectively assess ECV in HD patients.

Funding: NIDDK Support

SA-PO757

Impact of High Convective Volumes on Metabolic Profile and Body Composition of Diabetic Patients on Online Hemodiafiltration

Nicolas Macias,1 Tania Linares,1 Almudena Vega,2 Esther Torres aguilera,2 Alba Santos,3 Marian Goicoechea,2 Eduardo Verde,2 Soraya Abad.3 Gregorio Marañon, Madrid, Spain; HUGUM, Madrid, Spain; 3HOSPITAL GREGORIO MARAÑON, MADRID, Spain; 1Hospital Gregorio Marañon., Madrid, Spain.

Background: OL-HDF with high convective volumes improves patient survival compared with high-flux hemodialysis. It has been proposed to limit the amount of convective transport in patients with diabetes mellitus, due to glucose load that is administered with replacement fluid. The aim of this study is to analyze the influence of substitution volume(SV) in the evolution of metabolic profile of diabetic patients incident on OL-HDF.

Methods: Prospective observational study in 29 diabetic patients incident on postdialution OL-HDF, three 4-hours sessions weekly. Baseline data included clinical, demographic, laboratory and body composition(BIS) parameters. Laboratory and SV were collected every four months, and in 23 patients another BIS was performed after a minimum follow-up of one year. Variations of glycosylated hemoglobin(HbA1c), triglycerides(TG), total cholesterol, LDL-c, HDL-c, albumin, prealbumin and C-reactive protein(CRP) were calculated at one-two-three years, and at the end of follow-up. Also quarterly and annual variations were calculated, as well as changes in body composition. Variations were collected to evaluate the influence of SV in these changes.

Results: Age at baseline was 69.7±13.6years, 62.1%male, with 48.35.5 – 76months on dialysis, 72.3±13.9kg weight, 27.1±5.4kg/m2 BMI, 1.78±0.16m. BSA. 81.5%received insulin, 7.4%antidiabetic drugs and 51.9%statins. Mean SV was 26.9±6.29L per session and follow-up(time on OL-HDF) was 40.4±26months. We found significant correlation between SV and final changes in HDL-c(0.385,p=0.039), prealbumin(0.404,p=0.003) and CRP(-0.409,p=0.007). Also convective dose adjusted with BSA was related with changes in HDL-c(0.393,p=0.035) and inversely correlated with changes in TG(0.423,p=0.022) and CRP(-0.573,p=0.007) since the second year of follow up. Quarterly comparison in 271 showed that quarterly SV correlated with variations in HbA1c(0.416,p=0.021). No correlation was observed between SV and changes in weight, body weight, lean or fat tissue in the period between BIS measurements.

Conclusions: Higher convective dose is associated with a slight improvement in metabolic profile in diabetic patients in OL-HDF. There is no evidence to restrict the convective transport in diabetic patients due to the glucose content of the replacement fluid.

SA-PO758

In-Vitro Dialysate Regeneration Using Dharma, the EasyDial Portable Hemodialysis Machine

Osman S. Khawar,1 Timothy R. Menonar,2 Sarah L. Foster.1 1Balboa Nephrology Medical Group, Escondido, CA; 2EasyDial, Irvine, CA.

Background: Dharma is a unique, fully portable dialysis machine, which uses only 5 Liters of dialysate per treatment. In order to achieve this limited dialysate volume, dialysate is regenerated using a chemical filter through which dialysate in recirculated continuously during dialysis, while electrolytes are supplied via an infusion into the dialysate reservoir.

Methods: Bovine blood was tested during a 2 hour dialysis, using a 70 mL concentrated mixture of calcium, potassium, and magnesium administered continuously during into 5 Liters of dialysate using an ambIT peristaltic pump. Samples of dialysate were collected every 15 minutes and analyzed for electrolyte concentrations.

Results: The electrolytes were continuously present at acceptable concentrations, indicating that dialysate was regenerated during the dialysis. Concentrations are provided in table 1. Baseline and 2 hour concentrations for each ion were: Calcium 37.06 ppm 36.67ppm, Magnesium 10.63ppm and 13.58ppm, potassium 71.03ppm and 5.15ppm.

Conclusions: These results verify that continuous infusion of key electrolytes into the dialysate during dialysis with Dharma maintains electrolyte concentrations in regenerated dialysate. Dharma offers the unique features of portability (18 lbs), no fixed water connection (5L dialysate) and the possibility for significantly reducing dialysis treatment times.

Funding: Commercial Support - EasyDial Inc

Electrolyte Concentrations in Dialysate

<table>
<thead>
<tr>
<th>Time</th>
<th>Calcium (ppm)</th>
<th>Magnesium (ppm)</th>
<th>Potassium (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>37.06</td>
<td>10.63</td>
<td>71.03</td>
</tr>
<tr>
<td>30</td>
<td>36.5</td>
<td>10.28</td>
<td>68.78</td>
</tr>
<tr>
<td>60</td>
<td>37.17</td>
<td>13.42</td>
<td>42.02</td>
</tr>
<tr>
<td>90</td>
<td>38.04</td>
<td>17.32</td>
<td>9.49</td>
</tr>
<tr>
<td>120</td>
<td>41.35</td>
<td>15.06</td>
<td>3.83</td>
</tr>
<tr>
<td>150</td>
<td>38.17</td>
<td>13.21</td>
<td>2.48</td>
</tr>
<tr>
<td>180</td>
<td>36.03</td>
<td>17.45</td>
<td>3.5</td>
</tr>
<tr>
<td>210</td>
<td>36.67</td>
<td>13.58</td>
<td>5.15</td>
</tr>
</tbody>
</table>

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

Underline represents presenting author.
Quality Improvement Empowerment: Dialysis Clinic Staff Lead Projects for Change
Laura J. Maurer, University of Wisconsin School of Medicine and Public Health, Madison, WI.

Background: Quality improvement provides an avenue for delivering healthcare that meets the best practices standards across medicine. Dialysis centers strive to provide the optimal care but in the era of dialysis center ratings measures of care delivery become even more impactful. There are many centers that have provided examples where quality improvement projects have improved the delivery of care. There are none that have created a system where all staff are educated about quality improvement and encouraged to lead their own project.

Methods: In the fall of each year, a portion of the staff meeting is dedicated to quality improvement (QI). The dialysis director talks about the differences between quality improvement and research, noticing gaps in care, methods of analyzing and measuring a problem and thinking of interventions. Each staff member is encouraged to develop a index and is a simple QI curriculum available to assist in facilitating the project. Periodically the dialysis director and charge nurse discuss the projects with each leader and the results of the projects were brought to the hospital administration at the end of the year.

Results: After this program was started, there have been 12 projects initiated. In the first year of the program 80% of the staff developed a project. All types of staff led projects: these included the dietician, the social worker, 75% of the nurses, and 100% of the dialysis technicians. The project topics included improved patient knowledge of emergencies, improved knowledge of dialysis treatment options, discussions with patients about the importance of dialysis adequacy and maintaining the prescribed dialysis schedule, improvement in the time the staff spend with each patient, increase fun activities for patients during dialysis, improved referrals for positive depression screening, and improvement in the albumin level.

Conclusions: Creating an environment and formalized QI program that empowers employees to notice problems and create solutions was able to make an impact on the quality of care provided in this small dialysis center. This simple curriculum could be translated into larger dialysis units to improve the quality of care and satisfaction of the patients or employees of the unit.

UK Clinical Experiences of a New Expanded Hemodialysis Therapy with a Novel Medium Cut-off Dialyzer
Itaxi B. Baharani,1 Bernard Bartiox,2 Debbie Hopkins,3 Wyn Passmore,4 Heart of England NHS Foundation Trust, Birmingham, United Kingdom; 2Morriston Hospital, Swansea, United Kingdom.

Background: Middle molecules are associated with the pathology of uremia, and their removal is enhanced by increased convection with hemodiafiltration (HDF) therapy. However, HDF therapy may not be suitable for, or available to, all patients. A newly developed medium cut-off (MCO) membrane allows hemodialysis (HD) to be expanded in terms of middle molecule removal (HDx therapy) using conventional HD infrastructure. Here, we describe the experience of two UK clinics trialing HDx therapy.

Methods: At Heartlands Hospital (HH), the patient demographic (n=8) was: 48–90 years of age, mixed ethnicities, and 1–14 years of HD experience. Patients (treated thrice weekly) were switched from high-flux HD with a polysulphone dialyzer (FX60 or FX80, Fresenius) to HDx therapy with the MCO membrane (Theranova 400, Baxter). At Morriston Hospital (MH), patients (n=18) were 25–91 years of age with 2–16 years of HD experience. Patients who had failed to tolerate (n=14) or tolerated (n=4) HDF therapy were switched to HDx therapy with the MCO membrane. Reduction ratios (RRs) of beta-2-microglobulin (β2M) and albumin loss were assessed; data are based on averages of 3 dialysis sessions (HH) or 1 dialysis session (MH).

Results: At HH, average β2M RRs (post-vs-pre-dialysis level) with HDx therapy were 69.3% (Week 1) and 69.4% (Week 9) vs 48.8% with high-flux HD. At Week 9, serum albumin levels increased during dialysis by 0.8 g/L. Following 9 weeks of HD therapy, post-dialysis levels of β2M were reduced by 11.7%, and no difference in albumin level was seen. At MH, average β2M RRs with HDx therapy were 71.0% (Week 1) and 73.9% (Week 9). For patients who tolerated HDF, at Week 1 β2M RRs were 72.2% and 73.9% with HDx and HDF therapy, respectively. Based on serum albumin levels, albumin loss in both groups was minimal. No adverse events were noted; 1 patient with arthritis did not experience any arthritic flare-ups during HDx therapy.

Conclusions: HDx therapy was convenient, simple to implement, and achieved high β2M RRs with low albumin loss. It offers opportunity for achieving the clearance of middle molecules delivered by HDF, when patient factors exist or HDF is not available. Based on 2 of 4 HDF patients and all 14 HDx patients.

Comparison of Albumin Binding Capacity and Uremic Toxins in Hemodiafiltration versus Novel Dialysis Membrane
Sebastian Koballa,4 Christina Westphal,1 Silvius Frimmel,2 Michael Hinze,3 Sebastian Klammert,3 Steffen R. Mitzner,1 Fraunhofer Institute for Cell Therapy and Immunology, Rostock, Germany; 2Rostock University Medical Center, Rostock, Germany; 3University Rostock, Rostock, Germany; 4Universität Rostock, Rostock, Germany.

Background: Albumin is an important transport protein for non-water-soluble protein-bound drugs and uremic toxins. A decreased transport capacity may lead to endogenous intoxication and worsening of uremic symptoms. It is known that the albumin binding capacity (ABiC) is reduced in patients with advanced stages of chronic kidney disease. Moreover, ABiC is an important marker of the detoxification capacity of extracorporeal treatments. It is presumed that open-pored filters remove high molecular substances more efficiently than conventional treatment, thereby increasing the detoxification capacity. The Baxter-Theranova (HDx) filter is the first approved filter which could meet these requirements. The study aim was to evaluate the effectiveness of the HDx dialyzer with regard to the improvement of ABiC and the removal of albumin toxins (e.g. hippuric acid, paracresyglycoconulron, indoxylsulfate, paracresylsulfate, indolacetic acid), phosphate, urea, albumin concentration during standard hemodiafiltration/hemodiafiltration treatment.

Methods: The efficacy of HDx was assessed by comparing Baxter Theranova 500 filters with the standard Fresenius FX80 filters (HDF). We included 32 patients with dialysis-dependent chronic kidney disease (stage 5d); above age 18 who provided written informed consent. Key exclusion criteria were acute infectious diseases, bleeding and a hospital stay within the last 14 days. All patients were first treated with HDF for 14 days (3 times a week) and blood samples were drawn (15ml) before and after treatment at study entry, before and after first HDx treatment and before/after 6 HDx treatments, to determine ABiC and other clinically relevant parameters. Alteration of ABiC and other relevant parameters was assessed by using Wilcoxon matched pairs signed-rank test.

Results: ABiC improved significantly in both therapies (HDx/HDF), however, no significant differences were found between the two therapies. The same was true for phosphate, indoxylsulfate, urea, creatinine, and uric acid. A reduction of albumin concentration during HDx treatment was not observed, neither during single treatment nor over the 14 days period.

Conclusions: Expanded hemodialysis enabled by Theranova demonstrates equal effects on ABiC and uremic toxins in comparison to OL-HDF.

Funding: Commercial Support - Baxter Healthcare.

Influence of Dialysis Membranes on Bisphenol A Serum Levels in Online Hemodiafiltration
Sebastian Mas,1 Enrique Bosch,2 Alberto Ruiz,3 Esther Civantos,2 Jesus Egido,2 Alberto Ortiz,2 Emilio E. Gonzalez-parras,2 1IIS- FJD, Madrid, Spain; 2Fundacion Jimenez Diaz, Madrid, Spain; 3IIS-FJD, Madrid, Spain.

Background: In uremia, the environmental toxin Bisphenol A (BPA) accumulates bound to proteins. BPA-containing dialyzers contribute to increase plasma BPA concentration in conventional hemodialysis patients. Online hemodiafiltration (OL- HDF) more efficiently clears high molecular weight molecules, and this may improve BPA clearance. However, OL-HDF requires high infusion volumes of replacement fluid generated online by using BPA-containing membranes and, thus, can be a source of BPA load. Objectives: To assess plasma BPA levels in OL-HDF patients using BPA-free or BPA-containing dialyzers.

Methods: In a prospective study, plasma BPA was assessed at baseline and 3 months after switching from baseline BPA-free polysulfone to BPA-containing polysulfone (n=31) dialyzers, or from baseline polysulfone to polysulfone (n=27) dialyzers in OL-HDF patients. Results were compared to a prior study on conventional hemodialysis.

Results: OL-HDF patients had lower plasma BPA than those in conventional hemodialysis (12.1±15.91 vs. 64.5±93.8 ng/mL) and both were several fold higher than healthy controls (<2 ng/mL). However, this was influenced by the dialysis membrane. Thus, baseline BPA was 8.79±7.97 ng/mL in patients dialyzed 6 months with polysulfone versus 23.42±20.38 ng/mL with polysulfone. During the first single OL-HDF session with the switch membrane, BPA decreased in the polysulfone-to-polysulfone group (pre-dialysis 23.42±20.38 ng/mL to post-dialysis 6.44±10.77 ng/mL, p <0.01), but remained unchanged in polysulfone-to-polysulfone patients. After 3 months on polysulfone, BPA levels rose non-significantly from 8.79±7.97 to 11.02±16.17 ng/mL in the polysulfone-to-polysulfone group, while they decreased 51% in the polysulfone-to-polysulfone group (p=0.01).

Conclusions: Optimal reduction in BPA levels is achieved by using OL-HDF with BPA-free dialyzer membranes. Attempts at optimizing net BPA clearance in OL-HDF are justified by the residual higher plasma BPA levels when compared to healthy controls.
Dialyzer Reuse in Prevalent Hemodialysis Patients: Mortality and Clinical Outcomes

Background: Dialyzer reuse has been a common practice in the US. In Mexico, economical restraints related to CKD have forced to seek cheaper options to provide RRT among these patients. Thus, dialyzer reuse has become a common practice in most of the hemodialysis clinics across the country. It is regulated by the Ministry of Health. Previous studies have reported no difference in mortality among patients with dialyzer reuse versus single use. The aim of this study was to evaluate the clinical implications of dialyzer reuse in prevalent HD patients from Jalisco, Mexico.

Methods: A cross-sectional, multicenter study in prevalent hemodialysis patients in Jalisco. 2561 insured and uninsured patients conformed the national data base. Only patients who had a Kt/V ≥1.2 were included for analysis. Mortality, vascular access, clinical variables and laboratory values were compared among patients with reusable dialyzers and those with single use dialyzers.

Results: 2561 patients were evaluated for analysis. Only 597 patients (23.3%) had a Kt/V ≥1.2. Reuse of dialyzer was performed in 482 of them (80%). Average reuse was 5.5 times per dialyzer (range 1-12). Serum electrolyte, creatinine, urea, albumin, PTH, iron kinetics, urea pre/post did not differ among both patients who underwent reuse of dialyzer vs those with one single use dialyzer. Hemoglobin, urea pre and post values were statistically better for patients with dialyzer reuse. Time to death and mortality did not differ among both groups. Dialyzer reuse continues to be a controversial practice, but according these findings, it appears to be a safe. Further studies are needed to assess the long term clinical impact of this practice, since the financial panorama of KD points to an urgent and generalized need to optimize economical resources in order to provide safe treatments to more patients at lower costs.

Conclusions: Serum electrolyte, creatinine, urea, albumin, PTH and iron kinetics did not differ among patients who underwent reuse of dialyzer vs those with one single use dialyzer. Hemoglobin, urea pre and post values were statistically better for patients with dialyzer reuse. Time to death and mortality did not differ among both groups. Dialyzer reuse continues to be a controversial practice, but according these findings, it appears to be a safe. Further studies are needed to assess the long term clinical impact of this practice, since the financial panorama of KD points to an urgent and generalized need to optimize economical resources in order to provide safe treatments to more patients at lower costs.

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

Effect Modification by Age and Pulse Pressure (PP) on the Association Between Mediterranean Diet (MD) and Telomere Length (TL) in Hemodialysis (HD) Patients

Background: Dialyzers reuse has been a common practice in the US. In Mexico, economical restraints related to CKD have forced to seek cheaper options to provide RRT among these patients. Thus, dialyzer reuse has become a common practice in most of the hemodialysis clinics across the country. It is regulated by the Ministry of Health. Previous studies have reported no difference in mortality among patients with dialyzer reuse versus single use. The aim of this study was to evaluate the clinical implications of dialyzer reuse in prevalent HD patients from Jalisco, Mexico.

Methods: A cross-sectional, multicenter study in prevalent hemodialysis patients in Jalisco. 2561 insured and uninsured patients conformed the national data base. Only patients who had a Kt/V ≥1.2 were included for analysis. Mortality, vascular access, clinical variables and laboratory values were compared among patients with reusable dialyzers and those with single use dialyzers.

Results: 2561 patients were evaluated for analysis. Only 597 patients (23.3%) had a Kt/V ≥1.2. Reuse of dialyzer was performed in 482 of them (80%). Average reuse was 5.5 times per dialyzer (range 1-12). Serum electrolyte, creatinine, urea, albumin, PTH, iron kinetics, urea pre/post did not differ among both patients who underwent reuse of dialyzer vs those with one single use dialyzer. Hemoglobin, urea pre and post values were statistically better for patients with dialyzer reuse. Time to death and mortality did not differ among both groups. Dialyzer reuse continues to be a controversial practice, but according these findings, it appears to be a safe. Further studies are needed to assess the long term clinical impact of this practice, since the financial panorama of KD points to an urgent and generalized need to optimize economical resources in order to provide safe treatments to more patients at lower costs.

Conclusions: Serum electrolyte, creatinine, urea, albumin, PTH and iron kinetics did not differ among patients who underwent reuse of dialyzer vs those with one single use dialyzer. Hemoglobin, urea pre and post values were statistically better for patients with dialyzer reuse. Time to death and mortality did not differ among both groups. Dialyzer reuse continues to be a controversial practice, but according these findings, it appears to be a safe. Further studies are needed to assess the long term clinical impact of this practice, since the financial panorama of KD points to an urgent and generalized need to optimize economical resources in order to provide safe treatments to more patients at lower costs.

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

Underline represents presenting author.

876
SA-PO767

Variability of Pre-Dialysis Serum Sodium and Its Association with Survival in Hemodialysis Patients: Results of the MONDO Consortium

Xiaoling Ye, Jeroen Kooman, Bernard J. Canaud, Nathan W. Levin, Cristina Marelli, Albert J. Power, Frank van der Sande, Stephan Thijsen, Xiaojie Xu, Len A. Usyyat, Yuedong Wang, Peter Kotanko,1,2 Joschen G. Raimann,3,4 FMC Deutschland GmbH, Bad Homburg, Germany; 3Fresenius Medical Care Argentina, Buenos Aires, Argentina; 4Fresenius Medical Care Asia Pacific, Hong Kong, China; 5Fresenius Medical Care North America, Melrose, MA; 6Renal Research Institute, New York, NY; 7Richard Bright Renal Unit, Bristol, United Kingdom; 8University of California - Santa Barbara, Santa Barbara, CA; 9Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Pre-dialysis serum sodium (SNa) is the main determinant of plasma osmolality. Whereas hyponatraemia is associated with adverse outcomes in haemodialysis (HD) patients, variations in SNa may lead to fluid shifts between the extracellular and intracellular spaces and cell volume changes. The aim of the study was to explore the relationship between SNa; the rate of change (slope), and the SD of the residual (variability) of SNa with all cause of death.

Methods: All incident and prevalent pts from the MONDO initiative with at least 6 SNa measurements during baseline (1st year in HD) were selected. Follow-up defined as 2nd year on HD. Survival analysis were applied to study the effect of SNa, slope and variability on event. Smoothing spline logistic regression models were used to explore the joint effect of (a) SNa variability with variability, and (b) SNa with slope on event. Additionally, time to event analysis were used to delineate the association of various demographic and clinical parameters with event.

Results: 15, 335 HD pts (63.2 years, 59% males, 24% diabetics) from Europe (10,907), West Asia (1,991), South America (283) and US (2,154) were included. Lower SNa, positive and negative slope, and higher variability associated with an increased the risk of event. Increased risk of death with higher variability and slopes appeared to be present at all levels of SNa, with apparently stronger effects for variability than slope (Figure 1). However, the relation between SNa variability and slopes with outcome lost significance after adjusted for confounders.

Conclusions: Our findings suggest that SNa variability may constitute a novel prognostic indicator. Underlying pathological conditions may explain the relation between SNa and outcome.

SA-PO769

Effect of Fluid Status on the Fat Mass Estimated by Bioimpedance in Hemodialysis Patients

Samer R. Abbas, Stephan Thijsen, Erik L. Penn, Jochen G. Raimann, Nathan W. Levin, Peter Kotanko, Fansan Zhu, Medical Center Alkmaar, Alkmaar, Netherlands; None, New York, NY; Renal Research Institute, New York, NY; Icahn School of Medicine at Mount Sinai, New York, NY.

Background: This prospective study utilizes calf bioimpedance spectroscopy (cBIS) to guide the attainment of dry weight (DW) in chronic hemodialysis (HD) patients. In the present research we evaluate whether fat mass is altered when DWcBIS is attained.

Methods: Target post-HD weight was gradually reduced from baseline (BL) until DWcBIS was achieved. DWcBIS was defined as the presence of both flattening of the curve of extracellular resistance during HD and the attainment of normalized resistivity (CNR) in the normal range (Zhu, Physiol Mea 2008). Extracellular (ECV), intracellular (ICV) volume and total body water (TBW) were measured using whole body bioimpedance spectroscopy (Hydra 4200). Fluid overload (FO), lean body mass (LBM), and fat mass (FM) were calculated according to a body composition model (Chumney, Am J Clin Nutr 2007).

Results: Twenty-eight patients (13 females; 7 diabetic; age 53.7±12 years) achieved DWcBIS over a period of 43.8±30.1 days. On average 16±10 measurements per patient were required to attain DWcBIS. Although significant decreases in body weight, CNR and ECV pre and post HD were observed, LBM and FM at DWcBIS did not differ significantly from BL (Table 1). ECV/TBW and FO were non-significantly higher at BL compared to DWcBIS (Table 1).

Conclusions: This study showed that attainment of DWcBIS did not affect fat mass.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Wt (kg)</th>
<th>CNR</th>
<th>ECV (L)</th>
<th>ECV/TBW (L/kg)</th>
<th>FO (kg)</th>
<th>LBM (kg)</th>
<th>Fat (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre HD BL</td>
<td>78.1±16</td>
<td>14.2±2</td>
<td>16.8±2.6</td>
<td>0.48±0.05</td>
<td>1.0±3</td>
<td>34.7±13</td>
<td>31.2±16</td>
</tr>
<tr>
<td>DWcBIS</td>
<td>50.1±7</td>
<td>16.3±2</td>
<td>15.0±2.5</td>
<td>0.47±0.04</td>
<td>1.7±2.3</td>
<td>35.0±9</td>
<td>28.8±12.5</td>
</tr>
<tr>
<td>Post HD BL</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.79</td>
</tr>
<tr>
<td>Post HD DWcBIS</td>
<td>75.4±15.6</td>
<td>17.0±2.5</td>
<td>14.4±2.2</td>
<td>0.46±0.05</td>
<td>1.2±1.1</td>
<td>25.9±9.0</td>
<td>20.8±12.5</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.1</td>
</tr>
</tbody>
</table>

SA-PO768

Modified Compression Bioimpedance in Edema Quantification in Patients on Hemodialysis


Background: Quantification of edema in dialysis patients is subjective and problematic. Given the importance of fluid overload, objective measures are necessary.

Methods: We conducted a clinical study using bioimpedance and circumferential strain measurement to quantify edema in patients with lower extremity edema in haemodialysis patients. Eleven stable hemodialysis patients, 18-85 years of age, with varying grades of clinical edema participated. During their usual hemodialysis session, a series of compression cycles (30 seconds, 50mm Hg) were applied above one ankle using a blood pressure cuff. Bioimpedance and strain data were collected using the bioimpedance meter and plethysmograph, respectively. This procedure was repeated until the completion of the dialysis session.

Results: Using the strain data we calculated the volume of mobilized fluid during compression. Using the bioimpedance data we calculated the total volume of fluid underneath the cuff. The median volume of fluid estimate for each subject was used to normalize the volume of mobilized fluid obtained from the strain measurements. These data, along with the fit parameters for the strain data, were plotted as a function of the edema grades. Of the three strain fitting parameters (ε0, ε∞, and τ), the ANOVA revealed significant differences among edema grades for both the instantaneous strain ε0 (p < 2×10^-16) and the viscoelastic strain ε∞ - ε0 (p < 2×10^-16). ANOVA also revealed significant differences among edema grades for the strain-based estimate of the volume of mobilized fluid (Fp (p < 2×10^-16); bioimpedance based total fluid volume (p < 2×10^-16)) and relative volume of mobilized fluid (p < 2×10^-16).

Conclusions: Using this novel technique in dialysis patients we demonstrated the potential to quantify mechanical characteristics of edema, ε0, ε∞ - ε0 and τ, to better characterize peripheral edema.

Funding: Private Foundation Support

Violin plots of strain fit parameters and estimates of volume parameters.
SA-PO770

Lower Blood Flow Rate in the Last Quarter of Hemodialysis May Protect Against Hypotension: Rebecka Backenroth,1,2 Dvora Rubinger,1 Tasneem Kab,1 Irina Mor yosef levi,1 Dan Sapoznikov,1 1Hadassah U Med Center, Jerusalem, Israel; 2Barzilai U Med Center, Ashkelon, Israel; 3Hadassah u med center, Jerusalem, Israel; 4Nephrology, Hadassah, Jerusalem, Israel.

Background: In hemodialysis (HD), high blood flow rate (BFR) increases clearances and decreases clotting of the extracorporeal circuit. However, possible adverse effects are not well delineated.

Methods: A prospective crossover study compared the effects of higher vs lower BFR, with patients serving as their own controls. Consenting stable adults on chronic HD were studied for 2 sessions in random order usually a week apart. The control session, with “high” constant BFR, 300-450 cc/min, and the variable flow session, alternating high then low, 250 cc/min BFR in 4 equal periods of the session. Continuous beat to beat BP and pulse were monitored noninvasively by Finometer TM, O2 saturation by pulse oximeter, and subjective wellbeing by questionnaires.

Results: Twelve patients in 24 HD sessions were studied. Baseline weight, pulse, interdialytic weight gain and UF rates were similar in the sessions but initial systolic BP (SBP) was higher in the control HD. In the control HD, SBP declined while the diastolic BP (DBP) declined only in the 4th quarter. The variable flow HD was similar until the last quarter, when lower BFR was associated with significant reversal of the decline of SBP and DBP, and a rise in DBP. Pulse increased insignificantly during both sessions. Autonomic parameters were similar except LFx (index of baroreflex sensitivity) which increased in the control, but decreased in the 4th, lower BFR period (p=0.03). Total peripheral resistance also differed only in the 4th period, when it decreased in the control, but increased in the variable BFR group. Stroke volume was significantly higher in the 1st period of low BFR, and cardiac output decreased in both sessions. SBP did not correlate with cardiac output. Subjective feelings and O2 sat were similar in both sessions.

Conclusions: Low BFR during the last quarter of HD seems to attenuate decreases in both SBP and DBP.

Funding: Clinical Revenue Support

SA-PO771

Prediction of Residual Renal Function (RRF) in Hemodialysis (HD) and Hemodialfiltration (HDF) - Maria-Eleni Roumelioti 1, Christos Argyropoulos,2 Mark L. Urnur,2 V. Shane Pankratz,2 1Unim Health Sciences Center, Albuquerque, NM; 2University of New Mexico, Albuquerque, NM.

Background: RRF is associated with improved survival in HD patients but requires cumbersome urinary collections to measure. Beta-2 microglobulin (B2M), has been proposed as a measure of RRF, without the need for such collections. We validate the predialysis B2M from the first session of the week, as a predictor of RRF in pts receiving HD or HDF.

Methods: We simulated the distribution of the predialysis B2M concentration in a mixed cohort of pts (N=10,000) receiving HD or HDF at different levels of RRF using a recently described population kinetic (PopK) model for B2M (PLoS ONE 10(6):e0129575). Logistic regression models were used to derive cutoffs of B2M predicting the RRF in this development cohort (Dev). These models were then used to predict the Urea Clearance (as a measure of RRF) in a validation cohort (Val) of 350 actual patients receiving either HF or HDF (PLoS ONE 10(12):e0143813) in whom B2M had been measured. Characteristics of the Dev cohort were deliberately chosen to differ from the Val cohort to assess generalizability.

Results: Median (IQR) B2M in ml/min was 5.2 (2.5-7.5) in Dev & 6.0 (0.0-2.0 ml/min Urea Cr) in the Val. Median (IQR) B2M in ml/L was 18.9 (11.6-23.2) in Dev & 25.5 (19.5-32.1) in Val. Sensitivity (Sens), Specificity (Spec) were >75%, while AUCs were >0.8 in both the Dev and Val cohorts [figure]. Median (IQR) of the optimal (AUC maximizing) B2M (in mg/L) cutoffs for RRF >9ml/min & >2 ml/min were 22.1 (20.0-23.2) & 19.5 (19.2-20.3) respectively in the Dev cohort. Sens/Spec of these cutoffs were 0.53/0.93 & 0.60/0.90 in the Val cohort.

Conclusions: PopK derived cutoffs of B2M predict with high accuracy RRF in pts on HD or HDF. These cutoff values are nearly identical to the values previously estimated in actual pts, attesting to the validity of the PopK model. Such cutoffs may have utility when implementing the KDOQI incremental dialysis guideline & as enrollment criteria in ESRD studies.

Funding: Clinical Revenue Support

SA-PO772

Bedside BNP as a Marker of Overhydration in Hemodialysis Patients - Jan Melin1, Magnus Lindberg,2 Jenny Stenberg,2 Hans Furuland,3 1University Hospital, Uppsala, Uppsala, Sweden; 2University of Gavle, Gavle, Sweden; 3University Hospital Uppsala, Uppsala, Sweden.

Background: Management of hydration status in dialysis patients is a great challenge to nephrologists, and new tools to understand the hydration status (HS) are needed. The aim of this study was to investigate the usefulness of brain natriuretic peptide (BNP), analyzed bedside, as a marker of overhydration (OH) in hemodialysis (HD) patients.

Methods: We investigated the distribution of BNP, measured by Alere Triage® BNP Test, and analyzed the correlation between BNP and HS, defined by bioimpedance spectroscopy (BIS) in 64 HD patients. We assumed there would be a difference in HS between patients with high levels of BNP (h-BNP) and low levels of BNP (l-BNP) and choose an arbitrary cut off of 500 ng/ml, and then differences between the groups were tested for significance. HS, blood pressure (BP) and heart rate was measured, and BNP analyzed, before one mid-week dialysis session. Blood samples were also drawn for analysis of NT-proBNP and inflammatory markers. Demographic data, comorbidities, lab values and nutritional status were collected from medical records.

Results: A positive correlation was found between BNP and OH as defined by BIS in HD patients, on the other hand euvolemia was rare in patients with elevated BNP. This suggests that BNP might serve as a marker of OH in a subgroup of old and frail patients. In a further study we aim to investigate if the relationship between BNP, when elevated, and OH is reproducible at an individual level.

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

SA-PO773

Government Support in the Development of Hemodialysis in County Level Hospitals in China - Hua Liu,2 Hongli Jiang,1 1Dialysis Center of First Affiliated Hospital of Medicine School, Xi’an Jiaotong University, Xi’an, Shaanxi, China; 2First Affiliated Hospital of Medical College of Xi’an Jiaotong University, Xi’an, China.

Background: In 2013, there were 88 hemodialysis center in Shaanxi province in China and all equipment and medical personnel could only meet the demand of about 22% ESRD patients. This paper will explore the role of government decision-making and financial support in the construction of hemodialysis center projects in county level hospitals in Shaanxi province in China after increasing investment in health care reform.

Methods: After 2013, the hemodialysis room construction project in county hospitals in Shaanxi province was carried out. Under the support of the government, we prepared the blood purification training materials and recorded teaching physicians and nurses in blood purification standard operating procedures, arranged 150 hours courses and 135 days clinical practice stage from 2013 to 2015 in four times. The effect of the training
course of the projects and the status of the hemodialysis center in the county hospital of Shunxi province were analyzed retrospectively.

**Results:** From the May 14, 2013 to June 30, 2015, we held four consecutive training classes, training a total of 827 doctors, nurses and technicians. After the implementation of this project, the number of dialysis rooms increased by leaps and bounds Shunxi province. By the end of December 31, 2016, there were 66 new high-quality hemodialysis rooms throughout 57 counties, and there were 2066 new dialysis patients registered in national dialysis registration system, far higher than the previous year increasing level (more than 30%), also higher than increasing ratio of the world’s new hemodialysis patients.

**Conclusions:** The project construction of the hospital hemodialysis room at the county level is the policy of the provincial government to improve the level of medical treatment in patients with chronic kidney disease. The government give a strong financial support in the purchase of equipment, personnel training and other aspects, which is convenient for patients with end-stage renal disease to obtain renal replacement therapy, improve the ability of hospital hemodialysis services and comprehensive treatment.

Patients and hemodialysis room development by hemodialysis network reported in China from 2014 to 2016

<table>
<thead>
<tr>
<th>numbers of hemodialysis patients</th>
<th>In 2014</th>
<th>In 2015</th>
<th>In 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>The new HD center</td>
<td>613</td>
<td>785</td>
<td>915</td>
</tr>
<tr>
<td>hemodialysis room in county hospital</td>
<td>70</td>
<td>83</td>
<td>99</td>
</tr>
</tbody>
</table>

SA-PO777

Dry Mouth with Hemodialysis Patients Results in Hypogeusia

**Purpose:** The aim of this study was to investigate the taste disorder in hemodialysis patients and analyze the possible reasons for the occurrence of hypogeusia.

**Methods:** This study included 150 hemodialysis patients from three dialysis centers from May 2016 to June 2017. The patients were divided into two groups: the LS group (taste sensitivity lower than the median) and the NS group (taste sensitivity higher than the median).

**Results:** The results showed that the mean age of the LS group was 58.5 ± 14.1 years and the mean age of the NS group was 55.8 ± 14.1 years. The difference in age was not statistically significant (p = 0.353). The taste sensitivity of the four tastes showed no significant difference. However, salt taste sensitivity (5.0 ± 1.8 vs 3.2 ± 1.7 points p = 0.088) tended to be lower in the LS group than in the NS group. Salt intake showed no significant difference (6.3 ± 2.0 vs 8.1 ± 2.1 g p = 0.096).

**Conclusions:** There are many causes & symptoms of taste disorders. Dry mouth tends to result in hypogeusia, especially in patients with less salt taste sensitivity. However, salt intake showed no significant difference between the two groups. Therefore, it cannot be determined whether dry mouth results in a taste disorder which then results in an excessive intake of salt.

SA-PO775

Muscle Mass Measured by Multi-Frequency Bioimpedance and Intradialytic Hypotension Among Hemodialysis Patients

**Purpose:** The purpose of this study was to investigate the relationship between muscle mass measured by multi-frequency bioimpedance and intradialytic hypotension in hemodialysis patients.

**Methods:** This study included 150 hemodialysis patients from three dialysis centers from May 2016 to June 2017. The patients were divided into two groups: the LS group (taste sensitivity lower than the median) and the NS group (taste sensitivity higher than the median).

**Results:** The results showed that the mean age of the LS group was 58.5 ± 14.1 years and the mean age of the NS group was 55.8 ± 14.1 years. The difference in age was not statistically significant (p = 0.353). The taste sensitivity of the four tastes showed no significant difference. However, salt taste sensitivity (5.0 ± 1.8 vs 3.2 ± 1.7 points p = 0.088) tended to be lower in the LS group than in the NS group. Salt intake showed no significant difference (6.3 ± 2.0 vs 8.1 ± 2.1 g p = 0.096).

**Conclusions:** There are many causes & symptoms of taste disorders. Dry mouth tends to result in hypogeusia, especially in patients with less salt taste sensitivity. However, salt intake showed no significant difference between the two groups. Therefore, it cannot be determined whether dry mouth results in a taste disorder which then results in an excessive intake of salt.

Forrest plots of height decile and mortality. Figure 1, Figure 2, Figure 3.
SA-PO777

Psychological Distress in Dialysis-Dependent CKD Syed S. Zaidi,1 Andrew Nixon,1,2 Judi M. Todd,1 Dawn Brannigan,1 John Anderton,1 Mark Brady,1 Ajay P. Dhaygude,1 1Lancashire Teaching Hospitals NHS Foundation Trust, Preston, United Kingdom; 2University of Manchester, Manchester, United Kingdom.

Background: The burden of chronic kidney disease (CKD) and renal replacement therapy results in a high prevalence of psychological distress. It is not routine practice to screen for psychological distress in patients with CKD. The Distress Thermometer (DT) is a screening tool for psychological distress that has been validated in the renal population. Our aims were to establish healthcare provider ability to perceive patient psychological distress and to assess factors that are associated with psychological distress in those with dialysis-dependent CKD.

Methods: One-hundred patients with dialysis-dependent CKD were recruited. Patient age-modified Charlson Comorbidity Index (CCI) and WHO performance status were assessed. Dialysis unit nursing staff assessed patient psychological distress using the DT. Patients completed the DT on the same day as the nurse assessment. A DT cut off score of ≥7 was used to define severe levels of psychological distress. The correlation between nurse and patient DT scores was assessed using Pearson’s correlation coefficient. Linear regression was performed to assess the magnitude of associations. A p value of <0.05 was considered statistically significant.

Results: Mean age was 63.19 years (SD: 14.18) with 58 male patients. Median time on haemodialysis was 38 months (IQR 16.25 to 66.75). Mean CCI score was 5.65 (SD: 1.97). The prevalence of WHO score ≥4 was 37%. The prevalence of severe psychological distress was 29%. Mean nurse DT score was 4.34 (SD: 2.49) and mean patient DT score was 4.32 (SD: 3.37). There was a weak to moderate correlation between the nurse and patient DT scores (r=0.50, p= 0.00, 95% CI 0.32-0.65). After adjusting for age, gender, dialysis vintage and CCI, only WHO score was associated with patient DT score. Each 1 point increase in WHO score was associated with an increase in patient DT score by 0.91 (p=0.01, 95% CI 0.27-1.55).

Conclusions: Psychological distress is highly prevalent in those with dialysis-dependent CKD. Psychological distress is associated with performance status; however, it is not associated with multimorbidity. Healthcare provider perceptions of patient psychological distress do not correlate strongly with patient reported psychological distress. Therefore, patients should be offered the opportunity to complete a psychological distress screening tool, such as the DT.

SA-PO778

The Association Between Tobacco Use and Intradialytic Hemodynamics in Hemodialysis Mark T. Sondeman, Peter N. Van Buren. UT Southwestern Medical Center, Dallas, TX.

Background: Extreme changes in intradialytic blood pressure are associated with poor outcomes in hemodialysis patients, but the overall effect of traditional cardiovascular risk factors on these outcomes is poorly understood. We sought to explore the effect of traditional cardiovascular risk factors on vascular hemodynamics during dialysis.

Methods: We determined smoking status among a group of hypertensive hemodialysis (HD) patients concurrently enrolled in a cross-sectional study. We compared differences in pre, post, and intradialytic change in systolic blood pressure (SBP), total peripheral resistance index (TPRI), and cardiac index (CI) in subjects defined as never smokers or smokers (current or former) using unpaired t-tests and multivariable linear regression controlling for confounding factors, diabetes, baseline hemodynamics, and other baseline characteristics.

Results: The pre and post dialysis hemodynamics are shown in Table 1. The ATPRI was -582 dynes/sec/cm2/m2 in smokers and 102 dynes/sec/cm2/m2 in non-smokers (p-value = 0.003). The ΔCI was 0.249 L/min/m2 in smokers and -0.063 L/min/m2 in non-smokers (p-value = 0.02). The ΔSBP was -14.5 mmHg in smokers and -10.3 mmHg in non-smokers (p-value = 0.63). In multivariable linear regression, there was an independent association between smoking and ATPRI (p=0.012) with an average reduction of 522 dynes/sec/cm2/m2 in ATPRI in HD patients with a history of tobacco use.

Conclusions: Hemodialysis patients with a smoking history have reductions in intradialytic TPRI compared to non-smokers although overall BP changes were not different. Further research needs to be done to identify the role of smoking and smoking cessation on intradialytic hemodynamics.

Funding: NIDDK Support

Hemodynamic Values Before and After Dialysis

<table>
<thead>
<tr>
<th>Smokers</th>
<th>Never Smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic Blood Pressure (SBP)</td>
<td>153 (±10)</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (DBP)</td>
<td>84 (±15)</td>
</tr>
<tr>
<td>Mean Arterial Pressure (MAP)</td>
<td>115 (±17)</td>
</tr>
</tbody>
</table>

The p-value compares the delta between the two groups.

SA-PO779

Patient Characteristics Associated with the In-Center Hemodialysis Consumer Assessment of Healthcare Providers and Systems (ICH CAHPS) Survey in Hemodialysis Patients in the U.S. Taimur Tighiouart,1 Megan Grobért,1 Eduardo K. Lacson,2,3 Clemens B. Meyer,1 Dana Miskulin,1 Daniel E. Weiner,1 Michelle M. Richardson,2 Dialysis Clinic Inc, Boston, MA; 2Tufts Medical Center, Boston, MA.

Background: The In-Center Hemodialysis Consumer Assessment of Healthcare Providers and Systems (ICH CAHPS) Survey is a mandatory assessment of patient experience of ICH patients. To better understand performance on this quality metric, we evaluated patient characteristics associated with high ICH CAHPS scores.

Methods: Cross-sectional analysis of ICH CAHPS scores in 2012 to all ICH patients in Dialysis Clinic, Inc (DCI) facilities. Eligibility criteria determined by AHRQ included ≥ 18 years old and received dialysis at the current facility for ≥ 3 months. Measures include patient-level demographic, clinical, laboratory, and functional characteristics. Outcomes include “top box” scores for the three global rating scales for the nephrologist, dialysis facility staff, and dialysis facility and three composite scores ‘Nephrologists’ Communication and Caring’ (Comm), ‘Quality of Dialysis Center Care and Operations’ (Qual), and ‘Providing Information to Patients’ (Info). “Top box” was defined by AHRQ as ≥8 for global rating scores (scale 0-10 with 10 being the best) and either “Always” (from Always, Usually, Sometimes, Never) or “Yes” (from Yes, No) answer choice to questions within each composite.

Results: Among 11,055 eligible patients, 4,514 (41%) returned the survey or completed it by phone. In random intercept multivariable logistic models which accounted for dialysis facility effect, older age and lower education were consistently associated with higher odds of top box scores for all three global ratings. Among composite outcomes, higher Ki/V (Comm), lower education (Qual), and being active on the transplant list (Info) were associated with higher odds of top box scores. Shortened treatments were associated with lower odds for a top box score for all global ratings and the Comm composite. Results were similar after imputing missing predictor data.

Conclusions: Older age and lower educational level were associated with higher global rating scores while higher Ki/V, lower educational level, and being active on the kidney transplant list were associated with higher composite scores. Our findings raise concern about dialysis facility scores being influenced by patient case-mix with associated expectations of care experience.

Funding: Other NIH Support - T32DK077777 - T32 Training Grant. “Epidemiology, Clinical Trials and Outcomes Research in Nephrology,” Institutional Training Grant at Tufts University; PI: Andrew Levey MD, Commercial Support - Dialysis Clinic, Incorporated
The Standardised Outcomes in Nephrololgys-Haemodialysis (SONG-HD) Consensus Workshop on Establishing a Core Outcome Measure for Patients in Haemodialysis Angela Ju,1 Mark L. Unruh,2 Jonathan C. Craig,2 Allison Tong,1 (The University of Sydney, Sydney, NSW, Australia; 1University of New Mexico, Los Ranchos, NM; 2University of Sydney, Sydney, NSW, Australia; 1University of Sydney Children’s Hospital, Sydney, NSW, Australia.

Background: Fatigue is a critically important outcome for patients on haemodialysis, but is infrequently and inconsistently reported across trials and observational studies, which probably reflects the lack of suitable measures that are feasible and psychometrically robust to use in this setting.

Methods: At an international consensus workshop, 56 (15 patients/caregivers; 42 health professionals) participated from nine different countries in six facilitated breakout groups. All discussions were transcribed and analysed thematically

Results: Four themes were identified. Drawing attention to a distinct and all-encompassing symptom was explicitly recognising fatigue as a multifaceted symptom that is unique to haemodialysis. Emphasising the pervasive impact of fatigue on life participation confirmed the importance of addressing patient concerns about consequences of fatigue such as being limited in their ability to do usual activities such as work and hobbies, and justified the focus on assessing this restriction. Ensuring meaningfulness of the measure was advocated to facilitate treatment decision-making for both patients and clinicians. Minimising burden of administration meant that the measure should be simple, short, without imposing additional burden given the high level of fatigue in the haemodialysis population. These support a proposed core outcome measure that asks patients what the extent to which fatigue limits participation in usual activities.

Conclusions: Patients, caregivers and health professionals supported the need for a simple, short, and meaningful core outcome measure that focuses on the impact of fatigue on life participation to be used in haemodialysis trials.

Funding: Government Support - Non-U.S.

SA-PO781
Measurement of Fluid Shifts during 15 Minutes of Standing Using Bioimpedance in Hemodialysis Patients and Healthy Subjects Xia Tao,1 Fannamn Zha,1 Ohnmar Thwin,1 Priscila Preciado,1 Laura Rosales,1 Stephon Thijssen,1 Peter Kotanko,1,2 1Renal Research Institute, New York, NY; 2Icahn School of Medicine at Mount Sinai, New York, NY.

Background: The InBody 770 bioimpedance device allows measurement of fluid status and body composition. Due to gravity, body fluid can shift from the trunk to the legs while standing. The aim of this study was to investigate if gravity-induced fluid shifts produce detectable changes in fluid distribution and if the magnitude of fluid shifts differs between hemodialysis (HD) patients and healthy subjects (HS).

Methods: We studied ten HD patients (7 males, age 58.1±12 years, pre and post HD, and 12 HS (7 females, age 33.3±5.6 years). Two measurements were performed 15 minutes apart in a standing position with the InBody 770 (InBody USA, Cerritos, CA, USA). Extracellular (ECW), intracellular (ICW), and total body water (TBW), ECW in the right and left leg (ECW_r, ECW_l) and the trunk (ECW_t) were recorded. ECW/TBW ratio was calculated with measurements at the start of observation period. Repeat measurements were compared by paired t-test. Unpaired t-test was used to compare patients with normals.

Results: During the 15-minute observation period, no significant change in TBW, ICW, or total trunk ECW occurred. Leg ECW increased significantly for both patients and healthy subjects. In HD patients, the observations above were true both pre and post HD (average fluid removal on HD: 2.2 kg). Pre-HD ECW/TBW differed significantly and healthy subjects. In HD patients, the observations above were true both pre and post HD (P<0.01).

Conclusions: Fifteen minutes of standing did not produce measurable changes in whole body ECW or TBW. However, leg ECW did increase significantly over this period, and this was true in healthy subjects, HD patients before dialysis, and HD patients after HD.

Funding: Commercial Support - Fresenius medical care/ Renal Research Institute LLC

Table 1: The differences (Δ) were calculated as the respective fluid compartment changes over a period of 15 minutes.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>STBW (Δ)</th>
<th>ACW (Δ)</th>
<th>ECW (Δ)</th>
<th>ECW_r (Δ)</th>
<th>ECW_l (Δ)</th>
<th>ECW_t (Δ)</th>
<th>ECW/TBW (Δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-100</td>
<td>-0.50±1.727</td>
<td>+0.12±0.176</td>
<td>+0.12±0.176</td>
<td>-0.38±0.177</td>
<td>+0.12±0.176</td>
<td>+0.38±1.727</td>
<td>+0.03±0.176</td>
</tr>
<tr>
<td>Post-112</td>
<td>+0.38±0.177</td>
<td>-0.12±0.176</td>
<td>-0.12±0.176</td>
<td>+0.50±1.727</td>
<td>-0.12±0.176</td>
<td>-0.50±1.727</td>
<td>+0.03±0.176</td>
</tr>
</tbody>
</table>

*p<0.01, compared with the 15-minute interval. ** p<0.01, compared to pre-HD results.

SA-PO782
Osteocytic Perilacunar/canalicular turnover in dialysis patients with high and low serum PTH levels Aiji Yajima,1 Ken Tsuchiya,2 Kosaku Nitta,2 1Indiana University, Indianapolis, IN; 2Tokyo Women’s Medical University, Shinjuku-ku, Japan.

Background: Osteocytic perilacunar/canalicular turnover in hemodialysis (HD) patients has not yet been reported, despite its particular relationship to bone and mineral metabolism in these patients. Under these circumstances, we were prompted to investigate osteocytic perilacunar/canalicular turnover in CKD patients.

Methods: Osteocytic lacunae in lamellar bone and woven bone were classified as eroded surface-, osteoid surface-, and quiescent surface-predominant osteocyte lacunae (ES-Lc, OS-Lc, QS-Lc, respectively) in HD patients with high or low parathyroid hormone (PTH) levels and controls without CKD.

Results: While the number of ES-Lc per unit bone volume (N.ES-Lc/B.Ar) was higher than N.OS-Lc/B.Ar in all groups [high-PTH (P<0.001)-, low-PTH (P=0.002)-, and control (P<0.001)], N.ES-Lc/B.Ar was higher in the high-PTH group than in the low-PTH (P<0.001) and control groups (P<0.001). The total volume of ES-Lc per unit bone volume (ES-Lc/B.Ar) was greater than OS-Lc/B.Ar in the high PTH (1.2 ± 0.4 vs. 0.1 ± 0.5 %, P<0.001) and the low PTH groups (0.6 ± 0.3 vs. 0.1 ± 0.2 %, P<0.001). N.OS-Lc/B.Ar was higher in woven bone than in lamellar bone (P<0.001).

Conclusions: Osteocytic perilacunar/canalicular turnover depends, at least in parts, on serum PTH level. Thus, attention should be paid to bone loss from the viewpoint of osteocytic perilacunar/canalicular turnover in HD patients.

Acknowledgments - We acknowledge Professor David B. Burr for analyses of the bone histomorphometric parameters and capturing of the images of osteocyte lacuna under the backscattered electron microscope. And we also acknowledge Dr. Keith W. Condon for his excellent technique to make bone samples for the observation by electron microscopy.

SA-PO783
Sleep Disorders in ESRD Claire Kennedy,4,5 Thomas Kanz,2 Peter J. Conlon,1 Beaumont Hospital, Dublin 9, Co Dublin, Ireland; 2Department of Respiratory and Sleep Medicine, Beaumont Hospital, Dublin 9, Dublin 9, Ireland; 3Department of Nephrology, Beaumont Hospital, Dublin, Ireland; 4Royal College of Surgeons in Ireland, Dublin, Ireland.

Background: Sleep disturbance may be overlooked in patients with ESRD due to competing medical issues, as well as a perception that it is difficult to study and frustrating to manage. We aimed to study sleep quality in an ESRD cohort using subjective and objective tools, and to assess the impact of renal replacement therapy (RRT) modality change on sleep disturbance.

Methods: A detailed assessment of sleep quality was performed in an unselected cohort of dialysis patients using several validated subjective tools as well as unattended home polysomnography (PSG) and wrist actigraphy. Repeat assessment was performed in those who switched RRT modality.

Results: Baseline interviews were performed in 33 patients. The majority reported poor sleep quality (54.5%, n=18), troublesome restless legs syndrome (RLS; 54.5%; n=16), and fatigue (30.3%; n=10). Most marked RLS (p<0.05) and fatigue (p<0.01) occurred in severe anaemia and depression. PSG (n=19) and actigraphy (n=14) confirmed high rates of sleep fragmentation and disordered sleep architecture across all dialysis modalities. PSG identified periodic limb movement disorder (PLM) disorder in 42% (n=8) and sleep apnoea (apnoea-hypopnea index ≥5) in 58% (n=11). Four patients were medicated for severe PLM with good effect; CPAP was initiated in one patient with severe obstructive sleep apnoea with marked clinical improvement. There were six RRT modality changes. Three were transplanted with improved unreported sleep quality and RLS. A patient receiving nocturnal home hemodialysis (NHHD) who had severe reduced sleep apnoea and PLM, with increased sleep efficiency. Three switched from conventional to nocturnal home hemodialysis (NHHD); again this led to better self-reported sleep quality and fatigue scores. Repeat PSG (performed on and off NHHD at one and six months) demonstrated reduced PLM and increased sleep efficiency, with the improvement most marked on the on-dialysis nights.

Conclusions: This cohort of dialysis patients had poor sleep quality and reduced quality of life without features of depression. Simple therapeutic interventions, made on the basis of home PSG, made a big clinical difference. NHHD and transplantation improved sleep quality. Unattended home PSG and actigraphy were well tolerated, including by those on nocturnal dialysis.

SA-PO784
Quality of Sexual Life Is More Associated with Mental Aspect of Quality of Life Rather Than Physical among ESRD Patients Nien-Chen Li,1 Norma J. Ofsthun,2 Franklin W. Maddux,1 Nwamaka D. Eneanya,3 1Fresenius Medical Care, Waltham, MA; 2Fresenius Medical Care North America, Waltham, MA; 3Massachusetts General Hospital, Boston, MA.

Background: In the Kidney Disease Quality of Life Short Form (KDQOL-SF) survey, there is an item that specifically investigates quality of sexual life (QSL). Few studies have demonstrated associations of QSL with different subcales featured in the KDQOL-SF. We sought to elucidate the relationship of QSL with overall QOL among ESRD patients.

Methods: Between 1/1/2014 and 8/31/2016, we administered KDQOL surveys to 184,986 patients aged between 18 to 85 with ESRD. QSL was ascertained by analyzing the item: "How much does kidney disease bother you in your sex life?" with responses ranging from “Not at all” to “Extremely bothered”. To investigate the associations between QSL and overall QOL, two methods were used: 1) correlational analysis between the QSL item and all other items in KDQOL, and 2) correlational analysis between the QSL item and all 5 composite subscales derived from KDQOL.

Acknowledgments - We thank the patients, research staffs from Fresenius Medical Care, and Fresenius Medical Care North America for their support and dedication.

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

Underline represents presenting author.
Results: Among the sample cohort, the mean age at the time of survey was 60.8 (±14.0) yr; 57% males; 60% white race; and 41% married. Thirty-four percent of all patients indicated that their kidney disease bothered their sex life. QSL was more correlated with “emotional” or “mental” rather than “physical” items. For example, r=0.27 for “I feel frustrated dealing with my kidney disease”, but r=0.13 for “moderate activities”. For composite subscales, sex life was correlated with the effects of kidney disease subscale (after removing the sex item) by 0.48, followed by the symptom subscale (0.34), burden of kidney disease subscale (0.33), mental component summary (0.30), and physical component summary (0.19). All correlations had a p value <.001.

Conclusions: We demonstrated that QSL was more associated with mental (rather than physical) well-being among dialysis patients. To improve QSL among patients with ESRD, psychological evaluations and treatments should be prioritized.

Funding: Commercial Support - three authors are employees of Fresenius Medical Care, Private Foundation Support

SA-PO785
Intradialytic Laughter Therapy: A Qualitative Study
Paul N. Bennett,* Brigitte Schiller, Christine Kalife, John H. Vo. Satellite Healthcare, San Jose, CA.

Background: Hemodialysis patients experience poor physical function and increased anxiety and depression. Intradialytic Laughter Therapy is a group therapy that can be performed while patients are on hemodialysis. Laughter Therapy combines elements of physical activity, intentional laughter, controlled deep breathing and meditation. Laughter Therapy has been shown to increase exercise in the facial, chest, abdominal and skeletal muscles, reduce stress, reduce anxiety and counteract depressive symptoms in non-dialysis patients. The aim of this study was to explore patients’ and staff perceptions of an Intradialytic Laughter Therapy program.

Methods: Intradialytic Laughter Therapy was delivered in two separate regional US hemodialysis clinics consisting of 30 minute sessions during dialysis, once per week for 3 months. Patients and clinical hemodialysis staff were surveyed and then interviewed using semi-structured interviews immediately following the 3 month program of Intradialytic Laughter Therapy. Content analysis of survey free text and interview transcript data identified coded items that were categorized into themes.

Results: 58 patients and 25 clinical hemodialysis staff were surveyed and interviewed. The four major themes emerging from the survey interview data were: (1) dialysis is boring and depressing, (2) laughter improved mood, health and wellbeing, (3) improved connections and community and (4) not for everyone. Laughter therapy made people feel happy, and helped them forget about their problems and the boredom of dialysis. Laughter Therapy brought people together and established comradeship improving the rapport between staff and patients. Although Laughter Therapy was embraced by most patients those patients who felt indifferent still recommended continuing laughter therapy for the benefit of other patients and staff who they knew enjoyed the Laughter Therapy.

Conclusions: Intradialytic Laughter Therapy is a safe, complementary therapy that can be used during hemodialysis to improve interpersonal interaction, help build group identity, solidarity, and cohesiveness and increase intradialytic physical activity. Laughter Therapy has been shown to be a positive therapy and can be seen as an important element to improve patient and staff experience in US hemodialysis clinics.

SA-PO786
Quality of Sexual Life in ESRD Patients
Nien-Chen Li,* Norma J. O’Shun,* Franklin W. Maddox,1 Nuwamaka D. Encanyaa,2 Fresenius Medical Care, Waltham, MA; Fresenius Medical Care North America, Waltham, MA; Massachusetts General Hospital, Boston, MA.

Background: Sexual dysfunction is a highly prevalent problem for patients (pts) undergoing dialysis. This study investigated associations of QSL with quality of life (QOL) for different ESRD modalities.

Methods: In Jan14-Aug16, we administered KDQOL surveys to ascertain the effect of different modalities on quality of sexual life (QSL) (scaled from “not at all bothered” to “extremely bothered”) among a national cohort of dialysis patients. The sample consisted of 184,986 prevalent pts aged 18-85. Logistic model was used to derive odds ratios (ORs) of kidney disease on quality of sexual life (QSL) (scaled from “not at all bothered” to “moderate activities”) for composite subscales, the effects of kidney disease subscale (after removing the sex item) by 0.48, followed by the symptom subscale (0.34), burden of kidney disease subscale (0.33), mental component summary (0.30), and physical component summary (0.19). All correlations had a p value <.001.

Results: 58 patients and 25 clinical hemodialysis staff were surveyed and interviewed. The four major themes emerging from the survey interview data were: (1) dialysis is boring and depressing, (2) laughter improved mood, health and wellbeing, (3) improved connections and community and (4) not for everyone. Laughter therapy made people feel happy, and helped them forget about their problems and the boredom of dialysis. Laughter Therapy brought people together and established comradeship improving the rapport between staff and patients. Although Laughter Therapy was embraced by most patients those patients who felt indifferent still recommended continuing laughter therapy for the benefit of other patients and staff who they knew enjoyed the Laughter Therapy.

Conclusions: Intradialytic Laughter Therapy is a safe, complementary therapy that can be used during hemodialysis to improve interpersonal interaction, help build group identity, solidarity, and cohesiveness and increase intradialytic physical activity. Laughter Therapy has been shown to be a positive therapy and can be seen as an important element to improve patient and staff experience in US hemodialysis clinics.
SA-PO788

Resistance Training Improves Muscle Strength and Maintained Physical Performance in Patients with Maintenance Hemodialysis

Yoshifumi Moriyama,1 Sae Aratani,1 Masahiko Haru,1 Hideaki Ishikawa,1 Konan Kosei Hospital, Konan, Japan; 2Nagoya Kyoritsu Hospital, Nagoya, Japan; 3Nippon Medical School Hospital, Tokyo, Japan; 4Osaka City University Graduate School of Medicine, Osaka, Japan.

Background: It is reported that reduced muscle strength and physical performance are prevalent conditions in patients with maintenance hemodialysis, and deteriorative changes in these parameters are associated with elevated mortality.

Methods: We provided 306 patients with 6-month resistance training program during hemodialysis. Primary outcome measures included muscle strength measured by handgrip (mean of right and left), percent knee extension muscle power to body weight (pKEMP-BW; mean of right and left), and physical performance measured by short physical performance battery (SPPB). Differences of these variables during 6-month were compared using Wilcoxon signed rank test.

Results: Median age was 71 (quartile 64-77) years old, 160 patients (52.2%) were men, and median dry weight was 54.5 (47.5-62.0) kg. During the 6-month, handgrip showed a slight increase in lower quartile from 22.8 (16.8-28.5) kg to 22.8 (18.3-28.5) kg (p=0.001), pKEMP-BW showed significant increase from 41.0 (32.0-51.8) % to 43.1 (34.4-54.7) % (p<0.001), and SPPB did not change the median and quartile values from 11.0 (9.0-12.0) to 11.0 (9.0-12.0) (Figure).

Conclusions: Resistance training improved muscle strength and maintained physical performance in patients with maintenance hemodialysis. We speculate that resistance training has a potential to prevent progression of sarcopenia and frailty in patients with maintenance hemodialysis.

SA-PO789

Multicenter, Prospective, Randomized, Crossover Trial to Demonstrate the Benefits of Hemodialysis without Acetate (with Citrate): ABC-Treat Study

Patricia De Sequera,1 Rafael Perez-Garcia,1 Manuel Molina,1 Hospital Infanta Leonor, Madrid, Spain; 2H Santa Lucia, Murcia, Spain; 3Group Team Spanish ABC-treat group study.

Background: Dialysis fluid, essential element in hemodialysis, is manufactured in accordance with the standards and characteristics established by the standards. We analyze the safety of HD with C on calcium metabolism, acid base status, inflammation, coagulation, and hemodynamic stability compared to HD with A.

Methods: Multicenter, prospective, randomized and crossover study, 32 weeks, 16 with 3mmol/l A (SoftPac®) and 16 with 1mmol/l C (Select BagCitrate®). Inclusion criteria: adults in HD for at least 3 months, with no acute conditions, and signed informed consent. Exclusion criteria: allergy or intolerance to citrate, intercurrent inflammatory diseases, significant cognitive impairment. Epidemiological, dialysis, and biochemical data were collected. Visual clotting scores of the dialyser and venous chambers were quantified.

Results: 53 patients were included, 44(83%) males, average age 64(16.5) years, dialysis technique HD/HDF: 18(34%)/35(66%). Mean values of the dialysis parameters: Blood flow: 392±8(42.8) ml/min; kt: 53.8(8.2) L, infusion volume in HDF: 26.3(7.5) L, dialysate bicarbonate concentrations: 31.5(1.6) mmol/L. Results Of the 32 patients who completed the study on 03/31/2017 in table. Coagulation scores of either chambers and dialyser, as well as the number of hypotension episodes recorded during the sessions were lower with the C (p=0.00). We did not find differences neither in the inflammatory parameters measured with C-reactive protein and IL-6, nor in the pH with bicarbonate values.

Conclusions: Dialysis with C modifies most pharmacokinetic metabolism parameters, not only acutely as previously described, but also in the long term, and decreases/avoids postdialysis alkalinaemia. We have found lower coagulation scores and arterial hypertension episodes with C.

Funding: Commercial Support - Baxter

SA-PO790

Risks and Benefits of Novel Oral Anticoagulants across the Spectrum of CKD among Patients with Atrial Fibrillation

Jung-Im Shin,1 Alex Secora,1 Josef Coresh,1 Alex R. Chang,2 Morgan Grams,3 Johns Hopkins University, Baltimore, MD; 4Geisinger Medical Center, Danville, PA.

Background: The relative safety of novel oral anticoagulants (NOACs) vs. warfarin for treatment of atrial fibrillation (AF) in patients with chronic kidney disease (CKD) in real-world settings is unknown. The objective of the study was to evaluate risks and benefits of NOACs in comparison with warfarin across a range of estimated glomerular filtration rate (eGFR).

Methods: We analyzed a cohort of 3,206 patients with AF who used NOACs (Apixaban, Rivaroxaban, or Daripatran) and a 1:1 propensity-score matched cohort of 3,206 warfarin users between October 2010 and January 2017 in the Geisinger Health System. We estimated the incidence rates of bleeding and ischemic stroke, stratified by G-stage of CKD.

Results: Mean baseline age of the study population was 73.3 years, 46.6% were women, and mean eGFR was 68.5 ml/min/1.73 m2. There were 1,181 bleeding events, 466 ischemic strokes, and 310 deaths among 6,412 patient-years (PYs) of follow-up. The incidence rates of bleeding (NOACs vs. warfarin) were 17.4 vs. 16.9 per 100 PYs among those with eGFR<60, 25.2 vs. 19.0 among those with eGFR 50-59, and 38.1 vs. 30.4 for eGFR<30 m/min/1.75 m2, respectively (Figure 1). The incidence rates of ischemic stroke were 6.0 vs. 6.0, 8.8 vs. 7.5, and 9.2 vs. 10.6 for those with eGFR>60, eGFR 30-59, and eGFR<30 m/ml/1.73 m2, respectively. Similar findings were observed when each drug was analyzed individually. Among the 122 NOACs users with eGFR<30, 27% were not prescribed with renal dose adjustment.

Conclusions: In real-world settings, patients with CKD on NOACs for treatment of AF appeared to experience bleeding events more frequently than those on warfarin. Further large-scale studies are warranted to confirm our descriptive findings.

SA-PO791

Cardiac Output Changes Relate to Ultraltrafiltration Volume during Intermittent Hemodialysis and to Pre-HD Intravascular Volume Assessed by Inferior Vena Cava Ultrasonography in ICU Patients

Matthew Kaptein,1,2 Christopher Nguyen,1 John Kaptein,3 Elaine Kaptein,3 Keck School of Medicine of USC, Los Angeles, CA; 2Loma Linda University Medical Center, Loma Linda, CA; 3LAC+USC Medical Center, Los Angeles, CA.

Background: The goal of volume management is to optimize intravascular volume and maximize cardiac output (CO). CO tends to increase after volume administration in volume depleted patients, to increase with UF in volume overloaded ESRD patients, and to decrease with UF in ESRD patients prone to intradialytic hypotension.

Methods: We retrospectively studied 12 ICU patients in 29 intermittent HD (IHD) encounters who had relative intravascular volume assessed by respiratory changes in inferior vena cava diameter within 24 hours prior to IHD/UF and CO assessed by thermodilution before and after IHD/UF. IVC Collapsibility Index (ICI) = (IVCmax−IVCmin)/IVCmax*100%. CO change >10% was considered significant.

Results: For encounters with IVC CI<10% (volume overload), UF ≥2.6L was associated with increased CO (+14 to +66%) [A]. Larger (2.3 to -2.3L) [B] or minimal (-0.75 to +0.2L) [C] UF was associated with decreased CO (-15 to -22%). With IVC CI >30% (volume depleted) volume given during HD may increase CO [D], while UF (-2.4 to -3.0L) may decrease CO (-28 to -44%) [E]. With IVC CI of 10 to 30%, volume removal (-1.4 to -2.8L) may decrease CO (-4 to -20%) [F].

Conclusions: Changes in CO with respect to IVC CI and net volume change with IHD/UF (Fig 1a) may be consistent with changes in position along the Frank Starling curve (Fig 1b), assuming that relative intravascular volume is a primary determinant of IVC CI and CO. These data are consistent with IVC CI being an indicator of relative intravascular volume, and provide empiric evidence that “appropriate” volume removal can improve CO in ICU patients. Reference PMID: 1) 28261499, 2) 8420299, 3) 12059009, 4) 27539225

Figure 1. Incidence Rate of Outcomes by eGFR Category
SA-PO792

Individual-Level Changes in Interdialytic Weight Gain and Blood Pressure before Dialysis Treatment Are Associated with Same-Day Extreme Heat Events within Northeastern US Cities

Alice Topping, Richard V. Remiglio, Jochen L. Raimann, Peter Kotanko, Franklin W. Maddux, Patrick Kinney.

Boston University School of Public Health, Boston, MA; Fresenius Medical Care, Waltham, MA; Renal Research Institute, New York, NY; University of Maryland, College Park, Washington, DC.

Background: In previous work, we have observed the effect of seasonal changes on interdialytic weight gain (IDWG) and pre-treatment blood pressure among hemodialysis (HD) patients. We sought to understand this seasonal effect at a finer temporal resolution by joining averaged daily ambient weather data with individual-level patient data. We focused on patients residing within northeastern United States cities.

Methods: Clinical data were extracted from Fresenius Medical Care-North America (FMC-NA) database for HD patients in Boston (N=1439), New York (N=2241), and Philadelphia (N=3762) between 2001 and 2012. Using weather data from the National Oceanic and Atmospheric Agency (NOAA), we defined a heat wave event as average ambient temperature in the 99th percentile for each city. We applied linear mixed-effects regression modeling to estimate the effect of same-day heat wave event exposures on IDWG and systolic blood pressure (pre-SBP) and diastolic blood pressure (pre-DBP) for patients in each city.

Results: All three cities demonstrated associations between same-day heat wave events and IDWG percentage. When compared to non-heat wave events, individual-level IDWG percentage can decrease up to 0.34 % on average (Figure 1a). Same-day heat wave effects on blood pressure demonstrated associations for all three cities. When compared to non-heat events, pre-SBP and pre-DBP can decrease up to 3.28 mmHg and 1.45 mmHg on average, respectively (Figure 1b,c).

Conclusions: Same-day heat wave exposures demonstrated a consistent effect on IDWG percentage and blood pressure among individual patients in the northeastern region of the USA. Our preliminary findings demonstrate a potential relationship between outdoor heat events and important clinical measures in hemodialysis patients. Further work is needed to account for possible regional-specific variation related to these clinical measures.

Funding: Commercial Support - Renal Research Institute

SA-PO793

Evaluation of Gender Differences in the Association between Hemoglobin and Mortality Among Hemodialysed Patients in the JDOPPS

Juan C. Diaz, Verónica Miranda, Laura C. Fajardo, Ricardo A. Hermo.

CASMU-IAMPP, Montevideo, Uruguay.

Background: Anemia is frequent in hemodialysis (HD) patients (Pts) and is associated to increased morbidity and mortality, being the main cause decreased erythropoietin (EPO) production. The objective of this study is to measure endogenous EPO (EPOe), and assess its relationship with hemoglobin (Hb) and required dose of erythropoietin supplementation (EPOsup) in HD Pts.

Methods: EPOe was measured in HD Pts older than 18 years on treatment in the HD Unit of CASMU in February 2017. We excluded Pts with evident bleeding, neoplasia, acute infection or hospitalization in the previous months. Data was registered regarding gender, age, and residual renal function (RRF) (creatinine clearance when diuresis ≥300 ml/day) EPOe and Hb were measured after 1 week without EPOsup, in midweek HD, with Advia 2010, Siemens. EPOe was considered low when <4.3, normal value 4.3 to 11.1 g/dL, high EPOe >11.1 g/dL. EPO sup was considered as UI/kg/week, and its response as stable to non-responders.

Results: We studied 134 Pts, 83 men (61.9%), median age 70 (IQR 60-79) years, 44 diabetics (32.8%), HD vintage 28 months (IQR 14-49). Diuresis in 54 Pts was 800 (IQR 500-1350) ml/day, with RRF 6.4 (IQR 2.8-9.3) ml/min. Median EPOe was 9.4 (6.6-13.7) mlU/ml. Low EPOe in 10 (7.5%), normal in 116 (86.5%), and high in 8 Pts (6%). Pts who did not received EPOsup (19) not differ regarding sex, age, HD vintage or EPOe with those with EPOsup. Median Hb levels were significantly higher in those Pts without EPOsup (12.6 vs 11.1 mlU/ml). EPO categories did not differ regarding age, gender, diabetes, gender or EPO levels. Higher EPOe levels were significantly associated to higher values (low EPOe 36.7 ± 23.5, normal EPOe 35.7 ± 41.4 and high EPOe 77.6 ± 70.6 months).

Conclusions: Unexpectedly only 7.5% of the Pts had low EPOe, even though normal levels are inadequate in anemic Pts. Higher EPOe in Pts with longer dialysis vintage may suggest others sources for EPOe besides kidneys in these Pts.

Funding: Clinical Research Support
SA-PO795

Safety of Erythropoietin Administration among ESRD Patients long
hoon Lee,1 Byung ha Chung,1 Cheol Whee Park,4 Chul Woo Yang,1 Yong-
Soo Kim,3 Bumsoo Choi.2 Seoul St. Mary hospital, Seoul, Republic of Korea; 5The Catholic University of Korea, Seoul, Republic of Korea; 3Division of Nephrology, Department of Internal Medicine, Seoul, Republic of
Korea; 2Seoul St. Mary’s Hospital, Seoul, Republic of Korea; 1The Catholic University of Korea College of Medicine, Seoul, Republic of Korea.

Background: Erythropoietin (EPO) has been used to care for anemia in CKD patients. Concerns about the administration of EPO include CVD events and tumor progression, but definite associations were not fully identified. We performed the study to validate safety of EPO administration among ESRD patients.

Methods: 3432 ESRD patients were included to a prospective observational study in Clinical Research Center for ESRD registry. The patients were divided into HD group and PD group by dialysis methods. A dose of EPO, IV iron administration and serum Hb levels, CVD and cancer mortality were collected in the registry. Analyses were conducted to estimate hazard ratio (HR) for the EPO administration, dose of EPO and HD levels with mortality of CVD and cancer.

Results: The mortality rate of CVD was 1.71% in HD group and 1.94% in PD group. CVD mortality was increased by EPO administration in PD group (HR 1.72, p=0.04). But the mortality has no correlation with EPO dose and Hb level. Any factor did not relate to CVD mortality in HD group. The mortality rate of cancer in ESRD patients was 0.94% in HD group and 0.78% in PD group. Hb level, EPO administration and dose were not associated with cancer mortality in both groups. In multivariate risk factor analysis, the mortality of CVD was associated to diabetes (p<0.01) and age (p<0.01) in both groups. However, the mortality of cancer was not associated with any factor.

Conclusions: EPO administration was associated with an increase of CVD mortality in PD patients. Diabetes and age were independent risk factors of CVD mortality. On the other hand, the mortality of cancer in ESRD patients was not associated with EPO administration.

Cardiovascular disease survival among peritoneal dialysis patients

SA-PO796

The Impact of Dose of ESA and Iron on the Risk of Adverse Events in Hemodialysis Patients Takeshi Kuragano,1 Takashi Nakanishi.1 Hyogo College of Medicine, Nishinomiya, Japan; 2Internal Medicine Division of Kidney and Dialysis, Nishinomiya, Japan.

Background: Anemia treatment with higher doses of ESA in patients with maintenance hemodialysis (MHD) might increase the risk of cardiovascular disease (CVD). On the other hand, higher doses of iron might cause iron overload, which can induce oxidative stress and CVD. The effects of the dosage balance of ESA and iron on the adverse events of MHD patients have not been well established.

Methods: This work was a prospective observational multicenter study over a period of 3 years in 1095 patients on MHD. The patients were divided into 4 groups according to the dose of ESA (high ESA (≥3000 IU/week), low ESA) and intravenous iron (high iron (>15 mg/week), and low iron). Furthermore, in another analysis, the patients were divided into 4 groups according to the dose of ESA and iron storage (high ferritin (>50 ng/mL), and low ferritin). A time-dependent Cox hazard model was evaluated to evaluate the association between patient groups and adverse events.

Results: Doses of ESA and iron: There was no significant difference in CVD risk between low ESA/low iron and high ESA/low iron. However, the CVD risks for low ESA/high iron (HR: 2.6, P=0.03) and low ESA/high iron (HR: 3.1, P=0.01) were significantly higher than that for low ESA/low iron. The risk of death for high ESA/high iron was significantly (HR: 2.8, P=0.04) higher than for low ESA/low iron. Dose of ESA according to iron storage: There was no significant difference in CVD risk between low ESA/high ferritin and high ESA/low ferritin. However, the CVD risks for low ESA/high ferritin (HR: 3.3, P=0.01) and high ESA/high ferritin (HR: 3.3, P=0.01) were significantly higher than that for low ESA/low ferritin. The risk of death for high ESA/high ferritin was significantly (HR: 3.1, P=0.01) higher than that for low ESA/low ferritin.

Conclusions: We found that high doses of ESA and iron were significantly associated with higher risks of CVD and death. Regardless of ESA dose, a higher dose of iron was significantly associated with a higher risk of CVD. Interestingly, patients with iron deficiency treated with a high dose of ESA were not necessarily at high risk of CVD. We concluded that a higher dose of ESA is required for improving the responsiveness to ESA did not necessarily attenuate this risk of CVD and death.

SA-PO797

Association between Resistance to Erythropoiesis-Stimulating Agents and Carnitine Profile in Patients on Maintenance Hemodialysis Daigo Kamei,1 Ken Tsuchiya,1 Kouku Nitta,1 1Blood Purification, Tokyo Women’s Medical University, Shinjuku-ku, Japan; 2Blood purification, Tokyo Women’s University, Tokyo, Japan.

Background: Patients on dialysis are in a chronic carnitine-deficient state. This condition may be associated with abnormalities in fatty acid and organic acid metabolism; however, the details are unknown. We investigated the association between carnitine profiles and ESA before and after dialysis and the erythropoiesis-stimulating agent (ESA) resistance index (ERI), which is a significant prognostic factor in patients on maintenance hemodialysis.

Methods: cross-sectional study. We measured the carnitine profile of 79 patients on maintenance hemodialysis before and after dialysis using liquid chromatography-tandem mass spectrometry (LC-MS/MS). The associations between the ERI and pre-dialysis carnitine profile, removal rate of various carnitines, and previously-reported ERI-related factors were investigated. Significant factors were determined with stepwise multiple regression analysis and validated with the bootstrap method. SPSS version 22.0 was used for all analyses, and P<0.05 was considered statistically significant.

Results: The removal rate of long-chain acylcarnitine with dialysis was lower than that of short-chain or medium-chain acylcarnitines. Stepwise multiple regression analysis (r2=0.79) demonstrated that 3-hydroxy isovalericylcarnitine (C5-OH, P=0.001, β=0.469) and acetylcarnitine (C18, P=0.001, β=0.390) were independent significant factors (R2=0.239) of ERI. The bootstrap method similarly indicated these two to be significant factors.

Conclusions: ERI was positively correlated with long-chain C18 acylcarnitine and negatively correlated with short-chain C5-C7 acylcarnitines. C5-OH and C18 acylcarnitines at baseline might be contributing factors in distinguishing responders from nonresponders after L-carnitine administration.

SA-PO798

Hemoglobin Level and Dose of Erythropoietin Stimulating Agent Depending on Hemoglobin Measurement Day Soo Ya Baek, Su-Kil Park, Hysang Kim. Asan Medical Center, University of Ulsan College of Medicine, SEOUL, Republic of Korea.

Background: Hemoglobin (Hb) variability is frequently observed in end stage renal disease (ESRD) patients. There have been many discussions over true functional Hb in ESRD patients without any confirmative conclusion. Optimal dosing of Erythropoietin Stimulating Agent (ESA) based on Hb level is important, because high dose ESA is known to be related to poor outcomes with increased health care expenditure. We investigated changes in Hb level and erythropoietin stimulating agent (ESA) dose depending on the change of Hb measurement day in maintenance hemodialysis (HD) patients.

Methods: The day for predialysis Hb measurement was changed from days after long interdialytic period (Monday or Tuesday) to midweek days (Wednesday or Thursday) in Asan Medical Center in September 2013. We reviewed baseline clinical characteristics, laboratory data including Hb, dose of ESA, dose of intravenous (IV) iron, and parameters related to HD for two years before and after the change of Hb measurement day in 92 patients receiving maintenance HD.

Results: Mean age of patients was 61.6±12.1, and diabetes mellitus was the leading cause of ESRD (52.2%). Mean Hb level was 10.7±0.6 g/dL, a year before the change in Hb measurement day, 10.78±0.47 g/dL a year after the change (p=0.105). Mean ESA dose was 175.36±72.47 μg darbepoeitin alfa per month, 163.65±83.95 μg per month, before and after the change, respectively (p=0.022). Mean IV iron dose was 6.32±4.84 g iron (100 mg Fe3+1 amplt) iron hydroxide sucrose per year, 4.47±5.02 amplt per year, before and after the change, respectively (p=0.001). Mean interdialytic weight gain was 2.81±0.82 kg and 1.99±0.61 kg, before and after the change, respectively (p=0.001). The number of patients without achievement of target Hb requiring higher dose of ESA was decreased from 8 to 2, before and after the change respectively.

Conclusions: Significant decrease in the ESA and IV iron dose was observed without change in Hb level after midweek predialysis Hb measurement. Midweek predialysis Hb level would be better criterion for ESA dosing.
**SA-PO799**

Association of Predialysis ESA Anemia Treatment with Mortality after Dialysis Initiation

James B. Wetmore,1 Suying Li,1 Heng Yan,1 Hairong Xu,2 Marvin V. Sinsakul,1 Yi Peng,1 Jiannong Liu,1 David T. Gilbertson,1

1AstraZeneca, Bethesda, MD; 2AstraZeneca, Westlake Village, CA; 3Minneapolis Medical Research Foundation, Minneapolis, MN; 4Chronic Disease Research Group, Minneapolis, MN; 5Hennepin County Medical Center, Minneapolis, MN.

Background: Whether treatment of anemia in the setting of CKD prior to hemodialysis (HD) initiation may reduce post-initiation mortality is unknown.

Methods: Patients who initiated HD between April 1, 2012 and June 30, 2013 were identified from USRDS end-stage renal disease (ESRD) and pre-ESRD files. Hemoglobin (Hb) measurements at HD initiation and at least one other measurement in the subsequent 3-months, in the absence of transfusion, were required. Patients who either never had anemia (defined as Hb ≥ 9.0 g/dL) in the absence of treatment or those who had persistent post-initiation anemia despite treatment were eliminated. Patients who were consistently well-treated (Hb ≥ 9.0 g/dL) with ESAs were retained and compared with patients who appeared to have untreated or ineffectively-treated anemia prior to HD initiation, provided the latter responded to ESAs after initiation. Cox PH models, adjusted for patients’ demographics and comorbidities, were used to calculate the hazard ratio of all-cause and cardiovascular (CV) mortality after HD initiation.

Results: The study sample was comprised of 3662 consistently well-treated patients and 4461 patients in the compared group. Adjusted risks of outcomes are shown in the Figure. All-cause mortality was significantly less for the consistently well-treated patients at 3 (HR 0.79, 95% CI 0.65-0.95), 6 (HR 0.80, 95% CI 0.69-0.93), and 12 (HR 0.83, 0.73 – 0.95) months. A similar pattern was observed for CV mortality at 3 (HR 0.74, 95% CI 0.54-1.00), 6 (HR 0.74, 95% CI 0.59-0.94) and 12 (HR 0.78, 95% CI 0.64-0.94) months.

Conclusions: Failure to achieve Hb ≥ 9.0 g/dL through lack of treatment in the predialysis period may represent missed treatment opportunity to reduce mortality after HD initiation.

**Funding:** Commercial Support - AstraZeneca

---

**SA-PO801**

Definition and Validation of a Novel Metric to Assess Erythropoiesis Stimulating Agent Response in Hemodialysis Patients

Calvin J. Meaney,1,4 Spinel Karas,2 Ben Robinson,1 Jamie L. Gaesser,3 Alan Forrest,4 Wojciech Krzyzanski,1 Mandep Panesar,1 Gauri G. Rao,1 Williamville, NY; 2The University of North Carolina; 3Durham, NC; 4University at Buffalo, Glen Mills, PA; 5University at Buffalo School of Pharmacy and Pharmaceutical Sciences, Buffalo, NY; 6University of North Carolina, Chapel Hill, NC; 7University of North Carolina Eshelman School of Pharmacy, Chapel Hill, NC.

Background: Erythropoiesis stimulating agents (ESA) are the primary treatment of anemia in end-stage renal disease (ESRD) patients. Hemoglobin variability in and out of a narrow target range is common and associated with higher mortality and/or morbidity. More robust metrics of ESA response are needed to define optimal dosing and association to clinical outcomes.

Methods: In this cross-sectional, single-center, retrospective study, 49 ESRD patients on hemodialysis were followed for 12 months. To quantify the excursion of hemoglobin outside the target range (10-12 g/dL), the area-under-the-curve of hemoglobin versus time over a 12-month period (AUC-HGB) was calculated using the trapezoidal rule. Patients were categorized into 4 responder groups based on AUC-HGB quartiles. Comparative analysis of demographic and clinical characteristics between responder groups was performed using Chi-square and/or Kruskal Wallis tests as appropriate. Spearman correlations between AUC-HGB, erythropoietin resistance index (ERI) and time within therapeutic range (TTR) were performed.

Results: There were no significant differences in demographics, laboratory, or dialysis parameters between responder groups except hemoglobin and ESA dose. The median (range) AUC-HGB at 12 months was 68.8 (15.5-371) U/kg/week for the poor responder group compared to 167 (48.3-524) U/kg/week for the excellent responder group. There was a positive correlation with AUC-HGB and TTR (r=0.90, p<0.001) and hemoglobin concentration (r=0.85, p<0.01), while there was a positive correlation with AUC-HGB and ERI (r=0.70, p<0.001). The poor response group received higher median ESA dose (160 U/kg/week) compared to the excellent response group (68.8 U/kg/week, p<0.001) with a similar number of ESA dose changes between the groups. Over 2 years of follow-up, 5 patients died, of which 3 were in the poor response group.

Conclusions: AUC-HGB is a valid metric of ESA response in the hemodialysis population and may serve as a better maker of ESA response compared to conventional metrics.

---

**SA-PO802**

GX-E2 versus CERA for Anemia in Patients Receiving Maintenance Peritoneal Dialysis: A Phase 2, Randomized, Multi-Center, Active-Comparator, Dose-Finding Safety and Efficacy Study

Eun Jeong Ko,1 Byung ha Chung,1 Sug kyun Shin,2 Hyung Wook Kim,1 Byung chul Shin,2 Seok Joon Shin,2 Yong Sun Kang,2 Sang-Ho Lee,2 Ho Cheol Song,2 Su Hyun Kim,3 Ki Young Na,3 Young-Il Jo,3 Won Kim,4 Eun Young Seong,1 Yong-Lim Kim,1 Minkyu Heo,4 Jungwon Woo,5 Chul Woo Yang,11 Kangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; 2Kyung Hee University Hospital, Seoul, Republic of Korea; 3Seoul National University Bundang Hospital, Gyeonggi, Republic of Korea; 4St. Vincent's Hospital, Gyeonggi, Republic of Korea; 5Chosun University, Gwangju, Republic of Korea; 6Chonbuk National University Medical School, Jeonju, Republic of Korea; 7Pusan National University Hospital, Busan, Republic of Korea; 8Kyungpook National University Hospital, Daegu, Republic of Korea; 9Genexine, Inc., Seongnam-si, Republic of Korea.

Background: GX-E2 is hybrid Fe (byFe) -fused long-acting recombinant human erythropoietin. We conducted a phase 2, randomized, active-comparator, safety and efficacy study in patients with anaemia on maintenance peritoneal dialysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>Dose (U/kg/week)</th>
<th>snowy</th>
<th>snowy</th>
<th>snowy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>A</td>
<td>100</td>
<td>120</td>
<td>140</td>
<td></td>
</tr>
<tr>
<td>Study 2</td>
<td>B</td>
<td>150</td>
<td>160</td>
<td>170</td>
<td></td>
</tr>
</tbody>
</table>

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

Underline represents presenting author.

---

**SA-PO803**

Anemia Management in Hemodialysis Patients – Is Six-Weekly Monitoring of Hemoglobin Sufficient?

Abdullah A. Alarifi,1 M. Khaled Shamseddin,2 Frances Macleod,2 Eduard A. Iliescu,1 Kingston General Hospital, Kingston, ON, Canada.

Background: The KDIGO guidelines recommend monitoring of hemoglobin (Hb) in hemodialysis patients (HD pts) at least monthly (not graded). Canadian HD programs vary from every 4 to 6-weeks and protocols exist for both schedules. Our centre changed from monthly to every 6 weeks in March, 2014. The objective of this QI report is to examine the volume of CBC measurements, costs, and proportion of pts. with Hb on target before and after the change.

Methods: This is a retrospective study of prevalent HD pts. in South-Eastern Ontario including all in-centre, satellite and home HD. The primary variables were the number of CBCs performed (obtained from EMR) during the 252 days before and 252 days after Mar. 24, 2014 and the associated costs (CDN $ 8.27/CBC Ontario Provincial Fee Schedule). The 252 day equal periods represent exactly 8 complete monthly cycles and 6 dialysis cycles before and after the change. The proportion of pts. with Hb on target (100 – 120 g/L) was assessed for a longer period of 2 yrs. before and after the change to assess long term outcomes.

Results: The profile of HD pts. is 430 - 440 total, 46 % in-centre, 43 % satellite, 11 % home HD, majority Caucasian, mean age 66 yr., 44 % female, 46 % DM, and 45 % with CVC. The CBC numbers and costs decreased overall but more in satellite than in in-centre pts (Table 1). The proportion of patients with Hb on target 2 years before and after were similar, 60 and 60.5 % respectively.

Conclusions: The results of this study suggest that anemia management in HD pts. result in similar outcomes with CBC measured every 6 weeks as with monthly with reduced cost. The reduction in CBCs was lower in in-centre pts. who had more CBCs measured between the routine bloodwork likely due to higher acuity and overall this is rational use of more frequent testing in sicker pts. The results of this study provide a regional perspective as this is the only HD program in the region, but may not be generalizable to HD programs with different population characteristics.
Methods: Patients with a stable end-stage renal disease treated with peritoneal dialysis or a dose-finding study was conducted in 60 patients randomly assigned to 1 of 4 treatment regimens, a 4-week treatment of different dosing range of GX-E2. In Part B, 12-week treatment was conducted in 72 individuals with two selected doses of GX-E2 based on the Part A results, and with methylxoy polyethylene glycol-epoetin β (CERA) (0.6 µg/kg bi-weekly). Primary endpoint was mean hemoglobin change from baseline to the end of treatment.

Results: In Part A, mean Hb level was significantly increased after 4 weeks GX-E2 administration and mean Hb changes from baseline were 0.6±1.3 g/dL in 3 µg/kg, 1.3±1.1 g/dL in 5 µg/kg, and 1.4±1.0 g/dL in 8 µg/kg bi-weekly. In Part B, participants were assigned to the following groups, treated bi-weekly with 5 µg/kg, 8 µg/kg of GX-E2, and 0.6 µg/kg of CERA. Mean Hb level changes after 12 weeks GX-E2 administration were 2.2±1.3 g/dL in 5 µg/kg, 3.1±1.1 g/dL in 8 µg/kg, and 1.7±1.4 g/dL in CERA, GX-E2 showed comparable or better outcome compared to CERA (p-values for each 0.233, <0.001) with no safety issues observed.

Conclusions: In this phase II study of anemia treatment in patients with end-stage renal disease on maintenance peritoneal dialysis, GX-E2 was well-tolerated and effectively maintained Hb levels.

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

SA-PO803
Epoetin Alfa and Darbepoetin Alfa: A Cross-Sectional Study Comparing Doses According to Administration Intervals
Marie-Eve Dupuis,1 Caroline Lamarche,2 Robert Z. Bell,1 Katherine Desforges,1 Laurence Lapage,1 Visnja P. Pribanic,1 Michel Valler,1 Jean-Philippe Pichette,2 Jean-Michel Michel,1,2
1Centre de recherche Hôpital Maisonneuve-Rosemont, Montréal, QC, Canada; 2Hôpital Maisonneuve-Rosemont, Montréal, QC, Canada; 3Université de Montréal, Montréal, QC, Canada.

Background: Anemia is a common problem among patients with chronic kidney disease. Erythropoiesis stimulating agents (ESA) are frequently used to maintain haemoglobin between 95-115 g/L. Multiple studies suggest that longer intervals than those recommended in the product monographs of these ESA can be effective. Most of these studies were done in non dialysis patients. Fewer studies were done with population in hemodialysis, peritoneal dialysis and in transplanted patients.

Methods: In this retrospective, single center, cross-sectional study, we compared the dose, reported in IU/kg/week, between groups defined by the interval at which patients received ESA (more than once a week (G0), once a week (G1), every other week (G2), once every three weeks (G3), every four weeks (G4) and every more than four weeks (G5)). Charts of all patients receiving an ESA at a stable dose for at least three months and followed at the pre-dialysis, hemodialysis, peritoneal dialysis and transplant clinic were reviewed.

Results: Five hundred and ninety four patients were included. One hundred and twenty-two patients (22%) were on epoetin alfa and 462 (78%) were on darbepoetin alfa. The mean dose/kg/week was less when a longer interval was used: the mean dose/kg/week was 247 in G0, 195 in G1, 82 in G3, 67 in G4 and 28 in G5 (p<0.0001). In the epoetin subgroup, the mean dose/kg/week was 256 in G0, 124 in G1, 52 in G2, 37 in G3, 19 in G4, 17 in G6 (p<0.0001). In the darbepoetin subgroup, the mean dose/kg/week was 211 in G0, 152 in G1, 71 in G2, 35 in G3 and G4 in G5 (P<0.0001).

Conclusions: Doses were significantly lower in the longer interval groups, suggesting that longer intervals are efficient to maintain haemoglobin in the desired target in a large population of patients with chronic kidney disease. The mean dose remained smaller in the longer intervals when comparing both ESA types, however, the mean dose was generally less in the epoetin group compared to the darbepoetin group. A selection bias might explain some of the differences between groups. Nonetheless, using longer intervals seem possible in a significant number of patients. Since longer intervals are more acceptable to patients and are more cost effective, this approach might be favourable.

Funding: Clinical Revenue Support

SA-PO804
Conversion from Epoetin Alfa to Darbepoetin Alfa in HD: Optimization of Dose Conversion Algorithm and HB Stability Dongyang Shang,1 Alex Yang,1 Shijie Chen,1 Steven Chang,1 Sheila Doss-McQuitty,3 Brigitte Schiller,1,2
1Satellite Healthcare, San Jose, CA; 2Stanford University, Palo Alto, CA, CA.

Background: Previous conversion experiences from thrice weekly epoetin to once weekly darbepoetin resulted in inconsistent outcomes when using the conversion table in the prescribing information (PI). This study tested an improved conversion algorithm and assessed the accuracy through achieved target hemoglobin (Hb), Hb stability and speed to reach pre-conversion.

Methods: This is a prospective, controlled, open-label, multi-center interventional trial. Data from 5643 in-center HD patients from 54 dialysis centers from January 2016 to May 2017 are presented. Conversion occurred from June 2016 to February 2017. Doses in these patients were included in the conversion algorithm and Hb values were measured monthly for the 4 months before conversion, 1 month during the conversion, and up to 4 months after conversion. Hb consistency was defined as an increase or decrease of a 3% in the percentage of patients in each Hb category.

Results: The improved conversion table increases the number of dose categories, resulting in doses that overall are 8.8 times more closely aligned with the optimal dosing curve than the current PI. The distribution of patients (n=6634) treated with darbepoetin for 4 months reaching the target Hb 10.0-11.4 g/dL is clinically and statistically similar to pre-conversion. Within 2 months of conversion 54% of patients reached target Hb, similar to previous dose conversion.

Conclusions: In this real-world dosing conversion study switching from epoetin to darbepoetin, the improved conversion table reduces the risk of initial under-dosing and shortens the duration of time before patients achieve stable Hb. Appropriate therapeutic conversion provides more accurate darbepoetin dosing based on patients’ ESA needs.

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

SA-PO805
Levels of the EPO-Responsive Hormone Erythroferrone in Mice and Humans with CKD
Mark R. Hanuel,1 Maxime Rappaport,1 Victoria R. Gabayan,1 Isidro B. Salusuysky,1 Tomas Ganz,2 Elizabetta Nemeth,2
1Department of Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, CA; 2Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA.

Background: We previously demonstrated that, in mice with normal kidney function, erythropoietin (EPO) stimulates erythroblasts to secrete the hormone erythroferrone (ERFE), which acts to suppress production of the iron-regulatory hormone hepcidin. ERFE-mediated hepcidin suppression increases iron availability for RBC production. ERFE has not been assessed in humans or in the setting of CKD.

Methods: We measured serum ERFE levels in wild type mice, with and without adenovirus-induced CKD, and in a single EPO dose. We also measured serum ERFE in adults with normal kidney function after EPO treatment, as well as in 161 adult and pediatric healthy controls, 82 adult and pediatric non-dialysis CKD patients, and 101 adult and pediatric dialysis patients.

Results: In mice with normal kidney function, serum ERFE levels, undetectable at baseline, increased in response to EPO, peaking 6h post-injection. In mice with CKD, serum ERFE levels increased to a similar degree, but peaked later, at 24h post-injection. In both groups, serum hepcidin was decreased at 48h. In four adults with normal kidney function injected with a single EPO dose, serum ERFE increased 2.2-fold from baseline by 48-72h post injection. Concurrently, serum hepcidin levels decreased 2.3-fold from baseline by 48-72h hours post injection. Median serum ERFE did not differ between non-dialysis patients (61.1 vs. 7.8 ng/mL), but was significantly elevated in dialysis patients (15.7 ng/mL; p<0.05). In the non-dialysis CKD patients, serum ERFE correlated positively with ERFE (Spearman r=0.59, p<0.001), but ERFE did not correlate with hepcidin. Hepcidin correlated with TSAT (Spearman r=0.34, p=0.004), but not with CRP or eGFR. Similarly, in the dialysis patients, hepcidin correlated positively with ERFE (Spearman r=0.44, p<0.001), but ERFE did not significantly correlate with hepcidin. Hepcidin did not correlate with TSAT or CRP.

Conclusions: In humans with normal kidney function, EPO administration increases ERFE and suppresses hepcidin. In CKD patients, ERFE correlates with serum EPO or rEPO dose, but not hepcidin. These data suggest that ERFE is responsive to EPO in humans and mice regardless of kidney function, but that regulation of hepcidin in CKD is multifactorial, masking the hepcidin suppressive effects of ERFE.

Funding: NIDDK Support, Other NIH Support - NIH Loan Repayment Program

SA-PO806
Impact of Intravenous Ferri-Sucrose Hydroxide on Mortality in HD: MEDIAL Iron Cohort ECHO (MICE Study)
Victorio Menoyo,1 Malik Touam,4 Pierre-Yves Durand,1 A. Testa,1 1ECHOCANNE, France; 2HEMODIALYSIS, ECHO, NANTES, France; 3ECHO NANTES, NANTES, France; 4Necker Hospital, Paris, France. Group/Team: MEDIAL STUDY GROUP.

Background: Intravenous iron is the main component to Erythropoiesis Stimulant Agent (ESA) treatment for HD patients. Ferri Sucrose Hydroxide (FHS) is one of this. Previous retrospective studies have shown the potential toxicity of HSF, and have report increased mortality above some monthly dose. We aimed to study the toxicity of HSF, and to precise its relationship with this markers.

Methods: Medical Iron Cohort ECHO is a multicenter cohort of HD patients coming from 49 HD french centers. All incident patients were included from year 2005 to 2015. Data were retrospectively analyzed. Iron injections, ESA, hemoglobin and other biological data were recorded in a single database : MEDIAL. Statistical analysis used
a non-parametric test for exceedances of the Ferritin, TSAT and CRP standards as well as kV<1.3. We considered the usual demographies and anamnastics. We have defined 4 subgroups according to the dose of HFS: A: <100 mg / month; B: 100-200 mg / month; C: 200-300 mg / month; D: 300-400 mg / month; E: < 400 mg / month. The proportional risk regression survival analysis (Cox model) was performed using the STATISTICA software.

Results: 1,370 patients were included. The average follow-up was 41.5 months. 481 deaths occurred during the study period. It was a very strong relationship between mortality and HFS dose above 200 mg / month. (P <0.0000) The stratified analysis showed that this mortality rate was dose dependent and the effect appears above a dose of 100 mg / month. Although there was no significant difference between subgroups A, B, C, there was a trend towards it. There was no significant relationship between mortality and Ferritin or TSAT blood levels. There was no significant difference between the 5 groups regarding the received ESA dose or hemoglobin. Gender and diabetes were not linked to mortality, while other independent factors appeared to be significant at age of onset of dialysis, albuminemia, CRP and kV<1.3.

Conclusions: This study suggests that intravenous HFS in HD patients could be toxic, probably for doses considered to be low toxicity to date. Ferritin and TSAT blood levels are not good markers for HSF toxicity. Advanced age at the start of ESRD, undernutrition, inflammatory status, or poor dialysis dose are significant markers linked to mortality. Further prospective studies are required to confirm these results.

SA-PO807

Serum Concentration of Non-Transferrin Bound Iron in Hemodialysis Patients Is Increased after Oral Iron Administration

Noriko Saito,1 Kazuhide Saito,6 Tetsuo Moritaka,1 Hisaki Shimada,4 Kozo Ikariashi,2 Yutaka Tsatsbara,1 Taiji Sasagawa,1 Katuya Ikuta,1 Yutaka Kohgo,2 Shigeru Miyazaki,3 Asahikawa Medical University, Asahikawa, Japan; 2Institute of Health and Welfare, Asahikawa, Japan; 3Shinraku-en Hospital, Niigata, Japan; 4Shinraku-en hospital, Niigata, Japan; 5Shinraku-en Hospital, Niigata, Japan; 6Shinraku-en Hospital, Niigata city, Japan.

Background: Non-transferrin bound iron (NTBI), which appears in serum in end stage renal disease, is thought to cause organ damage through free radical production. We reported NTBI was increased after intravenous iron administration (IVIA) in hemodialysis (HD) patients (SNSAS2016), and their kinetics after oral iron administration (OIA) is unknown. The aim of this study is to assess the kinetics of NTBI concentration after OIA in HD patients.

Methods: 16 HD patients without any iron load during 4 weeks, whose Hb=12g/ dl, ferritin<100mg/ml and CRP<1mg/dl, were enrolled. They received oral ferrous sulfate 1200mg/day for 5 consecutive days as the first period. We evaluated the following parameters before and at 1,2,3,4 and 48 hours after OIA: 1) NTBI, hepatic iron concentration (HIC), high sensitive CRP(HsCRP), 8-oxo-2'-deoxyguanosine, serum iron, transferrin saturation(TSAT), transferrin(Tf), ferritin, soluble Tf receptor and standard hematological parameters. NTBI was measured by recently described reliable methods (Clin Chim Acta373(1-2):135-140, 2015).

4 HD patients without OIA were also enrolled as control.

Results:

1. Fe before OIA was 30(24-49)µg/dl and significantly increased to 45(27-57)µg/dl at 1hr and reached the peak level of 272(104-320)µg/dl at 4hr and then decreased to 52(34-81)µg/dl at 48hr (Medians(interquartile range)). 2. TSAT before OIA was 127(67-177)% significantly increased to 248(177-291)% at 2hr, reached the peak level of 74(50-80)% at 4hr and decreased to 17(14-26)% at 48hr. 3. NTBI before OIA was 0.02(0-0.10)µg/ml and significantly increased to 0.15(0.03-0.35)µg/ml at 4hr and decreased to 0.02(0-0.07)µg/ml at 48hr. 4. NTBI increased after OIA correlated with HIC at 4hr(r=0.894, p=0.001). 5. The percentage of NTBI 4hr after OIA was percentage of hypochromic red cells (%HypoHe) before OIA by stepwise analysis (r=0.548, p=0.028, R2=0.36). 6. Ferritin before OIA was 16(15-29)ng/ml and significantly increased to 33(19-48)ng/ml at 4hr. HPC was unchanged during 48hr. 7. NTBI and ferritin were not changed during 48hr.

Conclusions: TSAT and NTBI significantly increased at 2hr and 4hr after OIA, respectively and both peaked at 4hr. %HypoHe before OIA was negative predictor of NTBI at 4hr. Clinical significance of NTBI increment after OIA should be further examined.

Funding: Private Foundation Support

SA-PO808

Evaluating Iron Overload in Haemodialysis Patients with MRI: A Pilot Study

Elif Boral,1 Elyan Cockburn,1 Benjamin Mark,1 Elaine Rutherford,2,3 Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom; 2Cardiology and Imaging Group, British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom.

Background: Intravenous iron is prescribed in patients with haemoglobin levels <11.5g/dl and intravenous iron at a dose of 200-300mg/month is aimed to increase haemoglobin levels. We performed a retrospective analysis of patients in the NAPRTCS database, a voluntary, prospective registry of children with end stage renal disease. We assessed transfusions, anemia, epo dosing, and hospitalizations in 3 time periods: baseline (2003-2007), implementation (2008-2011) and post-implementation (2012-2016).

Results: 1,199 children enrolled in the NAPRTCS HD registry during the study period (54.7% male, median age 13.4 years). Children in post-implementation were significantly younger than children in baseline and implementation. 12.8% of patients had transfusions in baseline, 19.6% in implementation (p=0.008 vs. baseline), and 17.4% in post-implementation (p=0.08 vs. baseline). Mean Hgb 6 months after HD start was 11.8 g/dl in baseline, 11.1 g/dl in baseline, 11.1 g/dl in implementation (p=0.001 compared with baseline) and 11 g/dl in post-implementation (p=0.02 compared with baseline). Median epo dosing 6 months after starting HD was 211 µg/kg/week in baseline, 131 µg/kg/week in implementation, and 142 µg/kg/week in post-implementation. 6 months after starting dialysis, 42.7% of children were hospitalized in baseline, 43.4% in implementation, and 46.5% in post-implementation. The rate of anemia (Hgb <10) 6 months after starting dialysis was 17.4% in baseline, 23.5% in implementation, and 23.5% in post-implementation.

Conclusions: With implementation of adult epo dosing guidelines, epo dosing was lower, anemia rate increased, transfusion rate increased, and mean hgb levels decreased among NAPRTCS participants. There was no significant difference in hospitalization rates before and after guidelines. Further study of safe target hgb levels among pediatric HD patients is warranted.
SA-PO810
Iron Supplementation for Hemodialysis Patients: Less Oxidative Stress by Oral Ferric Citrate Hydrate as Compared to Intravenous Saccharated Ferric Oxide Masaki Nakayama, Yoshitomo Tani, Jun-Oh Nakazawa, Kazumasa Suyama, Akira Kiba, Hidemasa Yamauchi, Tadashi Misono, and Naohiro Nakashima
Background: Iron deficiency is prevalent in dialysis patients, and it is associated with adverse health outcomes. Oral ferric citrate hydrate (FO) may be a safer alternative for iron supplementation compared to intravenous (IV) saccharated ferric oxide (saccharated ferric oxide) due to its lower oxidative stress.
Methods: In a randomized, double-blind, placebo-controlled study of 31 hemodialysis patients, we compared the oxidative stress induced by FO and IV saccharated ferric oxide.
Results: The mean change in the level of thioredoxin (anti-oxidant) in FO, whereas no significant increases were seen in FC, whereas significant increases were seen in FO, despite the lower serum iron levels in the younger age group patients. FPC-HD showed a similar intradialytic and post-dialysis iron prole delivery as compared to the IV iron dose.
Conclusions: Oral FO may have benefits in terms of iron supplementation for anemia associated with chronic kidney disease.
Funding: Commercial Support - Japan Tobacco, Government Support - Non-U.S.

SA-PO811
Background: Daprodustat is an oral prolyl hydroxylase domain inhibitor that functions by increasing the expression of erythropoietin (EPO). This study evaluated the safety, efficacy, and pharmacodynamics of daprodustat administered twice weekly (TIW) in anemic dialysis patients.
Methods: This was a randomized, double-blind, placebo-controlled study conducted at 22 centers in Japan. Patients entered a 7-day baseline period followed by a 28-day treatment period. Dose escalation was performed in a 2:1 placebo:daprodustat treatment ratio, with 11 patients per dose level. Efficacy endpoints included change in hemoglobin (Hb) and change in erythropoietin (EPO) levels.
Results: Of the 35 patients enrolled, 29 completed the study. The mean change in Hb was 2.4 g/dL from baseline to end of treatment. The most common adverse events were deep vein thrombosis and upper abdominal pain.
Conclusions: Daprodustat administered twice weekly was safe and effective in increasing Hb levels in anemic dialysis patients.
Funding: Commercial Support - GlaxoSmithKline
SA-PO814

Labile Plasma Iron for the Early Detection of Iron Overload in ESRD

Aron Benayahu,1 Itzchak N. Slotki,2 Linda Shavit,2 Jolanta Malyszko,3 1Medical University, Białystok, Poland; 2Share Zedek Medical Center, Jerusalem, Israel; 3Share Zedek Medical Center, Jerusalem, Israel; 4shaare zedek, Jerusalem, Israel.

Background: The increased usage of intravenous iron (IVI) in hemodialysis patients during recent years has led to increasing concern over the potential development of iron overload (IO). Current methods for detecting iron overload, transferrin saturation (TSAT) and serum ferritin are neither sensitive nor specific. Labile plasma iron (LPI) represents a component of non transferrin bound iron that is both redox active and chelatable and may be a more accurate indicator of impending iron overload. We studied whether LPI measured using the FerRos LPI detecting system (Aferrix) can serve as an early indicator of impending IO in hemodialysis patients.

Methods: Chronic hemodialysis patients from two medical centers in Israel and Poland who received IVI were included. Demographic data, cause of ESRD, comorbidities, medications and the following laboratory parameters were recorded: Hb, serum iron, transferrin, TSAT, ferritin. LPI was measured before and 48 hours after a single IV administration of either iron sucrose 100 mg, iron gluconate 62.5 mg, iron (III)-hydroxide dextran complex 100 mg. A test result of 0.6 units of LPI or more indicated a potential for iron-mediated production of reactive oxygen species in the sample.

Results: 111 hemodialysis patients, aged 64 ± 15, were included in the study. 90 patients received iron sucrose, 14 iron gluconate and 7 iron dextran at mean monthly doses of 233 ± 133 mg; LPI was negative in all patients prior to IVI, but became positive post administration in 4 patients, all of whom received iron sucrose. Three of these patients were diabetic, had TSAT < 30% and ferritin ≤ 360 ng/ml and received monthly iron doses of 400-500 mg.

Conclusions: Doses of IVI routinely used in chronic hemodialysis patients appear to be safe. However, higher monthly doses may be associated with detectable LPI post administration, even in the absence of currently used laboratory parameters of IO.

SA-PO815

Low-Dose Iron Treatment and Erythropoiesis Efficiency in Hemodialysis Patients with Anemia Treated by Erythropoiesis-Stimulating Agents

Tadashi Kuki,1 Shota Suzuki,2 Tetsuya Fujikawa,3 1Yokodai Central Clinic, Yokohama, Kanagawa, Japan; 2Yokohama City University, Yokohama, Kanagawa, Japan; 3Yokohama National University, Yokohama, Kanagawa, Japan.

Background: Anemia is a common comorbidity and is a major cause of morbidity and mortality among hemodialysis (HD) patients. Iron deficiency is a major cause of resistance to erythropoiesis-stimulating agents (ESA) therapy; however, excessive iron intake has toxic and oxidative effects. An increased iron supply causes oxidative stress due to free iron in the blood, therefore low-dose iron is desirable to reduce the free iron release for optimal prognosis. We aimed to investigate whether low-dose iron supplementation is as effective for erythropoiesis as standard dose iron supplementation.

Methods: A randomized, controlled, parallel-group study was performed for six months. One hundred and two patients were randomized to receive 20mg intravenous elemental iron per week (Low-dose iron group: n = 53) or 40 mg intravenous elemental iron per week in 4 doses (Standard-dose iron group: n = 49). Ferritin and transferrin saturation were measured at two-month intervals. Iron was administered for two months when HD patients showed iron deficiency (transferrin saturation < 20% and ferritin ≤ 100ng/ml).

Results: No significant differences in baseline characteristics except systolic blood pressure were evident between the two groups. The mean numbers of two-month long iron supplementation were 7.4 ± 0.83 in low-dose iron group and 4.9 ± 0.56 in standard-dose iron group. Mean Hb levels during the evaluation period of 6 months were 10.5 ± 0.4 g/dl in the low-dose iron group and 10.4 ± 0.4 g/dl in the standard-dose iron group (p = 0.315). There was a tendency toward lower Hb levels in the low-dose iron group compared to the standard-dose iron group (411.6 ± 2170.4 IU/week vs. 493.5 ± 1792.8 IU/week, p = 0.079). There was a trend towards decrease in ferritin levels in low-dose iron group compared with the standard-dose iron group (36.4±50.9 ng/ml vs. -11.8 ± 65.2 ng/ml, p = 0.073). Reticulocyte hemoglobin levels (newly synthesized hemoglobin) and ESA resistance index were not significantly different between the two groups.

Conclusions: Low-dose iron treatment suppresses ferritin levels, but does not decrease hemoglobin levels and reticulocyte hemoglobin levels or does not increase required ESA dose.

SA-PO816

Link between Iron Deficiency and Thrombocytosis in Dialysis Patients - Are ADPKD Patients Different? Felix Nadrowitz,1 Klaus Stahl,1 Bernhard M. Schmidt,1 Gero D. von Gersdorff,1 Katherine Rascher,4 Hermann G. Haller,1 Roland Schmidt,1 1Hannover Medical School, Hannover, Germany; 2MHH, Hannover, Germany; 3Medizinische Hochschule Hannover, Hannover, Germany; 4University Hospital Cologne, Cologne, Germany.

Background: Secondary thrombocytosis has been reported in iron deficiency (ID) anemia. Maintenance hemodialysis (MHD) patients with adult polycystic kidney disease (ADPKD) often receive low iron supplementation due to their spontaneously high hemoglobin levels. We analyzed a possible correlation between ID and platelet count in MHD ADPKD and non-ADPKD patients.

Methods: We conducted a multi-center cohort study with 2387 ADPKD and 30923 non-ADPKD patients. Data between 2008 and 2015 were extracted from over 190 outpatient hemodialysis centers from the institutional K.H quality registry. Multivariable correlation as well as multivariable linear regression analysis with thrombocyte count and parameters of iron status were performed. To correct for inflammation dependent changes laboratory measurements were only included when CRP was in the normal range.

Results: While mean transferrin saturation (TSAT) in ADPKD patients indicated ID (16.6 ± 7.4 %), mean ferritin was not in the ID range (544.8 ± 416.9 ng/ml). Mean absolute thrombocyte count in the ADPKD cohort was 202.2 ± 65.0 x10^11/µl. A correlation coefficient of 0.12859 implicated a statistically significant, but minor negative correlation of thrombocytes with TSAT in non-ADPKD MHD patients mean TSAT was 17.9 ± 9.6 % and mean ferritin was 631.6 ± 446.2 ng/ml. Mean platelet count was 216.5 ± 73.7 x10^11/µl with a likewise significant, but small negative correlation coefficient to TSAT (-0.11974). Only an extremely low TSAT (< 2%) was associated with platelet counts above the upper limit of normal.

Conclusions: In MHD patients with ADPKD we could not find a relevant correlation of TSAT and platelet count. This was not different from non-ADPKD patients. Our study demonstrates that common degrees of ID in ADPKD and non-ADPKD patients on MHD do not result in thrombocytopoiesis.
SA-PO818
A Prospective Study Examining the Contribution to Renal Anemia Treatment of Ferric Citrate Hydrate, an Iron-Based Oral Phosphate Binder, in Hemodialysis Patients with Hyperphosphatemia: ASTRIO Study Keitaro Yokoyama,1 Masanumi Fukagawa,2 Takashi Akiba,3 Masaki Nakayama,4 Koji Hanaki,5 Ito Kyoko,1 Hideki N. Hirakata.1 1Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan; 2Fukuoka Renal Clinic, Fukuoka City, Japan; 3JAPAN TOBACCO INC, Tokyo, Japan; 4Kokura Hospital, Tokyo, Japan; 5Tokohu University, Tohoku University Hospital, Sendai City, Japan; 6Tokai University School of Medicine, Isehara, Japan; 7Tori Pharmaceutical Co., Ltd, Tokyo, Japan

Background: We conducted a prospective study examining the contribution to renal anemia treatment of Ferric citrate hydrate (FC) compared with non-iron-based oral phosphate binders (Control), in HD patients with hyperphosphatemia undergoing ESA therapy.

Methods: The study was designed as a multicenter, open-label, active-controlled, randomized, parallel-arm comparison study. HD patients who had been used non-iron-based oral phosphate binders were randomized to FC group (n=45) or Control group (n=48). In FC group, previous treatment was discontinued at registration and switched to FC, and for continued for 24 weeks. In Control group, previous treatment was continued. Serum P and Hb were controlled in the targeted range of 3.5 to 6.0 mg/dL and 10.0 to 12.0 g/dL, respectively. We evaluated the doses of ESA and IV iron.

Results: Mean changes in ESA dose (IU/week) from baseline to end of treatment (EOT) were –1211.8 ± 6662.8 in Control group and 1195.5 ± 6662.8 in Control group. It was significantly lower in FC group than Control group (p=0.0386). Cumulative dose of IV iron from baseline to Week 24 was also significantly lower in FC group than in Control group (p=0.0065). Other parameters are shown in the table.

Conclusions: We confirmed that FC decreased doses of ESA and IV iron. We also confirmed the differences of ERI, MCV, RDW and FGF23 between FC group and Control group. It was considered iron supplementation by FC was done in functional manner. FC showed stable dosing patterns and stable hemoglobin (Hb) outcomes. Predictive hierarchical modeling was applied to identify determinants of outcomes of interest.

Methods: A subset of 484 patients with complete 24-month data was used to investigate pre-specified potential determinants of the following outcomes: (1) mean Hb of last 4 visits, estimated using Wald test (hierarchical linear regression); risk for (2) chronic hyporesponsiveness, (3) overnight hospitalization, (4) thromboembolic events of last 4 visits, estimated using Wald test (hierarchical linear regression); risk for (5) mortality. Risks were estimated using adjusted odds ratios (OR; hierarchical logistic regression). The intraclass correlation coefficient (ICC) quantified the proportion of variance in outcome attributable to a center class effect.

Results: The following determinants were retained for each outcome of interest at p<0.05. For mean Hb of last 4 visits (ICC=-0.0477): age (+0.0067g/dL per 1 year over mean), chronic infection or inflammatory disease at baseline (0.3595g/dL if present); Kt/V at baseline (0.3150g/dL if present). For risk of chronic hyporesponsiveness (ICC=-0.1516): chronic infection or inflammatory disease at baseline (OR=3.055). For risk of hospitalization (ICC=-0.2349): no determinants retained despite ICC. For TEE risk (ICC=-0.0550): serum albumin a3g/dL (OR=0.396); Kt/V1.2 at baseline (OR=0.455); age (per 1 year of age; OR=1.021). For overall mortality (ICC=0.1156): deficient iron status (OR=2.354); Kt/V1.2 at baseline (OR=0.316); age (per 1 year old; OR=1.064).

Conclusions: In hemodialysis patients receiving Binocrit® for 2 years, determinants of poor outcome included Kt/V1.2 and serum albumin a3g/dL. The presence of chronic infection or inflammatory disease and deficient iron status were predictive of poorer Hb outcomes. Age was associated positively with Hb levels, but negatively with TEE and mortality risk. Consistent with findings from the DOPPS and ESAM observational studies, all determinants except for age are clinically modifiable or manageable. Funding: Commercial Support - Sandoz

SA-PO819
Predictive Hierarchical Modeling of Determinants of Outcomes of Anemia Management with Binocrit®, a Biosimilar Epoetin Alfa, in the Hemodialysis Setting (MONITOR-CKD5 Study) Frank Dellanna,1 David J. Coldsmith,2 Johnnes F. Mann,3 Philippe Zaoui,4 Christian Combe,5 Andriy Krendyukov,6 Ivo Abraham,7 Karen Macdonald.1 1MVZ DaVita Rhein-Ruhr GmbH, Düsseldorf, Germany; ‘Guy’s & St. Thomas’ NHS Foundation Trust, Great Maze Pond, United Kingdom; 2KfH Nierenzentrum, München, Germany; 3Clinic of Nephrology Chu Grenoble, Grenoble, France; 4CHU de Bordeaux, Bordeaux, France; 5Sandoz Biopharmaceuticals, Holzkirchen, Germany; 6University of Arizona, Tucson, AZ; 7Matrix 45, Tucson, AZ

Background: The European observational MONITOR-CKD5 study demonstrated the real-world effectiveness of Binocrit® in renal anaemia. Patients treated for up to 24 months showed stable dosing patterns and stable haemoglobin (Hb) outcomes. Predictive hierarchical modeling was applied to identify determinants of outcomes of interest.

Methods: A subset of 484 patients with complete 24-month data was used to investigate pre-specified potential determinants of the following outcomes: (1) mean Hb of last 4 visits, estimated using Wald test (hierarchical linear regression); risk for (2) chronic hyporesponsiveness, (3) overnight hospitalization, (4) thromboembolic events of last 4 visits, estimated using Wald test (hierarchical linear regression); risk for (5) mortality. Risks were estimated using adjusted odds ratios (OR; hierarchical logistic regression). The intraclass correlation coefficient (ICC) quantified the proportion of variance in outcome attributable to a center class effect.

Results: The following determinants were retained for each outcome of interest at p<0.05. For mean Hb of last 4 visits (ICC=-0.0477): age (+0.0067g/dL per 1 year over mean), chronic infection or inflammatory disease at baseline (0.3595g/dL if present); Kt/V at baseline (0.3150g/dL if present). For risk of chronic hyporesponsiveness (ICC=-0.1516): chronic infection or inflammatory disease at baseline (OR=3.055). For risk of hospitalization (ICC=-0.2349): no determinants retained despite ICC. For TEE risk (ICC=-0.0550): serum albumin a3g/dL (OR=0.396); Kt/V1.2 at baseline (OR=0.455); age (per 1 year of age; OR=1.021). For overall mortality (ICC=0.1156): deficient iron status (OR=2.354); Kt/V1.2 at baseline (OR=0.316); age (per 1 year old; OR=1.064).

Conclusions: In hemodialysis patients receiving Binocrit® for 2 years, determinants of poor outcome included Kt/V1.2 and serum albumin a3g/dL. The presence of chronic infection or inflammatory disease and deficient iron status were predictive of poorer Hb outcomes. Age was associated positively with Hb levels, but negatively with TEE and mortality risk. Consistent with findings from the DOPPS and ESAM observational studies, all determinants except for age are clinically modifiable or manageable. Funding: Commercial Support - AstraZeneca

SA-PO820
Development and Validation of a Transfusion Risk Score David T. Gilbertson,1 Heng Yan,2 Hairong Xu,2 Marvin V. Sinskukl,3 Yi Peng,4 James B. Wetmore,4 Jiannong Liu,5 Suying Li.1 1AstraZeneca, Bethesda, MD; 2Astrazeneca, Westlake Village, CA; 3Chronic Disease Research Group, Minneapolis, MN; 4Minneapolis Medical Research Foundation, Minneapolis, MN; 5Hennepin County Medical Center, Minneapolis, MN

Background: Following changes to CMS payment for dialysis services in Jan 2011 and an ESA label revision 6 months later, a decline in hemoglobin (Hb) levels and an increase in transfusions were observed in dialysis patients. Transfusions have decreased from their 2012 peak, and transfusion avoidance is the preferable option in dialysis patients. We sought to develop a predictive model for transfusions using comorbidity, markers of inflammation, previous transfusion, vitamin D use, IV iron use, ESA dose, Hb, ferritin and TSAT.

Methods: USRDS/Crownweb data from 2012-13 were used for model development. Point prevalent hemodialysis (HD) patients on 11/1/12 with a 6 months Medicare A/B coverage and mean Hb < 10 g/dL were included. Aug-Oct were used to assess anemia-related variables (Hb, ESA, TSAT, ferritin, IV iron use, vitamin D, and transfusion), and May-Oct were used to assess comorbidity from claims. Logistic regression with Lasso for variable selection was used to predict transfusion during the next 3 months. For model validation, similar cohort construction was used, with point prevalent HD patients on 8/1/13.

Results: Variables retained in the final model included Hb, ESA dose, ferritin, TSAT, iron vitamin D, prior transfusion, and interactions of these variables. In the validation dataset, a calibration plot showed good agreement between observed/predicted transfusions (Figure); c-statistic = 0.74. Conclusions: The addition of ferritin and TSAT, along with inflammatory comorbidities, aided in prediction of transfusions in patients with Hb levels < 10 g/dL. Future anemia management strategies involve balancing CV risk on the high end of Hb and ESA exposure with transfusion risk on the low end. The ability to identify patients at risk for transfusion may lead to improved anemia management outcomes. Funding: Commercial Support - AstraZeneca

SA-PO821
Association of Hepcidin with Anemia Parameters in Incident Dialysis Patients: Difference between Dialysis Modalities Eun Young Lim,1 Yong-Hak Lee,2 Man-hoon Han,1 Kyu Yeun Kim,1 Hee-Yeon Jung,3 Ji-Young Choi,1 Jang-Hee Cho,1 Chan-Duck Kim,2 Sun-Hee Park,2 Yong-Lim Kim,1 1Kyungpook National University Hospital, Daegu, Republic of Korea; 2Daegu Fatima Hospital, Daegu, Republic of Korea

Background: Hepcidin has been considered to be a key regulator of iron homeostasis in recent years. However, its relationships to other variables are not well understood. This study aimed to evaluate association of serum hepcidin level with iron parameters and inflammatory parameters, especially according to dialysis modality, in end-stage renal disease (ESRD) patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: A total of 110 incident dialysis patients, 68 on peritoneal dialysis (PD) and 42 on hemodialysis (HD), were prospectively followed up for 6 months. Serum hepcidin level was measured by a commercial ELISA kit (DRG Instruments, Marburg, Germany) at baseline and 6 months after initiation of dialysis. The relationship of hepcidin to clinical parameters was investigated using linear regression models.

Results: Serum hepcidin levels significantly increased in initial 6 month after start of dialysis. PD group showed higher hemoglobin after 6 months than HD group, in spite of less use of erythropoiesis-stimulating agents during study period. In multivariate regression model, independent predictors of serum hepcidin were aspartate transaminase (β=21.359, p=0.003), ferritin (β=0.056, p=0.008), transferrin saturation (β=0.644, p<0.009), and phosphate (β=0.946, p=0.001) in incident ESRD patients. At 6 months after initiating dialysis, serum hepcidin was independently predicted by urine volume (β=−0.008, p=0.043), alanine transaminase (β=12.091, p=0.008), ferritin (β=0.051, p=0.019), and total iron binding capacity (TIBC) (β=0.191, p=0.002) in all patients, whereas by ferritin (β=0.056, p=0.001) and TIBC (β=−0.184, p=0.023) in PD patients, and urine volume (β=−0.021, p=0.004), ferritin (β=0.048, p=0.005), and TIBC (β=−0.225, p=0.015) in HD patients.

Conclusions: Serum hepcidin was differentially associated with anemia parameter between PD and HD patients. Urine volume was an independent predictor of hepcidin in incident HD patients. It suggests preservation of urine volume may be important to reduce hepcidin concentration in incident HD patients.

Funding: Commercial Support - Roche Pharma AG, Fresenius Medical Care North America

SA-PO822
Difference in the Hepcidin/Ferritin Ratio among Non-Dialyzed CKD Patients, and Patients on Hemodialysis and Peritoneal Dialysis
Takahito IiKura,1 Yukio Maruyama,1 Satomi Nakashima,1 Nanae Matsuo,1 Yuto Tanno,1 Ichiro Okhido,1 Keitaro Yokoyama,1 Hiroyasu Yamamoto,1,2 Takashi Yokoi.1 Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan; 1Department of Internal Medicine, Atsugi City Hospital, Atsugi, Japan.

Background: The level of hepcidin, a key mediator of iron homeostasis, generally increases in patients with chronic kidney disease (CKD), attributable to inflammation or a decline in the glomerular filtration rate (GFR). Although the hepcidin/ferritin ratio is used in hepatic disorders (e.g., viral and autoimmune hepatitis) and hematological disease (e.g., hereditary hemochromatosis and thalassemia), its role in renal patients has never been investigated. We evaluated the hepcidin/ferritin ratio in non-dialyzed CKD patients, and in those undergoing hemodialysis (HD) or peritoneal dialysis (PD); we also used this ratio to explore iron homeostasis in CKD patients.

Methods: We recruited 285 CKD patients (117 non-dialyzed CKD patients, 80 HD patients, and 88 PD patients) and measured the levels of serum hepcidin-25, ferritin and markers of kidney disease. Serum hepcidin-25 levels were assessed via liquid chromatography/tandem mass spectrometry.

Results: The serum hepcidin-25 level was elevated in all CKD patients, and was significantly higher in PD than non-dialyzed CKD and HD patients (68.4 [0.4–262] vs. 32.8 [0.7–240] vs. 25.9 [0.4–196] ng/mL, p < 0.01). The serum hepcidin-25 level was positively correlated with that of serum ferritin in all CKD patients, whereas the hepcidin/ferritin ratio was higher in PD patients than in other CKD patients.

Conclusions: PD patients exhibited a higher serum hepcidin-25 level and the hepcidin/ferritin ratio did non-dialyzed CKD and HD patients. Several factors unique to PD patients, such as continuous peritoneal stimulus by the dialysate, and subclinical inflammation and infection, may explain the high hepcidin/ferritin ratio in such patients.

SA-PO823
Determinants of Hepcidin/Ferritin Ratio in Patients Undergoing Maintenance Hemodialysis
Takahiro Kuragano, Takeshi Nakanishi. Hyogo College of Medicine, Nishinomiya, Japan.

Background: Hepcidin is the key regulator of iron absorption. Although low serum levels of hepcidin allow iron uptake in patients with iron deficiency, an imbalance of hepcidin and iron storage might be associated with iron overload. As iron containing photon absorber has expanded the clinical use in chronic kidney disease patients, intestinal iron absorption should be properly evaluated.

Methods: Study design: Cross sectional study. Subjects: 317 patients undergoing maintenance hemodialysis (MHD). We measured the blood levels of Hb, ferritin, iron, transferrin saturation (TSAT), C-reactive protein (CRP), uric acid levels, and phosphate. Laboratory parameters (h) were used to estimate glomerular filtration rate (GFR). The hepcidin/ferritin ratio was used to guide treatment choices, whilst the relative effectiveness of the two available treatments has never been compared in a randomised trial.

Results: At 6 month follow-up, hepcidin concentration in incident HD patients. Serum hepcidin was differentially associated with anemia parameter between PD and HD patients. Urine volume was an independent predictor of hepcidin in incident HD patients. It suggests preservation of urine volume may be important to reduce hepcidin concentration in incident HD patients.

Funding: Private Foundation Support, Clinical Revenue Support

SA-PO824
Randomised Controlled Trial of Intravenous Iron versus Increased Erythropoietin in Haemodialysis Anaemia Sarah Hildebrand, Neill D. Duncan, Frederick W. Tam, Damien Ashby. Imperial College Renal and Transplant Centre, London, United Kingdom.

Background: Anaemia in haemodialysis patients is treated with both erythropoietin and intravenous iron, but response rates are suboptimal, and treatment thresholds remain controversial. Despite poor reliability, traditional iron indices such as ferritin are usually used to guide treatment choices, whilst the relative effectiveness of the two available treatments has never been compared in a randomised trial.

Methods: Stable haemodialysis patients who became moderately anemic (Hb 90-109 g/L) were randomised after 1 year of regular routine testing with non-extreme ferritin (<150 mg/dL) treatments were allocated to treatment with either intravenous iron (1 g divided over 5 consecutive sessions, IVFE group) or increased erythropoietin (starting 3000unit/week or median increase 50%, EPO group). No further treatment was given for 2 months.

Results: In 194 patients followed for up to 18 months (2438 patient-months observed), there were 160 anaemia episodes with completed randomisation and follow-up (mean age 63, 71% male). Intravenous iron and increased erythropoietin were equally effective: a positive haemoglobin response (increase by at least 5g/L by 2 months) was observed in 94.76% IVFE patients, and 95.04% EPO group patients; and both groups had similar levels of treatment response were assessed in both groups. In the IVFE group, compared to non-responders, those achieving Hb response had lower ferritin (101 vs 143mg/dL, p=0.031), lower mean cell volume (90.6 vs 94.5, p=0.034) and lower reticulocyte Hb (33.8 vs 35.5, p=0.037) in the EPO group. The EPO group only low CRP was predictive of a positive response (13.5 vs 28.6, p=0.003). Ferritin was not predictive of response in either group (p=0.9 and 0.2 respectively). Weaker associations with response were found for gender, B12 levels, previous erythropoietin dose and warfarin use.

Conclusions: Intravenous iron and erythropoietin are equally effective in the majority of haemodialysis patients who become anaemic. Ferritin does not predict treatment response, but hepcidin and several established biomarkers do: in combination they could be used in an evidence-based protocol with improved response rates.

Funding: Private Foundation Support, Clinical Revenue Support

SA-PO825
The Effect of Ferric Citrate on IV Iron, ESA Utilization, and Laboratory Parameters in Real-World Dialysis Practice Ciba P. Kovacs1,2, Frederick W. Tam1, Leslie A. Acree,1 Robin Lewinter1;2

Poster/Saturday

Methods: Objective: to determine whether controlled iron release system (CIRS) and/or anemia management system (AMS) can improve clinical outcomes in patients with CKD on dialysis. We retrospectively evaluated changes in healthcare resource utilization (HRU) and laboratory parameters before and after FC initiation in typical dialysis practice.

Results: In 194 patients followed for up to 18 months (2438 patient-months observed), there were 160 anaemia episodes with completed randomisation and follow-up (mean age 63, 71% male). Intravenous iron and increased erythropoietin were equally effective: a positive haemoglobin response (increase by at least 5g/L by 2 months) was observed in 94.76% IVFE patients, and 95.04% EPO group patients; and both groups had similar levels of treatment response were assessed in both groups. In the IVFE group, compared to non-responders, those achieving Hb response had lower ferritin (101 vs 143mg/dL, p=0.031), lower mean cell volume (90.6 vs 94.5, p=0.034) and lower reticulocyte Hb (33.8 vs 35.5, p=0.037) in the EPO group. The EPO group only low CRP was predictive of a positive response (13.5 vs 28.6, p=0.003). Ferritin was not predictive of response in either group (p=0.9 and 0.2 respectively). Weaker associations with response were found for gender, B12 levels, previous erythropoietin dose and warfarin use.

Conclusions: Intravenous iron and erythropoietin are equally effective in the majority of haemodialysis patients who become anaemic. Ferritin does not predict treatment response, but hepcidin and several established biomarkers do: in combination they could be used in an evidence-based protocol with improved response rates.
we observed small but statistically significant mean increases in hemoglobin, transferrin saturation (TSAT) and ferritin despite decreases in cumulative IV iron and ESA dose (all P<0.05). At 3-6 months post-FC (vs. pre-FC), the mean reduction in cumulative IV iron and ESA administration was -130 mg (P=0.001) and -17,127 IU (P<0.001), respectively. The Figure depicts mean % change for each HRU and lab parameter.

Conclusions: Despite significant reductions in IV iron and ESA utilization, hemoglobin and iron parameters improved within 3 months of FC initiation in pts on dialysis. Additionally, serum P control improved significantly in this patient population. Funding: Commercial Support - Keryx Biopharmaceuticals Inc.

Figure: HRU and Lab Mean Percent Change

SA-PO826
Patterns of Anemia Management and Response in the Predialysis Period
James B. Wetmore,4 Heng Yan,3 David T. Gilbertson,3 Hairong Xu,2 Marvin V. Sensakul,1 Yi Peng,1 Jiannong Liu,1 Suying Li,1 Astrazeneca, Bethesda, MD; 2Astrazeneca, Westlake Village, CA; 3Chronic Disease Research Group, Minneapolis, MN; 4Hennepin County Medical Center, Minneapolis, MN; 5Minneapolis Medical Research Foundation, Minneapolis, MN.

Background: The management of anemia in the predialysis period has not been fully described.

Methods: We used USRDS ESRD and pre-ESRD files to study patients initiating hemodialysis (HD) between April 1, 2012 and June 30, 2013. Patients had to have a hemoglobin (Hb) measurement at HD initiation and at least one other measurement in the 3 months after, in the absence of a blood transfusion. Patients were divided into those with predialysis Hb ≥ 9.0 g/dL and those <9.0 g/dL. Percent of patients receiving ESAs and associated Hb levels before and after dialysis initiation were reported.

Results: Of 20,454 patients, 15,599 (76%) had predialysis Hb ≥ 9.0 g/dL and 4855 (24% of the total) who had predialysis Hb <9.0 g/dL, only 1293 of these (27%) received ESAs; mean predialysis Hb was 8.2 ± 0.7 g/dL. The remaining 25% required ESAs, attaining a predialysis Hb level of 10.3 ± 1.1 g/dL. Of the 4461 (92%) who responded to ESAs after initiation, Hb increased markedly from 8.2 g/dL (predialysis) to 10.9 ± 1.2 g/dL (postinitiation).

Conclusions: One quarter of patients had predialysis Hb < 9.0 g/dL, of whom only one-quarter received ESAs. Since only 1 in 20 patients with Hb < 9.0 g/dL subsequently proved to be poorly responsive to ESAs after initiation, the vast majority of patients with predialysis Hb <9.0 g/dL appear to have been “rescuable” from anemia, suggesting that opportunities to effectively treat predialysis anemia are being missed. Funding: Commercial Support - Astrazeneca.

SA-PO827
Roxadustat Treatment of CKD Anemia Is Not Influenced by Inflammation
Lynda Szczec,1 Anatole Besarab,1 Khalil Saikali,1 Lona Poole,4 Gopal Saha,2 Thomas B. Neft,3 FibroGen, Inc., San Francisco, CA; 2FibroGen Inc, San Francisco, CA; 4FibroGen, Inc., San Francisco, CA; 5Fibrogen, Inc, San Francisco, CA.

Background: The efficacy of ESAs in the treatment of anemia is diminished in inflammation. The hypoxia-inducible factor prolyl hydroxylase inhibitor roxadustat is being developed for treatment of CKD anemia. This analysis of Phase 2 studies was undertaken to explore the efficacy of roxadustat in non-dialysis-dependent (NDD) and dialysis-dependent (DD) CKD patients with and without inflammation.

Methods: Data from five completed Phase 2 studies in NDD- and DD-CKD patients in both anemia correction and conversion of patients already treated for anemia were analyzed in this post hoc analysis. Among studies, roxadustat doses, study duration, and comparator (placebo or epoetin alfa) varied. Baseline (BL) hemoglobin (Hb) and change from BL (CFB) were summarized in the efficacy-evaluable populations among patient subgroups with BL CRP ≥ and < ULN (4.9 mg/L).

Results: A total of 234 NDD-CKD and 262 DD-CKD subjects were treated in these studies. Mean CFB in Hb with roxadustat versus comparator was summarized by study and inflammatory state. Roxadustat-driven erythropoiesis, at similar doses, is clinically similar in inflamed versus non-inflamed NDD-CKD and DD-CKD subjects. In all studies, Hb CFB with roxadustat versus comparator (placebo or epoetin alfa) varied.BL hemoglobin (Hb) and change from BL (CFB) were summarized in the efficacy-evaluable populations among patient subgroups with BL CRP ≥ and < ULN (4.9 mg/L).

Conclusions: Roxadustat corrected and maintained Hb similarly in NDD-CKD and DD-CKD subjects both with and without inflammation, in contrast to ESA comparators, for which inflamed subjects had a less robust response. Phase 3 trials are currently underway to further establish the efficacy and safety of roxadustat.

Funding: Commercial Support - FibroGen

Hemoglobin CFB among subgroups defined by inflammatory status

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment (%)</th>
<th>Baseline CRP(mg/L)</th>
<th>Baseline Hb(g/dL)</th>
<th>Change from Baseline in Hb without inflammation</th>
<th>Change from Baseline in Hb with inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>041</td>
<td>Roxadustat</td>
<td>7.45 (±2.06)</td>
<td>9.72 (±0.57)</td>
<td>1.39 (±0.12)</td>
<td>1.56 (±0.18)</td>
</tr>
<tr>
<td>042</td>
<td>Roxadustat(N=18)</td>
<td>7.45 (±2.06)</td>
<td>9.72 (±0.57)</td>
<td>1.39 (±0.12)</td>
<td>1.56 (±0.18)</td>
</tr>
<tr>
<td>043</td>
<td>Placebo(N=8)</td>
<td>4.88 (±2.06)</td>
<td>9.00 (±0.52)</td>
<td>0.77 (±0.16)</td>
<td>0.10 (±0.09)</td>
</tr>
<tr>
<td>040</td>
<td>Roxadustat(N=8)</td>
<td>7.45 (±2.06)</td>
<td>9.72 (±0.57)</td>
<td>1.39 (±0.12)</td>
<td>1.56 (±0.18)</td>
</tr>
<tr>
<td>041</td>
<td>Placebo(N=8)</td>
<td>4.88 (±2.06)</td>
<td>9.00 (±0.52)</td>
<td>0.77 (±0.16)</td>
<td>0.10 (±0.09)</td>
</tr>
<tr>
<td>042</td>
<td>Roxadustat(N=8)</td>
<td>7.45 (±2.06)</td>
<td>9.72 (±0.57)</td>
<td>1.39 (±0.12)</td>
<td>1.56 (±0.18)</td>
</tr>
<tr>
<td>043</td>
<td>Placebo(N=8)</td>
<td>4.88 (±2.06)</td>
<td>9.00 (±0.52)</td>
<td>0.77 (±0.16)</td>
<td>0.10 (±0.09)</td>
</tr>
</tbody>
</table>

Noninflamed subgroup = Baseline CRP <= ULN. Inflamed subgroup = Baseline CRP > ULN.

Means±SD for baseline CRP and Hb. LMeans±SE for Hb CFB.
SA-PO828

Relationship between History of Coronary Heart Disease at Dialysis Initiation and Onset of Events Associated with Heart Disease: A Propensity-Matched Analysis of a Prospective Cohort Study

Daisuke Inaguma,1 Shigehisa Koide,2 Kazuo Takahashi,1 Hiroki Hayashi,1 Midori Hasegawa,1 Yukio Yuzawa,1 Fujita Health University School of Medicine, Toyoake, Japan; 2Fujita Health University School of Medicine, Aichi, Japan; 3Nephrology, Fujita Health University School of Medicine, Toyoake, Japan.

Background: Few studies have reported serial observations during dialysis initiation and maintenance. Therefore, we examined whether the incidence of heart disease events during maintenance dialysis differed between CKD patients with and without a history of coronary heart disease (CHD) at dialysis initiation.

Methods: The subjects were patients in the 17 centers participating in the Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis (ACCORD) from October 2011 to September 2013. We excluded 9 patients whose outcomes were unknown, as determined by a survey conducted at the end of March 2015. Thus, we enrolled 1,515 subjects into the study. We classified patients into 2 groups according to the history of CHD (i.e., a CHD group and a non-CHD group). Propensity scores (PS) represented the probability of being assigned to a group with or without a history of CHD. Onset of heart disease events and associated mortality and all-cause mortality were compared in PS-matched patients by using the log-rank test for Kaplan-Meier curves. Factors contributing to heart disease events were examined using stepwise multivariate Cox proportional hazards analysis.

Results: There were 254 patients in each group after PS-matching. During observation, heart disease events occurred in 85 patients (33.5%) in the CHD group and 48 (18.4%) in the non-CHD group. The incidence was significantly higher in the CHD group (p < 0.001). Heart disease-related death occurred in 27 patients (18.9%) in the CHD group and 12 (10.6%) in the non-CHD group (p = 0.014). All-cause death occurred in 70 patients (27.6%) in the CHD group and 47 (18.5%) in the non-CHD group (p = 0.026). The CHD group was associated with higher incidence of heart disease events (vs. the non-CHD group, HR = 1.75, 95% CI = 1.16-2.64). In addition, comorbidities such as diabetes mellitus (HR = 1.77), low body mass index (HR = 0.92), and serum high-density lipoprotein cholesterol (10 mg/dL, HR = 0.86), were associated with higher incidence of events.

Conclusions: History of CHD at dialysis initiation was associated with a higher incidence of heart disease events and mortality and all-cause mortality.

SA-PO829

Trends and Outcomes of Surgical versus Transcatheter Aortic Valve Replacement in Patients on Maintenance Dialysis

Priti Poojary,1 Aparna Saha,1 Shanti N. Patel,2 Neha Debnath,1 Kinsuk Chauhan,1 Steven G. Coca,1 Giri N. Nadkarni,1 Lili Chan,1 Ichsan School of Medicine at Mount Sinai, New York, NY; 2Maimonides Medical Center, New York, NY.

Background: The prevalence of aortic stenosis in maintenance dialysis patients is high (28-55%). Dialysis patients generally have high operative risk for surgical aortic valve replacement (SAVR). While transcatheter aortic valve replacement (TAVR) in high-risk patients is associated with better survival in clinical trials, dialysis patients are generally excluded from these studies. We sought to assess outcomes and trends of SAVR vs. TAVR in dialysis patients from a nationally representative database.

Methods: Utilizing the National Inpatient Sample from 2008 – 2014, hospitalizations in dialysis patients for SAVR and TAVR were identified using ICD-9-CM codes. TAVR patients were propensity matched with SAVR patients on demographics, hospital type, primary payer type, income, and Charlson comorbidity index.

Results: The proportion of dialysis patients receiving SAVR procedures increased from 2008-2010 (annual percentage change(APC) of +2). The proportion of dialysis patients receiving TAVR has significantly increased over time (APC of 69) (Figure 1). Prior to propensity matching, patients in the TAVR group were older(75 vs. 63 years, P<0.001), more likely to be white(67% vs. 40%, P<0.001), and more likely to be female(48% vs. 31%, P<0.001). After matching, SAVR was associated with a longer length of stay (18 vs. 10 days, P<0.001) and higher cost (76,450 vs. 67,510, P=0.05). TAVR was associated with lower odds for in-hospital mortality OR 0.46 (95% CI 0.24-0.91).

Conclusions: TAVR in dialysis patients is increasing and is associated with lower in-hospital mortality. The decreasing trend in SAVR suggests that these patients are now getting TAVRs instead. Patients who are getting TAVRs have different demographics from those getting SAVR. Further investigation is needed to identify reasons for gender and racial differences and evaluation of long-term outcomes between SAVR and TAVR.

SA-PO830

Effect of Sodium Thiosulfate on Arterial Stiffness in ESRD Patients Undergoing Chronic Hemodialysis: A Randomized Controlled Trial

Donlalawat Saengpanit1, Monchol Siriburunwong2, Pawat Sussanitaphong1, Piaat Kataveerita3, Somchai Eiam-Ong4,1 Kriang Tungsangta,1 Visith Sitrirja,2 Kearsait Pradhiprinsila3,1 King Chulalongkorn Memorial Hospital, Thai Red Cross Society and Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; 2Lerdhis Hospital, Bangkok, Thailand; 3Queen Saovabha Memorial Institute, Bangkok, Thailand.

Background: End-stage renal disease (ESRD) patients undergoing chronic hemodialysis (HD) have an extremely poor cardiovascular outcome. Arterial stiffness (AS), a strong independent predictor of survival in HD patients, is related to vascular calcification (VC). Intravenous (IV) sodium thiosulfate (STS) can prevent VC in animal studies and delay progression of VC in HD patients, likely by catholic chelating and antioxidant properties. The effect of STS on AS has not been assessed in this patient population. This study is the first to evaluate the efficacy of STS on AS in HD patients.

Methods: We enrolled 50 HD patients with AS measured by Carotid-Akle Vascular Index (CAVI ≥ 8) into an open-label, randomized controlled trial. Patients were allotted to receive IV STS 12.5 gram during the last hour of HD twice weekly for 24 weeks (n=24) or usual care (control; n=26). CAVI, hemodynamics, and biochemical parameters were determined at baseline, 12 weeks and after 24 weeks. (Thai Clinical Trials Registry ID: 20160814001)

Results: All baseline parameters including CAVI (IV STS, 9.33 ± 0.87 vs. control, 9.34 ± 0.94) were comparable. Twenty-four weeks of twice weekly IV STS slightly lowered AS but insignificantly compared with the control group (mean difference of the change of CAVI between STS and control was -0.53; 95% CI -1.10, 0.02; P = 0.17). Significant improvement of AS was observed in those without diabetes mellitus (DM) (P<0.05). There were no significant changes in hemodynamic parameters in both groups. No significant changes in serum calcium, phosphate, calcium-phosphate product, intact parathyroid hormone, and 25-OH vitamin D levels at baseline and after 24 weeks were observed. High-sensitivity C-reactive protein was slightly but not significantly decreased in IV STS treated group than the control group. After STS treatment, anion gap significantly increased from baseline (P=0.05).

Conclusions: Intradialytic STS treatment has a trend toward improvement in AS measured by CAVI in HD patients. The subgroup results which demonstrated that ESRD patients without DM are affected differently by STS treatment are interesting and require further study for confirmation.

SA-PO831

The Effect of Far Infrared Therapy on Peripheral Artery Disease in Hemodialysis Patients

Chih-Ching Lin1,2 (Division of Nephrology, Department of Medicine, Taipei Veterans General Hospital, Taipei City, Taiwan; 1School of Medicine, National Yang Ming University, Taipei, Taiwan)

Background: In hemodialysis (HD) patients, peripheral artery disease (PAD) remains a critical cardiovascular complication which is usually diagnosed by ankle brachial index (ABI). Far infrared therapy improves access flow of vascular access but the effect on PAD in HD patients is still unknown.

Methods: We enrolled 198 maintenance HD patients in this study. PAD was defined as ABI ≥ 0.90. Only PAD patients received WSTY101 FIR emitter (Fireapy) for 40 minutes during each HD session, three times weekly for six months. The ABI was measured for bilateral lower extremities for 4 times [pre-dialytic timing (0 minute) and 40 minutes after the initiation of HD session at both day 0 and 4 months after the FIR therapy].

Results: Fifty-one out of 198 patients had PAD. In comparison with the period without FIR therapy in the 51 PAD patients, 6 months of FIR therapy significantly improved the ABI of right/ left side for 0 minute (from 0.77±0.19 to 0.81±0.20, P=0.027), 20 to 40 minutes (from 0.81±0.17 to 0.85±0.04), 40 minutes during HD (from 0.73±0.23 to 0.83±0.19, P<0.001)/ from 0.77±0.21 to 0.83±0.18, P<0.001) and incremental change between 0 and 40 minutes (from -0.04±0.14 to 0.02±0.13, P=0.007/ from -0.02±0.13 to 0.02±0.14, P=0.012) respectively.
SA-PO832

Effect of Physical Training on Echocardiographic Parameters during Hemodialysis: A Randomized Clinical Trial during Hemodialysis

Valeria Palma,

1Jonathan Chavez,

2Hospital Civil De Guadalajara, University of Guadalajara, Guadalajara, Mexico; 2Hospital Civil De Guadalajara, Guadalajara, Mexico; 2Hospital Civil De Guadalajara "Fray Antonio Alcalde"; Guadalajara, Mexico.

Background: On HD reduce their motor capacity over the time. It has been shown that physical training programs in HD are a safe intervention that positively impacts patients quality of life with positive effects on peak oxygen consumption, endothelial function and arterial stiffness index. Our objective was to evaluate the effect of a physical activity program with ergonomic bicycle during HD on the echocardiographic parameters of patients with conventional HD.

Methods: Randomized, controlled, unblinded clinical trial in prevalent HD patients, from September 2015 to May 2016, ≥18 years old. Patients with amputation of lower limbs, motor sequelae of cerebral vascular event and patients with vascular accesses in the lower extremities were excluded. Pre-dialysis biochemical test and echocardiographic parameters were taken at 0, 4 and 8 months. The intervention group included 14 pts who performed 135 min per week of moderate intensity exercise with ergonomic bicycle for a period of 35 weeks. SPSS software version 2.0 was used.

Results: 28 pts, average age 41 years, male (64%), HD vintage of 26 months. No difference was found in gender distribution, hereditary history, BMI, HbA1c, progression of CKD or hemodialysis time between the 2 groups. In the intervention group there was an increase in deceleration time with a baseline value of 157 ms to 220 ms at 8 months, with a statistically significant result which was not observed in the control group. In the control group, there was an increase in PSAP with an initial value of 35 mmHg which increased to 44.5 mmHg, with a statistically significant result. Comparisons of biochemical level did not show statistically significant changes between both groups at 8 months of follow-up.

Conclusions: HD pts with physical activity with an ergonomic bicycle for an 8-month period, compared against patients who did not perform physical activity, increased the deceleration time and did not increase PSAP. Intradialytic aerobic exercise is a feasible way to improve the myocardial function of HD pts, however, the design of new studies is required to further explore the impact of this intervention on other vascular function markers and to determine whether or not it reduces cardiovascular morbidity and mortality observed in patients with CKD.

SA-PO833

Dietary N-3 Polyunsaturated Fatty Acids (PUFA) Intake and Mortality in Adults on Hemodialysis: The DIET-HD Multinational Cohort Study

Valeria M. Saglimbene,1,4 Germaine Wong,1,3 Jonathan Craig,2 Jorgen B. Hegbrant,1 Giovannii F. Strippoli,5,6 Sydney School of Public Health, University of Sydney, Sydney, NSW, Australia; 1University of Sydney/Children’s Hospital, Sydney, NSW, Australia; 1Diaverum Medical-Scientific Office, Lund, Sweden; 2Diaverum Medical-Scientific Office, Lund, Sweden; 3Centre for Kidney Research, Children’s Hospital at Westmead, Sydney, NSW, Australia; 4University of Bari, Italy. Group/Team: For DIET-HD investigators.

Background: N-3 PUFA are protective factors for cardiovascular risk in the general population. However their role in hemodialysis patients, in whom the pathogenesis of cardiovascular disease is different, is uncertain.

Methods: The DIET-HD study is a prospective cohort study (January 2014-January 2016) in 9757 adults treated with hemodialysis in Europe and South America. The dietary N-3 PUFA intake was measured at baseline using the validated GA\LEN Food Frequency Questionnaire. Adjusted cox regression analyses clustered by country were conducted to evaluate the association between dietary N-3 PUFA intake and cardiovascular and all-cause mortality.

Results: During a median follow up of 1.5 years (8108 person-years), there were 1214 deaths of which 515 were attributable to cardiovascular causes. Compared to participants with the lowest dietary N-3 PUFA intake (<0.37 g/wk), the hazard ratios (95% confidence intervals) for cardiovascular mortality among patients in the middle (0.37 to <1.8 g/wk) and highest (≥1.8 g/wk) tertiles of N-3 PUFA were 0.80 (0.64 to 1.00) and 1.13 (0.88 to 1.45), respectively; the hazard ratios for all-cause mortality were 0.95 (0.82 to 1.09) and 1.08 (0.92 to 1.28), respectively. Only one third of the study population consumed sufficient N-3 PUFA (at least 1.75 g/wk) as recommended for primary cardiovascular prevention, and less than 10% as recommended for secondary prevention (7-14 g/wk).

Conclusions: Dietary N-3 PUFA intake was not associated with cardiovascular or all-cause mortality in patients on hemodialysis. The possibility that higher dose N-3 PUFA, reached from supplementation, might mitigate cardiovascular risk has not been excluded.

SA-PO834

Initiation of Hemodialysis Is Associated with Altered Protein Composition of High-Density Lipoprotein Ke Wang,2 Cassianne Robinson-Cohen,2 Andrew N. Hoofnagle,2 Bryan R. Kestenbaum,2 The HFM Study Group,1 1NIDDK, Bethesda, MD; 2University of Washington, Seattle, WA.

Background: High-density lipoprotein cholesterol (HDL-C) is composed of lipids and proteins that play important roles in cardiovascular disease development. The protein composition of HDL-C is altered in chronic dialysis patients compared to healthy controls. However, such differences confute potential effects of kidney disease with those of dialysis procedures. We compared HDL-C associated proteins in patients recently initiating hemodialysis to those of patients with advanced chronic kidney disease (CKD).

Methods: We used liquid chromatography-mass spectrometry to quantify 38 HDL-C proteins in participants from the Hemodialysis Fislata Maturation (HFM) Study. We used linear regression to compare differences in log-transformed HDL-C proteins between 110 CKD patients awaiting dialysis (mean estimated GFR 12.8 ml/min/1.73m2) to 143 patients who initiated dialysis within the previous year. We used a q-value false discovery rate threshold of ≤0.1 to select candidate proteins that differed by dialysis status. We adjusted for age, race, gender, diabetes, body mass, smoking, prior cardiovascular disease, and statin use.

Results: Eight HDL-C associated proteins met the specified false discovery rate threshold for statistical significance (Figure). After covariate adjustment, seven of these proteins remained statistically significant at the p<0.05 level with minimal changes in effect sizes.

Conclusions: HDL-C associated proteins in pathways of inflammation and thrombosis are higher among recent hemodialysis patients compared to those with late stage CKD. These findings suggest that the hemodialysis procedure itself may provoke adverse metabolic changes.

Funding: NIDDK Support

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

Dialysis: Epidemiology, Outcomes, Clinical Trials - Cardiovascular - II
Poster/Saturday
Health Literacy Improves Medication Adherence and Clinical Outcomes

**Table 1**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Poor (n=44,698)</th>
<th>N Poor (n=123,164)</th>
<th>2 poor (n=7)</th>
<th>≥3 poor (n=11)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence</td>
<td>54.6%</td>
<td>86.0%</td>
<td>5.7%</td>
<td>0.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Uncontrolled importance of BP control</td>
<td>46.0%</td>
<td>83.0%</td>
<td>8.1%</td>
<td>0.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Uncontrolled importance of Phosphorus control</td>
<td>29.0%</td>
<td>63.0%</td>
<td>0.0%</td>
<td>1.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP ≥90 mmHg pre-dialysis</td>
<td>63.1%</td>
<td>80.1%</td>
<td>1.4%</td>
<td>0.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Phosphorus level (mg/dL)</td>
<td>6.149.9</td>
<td>6.21.8</td>
<td>0.31</td>
<td>0.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Awareness of antihypertensive medications (%)</td>
<td>None</td>
<td>20</td>
<td>9</td>
<td>0.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Awareness of phosphorus-binding drugs (%)</td>
<td>None</td>
<td>56</td>
<td>9</td>
<td>0.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Awareness of optimizing dietary intake (%)</td>
<td>None</td>
<td>27</td>
<td>67</td>
<td>0.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Goal</td>
<td>Good</td>
<td>57</td>
<td>24</td>
<td>0.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;0.05 considered significant.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SA-PO838**

**Application of Extended Home Hemodialysis with the NxStage System One**

**Poster/Saturday**

**Background:** Extended hemodialysis, which is characterized by session duration beyond the usual interval of 3 to 5 hours, facilitates the removal of large fluid volumes at slow rates, likely resulting in fewer intradialytic hypertensive episodes and lower interdialytic blood pressure. There are few data about applications of extended hemodialysis with a low volume of dialysate per session. We used the telehealth platform to collect data about home hemodialysis (HHD) patients using the NxStage System One for extended hemodialysis.

**Methods:** We collected treatment factors and intermediate outcomes in HD patients using the NxStage System One in tandem with the Nx2me Connected Health platform. We analyzed digital flowsheets collected from US patients between November 2019 and March 31, 2020, and then included those patient-weeks with prescription of at least 3 sessions and receipt of at least 3 flowsheets with session duration ≥6 hours. We used descriptive analysis to summarize collected data.

**Results:** We identified 1932 patient-weeks of extended hemodialysis among 56 patients. Percentages of patient-weeks with 3.5, 4, and 5 prescribed sessions per week were 5%, 34%, and 65%, respectively. The mean number of delivered sessions per week was 4.22 (adherence, 90%). Mean session duration was 421 minutes, with 5% and 95th percentiles of 355 and 481 minutes, respectively; the mean number of cumulative treatment hours per week was 29.3. Sixty liters of dialysate were prescribed for 67% of sessions and the median blood flow rate was 300 mL/minute. Mean ultrafiltration rate was 212 mL/hour and had 5% and 95th percentiles of 0.6 and 3.9 L. In patient-weeks of extended hemodialysis, we identified 7429 digital flowsheets with complete data. Mean (standard deviation) ultrafiltration rate (UF) was 2.97 (1.37) mL/hour/kg. 99.9% of sessions had UFR < 10 mL/hour/kg. Before treatment, mean (SD) systolic blood pressure (SBP) was 127 (24) mmHg and mean (SD) diastolic blood pressure (DBP) was 72 (12) mmHg. After treatment, mean (SD) SBP was 122 (23) mmHg and mean (SD) DBP was 72 (12) mmHg. The percentages of sessions with predialysis and postdialysis blood pressure in KDOQI target ranges were 67% and 56%, respectively.

**Conclusions:** Extended HHD on the NxStage System One delivered almost 30 hours of treatment each week, partially due to excellent adherence. UFR was very low and BP control was generally very good.

**SA-PO839**

**Lymphopenia CD19+, a New Cardiovascular Risk Factor in Hemodialysis Patients**

**María Molina, Enrique Morales, Claudia Yuste, Manuel Praga. Nephrology Department, Hospital Universitario 12 de Octubre, Madrid, Spain.**

**Background:** Cardiac disease (CVD) is one of the most important causes of mortality in hemodialysis patients (HD). Traditional factors for CVD aren’t good predictors of events. On the other hand, trauma in HD induce have a proinflammatory environment that facilitate atheromatous lesions. Recently, the role of CD19+ lymphocytes in atheromatosis process has been described in non-uricemic patients. The role of CD19+ lymphocytes in CVD in HD patients is unknown.

**Aim:** To evaluate the role of lymphocytes CD19+ in cardiovascular deaths in HD patients.

**Methods:** A single centre prospective cohort study was started in 2011. We measured the lymphocytes CD19+ in 104 patients on HD and we followed them for 5 years. We defined myocardial infarction or coronary death or coronary transplantation or peripheral vascular disease as cardiovascular death in this study.

**Results:** We measured the lymphocytes CD19+ in 104 patients on HD and we followed them for 5 years. We defined myocardial infarction or coronary death or coronary transplantation or peripheral vascular disease as cardiovascular death in this study.

**Conclusions:** Extended HHD on the NxStage System One delivered almost 30 hours of treatment each week, partially due to excellent adherence. UFR was very low and BP control was generally very good.
SA-P0840
Aggravated Aging-Related Immune Changes Are Associated with Inflammation and Cardiovascular Diseases in ESRD Patients: Baseline Findings from the iESRD Study Kai-Hsiang Shiu,1 Yu-sen Peng,2 Yen-Ling Chiu,1,3 Far Eastern Memorial Hospital, Banciao, New Taipei City, Taiwan; 1Far Eastern Memorial hospital, Taipei, Taiwan; 3Division of Nephrology, Far Eastern Memorial Hospital, New Taipei City, Taiwan; 4Graduate Institute of Immunology, National Taiwan University, Taipei, Taiwan.

Background: Patients with end-stage renal disease (ESRD) exhibit accelerated aging of the immune system and increased risk for cardiovascular diseases, but the overall contribution of "immunosenescence" to cardiovascular disease is not clear.

Methods: We performed a comprehensive lymphocyte and monocyte immunophenotyping in 412 ESRD patients on maintenance hemodialysis and age-matched 47 healthy controls. Peripheral blood samples were sampled before both dialysis sessions and processed immediately for mononuclear cell isolation and staining. Using multicolor flow cytometry, lymphocytes were separated into subpopulations including naive T cells (CCR7+CD45RA+, TNaive), central memory (CCR7+CD45RA-, TEM), effector memory (CCR7-CD45RA+, TEM), terminally differentiated (CCR7-CD45RA-, TEMRA) and memory stem cells (naive cells with high CD28 andCD95, TSCM). Monocytes were separated into classical (CD14+CD16-), intermediate (CD14+CD16+) and non-classical monocytes (CD14+CD16+).

Results: Compared to healthy individuals, ESRD patients showed decreased levels of naive CD4+ and CD8+ T cells, increased levels of terminally differentiated TEMRA cells and intermediate monocytes (CD14+CD16+), and these changes not only significantly correlated with age but also enhanced by increasing dialysis vintage. Lymphocyte and monocyte aging also correlated with other established cardiovascular risk factors, including hemoglobin and high-sensitivity C-reactive protein. In multivariate-adjusted analysis, performed more studies about the role of CD19+ lymphocyte in CVD in uremic patients. The prognostic ability of obestatin is modified by age being very prominent in patients older than 71 years. In addition, we report on novel interactions between obestatin, inflammatory mediators and AG associated with mortality risk in the study population.

Conclusions: Low CD19+ lymphocyte could be a new cardiovascular risk factor as its level in isolation in HD patients might improve the immune system knowledge could decrease the CVD deaths of the HD patients. It is mandatory to perform more studies about the role of CD19+ lymphocyte in uremic patients.

SA-P0841
The Modification Effects of Age, Inflammation, and Acyl-Ghrelin on the Relationship between Obestatin Levels and Clinical Outcomes in Maintenance Hemodialysis Patients Ilia Beberashvili,1 Anna Katkov,1 Inna Sinuiani,1 Ada Azar,2 Gregory Shapiro,2 Leonid Feldman,3 Shai Efrati,2 Nephrology division, Assaf Harofeh Medical Center, Zerifin, Israel; 1None, Zerifin, Israel; 2Nephrology division, Assaf Harofeh Medical Center, Zerifin, Israel; 3Nephrology division, Assaf Harofeh Medical Center, Zerifin, Israel; 4Pathology division, Assaf Harofeh Medical Center, Zerifin, Israel; 5Nutrition department, Assaf Harofeh Medical Center, Zerifin, Israel.

Background: Obestatin, an anorexigen, was proposed as a physiological opponent of acyl-ghrelin (AG). While obestatin failed to reproduce the anorexigenic property in further studies, its potential marker of angiogenesis & endothelial repair might have a significant protective role. Further exploration into the pathophysiological effects of these pathways is required. 1

Methods: For each ng/ml increase in baseline obestatin level, in fully adjusted models and cardiovascular mortality (synergy index 4.81, p=0.02) emerged in multivariable analysis. Compared to low obestatin levels, which were associated with mortality risk. High AG and high obestatin interaction was negative (synergy index 0.76, p=0.03) in predicting lower risk for all-cause mortality and cardiovascular mortality (synergy index 0.80, p=0.008).

Results: The mean age was 64.8±15.5, 51% were male. Cardiovascular risk factors as arterial hypertension, diabetes mellitus and dyslipidemia were found in 76%, 29.8% and 51.9%, respectively. 62 (60%) patients had previous CVD: 28% (26) ischemic heart disease, 16% (15) hypertension, 14% (13) cardiomyopathy, 13% (12) cerebrovascular disease. The progression of CVD disease is not clear. The observation is modified by age being very prominent in patients older than 71 years. In addition, we report on novel interactions between obestatin, inflammatory mediators and AG associated with mortality risk in the study population.

Conclusions: The relations of CVD events to NLR or to neutrophil and lymphocyte counts were not significant. An interactions between high IL-6 (above median) and low obestatin (below median) levels were associated with increased risk for all-cause mortality (synergy index 1.5, p=0.001) and cardiovascular mortality (synergy index 4.81, p=0.02) emerged in multivariable analysis. Compared to low obestatin levels, which were associated with mortality risk. High AG and high obestatin interaction was negative (synergy index 0.76, p=0.03) in predicting lower risk for all-cause mortality and cardiovascular mortality (synergy index 0.80, p=0.008).
that an increased circulating number of monocytes might play a role in the development of atherosclerosis in chronic kidney disease patients, possibly through differentiation of monocytes into macrophages in plaques, or by other mechanisms.

Funding: Government Support - Non-U.S.

SA-PO844

Significant Association between Serum Magnesium and the Elevation of Troponin T in Maintenance Hemodialysis Patients

Jiro Yen-Ling,1,3 Kai-Hsiang Yang,1,3 Shigeichi Ishimura,1,3 Ken Nakatani,2, Akhiro Tsuda,3 Nobuyuki Kuwamura,2 Ryusuke Kakiya,1 Jiro Miyawaki,1 Senji Okuno,3 Tomoyuki Yamakawa,2 Shigeichi Shoji,3 Masaki Inaba.2 MeijiJiin Hospital, Osaka, Japan; 2Osaka City University Graduate School of Medicine, Osaka, Japan; 3Shirasagi Hospital, Osaka, Japan.

Background: Serum magnesium (Mg) levels is well known to be closely associated with cardiovascular disease in the general population. Troponin T has been reported to be a cardiac contractility modulating protein, and is measured as a biomarker for diagnosing myocardial injury. In hemodialysis patients, serum troponin T is elevated, and elevated serum troponin T has been reported to be a risk of death from all-cause mortality and cardiovascular disease. We hypothesized that serum Mg would be associated with the elevation of troponin T in hemodialysis patients.

Methods: A total of 432 stable maintenance hemodialysis patients were examined (age: 64.0±11.3 years, hemodialysis duration: 8.0±6.9 years, 63.7% men, and 37.5% diabetics). Troponin T was measured twice in one year interval. Patients were divided into two groups based on the elevation of serum troponin T (≤0.9 vs. >0.9 ng/mL in a year (241 patients of no elevation of serum troponin T in a year 98 patients of the group with its non-elevation (334 patients)).

Results: The group of elevation of serum troponin T showed significantly older age, compared to the group of no-elevation of serum troponin T (67± 10 vs. 63 ± 12 vs. years, p = 0.0009). Cardiac thoracic ratio (CTR) was significantly larger in the cardiovascular disease the latter (50.5 ± 4.7 vs. 49.3 ± 4.4 %, p = 0.0260). Body mass index or duration of hemodialysis did not significantly differ between the two groups. Serum magnesium concentrations were significantly lower in the group of elevation of serum troponin T in a year compared to group of no-elevation of serum troponin T in a year (2.6 ± 0.3 vs. 2.8 ± 0.4 mg/dL, p = 0.0015), although there were no significant differences in serum calcium, phosphate or intact PTH between the two groups. In a multivariable logistic analysis, serum Mg levels (OR = -0.394, 95% CI 0.177 to 0.877, p = 0.0224) were significantly and independently associated with the elevation of troponin T, in addition to other significant factors of age, hemodialysis duration, and smoking (R2=0.097, p < 0.0001), after adjustment of several clinical factors.

Conclusions: These results demonstrated that lower serum Mg concentration was significantly associated with the elevation of troponin T in hemodialysis patients, possibly suggesting that significant association of lower serum Mg and higher cardiac injury.

SA-PO845

Level of Anti-Cytomegalovirus Antibody Positively Correlates with Coronary Artery Disease and Cardiovascular Diseases in ESRD Patients

Feng-Jung Yang,1,3 Kai-Hsiang Shu,4 Yen-Ling Chiu,2,1 Graduate Institute of Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan; 2Far Eastern Memorial Hospital, Banciao, New Taipei City, Taiwan; 3Internal Medicine Department, National Taiwan University Hospital Yunlin Branch, Douliu, Taiwan; 4Internal Medicine Department, National Taiwan University Hospital, Taipei, Taiwan.

Background: Accumulating evidence indicates cytomegalovirus (CMV) infection is significantly associated with cardiovascular outcomes including all-cause and cardiovascular mortality in individuals with normal renal function. Patients with end-stage renal disease (ESRD) exhibit impaired immune function and may face higher risk of CMV-related adverse outcomes. Whether level of anti-CMV immune response may associate with cardiovascular mortality is unknown.

Methods: The immunity in ESRD study (iESRD) recruited 412 hemodialysis patients from both northern and southern Taiwan. By history taking and detailed chart reviews, baseline co-morbidities were recorded. Peripheral blood was sampled before hemodialysis session and processed immediately. Plasma levels of CMV-IgG and high-sensitivity C reactive protein were determined by ELISA. Peripheral blood monocyte and T cell differentiation subsets were determined by multicolor flow cytometry.

Results: Among these patients, 99% were CMV-seropositive. In the univariate analysis, log level of anti-CMV IgG was independently associated with the existence of coronary artery disease (OR=1.944, 95% CI 1.2–3.0, p=0.004) as well as cardiovascular diseases including stroke and peripheral arterial occlusive disease (OR=1.53, 95% CI 1.03–2.276, p=0.034). In a multivariable-adjusted logistic regression model, log level of anti-CMV IgG was independently associated with the existence of coronary artery disease (OR=1.53, 95% CI 1.2–1.9, p=0.019) as well as cardiovascular diseases including stroke and peripheral arterial occlusive disease (OR=3.98, 95% CI 1.5–10.8, p=0.007) after adjusting for age, gender, dialysis vintage, hemoglobin, DM, and hs-CRP. Level of anti-CMV IgG positively correlated with both percentage and absolute number of terminally differentiated CD8+CD57+CCR7- TEMRA cells, indicating the accumulation of these cells participate in the progression of atherosclerosis.

Conclusions: Anti-CMV humoral immune response positively correlates with the existence of coronary artery disease and cardiovascular diseases in ESRD patients. Role of anti-CMV humoral immune response should be further investigated in the pathogenesis of atherosclerosis in this patient population.

Funding: Government Support - Non-U.S.
SA-PO848

Differences between Home and In-Center BP Readings in Dialysis Patients

Dana Miskulin,1 Ambreen Gul,2 R. Schrader,2 Jennifer J. Gassman,2 Antonia Hartford,3 Philip Zager,2 Tufts Medical Center, Sommerville, MA; 2DCI, Albuquerque, NM; 1UNM, Albuquerque, NM; 4Cleveland Clinic, Cleveland, OH. Group/Team: For BID Study Investigators.

Background: Critics argue that ‘in-center’ pre-dialysis BP readings in hemodialysis patients are not reflective of ‘true BP’ because patients are at the extremes of fluid balance, are more anxious than usual and staff do not follow AHA guidelines for measurement. Few studies have compared home with in-center readings, and those that have, have been limited to 1-2 weeks of home readings. The BID was a pilot RCT in which 126 thrice weekly hemodialysis patients were randomized to 12 months of treatment to a pre-dialysis standardized dialysis unit (SDU) systolic blood pressure (BP) 110-140 or 155-165 mm Hg. Patients measured BP at home on the day following the mid-week treatment for one year.

Methods: The difference between the mid-week pre-dialysis SDU and home systolic BP the next morning was modeled using linear mixed regression with cubic splines.

Results: Systolic BP at home was a mean (SD) 6.1 (0.7) mm Hg lower than the pre-dialysis SDU (Figure 1) though, the range of the difference was wide and for 25% of the population, home was less than SDU by more than 15 mm Hg. The ‘within patient’ variability in systolic BP was slightly higher for home (16.9 mm Hg) as compared with pre-dialysis SDU (14.3) readings. Results were not different when SDU was compared with the average of the morning and evening home BPs.

Conclusions: The average difference between systolic BP taken pre-dialysis using a standardized protocol vs. at home of ~6 mm Hg is surprisingly consistent with the difference between office and home BP in the general population. However, for some patients, it is much larger, and the differences are likely to be even greater with routine (as opposed to standardized) in-center BP measurement. Obtaining home BP readings in dialysis patients may reduce ‘overtreating’ hypertension, which would be especially important in elderly patients and those prone to falls.

Funding: NIDDK Support, Other NIH Support - Dialysis Clinic Inc.

Difference between Home and Standardized Pre-Dialysis Systolic BP

SA-PO849

Effect of Spironolactone on Left Ventricular Mass in Hemodialysis Patients: The MiRENda Study – A Randomized Controlled Trial

Christoph Wanner,1,2 Uwe Malzahn,3 Julian Donnhauser,4 Christoph Betz,5 Clemens Grupp,6 Thomas Döltz,7 Nils Pollak,8 Sören Grebe,9 Esther Murilli,10 Severin Bausch,11 Tobias G. Hauser,12 Monika Mehling,13 Kirsten Hofmann,13 Christian O. Ritter,13 Vera Krane,13 Fabian Hammel,1,2 1University Hospital Würzburg, Würzburg, Germany; 2Department of Nephrology, Bamberg, Germany; 3Hospital of the university of Würzburg, Würzburg, Germany; 4KIH, Germany, Bamberg, Germany; 5University Hospital, Wuerzburg, Germany; 6University Hospital Wuerzburg, Wuerzburg, Germany; 7University Hospital Wuerzburg, Würzburg, Germany; 8University of Wuerzburg, Wuerzburg, Germany; 9University of Würzburg, Würzburg, Germany; 10University of Wuerzburg, Wuerzburg, Germany; 11University of Würzburg, Würzburg, Germany; 12Comprehensive Heart Failure Centre, University Würzburg, Würzburg, Germany; 13Medicine, University Hospital Frankfurt, Frankfurt, Germany.

Background: Hemodialysis (HD) patients are characterized by an extraordinary high cardiovascular (CV) morbidity and mortality but effective medical treatment is lacking. Left ventricular mass (LVM) constitutes an independent predictor of all-cause and CV mortality risk. We here evaluated the effect of spironolactone on LVM in HD patients.

Methods: We enrolled 118 HD patients of which 97 patients (female: 22.9%; mean age: 60.3±13.3 years; mean body mass index: 27.6±5.0 kg/m2; median duration of dialysis: 42.0 [16.6–76.0] months) were randomized 1:1 to spironolactone 50mg once daily (N=50) or placebo (N=47). The primary efficacy end point was the change in the LVM index as determined by cardiac magnetic resonance imaging before and at the end of the 40 week treatment period. Secondary outcomes included the effect on 24h ambulatory blood pressure and the development of severe hyperkalemia (potassium ≥6.5mmol/l).

Results: Treatment with spironolactone compared to placebo did not result in a significant change of the LVM index as determined by cardiac magnetic resonance imaging before and at the end of the 40 week treatment period. Secondary outcomes included the effect on 24h ambulatory blood pressure and the development of severe hyperkalemia (potassium ≥6.5mmol/l).

Conclusions: Treatment of HD patients with 50mg spironolactone had no effect on LVM or blood pressure and did not increase the risk of severe hyperkalemia.

Funding: Government Support - Non-U.S.
SA-PO850


Background: The ratio of extracellular (ECW) to total body water (TBW) is a widely accepted indicator of fluid status. However, ECW/TBW may differ between bioimpedance devices. We compared three commercially available bioimpedance devices in hemodialysis (HD) patients and healthy subjects (HS).

Methods: Ten patients (8 males, age 58±12 years) and 12 healthy subjects (7 females, age 33±5 years) were studied using two eight-point bioimpedance devices, InBody 770 (InBody USA, Cerritos, CA), Seca mBCA 514 (Seca North America, Cherokee, CA) and Hydra 4200 (Xitron Technologies, San Diego, CA). Measurements were performed pre and post HD in patients and once in HS. ECW, intracellular water (ICW), TBW, and ECW/TBW reported by the devices were compared between pre and post HD, and between patients and HS.

Results: ECW and ICW were significantly lower in InBody compared to Seca and Hydra (Table 1). Peridialytic changes of ECW (ΔECW), ICW (ΔICW), and TBW (ΔTBW) did not differ. Peridialytic weight loss (ΔWt; 2.58±0.51 kg) did not differ from ΔTBW reported by InBody and Hydra. ΔECW reported by InBody and Hydra was significantly lower than ΔWt. Seca measurements of ΔTBW was higher than ΔWt. In HD patients and HS, InBody measurements of ECW/TBW were lower compared to Seca and Hydra, respectively (Fig. 1). Pre and post HD ECW/TBW measured with InBody and Hydra did not differ (Fig. 2).

Conclusions: This pilot study indicates that ECW/TBW measurements differ between bioimpedance devices. InBody reports significantly lower ECW/TBW values compared to Seca and Hydra.

SA-PO851

Magnesium Prevents Vascular Calcification by Inhibition of Hydroxyapatite Crystal Formation Jeroen H. De Rauw, Anneke C. Ter braakse, Rene J. Bindels, Joost Hoenderop. Radboud University Medical Center, Nijmegen, Netherlands.

Background: Mg2+ has been shown to effectively prevent vascular calcification in multiple experimental calcification models. Vascular calcification is common in chronic kidney disease and contributes to increased mortality. Mg2+ has been hypothesized to prevent the upregulation of osteoblastic gene expression that drive calcification. However, extracellular effects of Mg2+ on Ca2+-Pi crystal formation have been largely neglected. This study aimed to investigate the effects of Mg2+ on both intracellular and extracellular changes associated with vascular calcification as well as effects on crystal formation in the extracellular space.

Methods: Bovine vascular smooth muscle cells (bVSMC) were calcified using β-glycerophosphate (BGP). Transdifferentiation was assessed by transcriptional analysis, cellular alkaline phosphatase (ALP) activity and development of apoptosis. X-ray powder diffraction, scanning electron microscopy and energy dispersive spectroscopy on crystals isolated from cell culture supernatants were used to map extracellular effects of Mg2+ on crystal formation and crystal composition.

Results: Mg2+ effectively prevented BGP-induced calcification in bVSMC. BGP did not cause changes in mRNA expression of the osteogenic genes BMP2, RUNX2 or ALP. Moreover, alkaline phosphatase activity was stable and apoptosis was only detected after calcification independent of Mg2+. In addition, blocking of the Mg2+ channel TRPM7 using 2-ABP did not abrogate the protective effects of Mg2+, indicating that intracellular Mg2+ is not involved in BGP-induced calcification of bVSMCs. Extracellular Mg2+ prevented the formation of hydroxyapatite crystals, which formed extensively after BGP treatment. Further analysis of the composition of the hydroxyapatite crystals showed that Mg2+ supplementation resulted in reduced Ca2+ and Pi fractions of 68% and 41%, respectively, without increasing the fraction of Mg2+.

Conclusions: This study demonstrates that Mg2+ inhibits vSMC mineralization through inhibition of Ca2+-apatite formation in the extracellular space, independent of VSMC transdifferentiation. These results emphasize the need for randomized-controlled clinical trials assessing the effects of Mg2+ supplementation on vascular calcification.

Funding: Government Support - Non-U.S.

SA-PO852

Bone Turnover in Patients with Calcific Uremic Arteriopathy Sagar U. Nigwekar, Jeffrey L. Hymes, Diane M. Rondeau, Franklin W. Maddux, Ravi I. Thadhani. 1Fresenius Medical Care, Waltham, MA; 2Massachusetts General Hospital, Boston, MA.

Background: Calcific uremic arteriolopathy (CUA) is an arteriolar calcification disorder with no effective treatment. Investigation of links between bone and vascular health in ESRD has largely focused on arterial calcifications; however the relationship between bone turnover and CUA is not well studied.

Methods: We examined the prevalence of bone turnover categories at hemodialysis (HD) initiation in patients who subsequently developed CUA. Bone turnover categories were defined by intact parathyroid hormone (iPTH) and alkaline phosphatase (ALK): high turnover if iPTH is >323 pg/mL and ALK >80 U/L; low turnover if iPTH is <103 pg/mL and ALK <25 U/L. We compared the prevalence of bone turnover categories between CUA patients and age, sex, and race matched controls. Univariate and multivariable logistic regression analyses were performed.

Results: We analyzed data from 1,030 CUA cases and 2,060 controls. High bone turnover at HD initiation was present in 8% of patients and low turnover in 9% of patients who subsequently developed CUA. Among controls, the prevalence of high bone turnover was 3% and of low turnover was 4%, both lower than in CUA patients (p<0.001). Both high and low bone turnover at HD initiation were associated with increased odds of subsequent CUA development in univariate and multivariable analyses adjusted for diabetes mellitus, obesity, and warfarin (figure).

Conclusions: The association between bone turnover at HD initiation and subsequent CUA development is U-shaped. Confirmation in future studies that apply bone biopsies will pave the way for targeted therapeutics to prevent/treat CUA (e.g. bisphosphonates, RANKL inhibitors for high turnover and teriparatide for low turnover).

Funding: Private Foundation Support
Vascular Calcification

The Specificity of Histologic Findings in Calciphylaxis

Background: The specificity of histologic findings in calciphylaxis (CUA), also known as calcific uremic arteriolopathy (CUA), usually depends on a skin biopsy but data on the specificity of histopathologic criteria are limited. To assess this, histology was compared in skin specimens and 55% of skin biopsies, but in 87% of skin biopsies from patients with a high clinical suspicion for CUA.

Methods: Skin biopsies in 38 patients with a clinical suspicion of CUA and 43 amputations in ESRD patients without CUA were assigned a low (16), moderate (6), or high (16) suspicion for CUA. With skin biopsies were performed a suspicion of CUA and in skin obtained from healthy margins of arteriolopathy (CUA), usually depends on a skin biopsy but data on the specificity of histopathologic criteria are limited. To assess this, histology was compared in skin specimens and 55% of skin biopsies, but in 87% of skin biopsies from patients with a high clinical suspicion for CUA. Comparison of amputations and high-suspicion skin biopsies is shown in the table. The combination of vessel calcification and thrombosis showed the greatest difference, being 6-fold more prevalent in high-suspicion skin biopsies. The combination of vessel calcification and intimal hyperplasia was not seen in any specimen. There were no significant differences between the findings in amputations and those in the skin biopsies from patients without a high clinical suspicion for CUA.

Results: Lesions in small arteries or arterioles were present in 35% of amputation specimens and 55% of skin biopsies, but in 87% of skin biopsies from patients with a high suspicion of CUA. Comparison of amputations and high-suspicion skin biopsies is shown in the table. The combination of vessel calcification and thrombosis showed the greatest difference, being 6-fold more prevalent in high-suspicion skin biopsies. The combination of vessel calcification and intimal hyperplasia was not seen in any specimen. There were no significant differences between the findings in amputations and those in the skin biopsies from patients without a high clinical suspicion for CUA.

Conclusions: Histopathologic findings historically associated with calciphylaxis also occur in viable tissue from unaffected ESRD patients. This calls into question the specificity of individual histologic findings for calciphylaxis. However, the combination of vessel calcification and thrombosis may provide more specificity.

Funding: Clinical Revenue Support

<table>
<thead>
<tr>
<th>Skin biopsies (%)</th>
<th>Amputations (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel calcification</td>
<td>63</td>
<td>73</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>47</td>
<td>14</td>
</tr>
<tr>
<td>Intimal hyperplasia</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Calcifications + intimal hyperplasia</td>
<td>73</td>
<td>5</td>
</tr>
<tr>
<td>Non-vessel calcif</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vessel + non-vessel calcif</td>
<td>13</td>
<td>9</td>
</tr>
</tbody>
</table>

SA-PO854

Protein Carbamylation Exacerbates Vascular Calcification

Daisuke Mori,1 Isao Matsui,2 Nobuhiro Hashimoto,1 Ayumi Matsumoto,1 Karim Shimada,1 Satoshi Yamaguchi,1 Tsutsumi Oka,1 Keiichi Kubota,1 Sayoko Yonemoto,1 Yusuke Sakaguchi,2 Takayuki Hamano,2 Yoshitaka Isaka.1 1Osaka University Graduate School of Medicine, Suita, Japan; 2Department of Comprehensive Kidney Disease Research, Osaka University Graduate School of Medicine, Osaka, Japan.

Background: Protein carbamylation is an irreversible posttranslational modification that can occur non-enzymatically in the presence of urea. Although carbamylation is recognized as a prognostic biomarker, the effects of protein carbamylation on organ dysfunction remain uncertain.

Methods: Using in vitro, ex vivo, and in vivo models, we investigated the effects of carbamylation on vascular calcification (VC), a life-threatening pathological condition that is common under carbamylation-prone situations.

Results: Protein carbamylation exacerbated the growth of human vascular smooth muscle cells (hVSMCs) by suppressing the expression of ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1), a key enzyme in the generation of pyrophosphate. By using immunoprecipitation in combination with mass spectrometry, we determined that several mitochondrial proteins, including ATP synthase subunits α and β, were carbamylated, although ENPP1 itself was not identified as a carbamylated protein. Rather, protein carbamylation reduced mitochondrial membrane potential and exaggerated mitochondria-derived oxidative stress, which downregulated ENPP1. The effects of carbamylation on ectopic calcification were abolished in mitochondrial-DNA-depleted hVSMCs and in hVSMCs treated with Mito-TEMPO, which indicated that mitochondria played essential roles in carbamylation-mediated effects. We also assessed the carbamylation effects by using ex vivo and in vivo models: Protein carbamylation suppressed enzymatic histochemical staining for cytochrome c oxidase and succinate dehydrogenase in rat aortae, exacerbated calcifying-medium-induced VC in aortic ring cultures, and exacerbated warfarin/vitamin-D-induced VC in rats.

Conclusions: Protein carbamylation exacerbates VC by exaggerating mitochondria-derived oxidative stress and the resultant suppression of ENPP1.

SA-PO855

Direct Inhibition of Phosphate-Induced Vascular Smooth Muscle Cell Calcification via Suppression of PiT2 Expression by 25-Hydroxyvitamin D

M Dasanori Tomokoto,2 Shunsuke Yamada,3 Kazuhiko Tsuruya,3 Takarani Kitzazono,1 Hiroaki Ooboshi.1 1Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; 2Department of Medicine, Fukuoka Dental College, Fukuoka, Japan; 3Department of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

Background: Inverse association between 25-hydroxyvitamin D (25(OH)D) level and cardiovascular (CV) risk has been reported. Recently, the low serum 25(OH)D levels, which are frequently recognized in chronic kidney disease, has been also connected with vascular calcification, but the mechanism remains fully unknown. In the present study, we examined whether 25(OH)D directly reduce phosphate (P)-induced vascular smooth muscle cell (VSMC) calcification and its mechanism.

Methods: Human VSMCs were cultured in high P media with the additional P load of 2.0 mM to induce calcification and treated with 25(OH)D of 10^{-10} ~ 10^{-6} M for a week. The degree of calcification and the expression of intrinsic calcification inhibitors and osteogenic differentiation markers were examined at Day 1 and 7. The degree of calcification was expressed as the calcium (Ca) content precipitated on the human VSMCs, and the content of calciprotein particle (CPP) was expressed as the Ca content in the precipitation of media, centrifuged by 16,000g for 2 hours at room temperature.

Results: Megalin and 1-hydroxylase were expressed in human VSMCs, and the PiT1 expression was not altered by administration of 25(OH)D, but the PiT2 expression was decreased with 25(OH)D of 10^{-10} ~ 10^{-6} M at Day 1 and 7 (p<0.01). The Ca contents at Day 7 were correlated with the PiT2 expression at Day 1 and 7 (r=0.01, r=0.66 and 0.57, respectively). Furthermore, the CPP content and the SOX9 expression were correlated with the PiT2 expression at Day 1 (r=0.01, r=0.55, and p<0.05, r=0.49, respectively). Our results indicate that 25(OH)D ameliorates P-induced calcification via the inhibition of PiT2 expression in human VSMCs.

Conclusions: Our results indicate that 25(OH)D ameliorates P-induced calcification via the inhibition of PiT2 expression in human VSMCs.

Funding: Government Support - Non-U.S.
the induction of different signaling pathways by recipient normal VSMC explains the different cell fate on calcification.

Methods: Cellular and Media derived MV from VSMC were examined for structure and content by transmission electron microscopy (TEM) and Western blots. Both types of MV were co-cultured with recipient VSMC and alteration of oxidative stress (ROS), intracellular calcium ([Ca^2+]i), and gene expression were determined by real-time PCR.

Results: TEM showed both types of MV are around 100 nm diameter membrane-bound vesicles of similar structure. By Western blot, both media and cellular MV contain the exosomal tetraspanins CD63 and CD81. Media MV contain significantly greater fetuin-A and lower annexins than cellular MV. The addition of media MV to recipient normal VSMC increased ROS production but had no effect on intracellular Ca^2+ ([Ca^2+]i). In contrast, the addition of cellular MV to normal VSMC had no effect on ROS but significantly increased [Ca^2+]i. Despite evidence that both are similarly endocytosed, both media and cellular MV increased gene expression of NOX1 but cellular MV also increased the expression of anti-oxidant superoxide dismutase-2 (SOD2) by 94% whereas media MV had no effect. Blockade of NOX1 activity with GKT137831 reduced media MV-induced ROS production by 25% in recipient VSMC and blocked cellular MV-induced calcification in recipient VSMC.

Conclusions: Cellular and media derived MV from CKD rats have different components and induce distinct cell signaling, gene expression and calcification in recipient normal VSMC. Cellular derived MV, as compared to media MV, do not induce ROS presumably due to a favorable oxidant/anti-oxidant ratio suggesting the ultimate cellular fate of the two MV types may be different.

Funding: Veterans Affairs Support

SA-PO857

CKD Patients with Calphalysiaxia and Sodium Thiosulfate Treatment: A Systematic Review and Meta-Analysis

Backgroud: Chronic kidney disease (CKD) patients with calcific uremic arteriolopathy (CUA, calphalysiaxia) are at high cardiovascular and mortality risks. Sodium thiosulfate (STS) is currently the most common treatment for CUA but the outcome is still unclear. Our objective is to systematically explore the outcome of CUA treatment with STS in CKD patients.

Methods: We searched MEDLINE, Scopus, and Cochrane Central Register of Controlled Trials from 1960 to April 2017 to identify case-control, cohort, and randomized controlled trials reporting the mortality rate and renal outcomes in CUA patients treated and fed the diets containing 2.5% oleic acid and 0.9% CaCl2. We included studies published in English language were included.

Results: From 1,071 articles searched, 24 cohort and case-control studies reporting mortality rate of CUA and STS were included into a systematic review. Ten of them were specified on STS treatment outcomes and had enough details for data analysis. No randomized controlled trials were found. There were total 284 patients receiving STS,27(12.2-32.7)% were male and 53.1(47.2-58.9)% had diabetes mellitus. The CUA lesions were mainly in the lower extremities (87.3±3.2%-96.5%). Mean accumulated STS dosages were 796±276 grams and mean duration of treatment were 8.0±2.2 weeks. After treatment with STS the wound completely resolved in 34.8 (22.6-46.55) and partially resolved in 35.5 (24.6-48.2)%. The overall mortality rate of CUA patients receiving STS was 57.8 (45.7-68.9%), as high as the pooled mortality rate from controlled trials reporting the mortality rate of CKD patients with CUA.

Conclusions: This is the first systematic review and meta-analysis of STS treatment in CUA patients. STS treatment with 796±276 grams for 8.0±2.2 weeks reduced the mortality rate from 57.8% to 34.8%. The outcome of CUA patients treated with STS is promising but more evidence is needed to confirm the results of this systematic review.

SA-PO858

Combined Therapy of Menagquinone-7 and Omega-3 Fatty Acid Prevents Progression of Aortic Calcification in Adenine and Low Protein Diet Induced Rat Model

Background: Vascular calcification is common and progressing in chronic kidney disease (CKD) patients. Diet with high dose menagquinone-7 (MK-7) (100 ug/kg diet) inhibited the development of cardiovascular calcification in 5/6 nephrectomy rat combined with high protein diet. Eicosapentaenoic acid (1g/kg/day), one of omega-3 fatty acid (FA), attenuates arterial medial calcification induced by warfarin. We evaluated the effect of omega-3 FA and MK-7 on aortic calcification in adenine and low protein diet induced vascular calcification rat model.

Methods: Male Sprague Dawley rats were fed the diets containing 0.75% adenine and 2.5% protein for 3 weeks. After 3 weeks, 4 rats were sacrificed for calcification evaluation of thoracic aorta. Thirty two rats were randomly divided into four groups, which were treated and received the diets containing 2.5% protein for 4 weeks: adenine control (0.9% saline), adenine control treated with omega-3 FA (300 mg/kg/day by gastric gavage), adenine control treated with MK-7 (50 ug/kg/day by gastric gavage), adenine control treated with omega-3 FA and MK-7. Control rats were fed the diets containing 2.5% protein for 7 weeks. For quantitative assessment of aortic calcification, von Kossa stain of aorta was done and calcium contents were measured with calcium colorimetric kit.

Results: Serum creatinine of adenine control group treated with omega-3 FA and MK-7 was lower than adenine control group without treatment. Serum calcium and BUN levels were not significantly different between adenine control group with treatment and without treatment. Two rats among 4 rats showed aortic calcification at 3 weeks. After 4 weeks, aortic calcification was progressed in adenine control group without treatment on von Kossa stain and calcium contents were the least progressed in adenine control group treated with combination of omega-3 FA and MK-7 compared to ovalbumin 3 FA or MK-7 single therapy.

Conclusions: Combined treatment with omega-3 FA and MK-7 definitely prevents progression of aortic calcification compared to rat without treatment in adenine and low protein diet induced vascular calcification rat model.

SA-PO859

Nrf-2 Attenuates Vascular Calcification in CKD-MBD by Suppression of Oxidative Stress

Background: Under pathological conditions in vascular calcification, uncontrolled production of ROS induced increased oxidative activities and impaired cellular antioxidant systems. NF-E2 p45-related factor-2 (Nrf-2) is a powerful factor to regulate oxidative stress. In our study, we aimed to elucidate the role and mechanism of Nrf-2 on vascular calcification in ESRD involving oxidative stress.

Methods: We selected 36 patients admitted at the Department of Nephrology in St. Vincent's Hospital between 2011 and 2012. 14 cases of age and sex matched biopsy-proven non-calcification were selected as negative control and 7 healthy volunteers as normal control. To mimick vascular calcification in ESRD, we used β-glycerophosphate to stimulate the rat vascular smooth muscle cells (RSMCs). 24 rats were randomly assigned to 4 groups: normal control group, vascular calcification group, vascular calcification group with DMF treatment group and DMF treated adenine control group. The rats were sacrificed 3 weeks later. The vascular calcification was induced by injection of Vitamin D3 and gavage nicotine.

Results: The blood phosphorus and iPTH in ESRD patients with vascular calcification was significantly increased. Nrf-2 expression was negatively correlated with vascular calcification in ESRD patients indicating by Alizarin-red S staining and immunohistological staining. To further elucidate the role of Nrf-2 in vascular calcification in CKD-MBD, we had knockdown or pharmacological blocked Nrf-2 in rat aortic smooth cells (RASMCs) followed by hyperphosphate treatment. Then we observed that knockdown or pharmacological blockade Nrf-2 could induce vascular calcification in CKD-MBD. Nrf-2 agonist treatment showed that activation Nrf-2 could ameliorate vascular calcification in RASMCs. Then ROS inhibitor NAC pretreatment increased the level of Nrf-2 and ameliorated vascular calcification in RASMCs. Activation of Nrf-2 inhibited oxidative stress and attenuated mitochondrial injury in RASMCs upon vascular calcification. Pathological examination revelead that Nrf-2 agonist could suppress vascular calcification in rat CKD aortas. Immunohistological staining about Nrf-2 expression in rat aorta were increased with DMF treatment group and DMF treated control group. The rats treated with omega-3 FA and MK-7 definitely prevents progression of aortic calcification compared to rat without treatment in adenine and low protein diet induced vascular calcification rat model.

Conclusions: This is the first systematic review and meta-analysis of STS treatment in CUA patients. STS treatment with 796±276 grams for 8.0±2.2 weeks reduced the mortality rate from 57.8% to 34.8%. The outcome of CUA patients treated with STS is promising but more evidence is needed to confirm the results of this systematic review.
SA-PO860

BMP7 Ameliorates Procalcific Gene Expression Patterns in the Calcified Uremic Aorta

Background: Hyperphosphatemia and vascular calcification (VC) are frequent complications of chronic renal failure (CRF). BMP7 has been shown to protect against development of VC in uremia. Thus the potential reversibility of established VC was examined in two experimental models; 1: by studying if BMP7 treatment could reduce the degree of VC in uremia and 2: by isogenic transplantation (ATx) of the calcified aorta from uremic rats to healthy littermates.

Methods: CRF and VC was induced in adult DA rats by 5/6 nephrectomy, high phosphate (P) diet and alfacalcidol treatment. After 14 wks, severe VC was present. In model 1, CRF rats were allocated either to 250 μg/kg of BMP7 ip once weekly or vehicle for 8 wks. In model 2, the abdominal aorta was transplanted orthotopically from CRF rats to healthy litters. Ctrl group had normal to normal ATx. Rats were sacrificed 4 wks after ATx.

Results: BMP7 treatment resulted in a significant reduction of plasma P from 2.06 ± 0.14 to 1.56 ± 0.07 mmol/L, p < 0.01, despite persistent uremia. Uremia induced increases in fibronectin 1.15 ± 0.11, peroxisin 1.31 ± 0.14 and activin-A 1.34 ± 0.06, and BMP7 treatment resulted in a significant decrease; Fni 0.82 ± 0.09, Postn 0.91 ± 0.09, Inhiba 0.97 ± 0.11, p < 0.05. In the BMP7 study Ca content was significantly increased in the uremic vehicle treated rats both in the distal abdominal aorta (1.96 ± 0.20 mg/g and in the proximal thoracic aorta 71 ± 15 mg/g), and similar levels were seen in the BMP7 treated rats; 2.2 ± 0.20 mg/g in the distal abdominal aorta and 54 ± 7 mg/g in the proximal thoracic aorta. In the ATx study Ca content of the aorta from uremic rats was significantly elevated to 17.0 ± 0.20 mg/g in the proximal abdominal aorta and similarly increased in the transplanted uremic aorta 15.9 ± 0.6 mg/g, confirming that established uremic VC is not reversible despite removal of the uremic milieu.

Conclusions: BMP7 treatment resulted in a significant decrease in the expression of procalcific genes and a significant decrease in plasma P. Despite these favorable changes no effect on aortic Ca content was seen. These results were confirmed in the ATx study where complete reversal of the uremic milieu neither reversed established uremic VC.

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

SA-PO861

Maintenance of Vascular Microna-145 Levels Effectively Attenuates Uremia- and High Phosphate-Induced Aortic Calcification

Aria Panizo, Natalia Carrillo-Lopez, Anabel Castro, Abigail Ramirez, Orlando Amenábar, Rafael Naves.

Background: Microna-145 is known to promote vascular calcification. We investigated the expression of microna-145 in normocalcemic rats and in uremic rats with high phosphate diets.

Methods: CA were treated with P (3 g/kg) or V vehicle for 10 weeks. Normal CA were obtained from control rats, and CRF CA were obtained from nephrectomized rats. The aorta was separated into proximal thoracic and abdominal segments, and gene expression was measured by qPCR.

Results: Microna-145 expression was significantly decreased in the proximal thoracic aorta of CRF rats compared to normal controls. In the abdominal aorta, a similar trend was observed.

Conclusions: Microna-145 is a potential target for the prevention of vascular calcification in uremic rats.

Funding: Government Support - Non-U.S.
SA-PO864

Do Hemodialysis and Peritoneal Dialysis Differ Regarding Their Effect on Coronary Calcification? Thijis T. Jansz,1 Franka Van reekum,2 Akin Ozylmaz,1,2 Marianne C. Verhaar,3,4 Brigit C. van Jaarsveld,14 'University Medical Center Groningen, Groningen, Netherlands; 2University Medical Center Utrecht, Amsterdam, Netherlands; 3VU medical center, Amsterdam, Netherlands; 4Department of Nephrology, Amsterdam, Netherlands; 5Diagrapy Dialysis Center, Amsterdam, Netherlands; 6Dialysis Center Groningen, Groningen, Netherlands. Group/Team: NOCTx investigators.

Background: Identifying modifiable risk factors of vascular calcification in endstage renal disease is crucial in light of the associated high cardiovascular morbidity and mortality. In this cross-sectional study, we compared coronary artery calcification and levels of biomarkers associated with vascular calcification in pts treated with hemodialysis and peritoneal dialysis (PD). Methods: We assessed coronary artery calcification using multi-sliced computed tomography in 121 pts treated with HD (± 16 hr/wk) and 46 pts treated with PD, who were included in the NOCTx study (NCT00950573). Biomarker measurements were performed in a subset of 25 HD and 33 PD pts using enzyme-linked immunosorbent-assay and multiplex assays. We adjusted for age, sex, dialysis vintage, diabetes mellitus, use of vitamin K antagonists, smoking and residual diuresis in multivariate analyses. Results: Pts treated with HD were somewhat older (53.1 ± 12.2 years versus 49.8 ± 15.1 years) and had been on dialysis longer (26.1 ± 12.7 years versus 14.1 ± 3.3 years, p < 0.01). In univariate and multivariate analyses, coronary artery calcification in HD pts (median score 208, IQR 1 – 899) was not significantly different from PD pts (median score 84, IQR 0 – 1066). In HD pts, phosphate levels tended to be higher compared with PD pts (1.7 mg/dL versus 1.59 ± 0.35 mmol/L). Osteoprotegerin was evidently lower in HD pts (2.95 ± 1.33 versus 3.43 ± 1.81 µg/L, p < 0.01), while inactive matrix Gla protein (dp-ucMGP) levels did not differ significantly between HD and PD pts. Only dp-ucMGP was independently associated with extent of coronary artery calcification. Inflammatory markers C-reactive protein, interleukin-1β and interleukin-6 did not differ significantly between HD and PD pts. Probably due to intermittent fluid overload in HD, NT-proBNP was significantly higher in HD pts (2217 ± 1817 versus 1045 ± 1372 pmol/L, p = 0.01). Conclusions: Uremia per se is detrimental for the coronary vasculature, seemingly irrespectively of treatment with HD or PD. Whether coronary artery calcification and its progression are affected by other renal replacement therapies needs further evaluation.

Funding: Commercial Support - The NOCTx study is performed with minor grants from: Baxter Nederland BV; Roche Nederland BV; Amgen Nederland BV; Fresenius Medical Care Nederland; Shire Pharmaceuticals Benelux; Novartis BV; and the “Wellerdieck-de Goede” Foundation with mediation of Stichting vrienden UMC Utrecht., Private Foundation Support

SA-PO865

Iron Stimulation Enhanced Calcification Along with TNF-Alpha in Human Vascular Smooth Muscle Cells Yasuyuki Nagasawa,1,2 Sayuri Kawada,1,3 Mutuki Kawabe,1,4 Aritoshi Kida,5 Yasuyoshi Nanami,5 Takahiro Kuragano,4,5 Yukiko Hasuike,6 Keiji Nakasho,7 Hiromitsu Kishimoto,8 Takeshi Nakashima,9 Hyogo College of Medicine, Nishinomiya, Japan; 2Division of Nephrology, Care Nederland, Shire Pharmaceuticals Benelux, Novartis BV; and the “Wellerdieck-de Goede” Foundation with mediation of Stichting vrienden UMC Utrecht., Private Foundation Support

Iron in vascular smooth muscle cells was shown to be involved in differentiation and growth of muscle cells. We investigated the mechanisms of vascular smooth muscle cell growth and calcification in iron overload in vitro and in vivo. Methods: Human umbilical endothelial cells (HUVEC) and aortic rings from normal and 5/6 nephrectomized uremic rats were used. Miners. Results: Iron increased the expression of the marker of vascular smooth muscle cells, such as smooth muscle actin (αSMA) and smooth muscle cell marker (SMC), in aortic media (aortic segments). Iron also increased the calcification of the aortic rings in normal rats but not in uremic rats. Conclusions: Iron is associated with vascular smooth muscle cell growth and calcification, which may be mediated by the activation of transcription factors and the down-regulation of matrix metalloproteinases. Funding: Private Foundation Support, Clinical Revenue Support

SA-PO866

Relationship between Bone Sialoprotein and Vascular Calcification in Maintenance Hemodialysis Patients Hongwei Wu, Fanna Liu. The First Affiliated Hospital of Jinan University, Guangzhou, China.

Background: Recent studies showed that vascular calcification was a osteoblast-like process involving multiple factors. Bone sialoprotein, a recently discovered protein, participated in the metabolism of bone-vascular axis and expressed in the medial layer of calcified vessel in uremia patients. The mechanism of vascular calcification that influenced by bone sialoprotein was not clear. This study was to evaluate the potential association of bone sialoprotein with the development of adventital aortic calcification (AAC) in maintenance hemodialysis (MHD) patients. Methods: Seventy-five patients who were on HD between May 2016 and May 2017 in the dialysis center were enrolled. Serum bone sialoprotein was tested. AAC was measured by abdominal lateral plain. Kaupplia score was used to assess the degree of CAF. Referring to CORD segmentation method, patients was divided into three groups: no or mild calcification group, moderate calcification group and severe group. Logistic regression analysis was used to determine the risk factor of AAC in MHD patients. The diagnostic value of serum bone sialoprotein for AAC was assessed using receiver operator characteristic curve (ROC).

Results: The AAC (AAC≥4) was present in 49.3% (37/75) patients, the median AAC score was 4.0 (24). The median of serum bone sialoprotein was 20.12 (18.63,24.21) ng/mL. The serum bone sialoprotein levels were significantly elevated in moderate calcification group and severe group compared to no or mild calcification group (22.43 (19.58,26.84) ng/L and 21.199 (18.87,26.18) vs 19.16 (17.23,32.3) ng/L, P<0.05). Multivariate logistic regression analysis showed that serum bone sialoprotein level was independent risk factor for AAC (OR=1.175,95%CI 1.004~1.375, P<0.05). The area under the ROC curve for serum sclerostin for AAC was 0.718 (95%CI 0.604~0.833,P<0.001), sensitivity was 0.711, and specificity was 0.595 for a cutoff value of 21.51 ng/mL.

Conclusions: Serum bone sialoprotein level is associated with AAC. Serum bone sialoprotein level may have a diagnostic value for AAC in MHD patients.

Funding: Private Foundation Support, Clinical Revenue Support

SA-PO887

Endothelial Hyperpermeability Induced by Mineral Stress Is Influenced by Vascular Calcium Yasuto Shikida,1 Masahide Mizobuchi,1 Hiroaki Ogata,2 Fumihiko Koivu,3 Takanoori Shibata,4 1Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan; 2Department of Internal Medicine, Showa University Northern Yokohama Hospital, Yokohama, Japan; 3Division of Nephrology, Department of Medicine, Showa University Fujioka Hospital, Yokohama, Japan.

Background: Uremia per se is detrimental for the coronary vasculature, seemingly irrespective of treatment with HD or PD. Whether coronary artery calcification and its progression are affected by other renal replacement therapies needs further elucidation. Methods: We assessed coronary artery calcification using multi-slice computed tomography in 121 pts treated with HD (± 16 hr/wk) and 46 pts treated with PD, who were included in the NOCTx study (NCT00950573). Biomarker measurements were performed in a subset of 25 HD and 33 PD pts using enzyme-linked immunosorbent-assay and multiplex assays. We adjusted for age, sex, dialysis vintage, diabetes mellitus, use of vitamin K antagonists, smoking and residual diuresis in multivariate analyses. Results: Pts treated with HD were somewhat older (53.1 ± 12.2 years versus 49.8 ± 15.1 years) and had been on dialysis longer (26.1 ± 12.7 years versus 14.1 ± 3.3 years, p < 0.01). In univariate and multivariate analyses, coronary artery calcification in HD pts (median score 208, IQR 1 – 899) was not significantly different from PD pts (median score 84, IQR 0 – 1066). In HD pts, phosphate levels tended to be higher compared with PD pts (1.7 mg/dL versus 1.59 ± 0.35 mmol/L). Osteoprotegerin was evidently lower in HD pts (2.95 ± 1.33 versus 3.43 ± 1.81 µg/L, p < 0.01), while inactive matrix Gla protein (dp-ucMGP) levels did not differ significantly between HD and PD pts. Only dp-ucMGP was independently associated with extent of coronary artery calcification. Inflammatory markers C-reactive protein, interleukin-1β and interleukin-6 did not differ significantly between HD and PD pts. Probably due to intermittent fluid overload in HD, NT-proBNP was significantly higher in HD pts (2217 ± 1817 versus 1045 ± 1372 pmol/L, p = 0.01). Conclusions: Uremia per se is detrimental for the coronary vasculature, seemingly irrespective of treatment with HD or PD. Whether coronary artery calcification and its progression are affected by other renal replacement therapies needs further evaluation.

Funding: Commercial Support - The NOCTx study is performed with minor grants from: Baxter Nederland BV; Roche Nederland BV; Amgen Nederland BV; Fresenius Medical Care Nederland; Shire Pharmaceuticals Benelux, Novartis BV; and the “Wellerdieck-de Goede” Foundation with mediation of Stichting vrienden UMC Utrecht., Private Foundation Support

Iron Stimulation Enhanced Calcification Along with TNF-Alpha in Human Vascular Smooth Muscle Cells Yasuyuki Nagasawa,1,2 Sayuri Kawada,1,3 Mutuki Kawabe,1,4 Aritoshi Kida,5 Yasuyoshi Nanami,5 Takahiro Kuragano,4,5 Yukiko Hasuike,6 Keiji Nakasho,7 Hiromitsu Kishimoto,8 Takeshi Nakashima,9 Hyogo College of Medicine, Nishinomiya, Japan; 2Division of Nephrology, Care Nederland, Shire Pharmaceuticals Benelux, Novartis BV; and the “Wellerdieck-de Goede” Foundation with mediation of Stichting vrienden UMC Utrecht., Private Foundation Support
Vascular Calcification

SA-PO868

Vitamin K and Vascular Health: A Systematic Review and Meta-Analysis
Jennifer S. Lee,1,3* Fiona A. Chapman,1 Patrick B. Mark,2,3* NHS Greater Glasgow and Clyde, Glasgow, United Kingdom; 1University of Glasgow, Glasgow, United Kingdom

Background: Vitamin K deficiency is prevalent among patients with chronic kidney disease. Matrix Gla protein, an important regulator of vascular calcification, is dependent on adequate vitamin K intake. We conducted a systematic review and meta-analysis of effect of vitamin K supplementation on vascular health, and assessed evidence that level of desphospho-uncarboxylated Matrix Gla protein (dpucMGP) is associated with incident cardiovascular disease (CVD) or mortality.

Methods: Two authors searched Medline, Embase, Cochrane and Google for: i) adult studies of vitamin K supplementation versus control which measured effect on vascular calcification, vascular stiffness or dpucMGP; and ii) prospective observational studies assessing effect of baseline dpucMGP on incident CVD or mortality. Random effects meta-analysis was conducted using meta and metafor packages for R statistical software package. Egger regression and Trim and Fill were used to assess for publication bias.

Results: Electronic searching identified i) 5095 and ii) 1850 references of which i) 8 and ii) 12 met our pre-specified inclusion criteria. In groups treated with vitamin K, there was a meaningful change in vascular calcification (see Figure, p=0.038) and dpucMGP (n=6, -235.5 ±292.1, -178.8 ±p<0.001), and a trend towards improvement in vascular stiffness (n=3, -3.70 ±7.77, 0.37 %, p=0.075). Over a median follow up period of 7.8 years (IQR 4.9-11.3), stepwise increase in dpucMGP was not associated with fatal or non-fatal CVD (log HR 0.06 ±0.1; 0.23, p=0.48) or mortality (log HR 0.02 ±0.11; 0.16, p=0.74). Egger regression and Trim and Fill analyses suggest a degree of publication bias in favour of positive results.

Conclusions: Vitamin K supplementation significantly reduces dpucMGP level, though dpucMGP is not associated with incident CVD or mortality. Supplementation appears to reduce progression of vascular calcification, with a trend towards improvement in vascular stiffness, though there are limited data available. Further clinical trials of the effect of vitamin K supplementation on vascular health are warranted.

SA-PO869

Mortality Prediction of Abdominal Aortic and Pelvic Calcification on Plain X-Ray in CKD, Hemodialysis, and Kidney Transplant Patients
Since Dishabanchong, Division of Nephrology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Background: Vascular calcification (VC) is highly prevalent in CKD and predicts poor outcomes. Both cardiovascular and CKD related risk factors participate in the development of VC. The gold standard for evaluation of VC is computed tomography but plain x-rays offer a less costly and less radiation exposure alternative. Lateral abdominal and pelvic x-rays have been utilized to evaluate the calcification of abdominal aorta, iliac and femoral arteries which was found to be highly correlated with abdominal aortic calcification (AAC) and CAC obtained by CT. The data regarding the predictability of AAC and pelvic arterial calcification (PAC) on patient outcomes are limited.

Methods: Four hundred and nineteen CKD stages 2-5 (CKD 2-5), maintenance HD (HD) and long-term KT (KT) patients were included. Only KT recipients who underwent transplantation for at least 1 year were enrolled in order to allow the time for stabilization of mineral metabolism. AAC score as described by Kauppila et al and PAC score as described by Adraga et al were applied to determine the severity of AAC and PAC on lateral abdominal and pelvic x-rays respectively. The median follow-up time was 62.7 months for CKD 2-5, 52 months for HD and 62.5 months for KT.

Results: AAC and PAC scores correlated well with the correlation coefficients (r) >0.4 in all 3 populations (p<0.001). Patients with AAC score >6 or PAC score >1 were older, had higher prevalence of DM, serum PO, and PTH but lower serum calcium and eGFR. Increased KT duration was associated with a more severe degree of AAC, whereas prolonged dialysis vintage was associated with a more severe degree of PAC. Kaplan-meier survival curves revealed AAC score >6 as a significant predictor for all-cause mortality in CKD 2-5 but not in HD or KT, whereas PAC score >1 was a significant predictor of mortality in all 3 populations. After an adjustment for age, the predictability of AAC in CKD 2-5 was lost, whereas PAC >1 remained an independent predictor of mortality in all 3 populations. Further adjustments for age, sex, BMI, serum albumin, calcium and PO4 revealed the predictability of PAC for mortality in CKD 2-5 patients and KT recipients but not in HD patients.

Conclusions: PAC was a better predictor of mortality than AAC in all 3 populations of CKD and should be considered in the evaluation of VC in CKD and KT patients.
Nephrology, Affiliated Drum Tower Hospital, Medical School of Nanjing University, China; 2Department of Nephrology, University of Oxford, United Kingdom; 3University College London, London, United Kingdom

Vascular Calcification

SA-PO873

Premature Vascular Smooth Muscle Cell Ageing Drives Inflammation and Calcification in Children on Dialysis: Catherine Liu1,2, Shanna E. Sanchis1,2, Sanchi H. Shroff3

Background: Children on dialysis have a cardiovascular mortality risk equivalent to the very elderly in the general population. Medial vascular calcification, an age-associated pathology, is prevalent in these children where we investigated whether premature vascular smooth muscle cell (VSMC) ageing might play a role in driving calcification.

Methods: Vessels from children with CKD and controls were harvested at time of surgery and subjected to histological analysis for parameters of ageing. VSMCs grown from these vessels were also phenotyped for calcification propensity and ageing markers including growth capacity, DNA damage, senescence and inflammation. Children with CKD with VSMC uptake and loss of vascular progeny including pulse wave velocity and spiral CT and these measures were correlated with serum markers of inflammation.

Results: Vessels from children on dialysis showed oxidative DNA damage as well as increased expression of the senescence markers p16 and p21. In vitro VSMCs from dialysis patients showed elevated levels of DNA damage, grew poorly and senesced early compared with control VSMCs. DNA damage correlated with increased expression of the osteogenic markers Runx2 and BMP2, and increased calcification in response to elevated levels of calcium (Ca) and phosphate (P). Ca and P treatment induced oxidative DNA damage in CKD vessel rings ex vivo, and accelerated VSMC senescence in vitro. Cytokine array analysis showed that VSMCs from CKD patients displayed a proinflammatory, pro-senescent, senescence associated secretory phenotype (SASP) in vitro, and blockade of ATM-mediated DNA damage signalling reduced senescence. Clinically, children on dialysis showed elevated circulating levels of SASP factors including BMP2, OPN and IL6 and these correlated with increased vascular stiffening and calciﬁcation in vivo.

Conclusions: Taken together, these data suggest that dysregulated mineral metabolism accelerates VSMC ageing by inducing oxidative DNA damage and premature senescence. In turn, the paracrine SASP promotes osteogenic differentiation, vascular calcification and systemic inflammation suggesting drugs that target DNA damage signalling or senolytics may be therapeutic agents for vascular calcification.

Funding: Private Foundation Support

SA-PO874

Loss of Secreted Frizzled-Related Protein 5 Contributes to Vascular Calcification in CKD by Activating Non-Canonical WNT Pathway: Yon Joon Chung1,2, Jae Hyun Chung3, Hyun Hee Lee3, Wookyung Chung4, Gachon University Gil Medical Center, Incheon, Republic of Korea

Background: Vascular calcification (VC) is frequently accompanied with bone loss in patients with chronic kidney disease (CKD). Wnt regulates osteoblast activation through canonical (β-catenin dependent) and non-canonical (-independent) signaling pathways. The common pathway between the pathways during VC and bone loss is still remains a conundrum. Therefore, we hypothesized that VC results from phenotypic conversion of vascular smooth muscle cell (VSMC) into an osteoblast-like cell involving induction of an osteoblast transcriptional program via a non-canonical WNT pathway, while bone loss is mainly regulated by canonical WNT pathway.

Methods: Adenine-induced CKD animal model with VC was induced in male Sprague Dawley rats fed 0.75% adenine (2.5% protein, 0.92% phosphate) and intraperitoneal calcitriol (0.08 μg/kg/day) injection for 4 weeks. In an angiotensin II (3μg)-induced VC in high phosphate milieu (3mM) through its effect on VSMC, the effect of WNT signaling on VC was determined by expression of osteoblastic transcriptional factor (RUNX2), Von Kossa stain and WNT downstream signaling factors.

Results: In mRNA profiler PCR assay of WNT signaling pathway from animal model, secreted frizzled-related protein 4 (sFRP4) were increased, while sFRP5 was decreased than those of control group fed with normal rat chow (0.62% phosphate). From the in vitro study, the protective effect of sFRP5 on VSMC differentiation was mediated through the inhibition of Rho/ROCK and JNK pathways. Moreover, the effect of Rho/ROCK and JNK pathways on sFRP5 repression through VSMC differentiation were aggravated by anisomycin (JNK activator), whereas recovered with SP600125 (JNK inhibitor). Those expressions of RUNX2 and WNT signaling factors in adenine-induced CKD animal model with VC showed in the similar patterns.

Conclusions: Our study suggests that loss of sFRP5 was associated with VC in CKD environment by activating non-canonical WNT pathway, which indicate that sFRP5 may be a new therapeutic target in VC in CKD environment.

Funding: Private Foundation Support

SA-PO875

Association between Circulating Osteogenic Precursors and Vascular Calcification in CKD Patients: Jamesong Chung1,2, Jae Hyun Chung3, Hyun Hee Lee3, Wookyung Chung4, Gachon University Gil Medical Center, Incheon, Republic of Korea

Background: Vascular calcification (VC) is frequently accompanied with bone loss in patients with chronic kidney disease (CKD). Wnt regulates osteoblast activation through canonical (β-catenin dependent) and non-canonical (-independent) signaling pathways. The common pathway between the pathways during VC and bone loss is still remains a conundrum. Therefore, we hypothesized that VC results from phenotypic conversion of vascular smooth muscle cell (VSMC) into an osteoblast-like cell involving induction of an osteoblast transcriptional program via a non-canonical WNT pathway, while bone loss is mainly regulated by canonical WNT pathway.

Methods: Adenine-induced CKD animal model with VC was induced in male Sprague Dawley rats fed 0.75% adenine (2.5% protein, 0.92% phosphate) and intraperitoneal calcitriol (0.08 μg/kg/day) injection for 4 weeks. In an angiotensin II (3μg)-induced VC in high phosphate milieu (3mM) through its effect on VSMC, the effect of WNT signaling on VC was determined by expression of osteoblastic transcriptional factor (RUNX2), Von Kossa stain and WNT downstream signaling factors.

Results: In mRNA profiler PCR assay of WNT signaling pathway from animal model, secreted frizzled-related protein 4 (sFRP4) were increased, while sFRP5 was decreased than those of control group fed with normal rat chow (0.62% phosphate). From the in vitro study, the protective effect of sFRP5 on VSMC differentiation was mediated through the inhibition of Rho/ROCK and JNK pathways. Moreover, the effect of Rho/ROCK and JNK pathways on sFRP5 repression through VSMC differentiation were aggravated by anisomycin (JNK activator), whereas recovered with SP600125 (JNK inhibitor). Those expressions of RUNX2 and WNT signaling factors in adenine-induced CKD animal model with VC showed in the similar patterns.

Conclusions: Our study suggests that loss of sFRP5 was associated with VC in CKD environment by activating non-canonical WNT pathway, which indicate that sFRP5 may be a new therapeutic target in VC in CKD environment.

Funding: Private Foundation Support

SA-PO876

RIPK-Independent Necroptosis Plays Significant Roles in the Progression of Vascular Calcification In Vitro: Yan Ding1,2, Qingle Liu1, Li-Hui Chen3,4, Yu-Chun Chang1, Yan Ding1,2, Qingle Liu1, Li-Hui Chen3,4, Yu-Chun Chang1

Background: Vascular calcification (VC) is a major complication in individuals with chronic kidney disease. A constant inflammatory state remains a key characteristic in the

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

Underline represents presenting author.
development of VC. Necroptosis is a programmed form of cell death that results in an inflammatory phenotype. Early descriptions of necroptosis involve phosphorylation of MLK by RIPK1/3 signaling. Many studies have shown that necroptosis is a key contributor in various inflammatory diseases, but none in VC. In this study, we aim to examine the roles of necroptosis in a model of VC in vitro.

Methods: We examined VC in HD patients by utilizing Human Aortic Smooth Muscle Cells (HASMCs) treated with SmnCaCl, and β-glycerophosphate for 7, 14, 21 days. VC was confirmed by Arsenazo III and Alizarin Red Staining and by expression of Klotho and Runx2. Necroptosis is assessed through the expression of MLK, phospho-MLK, RIPK1, RIPK3, CD33, Western Blot. Pan-caspase inhibitor Z-VAD.fmk (10μM), RIPK inhibitor necrosulfonamide, necrostatin-1 (20μM, 40μM), and MLK inhibitor necrosulfonamide (0.5μM, 1μM) were used to assess the effects of necroptosis inhibition.

Results: The VC was confirmed by down regulation of Klotho and up regulation of Runx2. VC expression was down regulated in a time-dependent manner in our VC model. The opposite was seen in MLK and phospho-MLK, indicating the presence of necroptosis in VC. Furthermore, treatment with MLK inhibitor, necrosulfonamide, alone displayed a dose-dependent reduction of calcification. Neither Z-VAD.fmk (Pan-caspase inhibitor) nor necrostatin-1 (RIPK inhibitor) resulted in significant changes in calcification.

Conclusions: Necroptosis is a major contributor to cardiovascular disease in patients with Chronic Kidney Disease (CKD). Our results indicate that RIPK-dependent activation of MLK may play a significant role in the development of VC. These findings suggest a new pathway of necroptosis whose inhibition may be a target in the treatment of vascular calcification.

Funding: Private Foundation Support

SA-PO877

OA1 Disruption Is Involved in the Development of Arterial Calcification in CKD

Fengying Guan,1,2 Junnan Li,1,3 Kenneth Lim,1,4 Linjing Feng,1,4 Yali Zhao,1 Fei Teng,1 Li-lun Ho,1 Thomas F. Hiemstra,1 Tongzhi Lu,1 Li Chen,1,2,4 Xiaomei Cao,1,2,4 Liang Chen,1,2,4 Qingsong Chen,5,6 Junhua Wang,1,2,4,7 Xiaotao Zhang,1,2,4,7 Xiaodong Hu,1,2,4,7 Guomin Zhao,1,2,4,7 Zhongwei Zhao,1,2,4,7 Li-ping Wang,1,2,4,7 Yoon-Joo Kim,7 Masahiko Sugawara,8,9 Yuji Muragaki,10,11 Motohiro Yamagata,12 Tomoyuki Shii,13,14 Katsunori Saito,15,16 Nobuyuki Goda,17,18 Kojiro Tsuchiya,19,20 Maozhi Zhang,21,22 Junjun Wang,21,22 Zhihong Wang,21,22 Baoshu Lin,22,23,24 Yang Shi,22,23,24 Hua Cui,22,23,24 Dongyun Zhao,22,23,24 Jinju Li,1,2,3,4,7,8,9,10,11,13,14,15,16,17,18,19,20,21,22,23,24,25 Jun Min,22,23,24,25 Junxia Chu,22,23,24,25,26 Junhua Wang,22,23,24,25,26 Min Xi,22,23,24,25,26 Junmin Li,22,23,24,25,26 Zhide Li,22,23,24,25,26 Xiusong Li,22,23,24,25,26 Dongshuai Zhao,22,23,24,25,26 Yuxing Wang,22,23,24,25,26 Ning Nie,22,23,24,25,26 Qianwei Gao,22,23,24,25,26 Shenglun Zhang,22,23,24,25,26 Weihua Hou,22,23,24,25,26 Yanliang Zhu,22,23,24,25,26 Jie Yin,22,23,24,25,26

Methods: OPA1 is a GTPase of the dynamin family that functions in the mitochondrial inner membrane. It is involved in 1) maintenance of the respiratory chain and membrane potential; 2) cristae organization and cristae remodeling; and 3) regulation of mitochondrial DNA. OPA1 protein could protect cells from mitochondrial dysfunction by blocking intramitochondrial cytochrome c redistribution, which proceeds remodeling of the cristae in the presence of mitofusin 1 (Mfn1). Our preliminary data has shown that OPA1 mediated disruption of mitochondrial dynamics may be involved in cell damage in type 2 diabetes. In this study, we investigated the role of OPA1 in human arteries from healthy and CKD patients.

Results: Human arteries were collected from healthy (n=15) and CKD (n=15) patients. Arterial calcification was assessed by automated digital analysis. The results are summarized in the tables. Furthermore, OPA1 expression was downregulated in human arteries compared to control.

Conclusions: OPA1 has a role in human arteries from healthy and CKD patients. OPA1 was significantly downregulated (Fold changes, FC, 2.33) in healthy controls, although they were slightly reduced in patients without VC (p=0.022) compared to those with VC (moderate and severe groups). However, the analysis of calcification expression may point to a non-regulatory phenotype of Treg in the latter. Additionally, OPA1 expression was higher in monocyttes from HD patients (p=0.020) compared to healthy counterparts. This increase was restricted to intermediate monocytess (CD4+CD16+), strongly increased in patients (p<0.001), and was found even in patients without VC. OPA1 expression on intermediate monocytess was negatively associated with vitamin D (r=-0.499, p=0.060) and positively with PTH (r=0.578, p=0.030). Finally, a higher percentage of low-density granulocytes (CD14++CD15+) was observed in CKD (p=0.001).

Methods: Several immune cell subsets related to inflammation, immunoenesence and vascular homeostasis are altered in CKD, even in the early stages of VC. Impaired vitamin D levels may be associated with this abnormal immune profile. This study paves the ground for the identification of early biomarkers to identify patients at higher risk of developing VC.

Funding: Government Support - Non-U.S.
Results: Four patients (11.4%) were excluded due to inadequate bone sample. Thirty-one patients were therefore analyzed. Twenty-six (79.0%) were male. Mean age was 67.3 ± 8.1 years. Mean serum creatinine and glomerular filtration rate were 2.2 ± 0.4 mg/dL and 27.6 ± 7.0 mL/min/1.73 m², respectively. Mean serum calcium, phosphorus, intact parathyroid hormone (iPTH) and native vitamin D (VD) levels were 9.0 ± 0.5 mg/ dL, 3.3 ± 0.6 mg/dL, 140.6 ± 130.2 pg/mL and 17.8 ± 11.9 ng/mL, respectively. Twenty- four patients (77.4%) had normal bone histology, 3 (9.7%) had adynamic disease, 3 (9.7%) had mild hyperparathyroid disease and one (3.2%) had mixed uraemic osteodystrophy. No cases of osteomalacia were found. Except for mineralization lag time and bone volume, histomorphometric parameters did not significantly differ between histological classes. Despite a trend for higher iPTH with rising bone formation rate, levels did not significantly differ between groups.

Conclusions: In a contemporary Portuguese pre-dialysis cohort, roughly 3/4 of the patients with renal bone disease, one tenth had adynamic bone disease and another tenth had mild hyperparathyroid disease. There was one case of mixed disease and none of osteomalacia. Our results also suggest that biochemical testing are not predictive of histological findings, thus highlighting the importance of bone biopsy as the gold-standard tool to evaluate ROD. Further histomorphometric studies are needed to enlighten the spectrum of ROD in pre-dialysis CKD.

SA-P0881
HIV/AIDS Is Associated with Bone Histomorphometric Abnormalities before Antiretroviral Therapy

Iran Sada, 1 Fayaz Alipour, 1 Masoud Lotfali, 2 Vahid Jordegi, 1 Long Sun, 3,4 1Department of Nephrology, 2Clinical Research Center, 3Clinical Research Center of Endocrinology and Metabolism, 4Department of Endocrinology and Metabolism, Tehran University of Medical Sciences, Tehran, Iran

Background: The reduction in bone mineral density (BMD) is a known metabolic complication of antiretroviral therapy (ART), especially tenofovir, which may cause tubular dysfunction, excess phosphaturia and osteomalacia. Low BMD and increased fracture risk, however, has been recognized in patients with HIV/AIDS even before treatment initiation. We aimed to identify and describe abnormalities in bone histomorphometry in ART-naïve HIV patients.

Methods: In 20 male patients with HIV infection, ART-naïve, we evaluated bone structure, turnover and mineralization by iliac crest bone biopsy with histomorphometry. Main exclusion criteria were eGFR < 60 mL/min/1.73m², metabolic bone disease, cirrhosis, diabetes, and medications affecting bone metabolism. HIV viral load and CD4+ T cell count (CD4) were determined. Serum 25-vitamin D (25(OH)D), PTH and RANKL levels were measured. BMD was assessed by DXA.

Results: Mean age was 29.6 ± 5.5 years, mean BMI was 24.7 ± 2.4, median time since diagnosis of HIV infection was 87 (71–231) days, with median viral load of 29,945 (IQR 5,485 – 53,118) copies/mL and mean CD4 of 375 ± 200 cells. Mean 25(OH)D was 22.3 ± 7.9 ng/mL and PTH was within reference range in all patients. RANKL levels correlated positively with HIV viral load (r = 0.48, p = 0.04) and negatively with CD4 (r = 0.65, p = 0.003). Three patients (15%) had low BMD (Z score < -2) at any site. By histomorphometry, 5% had low bone trabecular volume and 25% had decreased cortical thickness, whereas cortical porosity was normal in all of them. Decreased bone formation rate was seen in 80% and abnormal mineralization was detected in 60%. Increased osteoclastic and eroded surface were seen in 40 and 30%, respectively.

Conclusions: Abnormalities in bone volume, turnover and mineralization are common among HIV-infected persons, especially decreased formation and mineralization, even before ART exposure. Immune dysregulation, mediated by abnormalities in RANKL levels, may contribute. Further study is necessary to determine which factors (immunologic, hormonal or others) predict greater bone loss with ART initiation.

Funding: Government Support - Non-U.S.

SA-P0882
The Trabecular Bone Score as a Tool to Assess Bone Microarchitecture in CKD

Janaina da Rhamel, 1 Igor Marques, 1 Vanda Jordegi, 1 Rosa M. Moyses, 1 Didier Hils, 2 Thomas Nickolas, 2 1Columbia University Medical Center, New York, NY; 2Rosa M. Moyses, 3 Universidade Federal de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil; 3Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil; 4Universidade de Nove de Julho, Sao Paulo, Brazil, Brazil

Background: Recent studies have demonstrated that low bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) predicts fractures in CKD patients. However, as bone strength reflects the integration of both BMD and bone quality, BMD only partially describes fracture risk. The Trabecular Bone Score (TBS) is a novel clinical tool that uses grayscale variograms of the lumbar spine image from DXA to assess bone quality and fracture risk. Its ability to assess trabecular (TB) bone quality has been validated against bone biopsy in the general population but not in CKD. We hypothesized that TBS can reflect TB bone quality at the iliac crest in CKD patients.

Methods: In 52 CKD patients from Columbia University, USA and University of Sao Paulo, Brazil, we determined Spearman correlations controlling for age between TBS and mineral disease: CKD-Bone. In 52 CKD patients from Columbia University, USA and University of Sao Paulo, Brazil, we determined Spearman correlations controlling for age between TBS and mineral disease: CKD-Bone.

Results: Mean age was 29.6 ± 5.5 years, mean BMI was 24.7 ± 2.4, median time since diagnosis of HIV infection was 87 (71–231) days, with median viral load of 29,945 (IQR 5,485 – 53,118) copies/mL and mean CD4 of 375 ± 200 cells. Mean 25(OH)D was 22.3 ± 7.9 ng/mL and PTH was within reference range in all patients. RANKL levels correlated positively with HIV viral load (r = 0.48, p = 0.04) and negatively with CD4 (r = 0.65, p = 0.003). Three patients (15%) had low BMD (Z score < -2) at any site. By histomorphometry, 5% had low bone trabecular volume and 25% had decreased cortical thickness, whereas cortical porosity was normal in all of them. Decreased bone formation rate was seen in 80% and abnormal mineralization was detected in 60%. Increased osteoclastic and eroded surface were seen in 40 and 30%, respectively.

Conclusions: Abnormalities in bone volume, turnover and mineralization are common among HIV-infected persons, especially decreased formation and mineralization, even before ART exposure. Immune dysregulation, mediated by abnormalities in RANKL levels, may contribute. Further study is necessary to determine which factors (immunologic, hormonal or others) predict greater bone loss with ART initiation.

Funding: Government Support - Non-U.S.

SA-P0883
Clinical Characteristics of Susceptible Factors and Nutritional Status in 576 Secondary Hyperparathyroidism Patients Undergoing Parathyroidectomy

Nanping Wang, 1 Yao Jiang, 1 Guang Yang, 1 Chang Ying Xing, 2 Xiaoming Zhao, 2 Department of Nephrology, The First Affiliated Hospital with Nanjing Medical University, Nanjing, China; 1First Affiliated Hospital of Nanjing Medical University, Nanjing, China; 2Nanjing Medical University, Nanjing, China; 3First Affiliated Hospital with Nanjing Medical University, Nanjing, China.

Background: Secondary hyperparathyroidism (SHPT) is a common complication of chronic kidney disease-mineral and bone disorder (CKD-MBD). Parathyroidectomy (PTX) is the prior therapy for severe SHPT, however, few large samples studies on predisposing factors and nutritional status of severe SHPT were explored. We aim to analyze the characteristics of high risk group and summarize the nutritional status of CKD patients with PTX.

Methods: Clinical data of 576 PTX patients were collected and grouped according to the age and dialysis vintage.

Results: There were 55.9% males and the mean age of all PTX patients were (46.4±11.3) years. The major cause of CKD was chronic glomerulonephritis (91.5%). Severe SHPT was more common in middle aged patients with long hemodialysis vintage (Fig 1). Levels of serum intact parathyroid hormone(iPTH) were gradually reduced from young age group to old age group(Fig2). The levels of BMD were (21.9±3.5) kg/m², which was negative correlated with serum iPTH levels. Serum albumin in each age group was lower than the reference range, and in age groups of ≥18 and >70 years old were lower than the other groups.

Conclusions: Susceptible factors of severe SHPT include middle age, chronic glomerulonephritis and long hemodialysis vintage. Focused surveillance and timely treatment for mild or moderate SHPT patients with risk factors are suggested. The elderly and patients with severe SHPT patients may have more serious malnutrition and higher operation risk. We recommend personalized diagnosis and treatment strategy for CKD-MBD patients.

Funding: Government Support - Non-U.S.
Characteristics of blood bone metabolic indices in different age groups.

SA-PO884
Parathyroidectomy (PTX), KDOQI Targets, PTH Lowering Therapies, and Mortality in a Cohort of Italian Dialysis (D) Patients: A Multicenter Observational Study

Background: PTX might improve survival by improving biochemical control. We: prospectively collected data of 528 prevalent PTX cases (age: 57.63 ±12.52, 56% M, 14.63% MF, 44/56%) from 153 D units in Italy, out of 12515 patients on D (~4.2%) and evaluated KDOQI targets, therapies and survival. Control cases (n=418, nested case-control selection) were balanced for sex (45/55%) but not age (60.30±14.36 y.o, p=0.01) or duration (11.2±7.3 y, p<0.01).

Results: PTX cases were at lower KDOQI targets for Ca (50 vs 57 %, p<0.05) and PTH (19 ± 37%, p<0.01) and received more calcitriol and Ca-based phosphate binders and less calcimimetic than controls. Also PTX cases included in the follow-up were less frequently targeted at PTH and were confirmed to receive more calcitriol and Ca-based phosphate binders and less calcimimetic than controls (table 1). Univariate analysis adjusted for D age, showed lower HR of mortality for PTX (0.558, CI:0.387-0.800, p=0.000). Multivariate analysis confirmed PTX (HR 0.679, p=0.000). Indeed, PTX cases had higher albumin levels than controls (3.4±0.4 vs 3.3±0.4, p<0.01).

Conclusions: PTX associates with lower risk of mortality regardless of PTH control and despite “more risky” therapy. As a toxin, PTH could negatively affect serum albumin.

Funding: Commercial Support - Amgen

SA-PO885
Effects of Vitamin D Supplementation on Markers of Bone and Mineral Metabolism in Pediatric Patients with Early and Late CKD

Table 1

<table>
<thead>
<tr>
<th>Year</th>
<th>Control group</th>
<th>n</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>257</td>
<td>41%</td>
<td>0.675</td>
</tr>
<tr>
<td>2 year</td>
<td>252</td>
<td>40%</td>
<td>0.654</td>
</tr>
<tr>
<td>3 year</td>
<td>245</td>
<td>40%</td>
<td>0.677</td>
</tr>
<tr>
<td>4 year</td>
<td>240</td>
<td>40%</td>
<td>0.683</td>
</tr>
</tbody>
</table>

Table 1: Prevalences of therapies during follow-up

Background: Recent research findings suggest that vitamin D may have PTH independent effects on the regulation of bone and mineral metabolism. We investigated the effects of vitamin D supplementation on circulating fibroblast growth factor 23 (FGF23), and sclerostin levels in two pediatric cohorts with early and late D.

Methods: Eighty vitamin D deficient children were selected: 40 with early CKD from the ERGO Study, a randomized placebo-controlled trial of ergocalciferol supplementation in children (mean eGFR 55 ml/min/1.73m²), and 40 with advanced CKD from the observational 4C Study (eGFR 24 ml/min/1.73m², p<0.01). In each study 20 children received vitamin D supplementation, and 20 age and eGFR-matched children not on vitamin D served as controls. Z-scores (SDS) were calculated for serum levels of Klotho, FGF23, and sclerostin, at baseline and after a median period of 8 months.

Results: Untreated patients in the ERGO study had normal FGF23 (30.31±0.31 SDS) but decreased levels of klotho (-0.77 SDS) and sclerostin (-1.04 SDS), whereas untreated children in the 4C cohort had increased FGF23 (3.87 SDS) and sclerostin (0.76 SDS), but normal klotho (-0.27 SDS) levels. Vitamin D supplementation further increased FGF23 levels in 4C but not in ERGO patients. Serum klotho and sclerostin normalized during vitamin D supplementation in ERGO but remained unaffected in 4C patients. In the whole cohort significant differences between vitamin D treated patients and controls were noted for Klotho at eGFR 40-70 ml/min/1.73 m² and for sclerostin at eGFR 60-70 ml/min/1.73 m². 25-hydroxyvitamin D levels >75nmol/L was independently associated with changes in Klotho and sclerostin levels.

Conclusions: Vitamin D supplementation normalizes Klotho and sclerostin levels in vitamin D deficient children with early CKD, but further increases FGF23 levels in vitamin D deficient children with advanced CKD.

Funding: Commercial Support - AMGEN

SA-PO886
Bone Disease Post Kidney Transplantation – Beyond Bone Mineral Density

Background: Post-transplant bone disease in kidney transplant recipients (KTRs) is traditionally characterised by severe loss of bone mineral density (BMD) and increased fracture risk. Recent studies have shown less dramatic decrease in BMD at various skeletal sites. Bone microarchitectural changes post-transplant are not well defined and cannot be accurately evaluated with bone biomarkers and dual energy x-ray absorptiometry (DXA). Bone biopsy is invasive and infrequently performed. We longitudinally evaluated changes in BMD, microarchitectural and biomarkers post kidney transplantation, using high-resolution magnetic resonance imaging (MRI, distal tibia), peripheral quantitative computed tomography (pQCT, radius), DXA and biomarkers of mineral metabolism.

Methods: We prospectively included 12 patients (mean age 60±10.5x, 66% M, eGFR 33±12.5 ml/min/1.73m², 4C cohort: n=12) who received vitamin D supplementation, and 20 age and eGFR-matched children not on vitamin D served as controls.

Results: Compared with baseline, 12-month MRI (tibia) showed deterioration in indices of trabecular bone: -1.37% in trabecular mineral density and -2% in surface to curve ratio (S/C, -1.5%, p=0.042) and erosion index (EI, +19%, p=0.005). Changes were also seen in cortical thickness (+4.6%, p=0.0269) and cortical area (+11.5%, p=0.03). Numerical changes in areal BMD and volumetric BMD were not statistically significant. Interval changes in S/C and EI correlated with total hip T-score (DSC: r=−0.70, p<0.01) and for sclerostin at eGFR 60-70 ml/min/1.73 m² and for Klotho at eGFR 40-70 ml/min/1.73 m². 25-hydroxyvitamin D levels >75nmol/L was independently associated with changes in Klotho and sclerostin levels.

Conclusions: Post-transplantation, there was deterioration in trabecular bone quality and network without significant changes in trabecular volume, structural parameters and BMD at central or peripheral sites. Preservation of cortical structure in our cohort is evident from recent studies and highlighted the heterogeneous nature of histologic changes and multifactorial pathology of post-transplant bone disease.

Funding: Commercial Support - AMGEN

SA-PO887
Deterioration of Cortical Bone Microarchitecture in Renal Osteodystrophy – Under-Represented in the “Turnover Mineralisation Volume” (TMV) Classification?

Background: Cortical bone contributes significantly to mechanical strength of bone and its deterioration is associated with non-vertebral fractures. Recent imaging and histomorphometric studies demonstrate prevalence of thin cortices and increased cortical porosity in CKD which may have diagnostic and therapeutic implications.

Changes in bone microarchitecture as measured by TMV classification do not completely reflect deterioration in cortical parameters. We evaluated trabecular and cortical bone microarchitecture in patients with chronic kidney disease (CKD) by classical histomorphometry and microcomputed tomography (mCT) of iliac crest biopsies.

Methods: Iliac crest bone biopsies were performed in 14 patients undergoing kidney transplantation (n=12) and parathyroidectomy (n=2). Trabecular structural parameters

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

Underline represents presenting author.

909
SA-PO888

FRAX® Predicts Fracture Risk in Patients with CKD
Reid Whitlock,1 William Leslie,2 James A. Shaw,2 Claudio Rigatto,2 Paul Komenda,2 David T. Collister,3 Naoko Endo,3 SiBonneface General Hospital, Winnipeg, MB, Canada; 1University of Manitoba, Winnipeg, MB, Canada.

Background: FRAX® was developed to predict fracture risk in the general population but its applicability to patients with chronic kidney disease (CKD) is unknown.

Methods: Using the Manitoba Bone Mineral Density (BMD) Database, we identified adult patients with chronic kidney disease with serum creatinine measurements and BMD measurements within 1 year between 2005-2010. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Incident major osteoporotic fractures (MOF) and hip fractures were ascertained from population-based healthcare databases. The performance of FRAX, derived without and with adjustment to CKD eGFR, was compared with BMD, with age and GFR.

Results: We studied N=10,099 subjects (mean age 64 ± 13 y), including N=254 with CKD stage 3 with higher BMD/MOFR, and N=590 with GFR <30 mL/min/1.73m2 (CKD stages 4-5). During a 3 year observation period, there were 772 individuals with an incident MOFR and 266 with incident hip fractures. In Cox proportional hazards models, FRAX predicted risk for MOF and hip fracture in all eGFR strata. For every standard deviation increase in FRAX score derived with BMD, the HR for hip fracture was 4.54 (95% CI 3.57-5.77) in those with eGFR < 60 mL/min/1.73m2, 4.52 (95% CI 3.15-6.53) in those with 30-60 mL/min/1.73m2 and 4.80 (95% CI 3.86-5.97) in those with <30 mL/min/1.73m2. ROC for MOFR were lower than the equivalent hip fracture HRs in all eGFR categories, but greater for MOF in those with moderate and severe reductions in eGFR (FRAX/eGFR interaction P=0.001).

Conclusions: FRAX stratifies fracture risk in patients with moderate to severe CKD as well as in those with preserved eGFR. These findings support the use of the FRAX score to risk stratify patients with CKD for hip and major osteoporotic fractures.

Funding: Government Support - Non-U.S.

SA-PO889

Relationships between Vitamin D and Bone Formation and Mineralization in Adults and Children with Pre-Dialysis CKD
Thomas Nickolas,1 Renata C. Pereira,1 Maria Coco,2 Joachim H. Ix,2 Michel Chonchol,3 Stuart M. Sprague,2 Isidra B. Salusky,1 Columbia University Medical Center, New York, NY; Mattel Children's Hospital, Los Angeles, CA; 1Montefiore Medical Center, Bronx, NY; 2Montefiore Medical Center, Bronx, NY; 3NorthShore University HealthSystem University of Chicago Pritzker School of Medicine, Chicago, IL; 4UCSD, San Diego, CA; 5University of California, Los Angeles, CA; 6University of Colorado, Aurora, CO. Group/Team: Kidney Disease Bone Biopsy Working Group.

Background: The Institute of Medicine (IOM) recommends levels of 25-hydroxyvitamin D (25(OH)D) >20ng/ml to optimize bone quality for the general population. In contrast, optimal 25D levels in adults and children with pre-dialysis CKD have not been established. We used bone-tissue level data to investigate the 25D level that is associated with optimal turnover and mineralization in adult and pediatric patients with pre-dialysis CKD.

Methods: From Columbia University, Montefiore Medical Center, NorthShore University and UCLA, we pooled iliac crest bone biopsies with tetracycline double labeling and quantified relationships between 25D and 1,25-dihydroxyvitamin D (1,25D) and histomorphometry in 25 adults and 31 children with CKD. Spearman correlations were adjusted for kidney function (CKD-EPI in adults; Schwartz Formula in children). To determine 25D levels that optimized bone formation and mineralization we used receiver operator curve (ROC) analysis and defined high turnover renal osteodystrophy (ROD) as bone formation or mineralization in the upper tertile of respective adult and pediatric populations.

Results: In adults, meanSD age and GFR were 63±14yrs and 27±18mL/min, respectively, and levels of 25D and 1,25D were 28±17ng/ml and 34±20pg/ml, respectively. 25D was inversely correlated with bone formation rate (BFR; r=-0.48, P=0.02) and mineralizing surface (r=0.48, P=0.02) and was inversely related to trabecular thickness (r=0.60, P=0.024) at the iliac crest and cortical area (r=-0.59, P=0.045) at the radius. CtTh was also associated measured by 3D mCT. Bone mineral density (BMD) was measured by peripheral were analyzed by histomorphometry and 3D mCT. Linear and logistic regression analyses were adjusted for protein intake, the association was positively modified between PRAL or NEAP β coefficient were stratified for CKD stage.

Conclusions: FRAX stratifies fracture risk in patients with moderate to severe CKD as well as in those with preserved eGFR. These findings support the use of the FRAX score to risk stratify patients with CKD for hip and major osteoporotic fractures.

Funding: Government Support - Non-U.S.

SA-PO891

Relation of Dietary Acid Load to Bone Mineral Density (BMD) and Osteoporosis in Early CKD
Janice Reid,1 Paul Saran,2 Steven Stuck,3 Nilka Rios Burrows,4 Rajiv Saran,4 Neil P. Powe,5 Centers for Disease Control and Prevention, Atlanta, GA; 1Graduate Entry Medical School, University of Limerick, Limerick, Ireland; 2Priscilla Chan and Mark Zuckerberg San Francisco General Hospital & University of California SF, San Francisco, CA; 3University of California San Francisco, San Francisco, CA; 4University of California, San Francisco, San Francisco, CA; 5University of Michigan, Ann Arbor, MI.

Background: Acidosis is buffered by bone leading to the release of calcium and bone resorption. High dietary acid load (DAL) may contribute to low BMD with studies in the general population showing inconsistent results. Inconsistencies may be due to lack of consideration of protein intake in the etiology of bone loss. Further, it has not been explored whether high DAL is associated with a decrease in bone turnover in chronic kidney disease (CKD). We investigated the association between DAL and BMD osteoporosis by gender in early CKD and explored whether higher protein intake modifies these associations.

Methods: We studied 1,580 participants aged≥20 years with early CKD (stages 1 and 2, eGFR ≥60 and ≤90 mL/min/1.73m2). The National Health and Nutrition Examination Survey. Nutrient intake from 24-hour recall was used to calculate net endogenous acid production (NEAP) and potential renal acid load (PRAL) (mEq/d). BMD measurements were made at the lumbar spine or pelvis and osteoporosis was defined as a T-score ≤−2.5 standard deviation. DAL and protein intake were measured by 24-hour recall.

Results: Mean age in men and women was 52.5±7 and 49.7±8.9 years. Among men, a statistically significant inverse association was observed between PRAL with either pelvis or lumbar BMD (β [95% CI]: -0.03 [-0.05,-0.01], -0.12 [-0.14, -0.09], respectively) as well as with NEAP (β [95% CI]: -0.03 [-0.06,0.003], -0.13 [-0.15, -0.10], respectively). When adjusted for both PRAL and NEAP, the association was positively modified between PRAL or NEAP with BMD (p<0.05). In women, PRAL was positively associated with pelvis BMD (0.03 [0.01,0.06]) but not with lumbar BMD. NEAP was positively associated with both pelvis and lumbar BMD and was inversely modified by protein intake. Neither PRAL
Advanced Glycation End-Products (AGEs) Is Associated with Vascular Calcification and Osteoporosis in CKD Patients

Keicia R. Quadros, André B. Esteves, Renata A. Franca, Cynthia M. Borges, Cinthia E. Carbonara, Marzyla T. Watanabe, Maryanne Z. Silva, Fabiana S. Antonialli, Noemi A. Roza, Jacqueline T. Caramori, Vanda Jorgetti, Rodrigo B. de Oliveira, School of Medical Sciences, Department of Internal Medicine, University of Campinas, Campinas, Brazil; Medical School, Department of Nephrology, University of São Paulo, São Paulo, Brazil; Medical School, University of São Paulo State, Botucatu, Brazil.

**Background:** Chronic kidney disease (CKD) is associated with mineral and bone disorder (MBD) and cardiovascular disease (CVD). Advanced glycation end-products (AGEs) contribute to these complications and their tissue accumulation can be indirectly measured through skin autofluorescence (sAF) by AGE-Reader.12

**Methods:** To investigate the relations between AGEs intake, tissue and serum AGEs levels with CVD and MBD parameters in CKD patients stages 3-4 and in peritoneal dialysis (PD) patients, we performed a cross-sectional study with healthy subjects and CKD patients distributed in 2 groups: CKD stages 3-4 (N=20) and PD (N=28). Clinical and laboratory parameters, ankle-brachial index (ABI), AGEs-sAF levels and AGEs intake were analyzed. In addition, CKD patients performed hip, hands and lateral abdomen radiographs for investigation of vascular calcification (VC), echocardiogram, bone densitometry and serum carboxymethyllysine (CML) levels assay.

**Results:** AGEs-sAF was increased in CKD 3-4 and PD patients compared to the healthy subjects (3.05±0.6 vs. 2.4±0.4; p<0.05), despite similar AGEs intake (10.11±4.76 vs. 11.94±5.581; p>0.05). There are no differences in AGEs-sAF levels between CKD3-4 and PD patients (3.04±0.6 vs. 3.08±0.7; p=0.9); AGEs-sAF levels were positively correlated with interventricular septum (R=0.36; p=0.02), age (R=0.5; p=0.0001) and negatively correlated with the T score from bone densitometry (R=-0.36; p<0.05). In addition, AGEs-sAF levels were higher in patients with VC [N=14 (31%) (3.4±0.5 vs. 2.6±0.5; p=0.01) and among patients with osteoporosis (3.2±0.8 vs. 2.6±0.4; p=0.04).

**Conclusions:** CKD stages 3-4 and PD patients have increased AGEs-sAF levels, which can be measured non-invasively with the AGE-Reader.21 AGEs tissue accumulation might play a role on development of VC and osteoporosis in CKD patients.

**References:**

Cinacalcet Attenuates Bone Loss in CKD through Preventing the Endothelial to Adipocyte Transition  

**Background:** Recently, cinacalcet (CINA) has been proved to be beneficial to bone loss in chronic kidney disease (CKD), while the exact mechanism is largely unknown. Emerging studies have shown that the conversion into mesenchymal stem cells (MSCs) via the endothelial-to-mesenchymal transition (EndMT) could be triggered into adipocytes. In this study, we hypothesized whether CINA could attenuate bone loss in CKD rats by inhibiting the endothelium to adipocytes transformation.

**Methods:** Eight-week male Sprague Dawley rats were divided into three groups: a control group (CTL), vehicle-treated CKD group (CKD) and a cinacalcet-treated CKD group (CKD+CINA). CKD was induced by a 0.75% adenine diet. Bone marrow expression of EndMT- and adipocytokine-markers were also examined.

**Results:** In CKD rats, CINA treatment significantly decreased the serum PTH, phosphate (Pi), and Ca (Calcium) × P product (P < 0.05). The ECT images of the parathyroid glands indicated hyperparathyroidism in CKD rats but normal parathyroid function in CTL rats and CKD + CINA rats. Bone mineral density, trabecular BTBV, trabecular number, cortical area, cortical thickness, force and stiffness were decreased in the CKD group, which were alleviated in the CKD+CINA group (P < 0.05). The expression of endothelial marker (CD31) was significantly down-regulated in CKD rats, whereas the expression of mesenchymal marker (FSP1), mesenchymal stem cell markers (STRO-1, CD44, CD105), adipocyte-markers (PPARγ and LPL) were markedly up-regulated. These changes were inhibited by CINA treatment (P < 0.05).

**Conclusions:** This study firstly demonstrated that CINA exerted a beneficial effect on bone loss in CKD through a novel mechanism of preventing bone marrow endothelial-to-adipocyte transition.  

**Funding:** Clinical Revenue Support, Government Support - Non-U.S.

---

Bisphosphonate Skeletal Accumulation Is Increased in Early and Mid-stage CKD  

**Background:** Bisphosphonates represent the gold standard pharmacological treatment for skeletal disease. Despite limited data, this class of drugs is contraindicated in patients with chronic kidney disease (CKD) due to concerns of compromised excretion and thus increased skeletal accumulation. The goal of this study was to use an animal model of progressive chronic kidney disease (C/+) rat to study bisphosphonate distribution in the setting of reduced kidney function.

**Methods:** At 25 weeks of age, CKD and normal (NL) rats were administered a single bolus of fluorescently labelled zolendronic acid (Fam-ZOL). Animals were euthanized either 24 hours or 5 weeks later (30 weeks of age) and radius/ulna, distal femur, tibia, and 3rd lumbar vertebra (L3) were collected. Bulk levels of Fam-ZOL accumulation in trabecular bone was estimated using whole bone fluorescent imaging (NightOwl LB981). Skeletal perfusion, to estimate blood flow and thus Fam-ZOL delivery, was measured prior to euthanasia via intra-cardiac injection of fluorescent microspheres.

**Results:** CKD animals had blood urea nitrogen (BUN) levels 2x higher than NL at 24 hours post-dose, total bone fluorescence was higher in CKD (134%, P < 0.05), distal femur (+105%, NL, L3 body (+26%, NS) and tibia (+51%, P < 0.05) compared to NL. Five-weeks post-dose, levels of drug in bone were significantly higher in all four bone sites of CKD animals relative to NL. Levels of drug in the bone at 5 weeks was in chronic kidney disease (CKD) rats at 24-hours post exacution mechanism largely skewed. Skewness, perfusion was non-significantly higher in CKD relative to NL at 25 weeks of age. By 30 weeks (~20% NL GFR), perfusion was higher in CKD humeri (155%, P < 0.05), distal femur (+142%, NS) and L4 (+152%, NS) compared to NL.

**Conclusions:** Based on these data we conclude that animals with reduced kidney function have altered dynamics of zoldenate accumulation in the skeleton, but such accumulation might be driven by factors other than compromised kidney excretion and may be due to altered blood flow.

**Funding:** NIDDK Support, Veterans Affairs Support

---

Roles for Type III Sodium-Dependent Phosphate Transporter, PIT-2, in Bone Development and Growth in Mice with Normal and Impaired Kidney Function  

**Background:** Type III sodium-dependent phosphate transporters, PIT-1 and PIT-2, are expressed in bone but their exact functions remain unclear. In this study, the role of PIT-2 in bone homeostasis in normal and chronic kidney disease (CKD) mice was evaluated.

**Methods:** Global PIT-2 knockout (KO) and wild type (WT) male mice with intact kidneys were euthanized at 10 weeks of age and subjected to serum biochemical determination and micro CT analyses, which included measurement of bone length and bone mineral density (BMD) and calculation of static bone parameters. Furthermore, to determine the impact of PIT-2 deficiency on renal Pi handling, 10-week-old WT and PIT-2 heterozygous knockout (HET) female mice were subjected to 24-hour urine collection and serum measurement, followed by kidney collection. WT and PIT-2 HET mice also underwent two-step 5/6th nephrectomy and were subjected to micro CT analyses at 3 weeks after CKD induction.

**Results:** Bone length in PIT-2 KO mice was significantly shorter in femur, tibia, and lumbar vertebra column than the WT mice. BMD in systemic bones including mandibles and both trabecular and cortical bone of femurs were significantly lowered in the PIT-2 KO mice than the WT mice. When femurs were analyzed by micro CT, both cortical and trabecular bone thickness were decreased in the PIT-2 KO mice compared with the WT mice. No significant differences were observed in bone mineral density, serum calcium and Pi levels, kidney function, renal mRNA expression of Slc34a1 and Slc34a3, and fractional excretion of Pi between the WT and PIT-2 HET mice. However, in the setting of CKD and high Pi diet feeding, PIT-2 haploinsufficiency decreased trabecular bone volume and thickness but did not change cortical bone volume and had no effect on serum levels of creatinine, calcium, and Pi.

**Conclusions:** PIT-2 is required for bone development and growth under both normal kidney function and CKD, and enhancing its activity might provide benefits in CKD patients with bone disorders.

**Funding:** NIDDK Support

---

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
SA-PO900

Bone Expression of HIF-1 in Osteites Is Decreased in CKD Rats
Sarah-Kim Bisson,1,2 Roth-Visal Ung,1 Sylvain Picard,1 Darren E. Richard,1,2 Mohsen Agharazii,2 Richard Lariviére,1,3 Fabrice Mac-Way,1,3 CHU de Québec, Université Laval, HDQ, Québec, QC, Canada; 1Université Laval, Québec, QC, Canada.

Background: Different studies, including our own, have shown that hypoxia-inducible factor-1 (HIF-1) enhances vascular calcification. However, HIF-1's role in chronic kidney disease (CKD)-related bone disease is currently unknown. The aim of this study is to determine bone HIF-1 expression in chronic kidney disease (CKD) rats with vascular calcification.

Methods: CKD was induced by 5/6 nephrectomy and vascular calcification by a supplement of calcium, phosphorus and 1,25-dihydroxyvitamin D3 (Ca/P/VitD). Three groups were studied: control (n=8), CKD (n=14) and CKD + Ca/P/VitD (n=12). At 2 months, tibia bone and thoracic aorta were harvested for micro-CT, histomorphometry and vascular calcification quantification. HIF-1α expression, the essential HIF-1 subunit, was measured in the tibia using qPCR with the β-actin housekeeping gene.

Results: Vascular calcification occurred only in CKD + Ca/P/VitD rats. Compared to controls, CKD and CKD + Ca/P/VitD rats presented with a lower bone volume and bone mineral content, while trabecular thickness and separation were significantly increased in the CKD + Ca/P/VitD group. Osteoid volume and surface were also increased in CKD + Ca/P/VitD rats, which is compatible with a mineralisation defect (lower turnover and mineralisation parameters). HIF-1α was expressed in osteites. Interestingly, the proportion of positive osteites for HIF-1α was decreased in CKD and CKD + Ca/P/VitD rats as compared to the controls (respectively 63.0 ± 16.78% vs 60.91 ± 23.17% vs 89.93 ± 5.87%) in controls, p<0.01.

Conclusions: Our study is the first to describe HIF-1 expression in bone from CKD rats with vascular calcification. Since HIF-1 was previously suggested to play a role in bone formation, these results suggest that lower osteite HIF-1 expression could be involved in the development of bone anomalies during CKD.

Funding: Government Support - Non-U.S.

SA-PO901

Leptin Signaling Blockade Ameliorates Muscle Wasting, Bone Disease, and Growth Failure in CKD Wai W. Cheung,1 Urszula T. Iwancie,1 Sheng Hao,2 Zhen Wang,2 Russell T. Turner,1 Robert H. Mak.3 Oregon State University, Corvallis, OR; 1UCSD, La Jolla, CA.

Background: We showed that aberrant leptin signaling is important in the pathophysiology of CKD-associated wasting (Cheung W et al JCI 115:1659-65, 2005 & JASN 25:119-28, 2014). As muscle and bone health are related, we investigated whether leptin signaling blockade affects bone disease and growth failure in CKD.

Methods: We performed 5/6 nephrectomy (CKD) or sham-operation (S) in 8 week old c57BL/6 wild-type (WT), leptin-deficient (ob/ob) and leptin receptor deficient (db/db) mice. Then, WT-CKD mice were treated with a pegylated leptin antagonist (PLA) (7 mg/kg/day) or vehicle (V) for 4 weeks. Secondary hyperparathyroidism was restricted with low phosphorus diets. WT-CKD mice were fed ad libitum while all other mice were fed restricted V or PLA at 0.75 mg/kg/day. WT-S and ob/ob-S+V, db/db-S+V and ob/ob-S+PLA, db/db-S+PLA and WT-S+V mice were used as controls. Uremic rats with vascular calcification.

Results: Weight gain, lean mass and muscle function were normalized in WT-CKD+PLA relative to WT-S+V mice. Increased expressions of muscle inflammatory cytokines (IL-1β, IL-6 and TNF-α) were normalized in WT-CKD+PLA relative to WT-S+V mice. Leptin signaling blockade affects bone disease and growth failure in CKD.

Conclusions: Leptin signaling blockade ameliorates muscle wasting, bone disease and growth failure in CKD. Its blockade may represent a novel therapeutic strategy.

Funding: Clinical Revenue Support

SA-PO902

Increased Bone FGF23 expression Is Linked to Impaired Osteocyte Maturation in CKD Katherine Wesseling-Perry,1 Renata C. Pereira,1 Isidro B. Salusky,1 David Geffen School of Medicine at UCLA, Los Angeles, CA; 1Mattel Children's Hospital, Los Angeles, CA.

Background: Increased FGF23 expression and skeletal mineralization defects characterize bone in CKD. FGF23-expressing osteocytes are located in clusters at the trabecular periphery. Since young osteocytes are also at the trabecular periphery, we hypothesized that FGF23 is a marker of young osteocytes. We also hypothesized that increased numbers of young, FGF23-expressing osteocytes reflect an adaptive response to impaired osteocyte maturation, the consequence of which is defective skeletal mineralization, in CKD.

Methods: We evaluated bone from 32 pediatric CKD patients (stages 2-4; n=12; stage 5: n=20). Patients were dichotomized based on the presence (n=13) or absence (n=19) of skeletal mineralization defects, defined by increased osteoid volume along with prolonged osteoid maturation time. Co-expression of FGF23 (FGF23[225-244]; Quest) with markers of osteocyte maturity (early osteocytes: e1976; mid; late osteocytes: MEPE(ab108073, Abcam); late osteocytes: MEPE(ab108073, Abcam)) was evaluated by immunofluorescence. Numbers of FGF23 and MEPE expressing osteocytes were evaluated by immunohistochemistry.

Results: FGF23 co-localized with MEPE in all CKD patients. FGF23 co-localized with MEPE in patients with skeletal mineralization defects. Numbers of MEPE-expressing osteocytes did not differ between groups or between CKD patients and controls.

Conclusions: FGF23 is a marker of young osteocytes. Normal mineralization indices in CKD are associated with a robust increase in young osteocytes. Impaired osteocyte maturation may precede and contribute to the development of skeletal mineralization defects and secondary hyperparathyroidism in CKD.

Funding: NIDDK Support, Private Foundation Support

SA-PO903

Relationship between Sarcopenia and Bone Mineral Density in Hemodialysis (HD) Patients Senji Okuno,1 Hisanori Okazaki,2 Jiro Miyawaki,3 Kyoko Norimine,1 Shigehue Shoji,1 Tomoyuki Yamakawa,1 Eiji Ishimura,2 Masaki Inaba,3 Shirasagi Hospital, Osaka, Japan; 1Osaka City University Graduate School of Medicine, Osaka, Japan.

Background: Little is known about the relationship between sarcopenia and bone mass in HD patients. Moreover, definition of sarcopenia was made only in considering the muscle mass in most of the previous studies. The purpose of this study was to strictly assess sarcopenia by both muscle mass and muscle strength in HD patients, and to compare bone mineral density (BMD) between HD patients with and without sarcopenia.

Methods: A total of 287 patients on maintenance HD were examined. BMD at the 1/3 distal radius and appendicular skeletal muscle mass were measured by dual energy X-ray absorptiometry (DXA). Low muscle mass was defined as skeletal muscle mass index (SMM) of < 7.87 kg/m² for males and < 5.46 kg/m² for females. Low muscle strength was defined as hand grip strength of < 26 kg for males and < 18 kg for females, according to the criteria of Asian Working Group for Sarcopenia. Sarcopenia was defined as decline in both hand SMI and grip strength.

Results: There were no significant differences in HD duration or in prevalence of diabetes between patients with and without sarcopenia in both genders. Age was significantly higher in patients with sarcopenia than those without sarcopenia in both genders (62.2 ± 12.7 vs 53.3 ± 10.4 years, p < 0.0001 in males; and 65.3 ± 8.6 vs. 55.3 ± 11.2 years, p < 0.0001 in females). BMD of the 1/3 distal radius in patients with sarcopenia was significantly lower than that of patients without sarcopenia (0.62 ± 0.12 vs. 0.69 ± 0.09 g/cm², p < 0.0001 in males; and 0.44 ± 0.09 vs. 0.53 ± 0.09 g/cm², p < 0.0001 in females). In a multiple linear regression analysis, presence of sarcopenia (β = 0.196, p = 0.0075 in males; β = 0.188, p = 0.0340 in females) was significantly, independently associated with BMD of the 1/3 distal radius after adjustment with age, BMD duration, presence of diabetes, body mass index, and serum parathyroid hormone levels in both genders (β = -0.320, p < 0.0001 in males; and R² = 0.448, p < 0.0001 in females).

Conclusions: These results clearly demonstrate that sarcopenia, which was strictly assessed by muscle mass and strength, is significantly associated with decrease in BMD in HD patients, suggesting that sarcopenia should be regarded as a significant risk factor for either osteoporosis or renal osteodystrophy in these patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
SA-PO904

Bone Mineral Density by Quantitative Computed Tomography Can Predict Fractures in Kidney Transplantation Candidates

Hanne S. Jørgensen,1,2 Simon Winther,4 Ellen-Margrethe M. Hauge,3 Lars Rejnmark,2,3 My Svenningson,2,4 Per R. Iversen,2,3 Aarhus University, Aarhus N, Denmark; 4Nephrology, Aarhus University Hospital, Aarhus, Denmark; 5Nephrology, Akerhus University Hospital, Oslo, Norway; 6Cardiology, Aarhus University Hospital, Aarhus, Denmark; 7Endocrinology, Aarhus University Hospital, Aarhus, Denmark; 8Rheumatology, Aarhus University Hospital, Aarhus, Denmark.

Background: Fracture risk is increased in chronic kidney disease (CKD), but the role of bone mineral density (BMD) in assessing bone fragility is still controversial. This study investigates if BMD can predict incident fractures in late stage CKD.

Methods: Adult kidney transplantation candidates were included. Volumetric BMD of spine and hip was analyzed from computed tomography (CT) scans. Low trauma fractures were recorded from patient interviews and records.

Results: During a median follow-up of 3.7 years, 19 out of 157 patients (12%) sustained a clinical fragility fracture. Patients with fracture had reduced BMD at the hip, but not at the spine (Table 1). Type 1 diabetes (p = 0.001), bone specific alkaline phosphatase (p = 0.03), and hip T- and Z-scores (p < 0.05) were identified as predictors of fracture by univariate cox regression. Thus, patients with total hip or femoral neck T-scores ≤-2.5 were at increased risk (Figure 1). A 1 unit decrease in total hip Z-score was associated with a 2-fold increase in the risk of fracture (HR 2.01, CI 1.24 to 3.24, p<0.01) after adjusting for dialysis therapy at baseline and kidney transplantation during follow-up.

Conclusions: Hip BMD by CT may predict fractures in adult kidney transplantation candidates with severe CKD.

Funding: Private Foundation Support

Table 1 Bone density in patients with and without fracture

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fracture (n=19)</th>
<th>No fracture (n=138)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine -T-BMD</td>
<td>−25.60</td>
<td>−23.90</td>
<td>0.36</td>
</tr>
<tr>
<td>Z-score</td>
<td>−0.52</td>
<td>0.43</td>
<td>0.75</td>
</tr>
<tr>
<td>T-score</td>
<td>−1.02</td>
<td>−0.40</td>
<td>0.39</td>
</tr>
<tr>
<td>Total hip -BMD</td>
<td>210.45</td>
<td>225.64</td>
<td>0.04</td>
</tr>
<tr>
<td>Z-score</td>
<td>−1.82</td>
<td>−1.32</td>
<td>0.01</td>
</tr>
<tr>
<td>T-score</td>
<td>−2.47</td>
<td>−1.80</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data are means±SD with p values by Student’s t-test

Figure 1 Risk of incident fracture in kidney transplantation candidates, red line=total hip or femoral neck T-score≤-2.5 (n=58), green line=hip T-score≤-2.5 (n=99)

SA-PO905

Risk of Fracture in Glomerular Disease: A Population-Based Cohort Study Using the Health Improvement Network

Michelle Denberg,1 Laura H. Mariani,2 Dorey A. Glenn,3 Lawrence A. Copelovitch,4 Mary B. Leonard,4 Thomas Nickolais,1 The Children’s Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; 2University of Michigan, Ann Arbor, MI; 3University of North Carolina, Chapel Hill, NC; 4Stanford School of Medicine, Stanford, CA; 5Columbia University Medical Center, New York, NY.

Background: Current understanding of skeletal complications in glomerular disease (GD) is limited. To our knowledge, there have been no studies in children or adults addressing the risk of fracture associated with GD independent of kidney function.

Methods: We performed a population-based retrospective cohort study using the Health Improvement Network. The median calendar year at the start of observation was 2005 (1994-2015). We identified 16,111 patients with at least one diagnostic code for primary GD and 161,045 randomly selected age, sex, and practice-matched individuals. Exclusion criteria included age ≥90 years, systemic lupus or vasculitis, multiple myeloma, amyloidosis, inflammatory bowel disease, celiac disease, HIV, hepatitis B or C, malignancy, and non-renal solid organ transplant. Cox regression was used to estimate the hazard ratio (HR) for first fracture.

Results: Median age was 42 years, and 57% were male. Over a median observation period of 5 years, 1328 incident fractures (132 per 10,000 person-years) occurred in participants with GD versus 11,423 in those without GD (110 per 10,000 person-years). In multivariable analysis adjusted for age, sex, and diabetes and chronic kidney disease (stage 3-5D and/or renal transplant) as time-varying covariates, GD was associated with an increased risk of fracture (HR 1.13; 95% CI: 1.06, 1.19, p<0.001). The adjusted HR for first incident vertebral fracture was 1.47 (95% CI: 1.10, 1.95, p=0.008). The adjusted HR for first incident hip/femur fracture was 1.46 (95% CI: 1.21, 1.75, p<0.001), and the increased risk associated with GD was more pronounced in younger individuals (HR 2.65 for those <40 years old vs. 1.42 for those ≥40 years, interaction p=0.03).

Conclusions: In this large-population based cohort study, GD was associated with an increased risk of incident fracture, particularly at the hip and spine, independent of impaired kidney function.

Funding: NIDDK Support

SA-PO906

Effects of Parathyroidectomy on Blood Bone Markers and Heart Rate Variability in CKD Patients

Ningning Wang,1 Huimin Chen,2 Xiaoming Zha,3 Chang Ying Xing,3 Department of Nephrology, The First Affiliated Hospital with Nanjing Medical University, Nanjing, China; 1First Affiliated Hospital of Nanjing Medical University, Nanjing, China; 2First Affiliated Hospital with Nanjing Medical University, Nanjing, China; 3First Affiliated Hospital with Nanjing Medical University, Nanjing, China.

Background: Lower heart rate variability (HRV) in chronic kidney disease (CKD) patients is associated with increased risk of cardiovascular disease (CVD). We aimed to evaluate the relationships between blood bone markers and HRV in stage 5 CKD patients, longitudinal changes in severe secondary hyperparathyroidism (SHPT) subgroup with parathyroidectomy (PTX) were also explored.

Methods: This cross-sectional study included 134 CKD patients, 100 controls, and a prospective study in PTX group(n=45) with median follow-up time of 6.7 months. Bone parameters included (1) intact parathyroid hormone (iPTH), as classic bone remodeling regulators; (2) bone-specific alkaline phosphatase (BAP), representing bone formation; (3) tartrate-resistant acid phosphatase (TRACP-5b), indicating bone resorption; (4) bone-derived hormone, fibroblast growth factor 23 (FGF23). HRV were measured by 24h Holter.

Results: Circulating bone markers of the participants were shown in Table 1. Baseline iPTH, BAP and lnFGF23 levels were independently associated with decreased HRV in CKD patients. Elevated blood iPTH, BAP, TRACP-5b, FGF23 levels and attenuated HRV were associated with advanced iPTH, TRACP-5b and lnFGF23 levels(Fig1).

Conclusions: In CKD patients, circulating iPTH and FGF23 levels may play important roles in imbalances of cardiovascular autonomic nervous system while the roles of bone resorption/formation need more research.

Funding: Government Support - Non-U.S.

Circulating Bone Markers of Different Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n=100)</th>
<th>Stage 3 CKD Patients (n=134)</th>
<th>Stage 5 CKD patients (n=124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPTH/Hpg/mL</td>
<td>35.2±4.9 (9.0)</td>
<td>6.3±3.1 (1.6–14.6)**</td>
<td>25.0±8.0 (1.6–8.7)</td>
</tr>
<tr>
<td>BAP/µg/L</td>
<td>18.6±5.2 (9.6)</td>
<td>22.1±3.7 (10.0)</td>
<td>18.1±2.4 (12.0)</td>
</tr>
<tr>
<td>TRACP-5b/µg/L</td>
<td>5.8±1.7 (3.0)</td>
<td>5.8±1.7 (3.0)</td>
<td>8.9±3.0 (3.0)</td>
</tr>
<tr>
<td>FGF23(pM)</td>
<td>4.2±0.6 (1.2–3.6)</td>
<td>6.5±0.6 (1.2–3.6)</td>
<td>4.2±0.6 (1.2–3.6)</td>
</tr>
<tr>
<td>HRV/FDF3</td>
<td>4.1±0.2</td>
<td>3.8±0.2</td>
<td>7.8±0.2</td>
</tr>
</tbody>
</table>

**compared with controls, P<0.001; *compared with CKD with Non-PTX, P<0.001

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

Underline represents presenting author.
Kidney Stones Associate with Increased Risk for Fracture in Patients with CKD. Dang H. Shin,1 Jung-soo Noh,2 Jeonghan Lee.1 College of Medicine, Hallym University, Seoul, Republic of Korea; 2Hallym University, Seoul. Republic of Korea.

Background: Most of kidney stones may result from renal hypercalciuria, which is a systemic dysregulation of calcium homeostasis. Accordingly, fractures related with this dysregulation occur more frequently in patients with nephrolithiasis than in the general population. However, little is known about the potential influence of kidney stones on bone health status in patients with chronic kidney disease (CKD).

Methods: A total of 2284 patients with stage 3 – 4 CKD, who were treated at Kandong Scared Heart Hospital were included. Patients were divided into 2 groups according to the presence and absence of kidney stones, and clinical and laboratory data were compared between groups. The association of fractures with kidney stones analyzed using Cox proportional hazards analysis.

Results: Patients with kidney stones and without kidney stones were 502 and 1782, respectively. Among these patients, 172 (7.4 %) were diagnosed with fractures. Hip, pelvis, vertebra, proximal humerus or distal forearm fractures were 43, 31, 50, and 48, respectively. Compared to patients without kidney stone, patients with kidney stones had a significantly higher proportion of fractures (12.4 % vs 6.2 %, P = 0.02). In particular, Cox proportional hazard analysis revealed that kidney stones were a significant independent predictor of vertebral fracture even after adjusting for other factors in patient with CKD stage 3-4 (HR, 1.81, 95% CI 1.12 – 2.81, P = 0.04).

Conclusions: Kidney stones are at increased risk for fractures. Especially, kidney stones are independently associated with higher risk of vertebral fracture in patients with CKD.

Effects of Primary Kidney Disease on Bone Histomorphometry in Pediatric Dialysis Patients. Ornachai Sirintrongkolchaisavkul,1 Katherine Wesseling-Perry,1 Barbara Gales,2 Georgina Chow,1 Renata C. Perrin,1 Isimat B. Salusky,2 David Geffen School of Medicine at UCLA, Los Angeles, CA; 3Mattel Children’s Hospital, Los Angeles, CA; 4None, Calabasas, CA; 5UCLA, Marrietta, AL; 6University of California, Los Angeles, CA. 

Background: Little is known as to the effect of primary kidney disease on renal osteodystrophy. The current study was thus designed to assess the association between CKD etiology, mineral metabolism and bone histomorphometry in pediatric ESKD.

Methods: Demographic, biochemical and bone histomorphometric data were analyzed from 207 patients (aged 12.7 ± 5.6 years) with ESKD who underwent double tetracycline labeled bone biopsy at UCLA. Patients were divided into 2 groups according to CKD etiology: inflammatory (n = 85) vs. non-inflammatory (n=122) disease. Non-inflammatory disease was further divided into CUKAT (n = 87) vs. non-CKUKAT (n = 35). Serum Ca, P, ALP, PTH, 25D, and C-term FGF23 levels were measured at the time of biopsy.

Results: Serum Ca, P, PTH and 25D did not differ between groups. Serum ALP levels were higher, and eFGF23 levels were lower, in patients with CUKAT (Table). Bone turnover and volume did not differ between groups. Osteoid volume (OV/BV), osteoid surface (OS/BS), osteoid thickness (O.Th) and osteoid maturation time (OMT) were increased in patients with CUKAT. As previously reported, multiple regression analysis demonstrated that Ca, P, ALP and PTH were independent predictors of OV/BV and O.Th. ALP and PTH were independent factors affecting BF/BBS. Disease etiology was not an independent predictor of any histomorphometric variable.

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

Underline represents presenting author.

SAP0097

SAP0098

SA-PO907

SA-PO908

SA-PO909

Conclusions: After controlling for biochemical variables, ESKD etiology did not affect bone histomorphic parameters of turnover, mineralization, or volume.

Funding: NIDDK Support, Private Foundation Support

Poster/Saturday

Poster/Oral

Poster/Oral

Poster/Saturday

Poster/Saturday

Poster/Saturday
Mineral Disease: CKD-Bone

Effect modification by age on PPI use

**SA-PO910**
The Regina CKD-MBD Study Bhuwan Prasad, Shelley Giebel, Thomas Nickolas.
1Columbia University Medical Center, New York, NY; 2Inner Health, Regina, SK, Canada.

**Background:** Recent studies have demonstrated that measurement of areal bone mineral density (BMD) by dual energy X-ray absorptiometry predicts fractures in patients with chronic kidney disease (CKD). However, whether fracture risk prediction by BMD is enhanced by assessment of biochemical markers of CKD-mineral and bone disease or clinical risk factors is not clear. We hypothesized that in a selected cohort of patients managed in a CKD clinic, that combining T scores with biochemical markers would optimize fracture discrimination than using DXA alone.

**Methods:** We conducted a retrospective review of 374 consecutive patients who underwent mandatory DXA imaging at the point of entry into our multidisciplinary CKD program. BMD measurements were obtained from DXA scan reports from the Nuclear Medicine Department. BMD data were collected at four sites: the lumbar spine, total hip, mean of left and right femoral neck, and the 1-3- radius. We collected data on demographic, lab markers of mineral metabolism and fractures (identified through self-reported questionnaires, hospital electronic medical records and physician billing records.

**Results:** In our cohort, 14.3% of stage 3 CKD, 15.7% of stage 4 CKD and 19.7% of stage 5 CKD experienced a clinical fracture during the study period. In an unadjusted model, each standard deviation decrease in total hip T-Score was associated with a 47% higher odds of fracture (OR=1.47, 95%CI: 1.18-1.82, p=0.0066). After adjustment for clinical risk factors (age, sex, BMI and diabetes) the odds of fracture remained unchanged (OR=1.47, 95%CI: 1.14-1.89, p=0.0028), and after adjustment for clinical risk factors and intact PTH (CKD-MBD), BMI remained a significant predictor of fracture (OR=1.52, 95%CI: 1.17-1.99, p=0.0018). In the final model, additional adjustment for eGFR did alter the relationship between total hip T-Score and fracture (OR=1.53, 95%CI: 1.17-1.99, p=0.0017). Neither clinical risk factors nor markers of CKD-MBD were related to fracture in multivariate models and there was no interaction between total hip T-Score and eGFR (p=0.5).

**Conclusions:** We conclude that measurement of BMD by DXA scans predicts fractures in stages 3-5. However, fracture prediction risk was not further enhanced by the addition of biochemical markers of CKD-MBD.

**SA-PO911**
Risk Factors of Fragility Fracture in Patients with CKD Mark A. Kleeman, Waleed Zaafar, Alex R. Chang.
1Geisinger, Danville, PA; 2Geisinger Medical Center, Danville, PA.

**Background:** Measurement of chronic kidney disease-mineral and bone disorder (CKD-MBD) focuses mainly on parathyroid hormone (PTH), phosphorus, and calcium. However, little is known about fragility fracture risk factors in CKD patients.

**Methods:** The study population included 5,733 patients in the Geisinger Health System with CKD [estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m², or urine albumin/creatinine ratio >=30 mg/g], intact PTH measurements, and no prior history of fragility fracture or use of osteoporosis medications. Fragility fracture was defined by ICD-9 codes for wrist, humerus, hip, and clinical spine fracture.

**Results:** Over a median follow-up of 5.0 (3.4-7.5) years, 609 (10.6%) CKD patients experienced an incident fragility fracture. Median (interquartile range) values for age, eGFR, intact PTH, alkaline phosphatase (ALP) were 70 (60-78) y, 43 (31-54) ml/ min/1.73m², 57 (37-90) pg/ml, and 77 (63-97) L.U. and 68.0 ± 5.2%, were female, 98.1% were white, mean eGFR was 44.8 (22.1) ml/min/1.73m², and median Elevated alkaline phosphatase (ALP) = 100 L.U. was associated with increased risk of incident fragility fracture; intact PTH, 25-hydroxyvitamin D, serum phosphorus and bicarbonate levels were not. Other significant risk factors included older age, female gender, body mass index (BMI) < 20 kg/m², serum albumin < 4 g/dl, and history of non-fractional falls (Table).

**Conclusions:** Several routinely collected clinical factors are associated with increased risk of fragility fracture in patients with CKD. Future clinical trials aimed at improving bone health and reducing fracture risk may consider using clinical factors to identify CKD patients at high risk of fragility fracture.

**SA-PO912**
Influence of Vitamin D Receptor Polymorphisms on Biochemical Markers of Mineral Bone Disorders in South African Patients with CKD Bala Waleed 1, Alex Zafar.1 University of the Witwatersrand, Johannesburg, South Africa; 2Internal Medicine, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa.

**Background:** It remains unclear whether genetic factors may explain the reported variation in the levels of biochemical markers of chronic kidney disease mineral and bone disorders (CKD-MBD) across ethnic groups. Therefore, the aim of this study was to examine the influence of VDR polymorphisms on secondary hyperparathyroidism and its association with vitamin D levels in black and white South African study participants.

**Methods:** This was a cross sectional study involving 272 CKD stage 3-5D patients and 90 healthy controls. The four common VDR polymorphisms (Bsm I, Fok I, Tag I, and Taq I) were genotyped using the polymerase chain reaction-restriction fragment length polymorphism (PCR –RFLP) method. In addition, the biochemical markers of CKD-MBD were measured to determine their associations with the four VDR polymorphisms.

**Results:** With the exception of Tag I polymorphism, the distribution of the VDR polymorphisms differ significantly between blacks and whites. In hemodialysis patients, the Bb genotype was significantly associated with moderate secondary hyperparathyroidism (OR, 0.3;12; 95 CI 1.11-8.83, p=0.03) and severe hyperparathyroidism (OR, 2.55; 95 CI 1.19-5.47, p=0.02). This was consistent with the observed higher levels of median PTH and mean phosphate in patients with Bb genotype. This candidate risk genotype (Bb) was over represented in blacks compared to whites (71.0 % versus 55.6 %, p=0.0001). In an unadjusted regression model, Fok II genotype was found to be significantly associated with the risk of developing severe vitamin D deficiency < 15ng/ml (OR, 1.89; 95 CI 1.17-3.07, p=0.01).

**Conclusions:** The VDR Bb genotype is an independent predictor of developing secondary hyperparathyroidism in patients with end stage renal disease. In addition, study participants with the Fok II genotype are at increased of developing severe 25(OH) D deficiency.

**SA-PO913**
Integrative Point-of-Care Ultrasound (POCUS) Curriculum Imparts Diagnostic Skills Relevant to Nephrology Surekha U. Mollano, Stephen M. Sozio, Steven Menes, Tarig Shaf. Johns Hopkins University School of Medicine, Baltimore, MD.

**Background:** The utility of POCUS has been expanding as a multipurpose diagnostic tool for nephrologists. However, a clear, nephrology-specific, curriculum has not been established. We have developed and implemented a POCUS curriculum that teaches focused skills to nephrology fellows. The goal of our study is to describe our initial experience with this innovative program.

**Methods:** The Johns Hopkins Renal Fellow POCUS curriculum is a two-week elective that provides focused training to assess the following: heart (ejection fraction, pericardial effusion, chamber size), lungs (pulmonary edema, effusion, pneumonia), inferior vena cava (diameter, collapsibility), kidney (size, echogenicity, hydropnephrosis), bladder (volume), and fistula (depth, diameter). We teach these skills using a combination of didactic lectures, guided scanning, and independent scanning. We grade both image interpretation skills using a Qualtrics-based test and image acquisition skills using an AUCOS-Objective Structured Clinical Examination (OSCE). Pre-tests and post-tests were administered prior to and after completion of the program. Comfort with ultrasound skills was gauged using a 5-point Likert scale.

**Results:** 12 fellows and trainees have so far started the course; 4 have completed all modules and the remaining are continuing training. Of the 4 who completed training, fellows were mean (sd) 7.3 (2.2) years after graduation from the medical school. 25% of fellows had used POCUS before for diagnostic purposes, but none were formally trained in use. The fellows that completed the course reported significant improvement (p < 0.05) in assessing kidney pathology, bladder volume, ejection fraction, and pericardial effusion. Comparing pre-test to post-test scores, fellows felt significantly more comfortable identifying and assessing pathology across all domains following the course (2.40 (0.87) to 4.20 (0.65), p < 0.001). At the end of the course, 100% of fellows agreed or strongly
agreed that POCUS was easy to obtain, improved assessment of patients, should be a part of the residency, and that other nephrology evaluations and faculty should be trained.

Conclusions: A 2-week nephrology-specific POCUS curriculum is feasible and enhances fellows’ learning experience.

SA-PO914

Nephrology Practice and Training in the Intensive Care Unit: Results of a United States Survey

Paul J. McCarthy,2 Kemsha Z. Huslin,1 Farhan Ali.1
1Smithsburg, MD; 2University of Maryland, Baltimore, MD.

Background: Renal pathology is common in the intensive care unit (ICU). Understanding of the entire ICU patient is optimal. We conducted a survey looking at opinions of intensivists and nephrologists regarding renal replacement. There was agreement on many issues and disparity in some areas. We completed a second survey on ICU nephrology to identify potential areas for future study and improvements in our training program.

Methods: A survey on renal replacement was emailed to training program directors in critical care medicine and nephrology and to nephrologists from a department database. A second survey was emailed to program directors in nephrology and nephrologists from a department database with questions on practices and nephrology training related to the ICU. Questions in the second survey were the result of responses from the first survey.

Results: Respondents were from both academic and non-academic settings, large and small centers and were from all parts of the country. The 1st survey showed agreement among nephrologists and intensivists on indications to start renal replacement and dose for CRRT. There were differences based on specialty in volume assessment and rounding patterns. Half of responding to the second survey stated that up to 50% of their patients are on CRRT. Respondents report that they place dialysis catheters, manage hemodialysis, CRRT and half prescribe pheresis. 75% have not participated in a continuing medical education (CME) activity specific to ICU nephrology in the last year. Rarely respondents round on patients at night. For training programs, less than half reported teaching of proctored CRRT cases are required. 40% of training programs give renal fellows specific training in hemodynamics monitoring and 15% or less of programs report training fellows in ultrasound, mechanical ventilation or require a formal rotation as part of an ICU team.

Conclusions: Nephrologists spend a good portion of time seeing ICU patients. Most place dialysis catheters, manage hemodialysis, CRRT and many manage pheresis. 75% have not participated in a CME specific to ICU nephrology in the last year. Most nephrology training programs have no minimum requirement of proctored CRRT cases and most programs do not train fellows in hemodynamic monitoring, ultrasound, mechanical ventilation or require dedicated time as an ICU team member.

SA-PO915

Assessing Teaching Practices in Percutaneous Kidney Biopsy among Pediatric Nephrology Training Programs

Shanmugam Turgeon,1 John D. Mahan.2 Children’s National Medical Center, Washington, DC; 2Nationwide Children’s Hospital, Columbus, OH.

Background: Standardized approaches for teaching kidney biopsies in pediatric nephrology fellowship training have not been established. To date, there has not been a comprehensive assessment of kidney biopsy training practices among pediatric nephrology training programs. The purpose of this study was to determine common practice patterns for teaching kidney biopsies for pediatric nephrology fellowship training.

Methods: An online survey was piloted and administered to training program directors (TPD’s) at 40 ACGME accredited pediatric nephrology fellowship programs in the United States.

Results: 28 (70%) of TPD’s completed the survey. Trainees performed the majority of all kidney biopsies at 73% of the institutions with the majority (63%) of kidney biopsies performed by 1st year trainees. A supervising attending nephrologist was uncommonly in attendance in the procedure area. Less than 50% of programs used didactic instruction or simulations in teaching obtaining consent and performing kidney biopsies. “Observation” was uniformly employed (100%) as the primary teaching modality for these purposes. All institutions used ultrasound localization for kidney biopsies. In 22% of the institutions, the trainee performing the biopsy was responsible for ultrasound guidance of the biopsy needle. The majority of programs that have the nephrologist performing simultaneous ultrasound provided formal instruction in ultrasoundography to their trainees. There was a broad range in the number of kidney biopsies performed by each trainee through training ranging from 10 to 150 biopsies with 10-80% of these performed in renal allografts. Among TPD’s, the minimum number of kidney biopsies felt to be sufficient to attain competency for independent practice was 10 with the majority (57%) of TPD’s feeling that 20-40 biopsies were necessary for a trainee to achieve competency. 92% of training programs provide teaching in the interpretation of kidney biopsies using a combination of didactic instruction (73%), renal pathology conferences (93%), and formal rotations with pathology within or outside their institutions (63%).

Conclusions: Despite a lack of formalized guidance or national standards, pediatric nephrology training programs employ common practices in teaching pediatric nephrology trainees to competently perform kidney biopsies in children and adolescents.

SA-PO916

Virtual Patient Simulation Improves Clinical Decisions for Hyperkalemia Treatment in Patients with Heart Failure

Susan Gitzer,1 Donald Blathewick, Douglas Blevins. Medscape, Lexington, KY.

Background: This study was conducted to determine if an online, virtual patient simulation-based continuing medical education (CME) intervention could improve performance of nephrologists and cardiologists in the management of patients with heart failure and hyperkalemia.

Methods: The CME intervention comprised 2 cases presented in a virtual patient simulation (VPS) platform, allowing learners to choose from lab tests, diagnoses, and treatments matching the scope and depth of actual practice. Learner clinical decisions, captured using open field entries, were analyzed using a sophisticated decision-making tailored clinical guidance (CG) was provided based on current evidence and expert recommendation. Decisions were collected post-CG and compared with each user’s pre-CG data using a 2-tailed paired t-test to determine P values. Data is reflective of learners who participated in the assessment from 2/23/17 to 4/21/17.

Results: Significant improvements include: Case 1 (n=86 nephrologists; n=126 cardiologists): Nephrologists and cardiologists demonstrated statistically significant changes from pre-CG to post CG in (all P<0.001): Diagnosis of hyperkalemia (3% vs 37% of nephrologists; 0% vs 45% of cardiologists) Orders for patiromer (1% vs 29% of nephrologists; 1% vs 36% of cardiologists) Orders for a preferred beta-blocker (12% vs 51% of nephrologists; 26% vs 56% of cardiologists) Orders for an ACEi (12% vs 40% of nephrologists; 30% vs 56% of cardiologists) Orders for influenza vaccination (0% vs 35% of nephrologists; 0% vs 36% of cardiologists) Case 2 (n=60 nephrologists; n=102 cardiologists): Nephrologists and cardiologists demonstrated statistically significant changes from pre-CG to post CG in (all P<0.001): Diagnose CKD (17% vs 76% of nephrologists; 21% vs 63% of cardiologists) Orders for sacubitril/valsartan (10% vs 46% of nephrologists; 19% vs 59% of cardiologists) Orders for influenza vaccination (0% vs 46% of nephrologists; 0% vs 40% of cardiologists) Orders for pneumococcal vaccination (0% vs 49% of nephrologists; 0% vs 43% of cardiologists)

Conclusions: This study demonstrated the success of online, VPS-based education that engages nephrologists and cardiologists for an authentic and practical learning experience that can improve evidence-based clinical decisions in the management of hyperkalemia in patients with heart failure.

Funding: Commercial Support - Relypsa

SA-PO917

CKD-Related Hyperkalemia: Effectiveness of Online Medical Education on Clinical Decision-Making

Susan Gitzer,1 Karen Badal,2 Donald Blathewick.1 Medscape, Lexington, KY; 2WebMD, New York, NY.

Background: Inhibition of the renin-angiotensin-aldosterone system (RAAS) has become a cornerstone of evidence-based therapies in chronic kidney disease (CKD), diabetes, and heart failure. Despite this, RAAS inhibitors remain widely underutilized in current clinical practice. We sought to determine if participating in a case-based online educational intervention related to CKD management improves clinical decision-making of nephrologists and cardiologists in the United States.

Methods: An interactive, case-based, online CME activity was developed. The education reflects were assessed using a repeated pairs pre/post-assessment study design. For all questions combined, the McNemar’s chi-squared test assessed whether the mean post-assessment score differed from the mean pre-assessment score. P values are shown as a measure of significance; P values <.05 are statistically significant. Cronbach’s α was used to calculate the effect size (0.06-0.15 is a small effect, 0.16-0.30 medium, and >0.30 large). The activity launched on December 19, 2016, and data were collected through January 24, 2017.

Results: Improved clinical-decision making was seen among nephrologists (n = 130) and cardiologists (n = 107) pre- to post-assessment (in all P<0.001): Causes of CKD progression in individual patients (nephrologists: 73% to 92%, V=0.242; cardiologists: 53% to 81%, V=0.299) Optimization of RAAS inhibitors in CKD (nephrologists: 55% to 87%, V=0.335; cardiologists: 55% to 79%, V=0.259) Alternative options for management of hyperkalemia and safe polypharmacy in patients requiring maximization of RAAS inhibition (nephrologists: 64% to 83%, V=0.218; cardiologists: 43% to 68%, V=0.254)

Conclusions: Participation in this interactive, case-based, online CME activity resulted in improved clinical decision-making by nephrologists and cardiologists in the management of patients with CKD particularly in regard to safe and appropriate management of RAAS inhibitors. Significant improvements were seen in consideration of causes for CKD progression, the importance of effective RAAS inhibition and RAAS inhibitor maximization, and alternative management strategies in patients with hyperkalemia.

Funding: Commercial Support - Relypsa

SA-PO918

Success of CME at Improving Physicians’ Knowledge of Diagnosis and Treatment of Hepatorenal Syndrome

Susan Gitzer,1 Donald Blathewick,1 Julia A. Muñoz.1 Medscape, Lexington, KY; Medscape, LLC, New York, NY.

Background: Timely diagnosis and intervention are critical for improving outcomes for patients with hepato renal syndrome (HRS), yet most specialists are not fully confident in their ability to identify and classify HRS, or to select appropriate pretransplant
SA-PO920

Improvement in Self-Perceived Clinical Competence among Indiana University Nephrology Fellows after Intersession

Background: The first year of Nephrology fellowship training is a clinically intensive experience in the USA. Our Nephrology fellowship program introduced an Intersession for first-year fellows during the academic year 2016-2017. We hypothesized that an intersession will improve fellows' self-perceived competence in core nephrology disciplines.

Methods: A 2-week intersession included hands-on training in home hemodialysis, peritoneal dialysis, and temporary catheter placement. Instruction in acute kidney injury management, hypotension, acid-base disorders and resistant hypertension was conducted via didactics, independent readings, and case-based discussions. Small-group workshops emphasized consultant professionalism. Fellows were exempt from clinical duties with the exception of their once weekly continuity clinic. An anonymous survey of 8 questions was conducted before and two weeks after the intersession to rate self-perceived competence. A scale of 1 to 5 was used to assess self-competence.

Results: All five first-year fellows participated in the Intersession. Five pre-surveys and 4 post-surveys were collected. One pre-survey was not adequately filled and excluded from the analysis. The average competence pre- and post-intersessions are shown in table 1. There was an increase in competence in AKI, acid-base, hypertension, and home hemodialysis management (p<0.05 for all). There was an increase in overall competence (p<0.05).

Conclusions: An intersession for first-year nephrology fellows significantly improves self-reported competence. It is expected that intersessions will be continued in the following years in the Nephrology fellowship program and longer term outcomes will be available.

Table 1- Self-reported competence pre- and post-intersession

<table>
<thead>
<tr>
<th>Competence</th>
<th>Pre</th>
<th>Post</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Kidney Injury</td>
<td>3.0</td>
<td>4.0</td>
<td>0.015</td>
</tr>
<tr>
<td>Hypotension</td>
<td>3.15</td>
<td>3.75</td>
<td>0.001</td>
</tr>
<tr>
<td>Acid-base disorders</td>
<td>2.75</td>
<td>3.75</td>
<td>0.030</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4.50</td>
<td>4.25</td>
<td>0.004</td>
</tr>
<tr>
<td>Home Hemodialysis</td>
<td>5.00</td>
<td>5.00</td>
<td>0.002</td>
</tr>
<tr>
<td>Peritoneal Dialysis</td>
<td>5.00</td>
<td>5.00</td>
<td>0.002</td>
</tr>
<tr>
<td>Correlation &amp; Pressure</td>
<td>4.25</td>
<td>4.25</td>
<td>0.002</td>
</tr>
<tr>
<td>Diastolic Dysfunction</td>
<td>4.25</td>
<td>4.25</td>
<td>0.002</td>
</tr>
<tr>
<td>Overall Competence</td>
<td>5.00</td>
<td>5.95</td>
<td>0.018</td>
</tr>
</tbody>
</table>

SA-PO921

Comparison of Five Methods of Measuring Specific Gravity in Mock Urine Solutions

Heidi Saxton,1 Nirupama Ramkumar,2 Martin C. Gregory,1 Salt Lake City, UT; 1University of Utah, Salt Lake City, UT; 2University of Utah School of Medicine, Salt Lake City, UT.

Background: Urine specific gravity (SG) is commonly used as an indicator of urine concentration in the clinical nephrology setting. SG measurements can aid in distinguishing pre-renal etiologies from acute tubular necrosis, although the accuracy of these measurements by different methods remains unknown. Our main objective in this study was to compare five methods of measuring SG in solutions that resemble normal and pathologic urine specimens.

Methods: We measured the SG and osmolality of solutions with varying concentrations of salts, glucose, urea, albumin, and intravenous contrast using the methods of hydrometry (urinometer), refractometry, reagent strips, and pycnometry. Samples were also sent to the hospital clinical laboratory for measurement by automated refractometry. Slope of SG versus osmolality and Pearsen’s correlation coefficient was calculated for each method.

Results: Slopes of SG by hydrometry correlated most closely with slope of specific gravity by pycnometry across all solutions (r value of 0.996). Slopes of SG by refractometry and clinical laboratory methods correlated moderately well (r values of 0.950 and 0.927, respectively), while slopes of SG by reagent strip correlated very poorly (r value of 0.434).

Conclusions: As mock urine solutions become more concentrated, the method of hydrometry correlates most closely with pycnometry. Refractometry manually and by clinical laboratory have moderate accuracy, while the method of reagent strip performs very poorly. This latter method may have poor clinical utility, especially in pathologic urine from patients with kidney disease.

Correlation of slope of specific gravity against calculated osmolality with pycnometry slope

<table>
<thead>
<tr>
<th>All solutions</th>
<th>Refractometry</th>
<th>Reagent strip</th>
<th>Hydrometry</th>
<th>Clinical Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>r value</td>
<td>0.949</td>
<td>0.434</td>
<td>0.950</td>
<td>0.927</td>
</tr>
</tbody>
</table>

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

Underline represents presenting author.

918
Hospital, Boston, MA; 2 None, West Newton, MA; 3 University of Massachusetts Lowell, Lowell, MA.

Background: It is established that the more a patient knows about peritoneal dialysis (PD), the more likely he is to select it. At our center, patients with advanced chronic kidney disease (CKD) are referred to a dialysis options visit with a nurse educator to learn about PD and hemodialysis. In the current project, we spoke to CKD patients to collect feedback about the visit.

Methods: Patients with stage 4 or 5 chronic kidney disease (CKD) were invited to a semi-structured interview immediately following their education visit. The interviews were recorded and transcribed. Qualitative content analysis was conducted by two staff members using NVivo 11 software. Basic demographics were collected.

Results: The mean age of the 10 CKD patients interviewed was 62 years (SD = 9.4), 60% were female, 40% were married, and 40% were Caucasian. 40% were not educated beyond high school. The median annual income was $20,000. Most patients did research before their education appointment. This typically involved an internet search (n=7), however others also spoke to dialysis patients, talked with their doctors/nurses, and one patient visited a unit. Only three patients said they knew nothing about dialysis before the visit. The patients interviewed displayed a preference for PD because of the perceived ease of therapy. The major advantages described were the schedule (with days off) and the fact that the therapy was delivered by others (the notion of just needing to show up). Only a minority of patients identified shortcomings of HD. One patient described the time commitment and a few patients voiced concerns about the need for a fistula and needles. PD in contrast was overwhelmingly viewed as a burdensome therapy. Patients were dismayed by the need to store supplies at home, to complete dialysis daily on their own, and the potential for infection. A couple of patients did not want the nurse to explain PD. Only two patients seemed to be considering PD as an option.

Conclusions: The patients interviewed displayed little confidence they would be able to successfully complete PD and were left with a negative impression. In contrast, there was little perceived downside to HD. These results may reflect the shortcomings of our current model of education. Further research is needed to determine different styles of education can overcome these barriers and improve utilization of PD.

Funding: Commercial Support - Baxter

SA-PO923

Developing Partnerships to Advance Renal Care and Ameliorate "Brain-Drain" in Haiti in Haiti Brian D. Remillard,1 Philip C. Cleophas,1 Robert S. Brown.2 1 Beth Israel Deaconess Medical Center, Boston, MA; 2 Dartmouth Hitchcock Medical Center, Lebanon, NH; 3 Hôpital Universitaire de Mirebalais, Mirebalais, Haiti.

Background: Immediately following the earthquake in Haiti (Jan 2010), BR provided acute hemodialysis (HD) for several patients with acute kidney injury (AKI). This involved major support and equipment from the Dartmouth community and Partners in Health/Zanmi Lasante. Once the earthquake crisis ended, we recognized that it would require a concerted effort and multiple partnerships to bring ongoing renal care to Haiti. Furthermore, despite Haiti investing years of free training of health care professionals, over 90% leave the country creating a "brain-drain" due to lack of jobs, low pay, little ongoing medical education and few resources to provide adequate patient care.

Methods: Two academic institutions, DHMC and BIDMC, have established partnerships with Bridge of Life, Sustainable Care Kidney Foundation, Partners in Health and Zanmi Lasante and our new charity, TORCH, along with NxStage Medical, Inc, to initiate teleconsulting of AKI at HD at HUM. We have effectively used teleconsulting between DHMC and HUM to provide education, biomedical support, train staff, and build relationships. We subsequently have developed a "mini" fellowship program inviting Haitian physicians and nurses to DHMC and BIDMC for short (2-3 week) training venues to provide specific skill development and ongoing mentoring.

Results: With the help of our partners, nurses and residents came from HUM to the USA for specific training in HD, cental line placement, urinalysis, AKI diagnosis, care, supported the physicians and nurses at HUM, and may provide a partial answer to the problem of "brain-drain" that impedes Haitian medical care. Supported the physicians and nurses at HUM via teleconferencing and "mini" fellowships has advanced renal patient education, and variations in clinical practice among primary care providers in comparison to nephrologists regarding the diagnosis, evaluation and management of CKD-MBD especially in earlier stages of CKD when patients might not be followed by a nephrologist.

Conclusions: Our study was conducted using a questionnaire which was distributed to residents, fellows and faculty in primary care specialties and nephrology. Questions were derived from the 2009 practice guidelines from the Kidney Disease Improving Global Outcomes work group and the 2003 National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease.

Results: Nephrologists scored higher than primary care physicians in all areas tested including pathophysiology of the disease, screening parameters and intervals, target levels and treatment strategies. The difference in score was statistically significant in the majority of those areas. Overall, primary care specialists (n of 51) scored an average of 31.7 % while nephrologists (n of 11) scored an average of 80.3 % (p-value <0.01).

Conclusions: Our investigation showed there is a significant discrepancy in knowledge between primary care physicians and nephrologists regarding the diagnosis and management of CKD-MBD. It is necessary to improve primary care physicians’ knowledge and practice in this field to provide high quality care to patients. Our next steps include physician education and creation of best practice advisory alerts using the electronic medical record system which will include criteria for appropriate nephrology referral for this subset of patients.

Funding: Private Foundation Support

SA-PO924

Conflicts of Interest in Nephrology Clinical Practice Guidelines Madhuri Chengappa,1 Sandra Herrmann,2 Saurabh Gupta,2 Thijesswi Poonacha,3 Mayo Clinic, Rochester, MN; Mayo Clinic, Rochester, MN; University of Minnesota, Minneapolis, MN.

Background: Clinical practice guidelines (CPG) are evidence-based guidelines, which serve as a standard of care in practice, quality improvement and reimbursement. There are over 700 nephrology clinical practice guidelines (CPG) that are maintained by different organizations. Our study evaluated the extent of COI in the Kidney Disease Improving Global Outcomes (KDIGO) practice guidelines. We also attempted to correlate this to the level of evidence and strength of recommendations outlined in KDIGO guidelines.

Methods: We examined 9 of the most recent KDIGO’s CPG which developed between 2008 and 2013. Using disclosure lists, we catalogued COIs for participants in each CPG work group. The categories included: Advisor/ consultant, Honoraria, Travel stipend, Grant/Research support, Speaker, Equity interest, Employees, Board of trustees, Royalties, Board of Directors, Employment, Ownership interests, Data monitoring committee, Expert testimony and Development of education materials. We reviewed COIs for members of the evidence review team (ERT) as well. We cataloged the companies/ institutions involved in each disclosure. Episode descriptive instances of participation of an individual in 1 company in 1 category of each guideline. “Company” describes a commercial, industry or institute affiliation reported by an individual in each episode. We correlated this data to a previously published article: A systematic review of evidence underlying KDIGO guidelines (Am J Kidney Dis.2016 Mar; 67(3):417-22).

Results: 93 (65.9%) of a total of 141 individuals reported COIs. A total of 758 episodes were disclosed. Being a consultant/ advisor was the most common category (31%) followed by Grant/ research support (29%). The % of episodes varied between CPGs (6.3%-19.5%). A total of 127 companies were associated with COI disclosure. 1 company was the most frequently reported company involving 82 (10.8%) of the 758 episodes. Only 1 member in the ERT reported 1 COI. The guideline with the maximum episodes (19.5%) had 3% recommendations as Category 1A and 33% as 2C. Guideline with lowest number of episodes (6.3%) had the highest number of recommendations category 1A (19%).

Conclusions: COIs are prevalent in KDIGO guidelines with up to 2/3rds of participants disclosing COI. The ERT however had only one COI to report. We were not able to clearly correlate the strength of recommendations in each guideline with COI in the same guideline.

SA-PO925

Knowledge and Practice Patterns in the Diagnosis, Evaluation, and Management of Mineral Bone Disease in CKD among Primary Care Physicians and Nephrologists in Haiti, Brazil, Venezuela, Mexico, and the USA for specific training in HD, central line placement, urinalysis, AKI diagnosis, care, supported the physicians and nurses at HUM, and may provide a partial answer to the problem of “brain-drain” that impedes Haitian medical care.

Patients with stage 4 or 5 chronic kidney disease (CKD-MBD) is a systemic disorder encompassing mineral, bone, and calcific cardiovascular abnormalities that develop as a complication of CKD and contribute to morbidity and mortality in these patients. Despite the availability of guidelines, there continues to be a disparity in practice patterns contributing to therapeutic inertia. Our aim was to identify gaps in knowledge and variations in clinical practice among primary care providers in comparison to nephrologists regarding the diagnosis, evaluation and management of CKD-MBD especially in earlier stages of CKD when patients might not be followed by a nephrologist.

Methods: This study was conducted using a questionnaire which was distributed to residents, fellows and faculty in primary care specialties and nephrology. Questions were derived from the 2009 practice guidelines from the Kidney Disease Improving Global Outcomes work group and the 2003 National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease.

Results: Nephrologists scored higher than primary care physicians in all areas tested including pathophysiology of the disease, screening parameters and intervals, target levels and treatment strategies. The difference in score was statistically significant in the majority of those areas. Overall, primary care specialists (n of 51) scored an average of 31.7 % while nephrologists (n of 11) scored an average of 80.3 % (p-value <0.01).

Conclusions: Our investigation showed there is a significant discrepancy in knowledge between primary care physicians and nephrologists regarding the diagnosis and management of CKD-MBD. It is necessary to improve primary care physicians’ knowledge and practice in this field to provide high quality care to patients. Our next steps include physician education and creation of best practice advisory alerts using the electronic medical record system which will include criteria for appropriate nephrology referral for this subset of patients.

Funding: Private Foundation Support

SA-PO926

Examining Patients’ Knowledge about AKI in Hospital Survivors Followed in a Dedicated AKI Clinic Victor M. Ortiz-Soriano,1 Joseph L. Alcorn,1 Fabiola G. Gianella,2 Brian S. Armentrout, MS, PA-C,3 Taha Ayach,1 B. Peter E. Sawaya,2 Hartmut H. Maillucl,1 Javier A. Neyra.2

1 University of Kentucky, Lexington, KY; 2 University of Kentucky Medical Center, Lexington, KY.

Background: Acute kidney injury (AKI) survivors are at high risk of adverse outcomes. There are few clinics dedicated to improving the care of AKI survivors. Specialized post-discharge nephrology care may improve AKI literacy and prevent renal insult and complications. We obtained self-rated AKI knowledge in AKI survivors followed in a specialized AKI Clinic.

Methods: This is a prospective study of 62 non-diabetes dependent AKI survivors. Patients self-rated the level of knowledge about their AKI diagnosis and the level of understanding of what AKI is. The ERT was defined by KDIGO criteria. Patients’ ratings (scale: 1 lowest to 5 highest) were compared by KDIGO stages and by the occurrence of renal recovery (ratio of the first clinic encounter serum creatinine (SCr)/baseline SCr ≤ 1.5). Mixed-model ANOVAs were utilized.
Results: Mean (SD) age was 54 (14.7) years; 51.6% were males and 87.1% whites. Patients’ ratings of their knowledge about AKI significantly increased following the clinic encounter \((p<0.001\) for each KDIGO stage [Figure 1] and each renal recovery group). Patients with AKI KDIGO Stages 1 and 2 rated their AKI as less severe than patients with AKI Stage 3 \((p=0.049)\) and Stage 3D \((p=0.002)\). There were no differences in the level of severity of AKI ratings by renal recovery status.

Conclusions: Post-discharge specialized nephrology care increased patients’ self-assessed knowledge about their AKI diagnosis. Patients with higher KDIGO stages rated the severity of their AKI as more severe than those with lower KDIGO stages, indicating that the survey has face validity. Future studies should examine the impact of patients’ AKI literacy on patient-centered outcomes.

SA-PO927
Talking Animated Videos to Educate Patients with Kidney Disease
Jonathan Slater, Longmeadow, MA.

Background: Improved patient understanding of their disease state promotes engagement and facilitates partnership and shared decision making. Digital Health education utilizing animated videos (AV) are gradually being incorporated into EMRs (e.g. EMMI, EPOCH, etc.) to help fill this need; however, there is very limited data on their effectiveness in educating both low and high healthcare literate patients. Kidneyman (KM) had its beginnings 7 years ago with a mission for patient education. It has now created a library of AV for patient kidney education. This study provides a preliminary assessment of the effectiveness of these AV in educating different sub-populations.

Methods: The following AVs from the library of KM were used for this study: Understandig Chronic Kidney Disease (A) and Treamnt Options for patients with ESRD (B). The AVs, which are 3-7 minutes in length, were shown to different sub-population incuding: high-schoolers heath class ; attendees to community outreach Kidney Program and individual patients being seen in Nephrologists outpatient office. Viewers of the videos were given the same specific questionnaire, designed for that particular AV, before and after watching the videos and the results were culminated and analyzed. Videos can be watched by going to kidneyman.co

Results: The results for the Outreach to the Community participants for Video B, the high-schoolers for Video A and B as well as the office patients for both videos all showed significant improvement in number of correct answers after watching the video (see Table and Graph).

Conclusions: The results from this study do support these AVs as being effective in educating 3 different sub-group of populations. The style and format of all the AVs in the Kidneyman library have been specifically designed to reach both low and high healthcare literate people and further testing to validate this is ongoing.

SA-PO928
Enhancing Learning and Interest in Nephrology among United States Medical Students
Hitesh H. Shah, Nupur N. Uppal, Kenar D. Juaveri. Hofstra Northwell School of Medicine, Great Neck, NY.

Background: Interest in nephrology careers remains low among United States (US) medical graduates. The type of nephrology elective that US medical students experience may play an important role in creating and enhancing interest in nephrology career.

Methods: A redesigned 4-week nephrology elective was created at our institution for US medical students. Our redesigned elective included both 2-week inpatient (IP) and 2-week outpatient (OP) nephrology experiences. The OP rotation included 10 half-days of various nephrology clinic experiences, 2 half-days of immediate post-transplant clinic, 1 half-day of kidney donor evaluation clinic, 2 half-days of PD clinic and 3 half-days of outpatient HD rounding. Our redesigned elective also included educational conferences. To evaluate the elective experience, all medical students were asked to complete an online survey following the completion of their rotation.

Results: From July 2012 to April 2017, nineteen 4th year medical students (from 14 different US medical schools) completed our redesigned elective. All students responded to our survey. All reported adequate OP nephrology experience during their elective. 84% of the students had worked with 1 or 2 faculty members during the IP setting. In comparison, 90% were exposed to at least 4 different faculty members during the OP experiences. All students had interacted with at least 3 fellows. All reported that the elective experience enhanced their exposure and knowledge in nephrology. They also thought that this elective structure provided them with a better insight into what nephrologists do in practice. 84% of the students reported that this elective experience created an interest in nephrology career. Majority (68%) of the students responded that they would consider nephrology as one of their 3 top career choices as a result of this elective experience.

Conclusions: Measures to enhance learning and interest in nephrology among medical students are needed. We believe that the restructured elective provides the medical student with a much needed and realistic exposure to nephrology careers. Based on our experience, we recommend nephrology training programs to consider this elective structure for medical students.

SA-PO929
CKD Patient and Provider Feedback Surrounding Dialysis Modality Education
Kristin M. Corapi,1 Warissara Sorat,2 Ishir Bhan.1 Massachusetts General Hospital, Boston, MA; 2None, West Newton, MA; ‘university of Massachusetts Lowell, Lowell, MA.

Background: Both hemodialysis and peritoneal dialysis impact patients’ lifestyles. In an effort to help patients make an informed choice, the nephrology community is
encouraged to provide education about dialysis options. At our hospital, this involves a one on one visit with a nurse educator. In the current project, we talked with patients and providers to get feedback on our dialysis education.

Methods: Patients with chronic kidney disease (CKD) stage 4/5 and providers were invited for semi-structured interviews. The interviews were recorded and transcribed. Qualitative content analysis was conducted by two staff members using NVivo 11. Basic demographics were collected.

Results: The mean age of the ten CKD patients enrolled was 62 years (SD = 9.4). 60% were female and 40% were Caucasian. 40% were not educated beyond high school and 60% reported an annual income of < $20,000. The providers interviewed (n=11) were 5 MD’s, 4 RN’s, 1 social worker, and 10 dietitian. The mean age of providers was 49 years (SD = 13.1) with an average of 18 years in practice (SD = 9.1). 64% were Caucasian and 64% were female. Following the visit, half of the patients reported feeling scared, confused or disappointed to learn they might need dialysis. Similarly, staff depicted patients as in denial, resigned, overwhelmed, and stressed. The majority of patients felt that the single visit provided all of the information needed to choose a modality. The remaining patients (n=4) asked for additional information about diet, lifestyle changes, and how to slow further CKD progression. Staff agreed that diet and lifestyle changes are difficult for patients to understand and might be topics that would benefit from more explanation. Patients recommended the use of videos, written material, emails, and talking to peers as strategies to help improve their understanding. Staff agreed that the addition of a patient network would be beneficial.

Conclusions: The referral to dialysis education is stressful to patients as they begin to accept the severity of their disease. Employing various educational styles, venues, and peer support may help ease these emotions and help patients to choose the modality best for them.

Funding: Commercial Support - Baxter

SA-PO930
Lung Ultrasound in ESRD: Moving from Evidence to Practice
Daniel W. Ross,1 Mohammed Abbasi,2 Kenar D. Jhaveri,1 Mala Sachdeva,3 Richard L. Barnett,1 Mangala Narasimhan,4 Anna Mathew,3 Hofstra Northwell School of Medicine-Northwell health system, Great neck, NY; 4Montefiore Medical Center, Bronx, NY; None, Great Neck, NY; 3North Shore-Long Island Jewish Health System, Great Neck, NY; Medicine, Division of Nephrology, Hofstra Northwell School of Medicine, Great Neck, NY; 1Northwell, Sleepy Hollow, NY.

Background: Lung ultrasound (US) allows for enhanced ability to detect extravascular lung water compared to traditional physical exam or standard chest XRay. This is extremely important for our CKD and ESRD patients to assess volume status. Teaching in using point of care US that includes lung US is vital in this era for our fellows and faculty. We conducted a review of lung US use in dialysis patients and assessed how it was taught to researchers.

Methods: We conducted a strategic search in Medline, Embase, Cochrane, and Web of Science. Eligibility criteria for included studies were: (1) 5 or more adults (age ≥18) with ESRD on chronic dialysis; (2) measured and reported lung US findings; and (3) reported another comparator outcome measure of volume status. Articles that looked at IVC and not lung US were excluded. Titles and abstracts were screened by a single reviewer. Discrepancies were resolved by a third reviewer.

Results: We identified 1,249 articles of potential interest. After title and abstract screening, we reviewed 352 full-text articles. We identified 12 studies where lung US was used to detect extravascular lung water in dialysis patients. In two studies nephrologists were trained but in most studies residents were trained. Reported training time varied from 2 to 3 hours. Time to perform lung US ranged from 6 to 15 minutes. All studies reported high concordance between novice and expert sonographers.

Conclusions: Lung US can be reliably taught to learners in a short 2 to 3-hour training course. Teaching lung US to our nephrology/fellows is an important step to improve care collaboration with our critical care and emergency medicine colleagues and improving volume assessment in our CKD and ESRD patients.

SA-PO931
Patient Engagement in ESRD: Do Patients Know Who Their Nephrologist Is?
Arijun Sekar,1 Leslie P. Wong,2 Cleveland Clinic Foundation, University Heights, OH; Cleveland Clinic, Solon, OH.

Background: Patient engagement describes how involved patients are in their care. We observed that some hospitalized dialysis patients are unable to describe their care, including who their nephrologist is. We hypothesized that patients unaware of these basic details may not actively participate in their care. We performed a survey to assess perceptions of the patient-doctor relationship and dialysis care.

Methods: We included hospitalized adult ESRD patients requiring hemodialysis. Intensive care, peritoneal dialysis and non-English speaking patients were excluded. Subjects completed a questionnaire about routine aspects of their dialysis care. We did a descriptive analysis of their responses and attempted to identify trends based on whether or not they knew their nephrologist’s name.

Results: Of 66 patients approached, 44 completed the survey. Over one-fifth (23%) did not know their attending nephrologist and 54% said a different nephrologist also rounded on them at dialysis. 74% felt their nephrologist answered their concerns promptly; 44% raised their health concerns with the nephrologist all the time. Only 24% were aware of palliative options. While 93% felt maintaining their dry weight was important to their health, only 60% knew their dry weight. Though 90% thought fluid restriction was important, only 60% stated they were compliant. Most (86%) thought controlling phosphorus was necessary but fewer (64%) were aware of its adverse effects. Sub-analysis of responses (Table) was done based on whether or not patients knew their attending nephrologist.

Conclusions: This study aimed at assessing patient engagement in ESRD. A number of patients reported disjointed perceptions of their dialysis care, including an inconsistent relationship with an attending nephrologist. This might impact discussions about palliative care and willingness of patients to follow advice. Better awareness and focus on the patient-nephrologist relationship in dialysis is needed.

RESPONSES BASED ON WHETHER PATIENTS KNEW THEIR NephROLOGIST

SA-PO932
Penile Calciphylaxis: Suspicion Is the Key
Abhilash Koratla,1 Gaineville, FL; 2University of Florida, Division of Nephrology, Gainesville, FL.

Background: Calciphylaxis or calcific uremic arteriolopathy (CUA) is a rare and potentially fatal condition that presents with skin ischemia and necrosis, typically seen in end stage renal disease (ESRD) patients on dialysis. Historically, it is characterized by medial calcification of dermal arterioles. CUA commonly involves legs, abdomen and gluteal region. Herein, we present a case of CUA of the glans penis.

Methods: An 81-year old white man with history of hypertension and CKD stage 5 was admitted to the hospital for uremic symptoms necessitating initiation of haemodialysis. He complained of pain and redness of the glans penis that first appeared 3 weeks ago. At that time, he was treated for possible balanitis with antibiotics and had partial relief. He denied having any fever, chills, difficulty urinating or discharge from the urethra. On examination, he had purpuric patches, erosions and superficial necrosis of penile glans with minimal tenderness (Figure 1A). His labs were significant for serum...
Fellows/Residents Case Reports: ESRD: HD, PD, Transplant

SA-PO933

A Wolf in Sheep’s Clothing: Calciphylaxis, Inocuous at First Glance

Stefan C. Hemmings, Derek M. Fine. Johns Hopkins University School of Medicine, Baltimore, MD.

Background: Calciphylaxis is a debilitating skin condition with high mortality seen in patients on dialysis who are at particular risk due to disordered calcium and phosphorus metabolism. Its early features are unfamiliar to many clinicians.

Methods: A 61 year old woman with diabetes on peritoneal dialysis for 5 years with adequate clearance by Kt/V was noted to have an erythematous painful lesion on the left leg (fig. 1A), which was diagnosed as shingles by her primary physician. She presented 2 days later to hospital for complaints of abdominal pain and was noted to have shallow ulceration of the lesion (fig.1B). She was evaluated by dermatology who felt that is was most consistent with venous stasis. Labs results: Calcium 10mg/dL, Phosphorus 6.4mg/dL, Cal-Phos product 58, iTPTH 244pg/dL and 25-hydroxyvit D 47.5ng/mL. She was on 30mg cinacalcet for hyperparathyroidism. She followed up in dermatology clinic a few days after discharge and the ulceration had deteriorated as shown in fig. 1C. Concern for its progression prompted a skin punch biopsy that confirmed the diagnosis of calciphylaxis with histopathological features of vascular medial calcification (figs. 2A and 2B). She was re-admitted and transitioned to hemodialysis for aggressive therapy with sodium thiosulfate. Despite this, the area of involvement progressed extensively in the left leg and new lesions on the fingers developed. After 10 weeks of treatment the leg lesion appeared to stabilize with eschar formation and healing skin at the borders (fig. 1D).

Results: Nephrologists and internists alike need to be aware of the initial innocuous presentations of calciphylaxis that may not raise clinical suspicion. The classic eschar is oftentimes a late feature. Early recognition can prevent the morbidity and mortality related to infections and amputations associated with delayed treatment, as the condition can progress rapidly. High vigilance for painful skin lesions is required in patients on dialysis.

SA-PO934

A Rare Case of a Large Calcified Mass in a Calciphylaxis Patient

Raja A. Pattil,1 Jason Cobb,1 Peter Darin,1 Carol A. Gray,2 William McKinnon.2

1Colorado College, Decatur, GA; 2Emory Healthcare, Atlanta, GA; 3Emory University School of Medicine, Atlanta, GA; 4Peachtree Vascular Surgery, Atlanta, GA.

Background: Calciphylaxis is a rare clinical disorder in patients with ESRD and is characterized by painful skin ulcerations due to ischemia and necrosis of the skin and subcutaneous adipose tissue. The disorder carries a mortality rate of 80% in the first year, and death is often due to recurrent infections leading to sepsis. The pathogenic mechanism is not clearly understood and therapeutic options are limited. We present a rare case of a calcified tumor from a patient suffering from calciphylaxis measuring 23.0 x 22.0 x 6.5 cm and 27 x 26 x 7.5 cm on the medial aspect of the thigh.

Methods: A 58 year old female with ESRD due to a collapsing glomerulopathy, diabetes, developed symptoms of pain and skin ulcerations over her bilateral lower extremities and abdomen. A tissue biopsy of the lesions revealed necrotic ulcerations of the epidermal and dermal layers, and focal calcium deposition in the subcutaneous adipose tissue. She presented to the hospital with symptoms of fever, weakness and pain, with large areas of induration and skin ulcerations (the largest measuring 20 cm) over the inner aspects of the thigh bilaterally. Examination revealed a large area of induration and skin ulcerations with a large firm mass. Lab levels included PTH <100 pg/ml (she presented on cinacalcet), serum phosphorus within normal limits, and unfortunately she had been on long-term warfarin due to chronic dialysis access thrombosis. She was transferred to our hospital for further management of calciphylaxis which included wound care, surgery debridement, and hyperbaric oxygen therapy. Vascular surgery excised 23 x 26 x 7.5 cm and 23.0 x 22.0 x 6.5 cm masses from the right and left inner thigh. Histopathology examination confirmed vascular calcifications, fat necrosis with fibrosis, inflammation, and subcutaneous calcification classically described in calciphylaxis. Approximately one month after surgery the patient subsequently succumbed to sepsis.

Conclusions: Although calciphylaxis most commonly presents with skin ulcerations and calcified deposition under the skin, this is an unusual case of calciphylaxis which manifested in the form of a large calcified mass. This is rarely described in the literature and one of the first cases of an excised mass with a pathological diagnosis. The pathogenesis of this proliferation of tissue in calciphylaxis needs to be further identified and studied.

SA-PO935

Acute Esophageal Necrosis (Black Esophagus) Complicating Calcific Uremic Arteriopathy

Jawed Akhtar, Vijaya Kumar Gorantla,1 Barry M. Wall,2,3 UTCSC, Memphis, TN; 2Veterans Affairs Medical Center, Memphis, TN.

Background: Calcific uremic arteriopathy (CUA) is associated with medial arterial calcification with vascular thrombosis and necrosis. While skin manifestations predominately, CUA rarely involves the gastrointestinal tract.

Methods: A 76-year-old male receiving chronic hemodialysis for 7 years presented with severe penile pain with ulceration due to phimosis and balanitis, requiring surgical debridement. Pathology confirmed medial artery calcification and tissue necrosis, consistent with CUA. He later developed nausea and melena. Endoscopy revealed black, friable mucosa of nearly the entire esophagus with a clear transition to viable tissue at the gastroesophageal junction. Pathology confirmed necrosis and the diagnosis of acute esophageal necrosis was made. He was placed on IV proton-pump inhibitors (PPI) and TPN. Workup for vasculitides was negative. HIV, fungal, HSV-2, and CMV tests were all negative. Calcium (11.4 mg/dL) and parathyroid hormone (PTH: 525 pg/mL) were noted to be elevated. Parathryoid scan confirmed a hyperparathyroidism. Patient received non calcium phosphate binders, pamidronate and sodium thiosulfate with dialysis. Patient declined daily dialysis or parathyroidectomy. Cinacalcet was started when oral intake improved. Follow up: PTH improved to 390 pg/ml, calcium 9.0 mg/dl and PO4 3.5 mg/dl. Repeat endoscopy revealed significant improvement with persistent severe esophagitis in the distal and middle third of the esophagus with a normal proximal third. He was started on a clear liquid diet and transitioned to oral PPI. TPN was discontinued 5 days later. He was discharged to a rehabilitation center, receiving oral liquid nutritional supplement (1800 cal/day) with no further gastrointestinal symptoms or bleeding.

Results: Gastrointestinal manifestations of CUA include mucosal erosion, diffuse ulcer formation, and bowel perforation arising from bowel infection. Gastrointestinal bleeding is a common presentation. Acute esophageal necrosis, a rare cause of upper gastrointestinal bleeding is found in patients with significant morbidities and is associated with high mortality. To our knowledge, there have been no prior reports involving coexistence of these conditions.

Funding: Other U.S. Government Support

SA-PO936

Native Kidney Ossseous Metaplasia – Incidental Finding or a Disease to Treat

Groyegi Okechuku,1 Saed Shawar,1 Jingyin Yan,2 Baylor College of Medicine, Houston, TX; 2None, Houston, TX.

Background: Ossesous metaplasia is an atypical phenomenon involving the formation of the bone tissue outside the skeletal system. This pathologic process may occur in sites such as the skin, subcutaneous tissue, and skeletal muscle, occasionally seen in visceral.
organ like intra-abdominal sites. We describe a case of osseous metaplasia in a native kidney.

Methods: We present a 26 year old African American woman with biopsy proven minimal change disease (MCD) at age of 5. Her disease course is significant for been steroid dependent initially with multiple relapses upon steroid taper and partial remissions. She had 3 biopsies in childhood. All 3 were consistent with minimal change disease. Her treatment regimen consisted of steroids, cellcept, started after she had side effect from cyclosporine and Lithisoprin. She presented to our Nephrology clinic with worsening SOB, orthopnea and PND. Physical examination was significant for fine crackles in lungs, and 3+ bilateral pitting edema. Labs showed serum calcium 8.2, phosphorus 4.1, vitamin D 34, and bicarbonate of 28, BUN of 15 and creatinine of 0.6. Her white cell count was 6.8, with hemoglobin 6.6, Platelets were 113. Her urinalysis was notable for 2+ proteinuria. C3 and C4 were normal. Negative RF; negative ANA; normal serum protein electrophoresis and light chain assay, dsDNA, ANCA were negative. A renal scanogram was unremarkable. A repeat renal biopsy was done findings suggested Minimal change disease. However, we found unmineralized osteoblast within 1 glomerulus.

Results: Osseous metastasia (OM) pathophysiology is not well known, but many factors have been incriminated including chronic ischemia, trauma, and chronic inflammation. The pathogenesis of this finding is not well understood. Osseous metastasia has been described in some transplant allograft, and associated with malignancies affecting the kidney, some leukemias and basal cell carcinoma. Ectopic calcifications are different entities. OM is asymptomatic and probably often confused with ectopic calcifications since their radiological aspects are identical. Treatment usually is watchful waiting approach.

Conclusions: 1

SA-PO937

Perioperative Acute Systolic Cardiac Dysfunction as Complication of Parathyroidectomy Itunu O. Owoyeni,1 Angie G. Nishio-Lucar,4 Sundaramaran Swaminathan,7 Karen M. Warburton,1 Gayle M. Vranic,2 Peter I. Lobo,5 Alden M. Doyle,1 Charlottesville, VA; University of Virginia Health System, Charlottesville, VA; University of Virginia, Charlottesville, VA; University of Virginia HS, Charlottesville, VA.

Background: Several factors including hypocalcemia have been incriminated in the pathogenesis of abnormal cardiac function in End Stage Kidney Disease (ESKD).

Methods: We report a case of a 57 yo woman with ESKD due to hypertension failed kidney transplant graft from BK nephropathy 8 years ago referred for management of severely elevated parathyroid hormone levels (PTH). Patient had undergone subtotal parathyroidectomy 5 years prior. Despite intensive therapy with calcitriol and cinacalcet, her PTH levels had remained around 2000 pg/mL. She had stress test done 2 months prior to operation that showed no evidence of inducible myocardial ischemia and preserved ejection fraction. Her evaluation included a sestamibi scan with showed activity within the mediastinum prompting the decision for resection and auto-transplantation. A day prior to surgery, she received IV calcitriol during dialysis and was down to her target weight. Cinacalcet was discontinued. Her surgery was uncomplicated. She received 1 g of IV calcium chloride. She was extubated quickly in the recovery room and initially did well.

Over the next hour, she developed acute shortness of breath with hypercapneic respiratory failure. A stat chest X-ray revealed left pleural effusion and mild cardiomegaly, which were new findings compared to chest X-ray done a day before surgery. Pertinent laboratory findings prior to this episode include hemoglobin 10.7mg/dL, ionized calcium 3.9 mg/dL, and phosphorus 7.7 mg/dL. PTH was 190 pg/mL, down from 1399 pg/mL at beginning of surgery, troponin 0.03 with no EKG changes. An Echocardiogram done showed decreased left ventricular systolic global function and small pericardial effusion adjacent to the right ventricle. A protocol for prevention of hypocalcemia was done to discontinue the medications.

Conclusions: Modifications of myocellular calcium interactions or sensitivity which may alter relaxation and contribute to cardiac dysfunction. Patients with severe hyperparathyroidism are at risk in the early post-operative period and should be monitored closely for hypocalcemia and, less commonly, acute cardiac dysfunction.

SA-PO938

Acute Neurological Syndrome Complicating Secondary Hyperparathyroidism Ravina Patel,1,2 Michael R. Wiederkehr,2 Baylor University Medical Center, Dallas, TX; ‘Dallas Nephrology Associates, Dallas, TX; ’Methodist Dallas Medical Center, Dallas, TX.

Background: Long-term severe secondary hyperparathyroidism in dialysis patients can lead to formation of “brown tumors,” a benign but locally aggressive neoplasm of predominantly osteoclast-like giant cells in a fibrous stroma. They present as single or multiple lesions and are locally destructive; they are lytic and expansive processes. Parathyroidectomy is preferred over medical management. Here we describe a case of acute cord compression caused by a brown tumor.

Methods: A 33-year-old Hispanic female, dialysis dependent for 9 years, presents with progressive lower extremity weakness and back pain. She had many years of uncontrolled hyperparathyroidism. Levels of iPTH were consistently above 2000, but recently up to 5500. Addition of cinacalcet improved PTH but it remained above 3000. Hypercalcemia indicated development of tertiary hyperparathyroidism. Imaging now revealed numerous lytic lesions through the spine, ribs, and sternum, and two expansive masses at T3 and T12 with severe spinal cord compression is at T3 with associated cord edema (see image), moderate spinal canal stenosis at T12. She underwent emergent T2-T4 laminectomy with resection of the tumor, followed by subtotal parathyroidectomy one week later. Intraoperative PTH dropped from 2558 to 268, and to 11 the following day.

Results: A 61 year old female with lupus nephritis causing ESRD, on dialysis for 8 years, underwent deceased donor KTxs with immediate graft function. Basiliximab was used for induction and Tacrolimus, Mycophenolate and Prednisone for maintenance immunosuppression (IS). Hypercalcemia early after transplant prompted Cinacalcet initiation and its persistence required dose up-titration on follow up. A 3.5 gland parathyroidectomy (PTX) performed 4 months after KTxs was complicated by post-op acute kidney injury, with moderate hydropnephrosis and distal ureter obstructing calculus seen on allograft imaging. Impacted stones in the ureteral orifice were partially removed by cystoscopy, but stent placement was unsuccessful requiring percutaneous nephrostomy. Serum creatinine (Scr) improved. Kidney biopsy was performed 6 months post-PTX for elevated Scr, BK Viremia and de-novo donor specific antibody to DR14 and DR52 HLA antigens. Morphologic examination revealed acute tubular epithelial cell injury in addition to luminal depositions of calcium phosphate, consistent with NC, with no evidence of rejection or BK nephropathy. Allograft function stabilized after percutaneous nephrolithotripsy and nephroureteral catheter placement. Stone analysis revealed calcium oxalate (20%) and calcium apatite (80%).

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

Underline represents presenting author.

Poster/Saturday

923
SA-PO940
Disseminated Bartonellosis Masquarading as PTLD in a Renal Transplant Recipient

Nrijan Tandukar, Christine Wu. University of Pittsburgh Medical Center, Pittsburgh, PA.

Background: A solid organ transplant recipient is at high risk for infections due to immunosuppression. We report a case of a renal transplant recipient presenting with diffuse lymphoproliferative disorder concerning for PTLD who was found to have disseminated bartonellosis.

Methods: A 52 year old male presented 11 months following his renal transplant (CMV +/-, EBV +/−) with complaints of malaise, drenching night sweats and fever to 103.8°F while on tacrolimus and mycophenolate mofetil. Review of systems was positive for a cat scratch on his knee several months back. He was hemodynamically stable on presentation. On exam, he had tender right inguinal lymphadenopathy. Urethral, chest x-ray and blood cultures were negative. His WBC count was 6,700/mm₃ and creatinine was 1.4 mg/dl (baseline 1.2 mg/dl). CT scans showed left supravacular, axillary, retroperitoneal and iliofemoral lymphadenopathy with hypodense lesions in the liver, spleen and renal allograft. PCR showed 110 copies/ml EBV and no CMV. Serologies for Bartonella henselae were positive for IgG (1.512) and IgM (1.80). Lymph node biopsy showed necrotic areas, neutrophilic abscesses with focal positivity for Bartonella and large abnormal cells that were EBV positive. He was treated with azithromycin and doxycycline for 8 weeks. His symptoms, along with lymphadenopathy, splenic and liver lesions on repeat CT scan resolved completely. His creatinine stabilized at 1.3-1.7 mg/dl.

Results: Conclusions: PTLD is characterized by lymphoid proliferation of B cells that may be monoclonal or polyclonal in origin and affects up to 1-2% of kidney transplant patients. As in our case, patients with PTLD often present with fever, malaise and lymphadenopathy. Bartonella henselae is a bacterium that is transmitted from cats to humans from a scratch or bite. Infected patients often present with fever, lymphadenopathy and night sweats. Dermatologic and neurologic findings may also be present. In an immunocompromised patient, the features may be more severe, with dissemination to other organs. In our patient, complete resolution of symptoms and CT findings following antibiotic treatment confirmed the diagnosis of bartonellosis. Disseminated bartonellosis should be considered in transplant patients presenting with fever and lymphadenopathy.

SA-PO941
Rapid Onset Donor Cell Transformation into Plasmacytoid Post-Transplant Lymphoproliferative Disorder (PTLD) in a Kidney Transplant Recipient

Mahmoud A. Mahmoud,1 Barry M. Wall,2 Manish Talwar.1 University of Tennessee Health Science Center, Memphis, TN; 2Veterans Affairs Medical Center, Memphis, TN.

Background: Post-transplant lymphoproliferative disorder (PTLD) is a complication of both solid organ transplant and allogeneic bone marrow or stem cell transplants. PTLD is most often recipient B cell lineage and is typically associated with Epstein-Barr Virus (EBV) infection.

Methods: A 56-year-old AA male with ESRD secondary to hypertension received a kidney transplant from a 9 year-old deceased female donor. Donor and recipient EBV IgG were positive. He received induction with thymoglobulin and maintenance therapy with mycophenolate, tacrolimus, and prednisone. Hospital discharge creatinine was 4.9 mg/dl and 1.8 mg/dl on post-op day 15. Alloagraft biopsy (Figure 1), performed on post-op day 48 due to rising creatinine and fever, revealed a massive plasma cell infiltrate with multiple negative for EBV, but strongly CD38 positive with monotypic lambda light chain expression by in situ hybridization, consistent with PTLD. Receiver EBV IgM and early D antigen were negative posttransplant, and EBV serum PCR was <500. There was no evidence for cellular or vascular rejection. FISH studies revealed a female cell population comprising the plasmacytoid infiltrate. Recipient bone marrow examination was negative for PTLD. Immunosuppression was withheld and treatment was attempted with bortezomib and cyclophosphamide; however, renal function declined and he resumed hemodialysis. Alloagraft nephrectomy showed diffuse hemorrhagic necrosis of parenchyma with persistent plasma cell infiltrates.

Results: Conclusions: FISH studies performed on the preserved kidney tissue showed a predominant female cell population comprising the atypical plasmacytoid infiltrate, confirming that PTLD was donor derived. There has been no evidence of persistent PTLD in the patient during 10 months of followup. Recipients of other organs from the same donor have not developed PTLD after 10 months of followup.
SA-PO944
One Drug’s Promise Leads to an Unavoidable Complication
Andrew Kowalski,1 Daniel Fantus,1 John J. Friedewald,2 1Comprehensive Transplant Center, Northwestern University, Chicago, IL; 2Northwestern University, Lombard, IL.

Background: CMV is a major pathogen for immunocompromised patients, especially including solid organ transplant recipients resulting in a broad range of syndromes and inducing organ rejection. This case study examines the course of denovo CMV infection in the setting of immunosuppression with belatacept.

Methods: 48 yo male, with a history of CKD stage V due to IgA nephropathy who underwent a successful living related kidney transplant in 7/2015. Due to his HLA status he received a steroid protocol induction and then transitioned to mycophenolate mofetil and tacrolimus. In the next few months he was transitioned to belatacept and off tacrolimus based on a study protocol. A year later he presented with complaints of vague abdominal pain and diarrhea. He was found to have a CMV viral load of 439,804 IU/mL, and placed on ganciclovir. His viral load decreased and then rose to 55,267 IU/mL the following month despite continued ganciclovir. He complained of worsening gastroenteritis symptoms and his viral load was 152,305 IU/mL. Belatacept was discontinued to boost his white cell count and his CMV viral load decreased to 7000 IU/mL, but his creatinine increased to 17. He was then started on ganciclovir.

Results: Belatacept binds to CD80 and CD86 receptors and blocks the required CD28 mediated interaction between APCs and T cells needed to activate T lymphocytes. The nature of belatacept prohibits the body to mount a response against EBV leading to an increase in PTLD. We recommend that this concern be extended to CMV negative patients as this case shows that the use of belatacept hinders the ability of the body to mount a response leading to uncontrolled infection and necessitating the use of nephrotoxic medications.

SA-PO946
Bullous Pemphigoid and Renal Transplant Rejection: More Than a Mere Coincidence?
Abhilash Koratala,1 William L. Clapp,2 Olarerewu A. Olayo,3 Alfonso Santos,2 1University of Florida, Division of Nephrology, Gainesville, FL; 2University of Florida, Gainesville, FL.

Background: Bullous pemphigoid (BP) is an autoimmune blistering disorder characterized by subepithelial blister formation and deposition of immunoglobulins and complement in the epidermal and/or mucosal basement membrane zone. There are few case reports on the association between BP and allograft rejection, and membranous nephropathy (MN). We report a unique case of BP associated with both acute cellular rejection (ACR) and de novo MN in a renal transplant recipient.

Methods: A 63-year-old man with a history of ESRD secondary to MN, with post living related kidney transplant 5 years ago who has been compliant with his immunosuppressant regimen was admitted for worsening skin rash that started 3 weeks ago and acute kidney injury. Skin exam revealed multiple scattered bullae with clear fluid and erosions with a collarette of scale on the neck, chest, back and limbs. His serum creatinine (Scr) was 7.3 mg/dL at presentation (~1.5). Urine exam showed 45/100 hpf RBC, 1/100 WBC and an albumin-creatinine ratio of ~0.5 g/g. BK virus, CMV, Herpes simplex and Varicella zoster serologies were negative. Skin biopsy revealed BP. His Scr minimally improved with supportive measures and allograft biopsy showed Banff 2A ACR with de novo MN and ~50% interstitial fibrosis and tubular atrophy (IFTA). He was treated with pulse corticosteroid and antithymocyte globulin but his Scr remained unimproved after 1 month. Further immunosuppression was not attempted due to the severity of IFTA on repeat biopsy. His skin lesions eventually improved with high-dose steroid therapy.

Results: Conclusions: Though the possibility of multiple distinct autoimmune processes cannot be excluded, allograft rejection-induced immune stimulation or anti-basement- membrane antibodies or antibody interactions and cross-reacting mechanisms for the simultaneous skin and renal involvement. Whether the diagnosis of BP in a renal transplant recipient warrants kidney biopsy remains unanswered.

SA-PO947
Long-Term Outcome after Treatment of Plasma Cell-Rich Rejection of the Kidney in Simultaneous Kidney and Pancreas and Kidney and Liver Transplant Recipients
Ksenija Vučur,1 Zeljka Jureković,1 Branimir Cingel,2 Danica G. Ljubanovic,1 Mladen Knoteč,1 1University of Zagreb School of Medicine, Clinical Hospital Dubrava, Zagreb, Croatia; 2Department of Nephrology, University of Zagreb School of Medicine and University Hospital Merkur, Zagreb, Croatia.

Background: Although plasma cells (PC) participate in the kidney graft rejection, their major involvement (i.e., plasma cell rich rejection - PCRR) is rare. We identified three cases with PCRR among simultaneous kidney-pancreas (SPKT) and liver-kidney (SLKT) recipients in our center.

Methods: Case I: A 35-yr old Caucasian male who had SPKT in 2006 presented three months posttx with renal dysfunction. Kidney biopsy (bx) showed acute cellular rejection (ACR) IB with infiltrate consisting of 17% of PC. Donor-specific antibodies (DSA) were negative. After treatment with steroid boluses there was only a mild decrease in serum creatinine, and the second bx revealed again PCAR. Treatment with high-dose (2 g/kg) IVIG and boluses of steroids led to normalization of renal function. On a follow-up bx at 1 yr, there were no signs of rejection. Eleven yrs later, both graft function is excellent. Case II: A 55-yr old Caucasian male who received SLKT in 2006 presented two yrs after tx with renal dysfunction. Kidney bx revealed ACR IB. The infiltrate consisted of 27% PC. After treatment with high-dose IVIG and steroid boluses, a repeat bx showed no signs of acute rejection. Subsequently, the patient had persistent stable renal dysfunction. He died in 2012 from sepsis. Case III: A 36-yr old Caucasian male presented in 2009, four yrs after SPKT with worsening of renal function. Kidney bx revealed acute PCRR with microvascular injury (MVI) that was treated with steroid boluses. At that time he had DSA against DQ and DR. Subsequent two bx showed persistent ACR and the treatment included high-dose IVIG. Afterwards renal function improved, but five yrs later serum creatinine increased again, and on biopsy PCRR with MVI was again diagnosed. He was treated with bolus of steroid boluses and was eventually discharged. On the last visit in 2017 patient had both graft function stable with creatinine 155 µmol/L.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
AKI Post Kidney Transplant Associated with Macroscopic Glomerular Hematuria Secondary to Rivaroxaban Magdi H. Abdelrahman,1 Muhammad R. Mustafa,2 Praveen N. Chander,1 1New York Medical College, Valhalla, NY; 2Westchester Medical Center, West Harrison, NY

Background: Reversible AKI secondary to macroscopic glomerular hematuria (MGH) has been described in IgA nephropathy, Anticoagulant-related nephropathy (ARN) and rarely in Thin GBM disease in the native kidneys. Acute tubular damage and widespread intraluminal obstructive RBC casts are salient histologic features. ARN is classically caused by warfarin; however other anticoagulants have been reported to cause it. We report a case of reversible AKI associated with rivaroxaban post heart and kidney transplant.

Methods: A 51 yo male with a history of non-ischemic cardiomyopathy and ESRD due to ANCA-associated vasculitis underwent combined heart and kidney transplantation from his deceased donor. He received Induction with basiliximab and methylprednisolone. Post-operative course was complicated by the development of catheter-related intra-jugular vein thrombosis and he was started on intravenous heparin. His maintenance immunosuppression regimen and then the sarcoma was significantly reduced. The diagnosis of Kaposi’s sarcoma. Everolimus was added to immunosuppression therapy in an attempt to treat the sarcoma but without success. The patient received a kidney transplant from her husband. Because of ABO-incompatible KT, she was treated with rituximab, and pulse steroids. SCr dropped to 1.6 mg/dl in 2 weeks. Tacrolimus level was 11.6; ANCA titer was 1:640. Large numbers of RBCs were detected on urinalysis. A transplant kidney biopsy showed a small segmental epithelial crescent in 1/11 glomeruli and numerous RBCs in the Bowman’s space of another, without any necrotizing or other significant lesions. Widespread intraluminal obstructive casts were present in tubules. The degree of renal impairment and tubular RBC casts were disproportionately greater than the glomerular disease suggesting coexistent ARN. Rivaroxaban was stopped; the patient was treated with rituximab, and pulse steroids. SCr dropped to 1.6 mg/dl in 2 weeks.

Results: Common etiologies of renal dysfunction in the early period post-transplantation are acute rejection, recurrent primary disease, or calcineurin inhibitor nephrotoxicity. To our knowledge, this is the first case of AKI post combined heart and kidney transplantation due to ARN (rivaroxaban). In conclusion, MGH of any type-rivaroxaban obstructing renal tubules should be considered in the differential diagnosis of early post-transplant acute kidney injury especially in patients on anticoagulants. Renal histology can be of help in evaluating such cases.

Conclusions: Kidney transplant patients with Kaposis’s sarcoma are supposed to increase in number with the progress of immunosuppression therapies. Everolimus, which is expected to have an anti-angiogenic effect, may be one of therapeutic options for Kaposis’s sarcoma associated with immunosuppression therapies.
Hiden, Donor-Derived Malignancy: A Tale of Two Kidneys Amalewari Pamarthy,1 Pradeep Vaitla,1 Madisson, MS,2 UMCAD, Madison, MS.

Background: PTLD (Post-transplant lymphoproliferative disorder) is a relatively common malignancy but rarely donor derived. PTLD includes clinical syndromes ranging from uncomplicated post-transplant infectious mononucleosis to true neoplasms with monoclonal chromosomal abnormalities which may or may not be associated with EBV infection. Most cases occur in the first year. Mortality is as high as 50-80% in monocular form. High index of suspicion and clinical vigilance is critical since patients can present with nonspecific symptoms & signs. Pathophysiology is not well understood. Hence anticipation and prevention of PTLD remains a challenge.

Methods: Mate kidneys obtained from EBV and CMV IgG negative donor were transplanted to 69-year-old male and 68-year-old female who were positive for EBV IgG and CMV IgG. Kidney and spleen biopsies were done at procurement. Both patients received induction with Anti-thymocyte globulin and maintained on Tacrolimus, Mycophenolate mofetil, Prednisone. Kidney biopsies at the time of transplant and imaging revealed a large para-aortic mass arising from transplant kidney, the biopsy confirmed plasmacytoma. The second patient presented with urinary retention and imaging revealed a large para-aortic lymph nodal mass. Biopsy confirmed plasmacytoma as well. Both patients were started on chemotherapy and doing fairly well now.

Results: Despite having a normal kidney biopsy at the time of transplant, donor-derived malignancy can be transmitted through lymphatics of the donor organs. If suspicion for PTLD is high, more aggressive screening and high clinical vigilance is indicated. Negative homonarrows biopsies might not preclude from having PTLD. If high suspicion for EBV-related PTLD presents, prophylactic therapies including antiviral agents and immunoglobulins were proposed but need to be tested in randomized, placebo-controlled trials to determine their true efficacy. Decreasing the immunosuppression is the cornerstone and might help with regression of the PTLD.

Conclusions: Despite having a normal kidney biopsy at the time of transplant, donor-derived malignancy can be transmitted through lymphatics of the donor organs. If suspicion for PTLD is high, more aggressive screening and high clinical vigilance is indicated. Negative homonarrows biopsies might not preclude from having PTLD. If high suspicion for EBV-related PTLD presents, prophylactic therapies including antiviral agents and immunoglobulins were proposed but need to be tested in randomized, placebo-controlled trials to determine their true efficacy. Decreasing the immunosuppression is the cornerstone and might help with regression of the PTLD.

An Unusual Case of Renal Cell Carcinoma (RCC) with Sarcomatoid Changes in a Renal Transplant Allograft Muhammad O Salmon, Laura L Mulloy, Carlos F Zayas, Rajan Kapoor, Augustana University, Medical College of Georgia, Augusta, GA.

Background: Renal transplant recipients are at a higher risk of developing RCC than general population. RCC in renal transplant allograft is unusual. We present a rare case of highly aggressive RCC with sarcomatoid changes in an allograft.

Methods: A 69-year Caucasian female with CKD stage 5 due to Autosomal Dominant Polycystic Kidney Disease (ADPKD) received a preemptive deceased donor kidney transplant. She presented 2 years post transplant with persistent hematuria. CT scan revealed 3.4 x 2.9 x 2.3 cm hypo-enhancing structure with mild to moderate enhancement and mild surrounding inflammatory change. Sonography-guided percutaneous needle biopsy of pelvis mass in the graft kidney revealed a low grade urothelial cell carcinoma. Radical graft nephrectomy and ureter lumen, which invaded to periuretal fat and renal parenchyma with lymphovascular presence (pT3N0M0). The patient started with adjuvant concurrent chemo-radiation therapy and returned to regular hemodialysis.

Conclusions: RCC in renal transplant allograft is unusual. Although the use of potent immunosuppressive agents increases graft survival in kidney transplantation recipients (KTRs), it may lead to the development of malignancy, including transitional cell carcinoma (TCC). TCC developing in the pelvis of graft kidney is very rare in KTRs.

Successful Kidney Transplantation and Chronic Lymphocytic Leukemia: A Case Report Mohammad Nazmul,2 Clifford D. Miles,2 Vannsi Krishna Chilla,1 Ryan Mullane,3 Scott G. Westphal.2 1Omaha, NE; 2University of Nebraska Medical Center, Omaha, NE.

Background: Active malignancies are typically considered as contraindication to kidney transplantation. Chronic lymphocytic leukemia (CLL) has variable prognosis; many have indolent course, with median survival up to 10 years. Some centers are considering the role of kidney transplantation in patients with active CLL who develop advanced kidney disease. Concerns related to transplantation include influence of immunosuppression on disease progression, possibility for leukemic infiltration of the graft, and increased risk of infectious complications. Few cases of kidney transplantation into patients with CLL have been described, however allograft and patient outcomes have been discouraging with high rate of graft failure and mortality. We report a patient with CLL treated with Bruton Tyrosine Kinase inhibitor, ibrutinib, underwent successful renal transplantation with relatively uncomplicated post-transplant course.

Methods: A 50-year-old man was diagnosed with CLL/small lymphocytic lymphoma Rai stage 0 with favorable cytogenetics. He was managed conservatively initially, but later treated with cyclophosphamide and maintenance rituximab due to declining kidney function. Kidney biopsy revealed IgA nephropathy with CLL renal involvement characterized by lymphocytic interstitial infiltrate. He progressed to end-stage kidney disease requiring hemodialysis. He completed two years of rituximab and was later transitioned to maintenance therapy with ibrutinib which controlled his CLL with stable WBC counts and no infections. Given clinical stability and favorable prognosis, he was approved for kidney transplantation and received a deceased donor kidney transplant (KDP 66%) with basiliximab induction followed by maintenance immunosuppression including tacrolimus, mycophenolate sodium and prednisone. He is now 1.5 years out from his transplant and has a successful allograft outcome with serum creatinine 1.0 mg/dl (gFR 76 ml/min) at last check. There have been no infectious complications. He has maintained a persistent lymphocytosis, but has not had adverse allograft injury related to his CLL.

Results: Patients with CLL have often been excluded for consideration for kidney transplantation, newer therapies and improved understanding of favorable prognostic markers may allow for safe kidney transplantation in carefully selected patients.


Background: Pediatric en bloc kidneys are considered “marginal” and many transplant centers are reluctant to use them. However, these kidneys double the number of nephrons and previous studies have shown that when exposed to adult hemodynamics these kidneys grow to adult size within first year. We aimed to compare extended long term function of pediatric en bloc kidneys to living donor kidneys performed at our institution.

Methods: This is a single center retrospective study of pediatric en bloc and living donor kidney transplants performed at our center between January 1990 and December 2001 who had functioned graft beyond 5 years. Graft survival, yearly serum creatinine and
estimated GFR using modified MDRD equation were calculated and compared between en bloc and living donor recipients.

Results: There were 72 patients in the en bloc and 75 in the living donor group who were transplanted during the study period. Maximum available follow up for serum creatinine value was 17 years following transplantation. Kaplan-Meier survival analysis showed no difference in graft survival between the groups over 27 years of follow up (log rank p=0.78). However on regression analysis, allograft function was found to be superior for en bloc vs. living donor kidney recipients longitudinally as evidenced by higher estimated GFR (33.0 ± 7.8 ml/min, p<0.0001) as shown in figure.

Conclusions: Our single center study showed similar graft survival but superior long term graft function as measured by estimated GFR among pediatric en bloc kidneys compared to living donor kidneys. This could be related to increased “nephron dose” among en bloc kidneys which could likely make them less susceptible to hyperfiltration injury in the long term. Our study encourages more widespread use of en bloc kidneys which could likely make them less susceptible to hyperfiltration compared to living donor kidneys. This could be related to increased “nephron dose” showing no difference in graft survival between the groups over 27 years of follow up.

Conclusions: Infection was the main complication of therapy observed in our patients, treating refractory gout arthritis in renal transplant patients, even with chronic kidney disease stage 4. Infection was the main complication of therapy observed in our patients, therefore, close monitoring is recommended.

SA-PO958
Renal Allograft Malakoplakia: A Rare Cause of Allograft Failure
Pavaswini Vyasanth1, Jeffy Kenny Thomas1, Thomas E. Rogers2, Sharon M. Graves1

1Nephrology, Emory University, Atlanta, GA; 2Emory University, Atlanta, GA.

Background: Malakoplakia is an unusual granulomatous inflammatory disorder associated with diminished bactericidal action of leukocytes. Cases of renal allograft malakoplakia are rare and generally associated with a poor graft and patient survival.

Methods: We present a case of renal allograft malakoplakia triggered by repeated UTIs in the setting of recent increase in immunosuppression.

Results: A 50-year-old female with history of pediatrics en bloc kidney transplant with baseline allograft function ranging between 2-2.5mg/dl on immunosuppression regimen of low dose cyclosporine (150mg twice daily), low dose MMF (250mg twice daily) and FK506 2mg/dl, was admitted with fever and UTI. She was discharged and returned to her tertiary care center for further management. She developed 14 days post transplantation hematuria and UTI and started on a course of antibiotics. She developed septicemia and UTIs. Laboratory investigations showed hematuria, proteinuria and pyuria. Urine cultures grew E.coli. She was managed with prolonged antibiotic courses, and experienced worsening of renal function. She was a candidate for allograft biopsy. Biopsy showed epithelioid histiocytes with PAS positive cytoplasm along with basophilic inclusions suggestive of malakoplakia with severe IFTA. Her creatinine remained at 4mg/dl and we maintained her on low immunosuppression in the setting of malakoplakia.

Conclusions: Renal parenchymal malakoplakia is a rare cause of renal allograft failure. Currently, malakoplakia is thought to be associated with infection, E coli is the most common. Therefore, agents targeting Gram negative bacteria with high bioavailability in macrophages are most commonly chosen, such as quinolones and sulfonamides. In malakoplakia, macrophage dysfunction and persistent antigens within cells cause progressive delivery of cytokines, resulting in renal inflammation and further injury. If the early interstitial injury is not controlled, renal injury continues to deteriorate and even progresses to interstitial fibrosis even when bacteria is removed and is associated with poor graft outcome, as demonstrated in this case.

SA-PO959
Pazopanib (Votrient) Induced Podocytopathy in a Transplant Kidney
Masumi Merkan1,2, Kenar Davari1,3, James M. Pullman,1 Mirinda Wanchoo1,2

1Pathology, Montefiore Medical Center, Bronx, NY; 2Nephrology, Hofstra Northwell School of Medicine, Great Neck, NY.

Background: Glomerular endothelial cell injury and podocyte damage, resulting in glomerulopathy including thrombotic microangiopathy (TMA) and focal segmental glomerulosclerosis, are well recognized complications of tyrosine kinase inhibitors(TKI) used in targeted therapy for cancers. TKI use in kidney transplant recipients is not well described. We report a case of nephrotic syndrome in a kidney transplant recipient with metastatic renal cell cancer treated with the TKI pazopanib(Votrient).

Methods: A 58 year old male with a living unrelated renal transplant 15 years ago was diagnosed with metastatic renal cell cancer (RCC). Immunosuppression was changed to minimal dose mycophenolate mofetil, tacrolimus was replaced with sirolimus, and low dose prednisone was continued. Renal function was normal without proteinuria. The TKI pazopanib was started to treat the metastatic RCC. Within three months of starting treatment, he developed worsening hypertension, edema and nephrotic range proteinuria (7 gms/day) with low serum albumin (3.4g/dl). A kidney biopsy revealed podocytopathy and early glomerular damage. There was no evidence of ABO incompatibility or antibody mediated rejection. Proteinuria improved with discontinuation of sirolimus and pazopanib but worsened again with re-initiation of pazopanib alone. We therefore conclude that pazopanib caused the podocytopathy as well as the endothelial injury. Without other options for RCC treatment, pazopanib was continued with conservative management of proteinuria by angiotensin receptor blockade and blood pressure control.

Results: We report the first case of biopsy proven podocytopathy with endothelial injury secondary to the TKI pazopanib in a kidney transplant recipient. Nephrologists, transplant physicians and oncologists need to be aware of complications of this and other targeted therapies in transplant recipients.

SA-PO960
Transplant Associated Thrombotic Microangiopathy (TA-TMA) in a Child with Neuroblastoma and Complement Factor Deletion: A Novel Association
A Child with Neuroblastoma and Complement Factor Deletion: A Novel Association

Anagha A. Kodagadula1, Ali Y. Suliman2, Michael Kent1, Alda Tufo1,3
1Yale University, New Haven, CT; 2Pediatric Nephrology, Yale University School of Medicine, New Haven, CT; 3Yale university School of medicine, Hamden, CT; 4Yale University School of Medicine, New Haven, CT.

Background: TA-TMA is an increasingly recognized morbidity following stem cell transplantation. It is uncommon in autologous stem cell transplantation (auto-SCT). Risk factors for TA-TMA following auto-SCT include specific malignancies such as neuroblastoma, platinum based chemotherapy, total body irradiation and infections. To our knowledge, there are no previous reports of genetic predisposition as a cause of TMA in neuroblastoma following auto-SCT.

Methods: A 3-year-old Hispanic boy with stage IV poorly differentiated neuroblastoma, received 6 cycles of high dose chemotherapy, primary tumor resection...
and underwent auto-SCT two months later. His post-stem cell transplant course was complicated by fevers and multi-organ dysfunction syndrome, fungal (Aspergillus) and recurrent suppurative tachycardia and acute kidney failure requiring continuous renal replacement therapy, which subsequently resolved and the neuroblastoma remained in remission. Two months after auto-SCT, he developed refractory hypertension on multiple anti-hypertensive therapy, seizures associated to acute posterior reversible leuкоencephalopathy syndrome, recurrent acute kidney injury and severe thrombocytopenia and anemia, dependent on daily transfusions. The diagnosis of TMA was then established with the presence of schistocytes, low serum haptoglobulin, elevated lactate dehydrogenase, normal white blood cells, normal platelet counts, and C3 and C5 levels were markedly decreased, suggesting type 3, marked deficiency, or complement component 5 activity. Complement gene panel revealed homozygous deletion of CFHRI gene. He received weekly eculizumab for two months leading to normalized renal function, eGFR of more than 100mL/min/1.73m2 (modified Schwartz), resolved hypertension, proteinuria, anemia and thrombocytopenia. Eculizumab therapy was tapered as all TMA signs resolved, and remains in remission to date (23 months from onset), while receiving Eculizumab every two months.

**Results:**

**Conclusions:** We report for the first time a case of TMA in a child with neuroblastoma harboring a complement genetic mutation known to cause TMA or atypical hemolytic uremic syndrome. It resolved upon Eculizumab and remains in remission after extending the therapy interval to 8 weeks. We hypothesize that complement variant may contribute a risk factor for sporadic TA-TMA.

SA-PO961

Kidney Transplantation in a Patient with Severe Pulmonary Hypertension on Macitentan Therapy

Sandhya L. Kommanda,1 Erik L. Lumin,2 Harbor ULCA MEDICAL CENTER, Harbor City, CA; 1UCLA Ronald Reagan Medical Center, Westwood, CA.

**Background:** Pulmonary Hypertension (PH) is associated with a significant reduction in patient survival and graft function following kidney transplantation. Patients with PH secondary to connective tissue disease, defined as a 6 minute walk of 300 meters or ventricular systolic pressure (RVSP) > 55 mmHg, are at increased risk for peri-operative complications and is considered a contraindication to kidney transplantation. Here we report a case with severe PH on maintenance Macitentan (Endothelin receptor antagonist) therapy who underwent successful kidney transplantation.

**Methods:** A 65-year-old male with ESRD secondary to autoimmune vasculitis was evaluated for kidney transplantation. His past medical history was notable for dermatomyositis, interstitial lung disease, pulmonary hypertension, and coronary artery disease. Two years prior to evaluation he was noted to have increasing dyspnea. A CT scan of the chest revealed pulmonary fibrosis. Pulmonary function tests revealed restrictive lung disease with FEV1 75% predicted, FEV1/FVC 57% and significant DLCO impairment of 28%. An Echocardiogram showed RVSP of 70 mmHg and was started on nocturnal oxygen therapy. His symptoms continued to worsen and was started on Macitentan, with improvement in his pulmonary pressures (32 mmHg) and nocturnal oxygen was discontinued. One year prior to transplantation he developed worsening dyspnea as a result of pulmonary edema in association with progression of his renal disease and was initiated on hemodialysis. His symptoms improved and he was cleared for kidney transplantation. The patient underwent living unrelated kidney transplantation without complications. His Macitentan was continued during the perioperative period. We used caution not to use Diltiazem or Fluconazole postoperatively due to drug interaction with S Cr. He was discharged with S Cr of 1.2 mg/dL.

**Results:**

**Conclusions:** The prevalence of pulmonary hypertension in ESRD patients has been estimated between 9-15% and when severe may preclude patients from getting kidney transplantation. However, the recent development of effective pharmaceutical therapies may improve these outcomes. To our knowledge, this is the first reported case where kidney transplantation was performed in a patient with pulmonary hypertension on drug therapy.

SA-PO962

Acyclovir Neurotoxicity Occurring in Two Patients on Peritoneal Dialysis with Varicella-Zoster Virus Encephalitis

Xunxi S. Guo,1 Vesh Srivatana,1 NYU-Cornell, New York, NY; 1The Rogosin Institute, New York, NY.

**Background:** Acyclovir neurotoxicity which can have varying symptoms including agitation, delirium, myoclonus and coma is known to appear more commonly in patients with varicella-zoster virus (VZV) encephalitis with improved mental status after transitioning to HD.

**Methods:** Case 1: A 56-year-old female with ESRD on CAPD for 3 months, recently started on valacyclovir for 2 days for herpes zoster ophthalmicus presents with acute onset of confusion and agitation. Her Cerebrospinal fluid (CSF) analysis showed 3,500 Varicella DNA copies/mL. Her encephalopathy worsened and neurological evaluation with EEG and MR/IMA was unrevealing. On hospital day 4, she underwent HD with subsequent improved mental status. Acyclovir level was 3.1 mcg/mL on Day 4 with normalization of mental status post-HD. She was discharged home after 2 weeks of IV Acyclovir and intermittent HD with return to normal mental status and transitioned back to CAPD at discharge.

Case 2: A 50-year-old female with ESRD on automated PD for 6 years presents with worsening mental status in setting of zoster ophthalmicus and superinfection with Aspergillus and Acinetobacter. She was started on IV Acyclovir. Her mental status quickly deteriorated, only grimacing to pain. CSF analysis showed 81,700 Varicella DNA copies/mL. Acyclovir level was 8.1 mcg/mL. On hospital day 3, she was started on HD. Her course was complicated by troponinemia, hypotension, and reduced mentation. She was transitioned to HD to maintain stable renal replacement therapy. Her mental status returned to baseline 5 days after start of HD. She completed a course of acyclovir and was transitioning back to PD at discharge.

**Results:**

**Conclusions:** We present two unique cases of acyclovir neurotoxicity in PD patients with VZV encephalitis. They highlight that acyclovir even at appropriate dosing can lead to toxic levels and neuropsychiatric effects in the PD population due to non-appreciable clearance.

SA-PO963

A Unique Case of Valganciclovir Associated Reversible Azoospermia in a Renal Transplant Patient

Al J. Lee, Myriam C. Vela-Ortiz, Karthik M. Ranganna, Sandeep Aggarwal. Drexel University College of Medicine, Philadelphia, PA.

**Background:** Azoospermia with secondary infertility has not been reported as an adverse effect associated with valganciclovir. We present a case of reversible azoospermia in a renal transplant patient associated with valganciclovir therapy.

**Methods:** A 30-year-old male with past medical history of surgically corrected Tetralogy of Fallot whom developed dialysis dependent renal failure post cardiac surgery and required renal transplant 11 years ago. Patient presented for routine outpatient transplant appointment with complaints consistent with chronic kidney disease. He had history of trauma, ED dysfunction, family history of infertility, or exogenous use of androgens. He was a well-nourished, well developed male who appeared as stated age and had an unremarkable physical examination. Referral was made to fertility clinic. The patient’s semen analysis results are: semen volume 3.8mL and no sperm identified. Diagnosis of primary male infertility secondary to azospermia was made. At this time the patient was on stable immunosuppression with tacrolimus 1mg BID and prednisone 5mg daily and valganciclovir 900mg BID (for 3 years)secondary to persistent EBV viremia. Autimmune, hormonal, and radiological workup for infertility was negative. In an attempt to uncover medication related azospermia, valganciclovir was stopped. 1 month later semen analysis results were: semen volume 2.9mL, sperm concentration 21mL/mL, total sperm number 60.9mL/mc, progressive motility 41%, total motility 63%, vitality N/P, sperm morphology 3%, pH 8, leukocyte <1. There were no further medication changes. Patient was able to conceive a child and had semen cryopreserved.

**Results:** Patient currently on valganciclovir with stable EBV PCR of 7272 copies/mL; unchanged since initial stoppage of valganciclovir 10 months prior.

**Conclusions:** In animal studies gancyclovir has been a potent inhibitor of spermatogenesis but to our knowledge this is the first human reported case of valganciclovir associated azoospermia. Further studies needed including careful post-marketing analysis to confirm this association.

SA-PO964

Rapidly Growing Mycobacteria (RGM) – An Unusual Cause of Peritoneal-Dialysis-Associated Mycobacterial Peritonitis

Nasir Khan,2 Valerie Jorge Cabrera, Neera K. Dahl.1 Madison, CT; 1Yale School of Medicine, New Haven, CT.

**Background:** Non-tuberculous mycobacteria are a rare but serious cause of peritoneal dialysis-related peritonitis. M.chelonae, a member of the rapidly growing Non-tuberculous mycobacteria (NGM) group, is an atypical organism most often found in soil and water and known to cause skin and soft tissue infections. We present a case of M.chelonae infection manifested with chronic skin lesions and peritonitis in a diabetic peritoneal dialysis patient.

**Methods:** A 54 year old African American male developed 2 nodular lesions on the mid abdominal area. His past medical history included diabetes, hypertension and end-stage renal disease due to diabetic nephropathy. He had been started on peritoneal dialysis (PD) around 2 years ago. Over the course of 7 months these nodular skin lesions developed into enlarging nodules with purulent discharge. The skin lesion were cultured and found to be M.chelonae, an atypical fungus and acid-fast bacilli (AFB) cultures were repeatedly negative. Several days prior to admission, his peritoneal effluent became cloudy without any systemic symptoms. Two ulcerated nodules with purulent drainage were noted on the mid abdomen. Peritoneal fluid cell count showed 4256 nucleated cells. Computed tomography (CT) of the abdomen confirmed the lesions to be interconnecting. A discrete 1.5 x 2.5 cm collection was also reported along the peritoneal catheter track. Four days later preliminary peritoneal fluid cultures revealed gram-positive acid fast bacilli, later identified as M.chelonae. The PD catheter was surgically removed and the patient was transitioned to hemodialysis. Deep wound cultures obtained in the operating room also confirmed the diagnosis. He was started on a 4-month course of Tigecycline and Amikacin based on culture sensitivities.

**Results:**

**Conclusions:** M.chelonae characteristically causes chronic nodular lesions with a purple discoloration. Very few cases of M.chelonae peritoneal dialysis-related peritonitis have been reported. Management of treatment is removal of the source as well as antibiotics. As M.chelonae is considered to be cutaneous and not enteric, mycobacteria should be maintained in peritoneal dialysis patients with routine negative dialysate cultures who are unresponsive to standard empirical antibiotics.
Fellows/Residents Case Reports: ESRD: HD, PD, Transplant

Health Network, Toronto, ON, Canada

Abu Dialysis Patient – A Case Report

Toronto General Hospital, Toronto, ON, Canada; 2Nephrology, University

Klebsiella pneumonia Renal Abscess and Peritonitis in a Peritoneal Dialysis

Patients?

SA-PO966

SA-PO967

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

Underline represents presenting author.

SA-PO965

Peritonitis Following Fecal Microbiota Transplantation *(2) via Coloscopy in a Peritoneal Dialysis Patient Shree R. Mulay, Sana Wahedez, University of Wisconsin, Madison, Madison, WI.

Background: Fecal microbiota transplantation (FMT) is commonly utilized in the treatment of recurrent Clostridium difficile (C. diff) infection. However, there is no consensus on how best to manage these patients who are on peritoneal dialysis (PD) for preventing and treating C. diff infection. We share our experience with one such case requiring an FMT who subsequently developed peritonitis.

Methods: A 50-year-old female on peritoneal dialysis for end stage renal disease secondary to ANCA vasculitis and recurrent C. diff infection was admitted with abdominal pain and severe peritonitis. She was found to have another C. diff infection and since she had already failed treatment with oral vancomycin and fidaxomicin a decision was made to proceed with FMT via coloscopy. Given the concern that she may not have a successful FMT if given prophylactic antibiotics, she was not given any antimicrobial prophylaxis and all antibiotics were held 48 hours prior to the procedure. She resumed peritoneal dialysis after the procedure and her fluid remained clear. However, 2 days later her diarrhea and abdominal pain recurred. She had an extensive GI work up and no alternative explanation could be found for her abdominal pain and her C. diff remained positive. She underwent another FMT considering the fact that there could be a 5-10% failure rate with the procedure. Again, she was not given prophylactic antibiotics. Her PD fluid turned cloudy the next day and she had low grade fever and her PD fluid cell count showed a total of 404 nucleated cells with 29% polymorphic neutrophils. Her PD culture grew Enterococcus faecalis and she was treated with intraperitoneal daptomycin daily for 3 total of 3 weeks. Her abdominal pain and diarrhea have not recurred since the second FMT.

Results:

Conclusions: FMT can be used to successfully treat patients on peritoneal dialysis with recurrent C. diff. However, our patient developed peritonitis as a result of the procedure which can be a risk if prophylactic antibiotics are not administered. We suspect she developed peritonitis from the second FMT because it was associated with a more thorough diagnostic (exploratory) colonoscopy. We recommend that the risk of peritonitis be discussed in detail with patients who are on peritoneal dialysis undergoing FMT.

Klebsiella pneumonia Renal Abcess and Peritonitis in a Peritoneal Dialysis Patient: A Novel Route of Infection Miten Dhruve,1 Joanne M. Bargman.1 Toronto General Hospital, Toronto, ON, Canada; 2Nephrology, University Health Network, Toronto, ON, Canada.

Background: We present a route of bacterial translocation leading to peritoneal dialysis (PD) peritonitis never before reported in the literature.

Methods: A 60 year old patient with newly-diagnosed CKD of uncertain cause underwent a kidney biopsy inadvertently performed during an episode of Klebsiella urosepsis. The biopsy was consistent with advanced diabetic nephropathy and after appropriate education and preparation, a PD catheter was placed and training commenced. The patient presented soon thereafter with abdominal pain and cloudy effluent consistent with PD peritonitis. Imaging revealed a renal abscess at the biopsy site. Microbiology from the PD effluent and from needle drainage of the renal abscess were both positive for Klebsiella pneumoniae.

Results:

Conclusions: We propose that the PD peritonitis was the result of seeding of the peritoneal cavity across the retroperitoneum with bacteria from the renal abscess. Successful treatment was achieved through drainage of abscess and antibiotics. The patient’s course is consistent with a novel route of bacterial entry into the peritoneal cavity culminating in PD peritonitis.

Atypical Presentation of Acute Type A Aortic Dissection in a Peritoneal Dialysis Patient – A Case Report Wagas J. Siddiqui,1 Muhammad Aslam,2 Abu Bakar,3 Hasan Arif,4 Sandeep Aggarwal,1 Ellie Kelepouris.1 1Division of Nephrology and Hypertension, Drexel University College of Medicine, Philadelphia, PA; 2Dow University of Health Sciences, Karachi, Pakistan.

Background: Clinical presentation of dialysis patients if often atypical. A commonly encountered clinical sign of dyspnea in dialysis patients is often secondary to fluid overload, but this generalization can often times lead to delay in diagnosis of important underlying causes. We present a case of acute aortic dissection (AoD) in a peritoneal dialysis (CCPD) patient with dyspnea refractory to fluid removal as the only presenting clinical symptom.

Methods: 53 year old man with a history of HIV, ESRD on CCPD awaiting renal transplant, hypertension, cardiomyopathy and recent negative peritoneal tests presented with 3 days of exertional dyspnea and orthopnea. He is compliant with his CCPD exchanges and medications, having recently started Furosomide 40 mg orally for better volume control. His baseline creatinine was 4.1 mg/dL, his blood pressure was 120/80 mmHg, heart rate was 94 bpm, respiratory rate 16/min, temperature = 98.0 °F orally, respiratory rate = 18/min and O₂ saturation on room air = 98%. His EKG showed prolonged QTc > 530 milliseconds. Remaining EKG and blood workup were unremarkable. Chest x-ray revealed mild congestion. The patient was diagnosed with dyspnea with fluid overload likely due to acute AoD failure. He was started on intravenous diuretics and transferred to CT chest with contrast confirmed severe aortic regurgitation with Type-A AoD. An emergent surgical repair was done. Post operatively he received Continuous Venous-venous Hemodialysis, later on, transitioned to intermittent hemodialysis and subsequently discharged.

Results: Conclusions: Acute AoD is a rare but potentially life-threatening vascular catastrophe with a high associated mortality. This case reminds us that dialysis patients can have an atypical presentation of acute AoD and should be considered if a patient is not improving with conventional renal treatment. Patients at risk of acute AoD include patients with T2DM, advanced age, atherosclerosis, high BUN, connective tissue diseases and uncontrolled hypertension.

Successful Placement and Follow Up of ESRD Patient on Peritoneal Dialysis with an LVAD Valerie S. Bart, Kenar Barta,2 Hasan Dhruve,1 Joanne C. anchoo.

Nephrology, Hofstra Northwell School of Medicine, GREAT NECK, NY.

Background: Left ventricular assist devices(LVADs) have been shown to improve cardiac function in patients with advanced congestive heart failure(CHF) that are refractory to medical therapy. LVADs are contraindicated in patients with end stage renal disease(ESRD) on hemodialysis(HD). Peritoneal dialysis(PD) is widely considered a contraindication as well, given the close proximity of the peritoneal catheter to the device as well as risk of systemic infections. We report a successful placement of LVAD in an ESRD patient on PD with short and long term follow up.

Methods: A 52 year old Caucasian male with ESRD secondary to chronic heart failure on PD for five years got evaluated for a heart-kidney transplantation. Due to the patient’s worsening heart failure and significant symptom burden, he underwent LVAD (HeartWare) placement while continuing PD. He tolerated the procedure well and there were no infectious complications related to his PD catheter. Post LVAD follow up his LVAD has not required adjustment and his hemoglobin improved from a baseline of 7 to 12 g/dl. His creatinine remained > 60 mg dl. As blood pressure monitoring is not possible in LVAD patients, MAP values using arterial Doppler ultrasound are used to assess volume status. His fluid management was adjusted using these MAP values in combination with physical exam.

Nine months following the LVAD, the patient remains stable on PD awaiting heart-kidney transplantation.

Results:

Conclusions: Our case highlights that PD can be safely performed in LVAD patients. There is a trend towards management of volume management, interrupted LVAD disconnection or peritonitis in our patient. PD should not be a contraindication for placement of LVADs. Additionally, it is our recommendation that in cases of acute kidney injury requiring initiation of dialysis post LVAD, the option of PD should be offered.


Background: Ferric citrate (FC), a novel oral phosphorus binder, is FDA approved for treatment of hyperphosphatemia in patients receiving dialysis. FC binds to dietary phosphate in GI tract producing ferric phosphate and is excreted in feces. However, small quantity of iron is systemically absorbed through drainage of dialysate and antibiotics. We report a case of a 65 year old man with ESRD due to IgA nephropathy, status post failed kidney transplantation, on CCPD for 3 years with adequate clearance, started on ferric citrate in 1/2016, dose adjusted to 3 tablets tid with meals and 1 with snack; maximum total dose of 11 tablets/day resulting in acceptable phosphorus control. No IV iron or transfusion during subsequent 12 months. Iron studies summarized in Table. FC discontinued at 12 months. Hematology work up consistent with acquired hemosiderosis.

Patient 1-51-years old woman with ESRD due to systemic sclerosis, on CCPD for 7 years with good clearance, started on ferric citrate in 1/2016, dose titrated up to maximum of 12 tabs/day with good phosphorus control. No IV iron or transfusion during subsequent 12 months. Iron studies summarized in Table. FC discontinued at 12 months.

Patient 2-37-years old man with ESRD due to AL amyloidosis, on CCPD for 1.5 years with adequate clearance, started on ferric citrate in 10/2016, dose titrated up to max of 11 tablet/day with acceptable phos control. No IV iron or transfusion after FC initiation. Iron studies summarized in table. FC discontinued at 6 months.

Results:

Conclusions: PD patients may be more prone to developing iron overload with the use of ferric citrate. This may be due to less ironloses in PD patients as compared to HD patients. These cases highlight the importance of close monitoring of iron studies in PD patients while receiving ferric citrate as phosphate binder. Further studies are needed to assess the safety of maximum approved dose of ferric citrate among PD patients.

Funding: Clinical Revenue Support

Iron Studies
SA-PO970
HbA1c Underestimated Glucose Level in Diabetic PD Patients Compared to Normal Kidney Function Diabetic Patients
Hua Zheng, Peking Union Medical College, Beijing, China.

Background: HbA1C is widely used as glycemic marker for general DM patients. However, its accuracy has been questioned in ESRD patients for potential effect of renal anemia, EPO usage and uremia on glycation physiology. Most research relevant to the topic was done in hemodialysis. Yet, reports on whether HbA1C underestimated glucose level in PD patients were contradictory. This research aimed to compare HbA1C value adjusted with mean glucose in PD DM and PD patients with normal kidney function (NKF) and the potential cause of the difference.

Methods: Twenty DM PD patients were enrolled in this single-entered prospective research for 72-hour Continuous Glucose Monitoring (CGM). PD patients were matched with twenty DM NKF patients based on 72-hour mean glucose (MG), age and gender who underwent CGM during the same period.

Results: One PD patient was discarded for incomplete data. No significant gender and age difference was detected between PD and NKF patients. For PD patients, mean EPO dose for previous three months was 8000 IU per week. Mean Hgb was 106.8g/L. PD and NKF patients had negligible MG (8.8±1.9 vs 8.7±1.7 mmol/L, p=0.688) with significantly different HbA1C value (6.17±0.87% vs 6.93±0.12%, p=0.043). PD patients also had worse linear correlation than NKF patients. Significant different regression formula was found between PD and NKF patients (p for intercept=0.02). PD patients had 0.79% lowered absolute value than NKF patients for HbA1C (6.15% vs 6.94%, p < 0.001) at pooled mean MG (8.74mmol/L). Further analysis on regression residuals or residuals over estimated HbA1C found that this difference could not be explained by EPO dose (p=0.733), hemoglobin (p=0.727), urea (p=0.934), creatinine (p=0.648), albumin (p=0.582), residual GFR (p=0.767) or nPCR (p=0.408).

Conclusions: HbA1C significantly underestimated glucose level in diabetc PD patients compared to normal kidney function diabetic patients. The difference might not be simply explained by hemoglobin, EPO injection dose, uremia, residual GFR, albumin, or nPCR.

SA-PO971
Hematuria in a Chronic Hemodialysis Patient
Anuradha Konkasa,1 Srikanth Thiruvarudsothy,2 Neeraj Sharma,3 Arvindan V. Jeyarajasingam,1 Sushma Munugoti,2 Alluru S. Reddi,2 Farah Piracha,2 (Swedesboro, NJ: 1Rutgers NJ Medical School, Staten Island, NY; 2Rutgers, Morrisplains, NJ; 3Rutgers NJMS, Belleville, NJ; 4Rutgers New Jersey Medical School, Newark, NJ; 5Rutgers UNIVERSITY, Montclair, NJ; 6Rutgers University, Bloomfield, NJ)

Background: Spontaneous gross hematuria in a chronic hemodialysis patient is an uncommon finding which can be a consequence of renal cyst rupture, renal cell carcinoma, angiosarcoma, stones, or vascular diseases. We recently treated a patient on chronic hemodialysis for spontaneous gross hematuria who was found to have renal cysts and renal cell carcinoma.

Methods: A 47-year-old African American man with past medical history of AIDS, hyperension, and ESRD on HD due to HIV ANS 2002 was evaluated for gross hematuria (1 to 2 ml). Hematuria was not associated with flank pain, weight loss, dysuria, or trauma. A CT scan of the abdomen and Pelvis with contrast showed a 6.3x6.2x5.1 cm mass in the mid to upper pole of right Kidney. There were bilateral renal cysts and both kidneys were atrophic. He underwent a right laparoscopic nephrectomy. Histology revealed clear cell renal carcinoma.

Results: There was no evidence of metastasis or regional lymph node involvement.

Conclusions: Acquired cystic kidney disease (ACKD) is recognized as a disease of consequence affecting patients on long-term hemodialysis (~3 years), and the prevalence of ACKD increases linearly with duration of dialysis. Approximately 1-4% of patients with ACKD develop renal cell carcinoma (RCC), and the development of cysts and their degeneration into carcinoma is poorly understood. The range of patients affected by ACKD-RCC is very narrow. Compared to the general population, the risk of developing RCC in ACKD is increased by more than 100-fold. In general, RCC associated with ACKD is considered to be less aggressive than sporadically occurring RCC. A CT scan should be performed to rule out other causes of spontaneous renal rupture. Recommendation to screen patients with ESRD for ACKD and renal cell cancer has not been uniformly accepted, due to limited life expectancy; however we believe screening will be valuable for patients in good general health with a good life expectancy.

SA-PO972
Successful Fecal Microbiota Transplant in an ESRD Patient
Jeffy Kenny Thomas,1 Jason Cobb,2 Jung W. Suh,1 (1Atlanta Gastroenterology Associates, Atlanta, GA; 2Emory University School of Medicine, Atlanta, GA)

Background: The incidence of clostridioides difficile (c. difficile) colitis is increasing and there are reports of 10-25% of patients treated with medical therapy (metronidazole or vancomycin) having relapse of colitis despite medical therapy. A treatment option in these refractory or recurring c. difficile colitis cases is fecal microbiota transplant (FMT). There is a paucity of data of c. difficile colitis in patients with kidney disease. We present a case of an ESRD patient with refractory c. difficile colitis that underwent a successful FMT.

Methods: Results: 60 year-old African-American female with ESRD requiring hemodialysis for 3 years. Her ESRD is due to diabetic nephropathy. She was admitted to an outside hospital in March 2017 for coronary artery disease and atrial fibrillation, and was transferred to our hospital for further cardiac care. She received intravenous antibiotics at the outside hospital for 1 day. Upon presentation to our hospital, she had severe diarrhea which required the placement of a fecal management system. Her stool was positive for c. difficile and due to the severity of her disease oral vancomycin was initiated. Despite treatment for 12 days with oral vancomycin, intravenous metronidazole was added. She continued to have persisting diarrhea despite treatment. She received bezlotoxumab (human monoclonal antibody for the treatment of c. difficile infections) but continued to have severe watery diarrhea. Gastroenterology was consulted and a decision was made to perform a FMT. The patient received a FMT on April 14th and April 25th, 2017. It was performed per colonoscopy with 60 ml syringes of fecal material being injected in the terminal ilium and cecum for a total of 240 ml each time. At the time of discharge (14 days after initial FMT) the patient was off antibiotics, off probiotics, and having only one semi-formed stool each day.

Conclusions: This is the first case of an ESRD patient undergoing a FMT and shows that it is a safe treatment option in ESRD patients with refractory or relapsing c. difficile colitis.

SA-PO973
Clinical Picture: Central Venous Catheter-Related Oclusive Disease
Jin Wen,1 Yang Yu,2 Tianlei Cui,2 (1Nephrology and Rheumatology Department, Tongchuan Hospital of Chongqing Medical University, Chongqing, China; 2Nephrology Department, West China Hospital & Sichuan University, Chengdu, China)

Background: The central venous catheter (CVC)-related occlusive disease is a major and serious complication of central venous cannulation, posing a huge challenge to end-stage renal disease (ESRD) patients, especially for the growing group of hemodialysis patients when CVC becomes the only available form of access. Herein, we report a successful case of multiple central venous occlusion and thrombosis by percutaneous superior vena cava (SVC) cannulation technique under cross-located fluoroscopy.

Methods: A 50-year-old male with ESRD for 7 years presented with 3 weeks of hemodialysis catheter dysfunction. Before transferred to our hospital, he had undergone a maintenance hemodialysis via a tunneled right femoral vein catheter for 6 months, when other possible vascular accesses had been tried but failed, unfortunately. Physical examination showed collateral tortuous veins in the right chest wall. CT venography of the chest demonstrated chronic occlusion of the entire right brachiocephalic vein (BCV), left brachiocephalic vein (LBV) and the distal end of SVC. Meanwhile, venography revealed inferior vena cava (IVC) long segment total occlusion with thrombosis (Fig1). Under this situation, we successfully implanted a new tunneled catheter by percutaneous SVC cannulation technique under cross-located fluoroscopy (Fig2), and then removed the previous malfunctioned catheter. The patient discharged 2 days after the new functional catheter establishment.

Results: Conclusions: The CVC-related occlusive disease is usually so troublesome that leaves a high mortality of ESRD patients, especially for those who suffer from exhausting hemodialysis vascular access. Although many patients are asymptomatic, some can present with symptoms of venous hypertension, such as edema of upper extremity and collaterals of the chest or abdominal wall, which require our more attention and supervision. However, it remains challenging to deal with such severe CVC-related occlusion when almost all the principal venous are occlusive. Notably, we implanted a new CVC under cross-located fluoroscopy.

Funding: Other NIH Support - No.
SA-P0974

Long-Term Clinical Spectrum and Circulating RAS Evaluation of Anephric Patients on Hemodialysis: A Series of 4 Cases and Literature Review

Lin Liu, Yumei Zhang, Fangting Fu, Wenge Li. China-Japan Friendship Hospital, Beijing, China; Department of Nephrology, China-Japan Friendship Hospital, Beijing, China.

Background: Blood pressure decline is one of the short-term complications of bilateral nephrectomy mainly due to sharp change of circulating renin-angiotensin system (RAS), but data about long-term outcome of clinical status and the development of circulating RAS of these patients is limited.

Methods: We enrolled 4 Chinese cases with both their kidneys removed for 2, 6, 8, and 10 years, respectively, from 304 patients on maintenance hemodialysis in December 2016 in our center. The blood samples for RAS tests were drawn after the subjects seated for 30 minutes immediately before hemodialysis was started. Radioimmunoassay was performed to assess their circulating RAS. Their ages ranged from 49 to 80, and 3 out of 4 were female. The reasons of nephrectomy included polycystic kidney disease (n=1), cancer (n=2), and hydronephrosis (n=1). Hypotension after surgery occurred in 2 patients, and mostly happened during dialysis. They suffered embolism of arteriovenous fistula, but not any life-threatening complications happened. At present, the SBPs in 24 hours of the 4 subjects were all above 90 mmHg, and the last SBP of 90 mmHg and DBP of 46 mmHg occurred during dialysis and at midnight, respectively. Only one patient developed severe hypertension again since 4 years after surgery, whose BP now was not well-controlled despite 6 kinds of antihypertensive drugs including ACEI and ARB. The average hemoglobin level was 103.3±12.5 g/L. Two of them complicated with hemorrhage of digestive tract, resulting in the need of high erythropoietin (EPO) dosages. The other two patients without hemorrhage received intravenous EPO of only 4500-8000IU/week. The 3 patients receiving blood tests all presented with extremely low plasma renin activity (PRA) of 0.08±0.03 ng/mL compared with normal range of 0.93-6.5 ng/mL. Surprisingly, plasma Ang II concentration of 71.3±6.28 pg/mL and aldosterone of 0.17±0.02 ng/mL were within normal limits.

Results: Conclusions: In conclusion, in 2 to 8 years after surgery, the 4 anephric cases did not suffer from transient rising or persisting hypotension, gradually recovering the baseline EPO dosage relatively small. Although their PRA was extremely low, they produced normal Ang and aldosterone in plasma, indicating the kidney-independent mechanism of Ang production compensated well in 2 years after removal of kidneys.

Funding: Government Support - Non-U.S.

SA-P0975

Acute Pancreatitis Related to Hemolysis During Hemodialysis Due to Defective or Kinked Blood Tubing

Muataz Yazji, Sobia N. Khan, Leonard A. Arbeit, Kyung Ho Kim, Nand K. Wadhwia. Stony Brook Medicine/ University Hospital, Stony Brook, NY.

Background: Hemolysis during hemodialysis (HD) may be related to dialyzer, extracorporeal circuit or patients’ disease. Extracorporeal hemolysis may result from blood pump occlusion, miss-size needle and partial occlusion of catheter in relation to high BFR, and kinked or faulty tubing. We report a case with massive hemolysis during HD related to faulty or kinked blood tubing presenting as acute pancreatitis.

A 32-year-old man with ESRD due to obstructive uropathy has been on HD since 2014. On his HD day, he started HD at 5:37 AM at BFR 400 mL/min with a 14 gauze needle using right brachiocephalic AV fistula. At 6:08 AM, arterial pressure increased from -80 to -10 mmHg and venous pressure dropped from 170 to 50 mmHg at a BFR of 360 mL/min. He continued HD until 6:43 AM with repeated alarms. He was moved to another HD machine and completed HD for 3.45 hrs with no issues. He presented to the ER the next morning with gradual, progressive worsening abdominal and back pain, nausea and vomiting since HD yesterday. On departure, the patient felt well but staff noted that his color had changed to dark red. On way home, he began to feel unwell and progressed until presented to the ER where labs were repeatedly reported hemolyzed. Physical exam: Alert and oriented, BP 122/88 mmHg, HR 98 bpm, RR 18/min, Temp 36.7°C. He was jaundiced with a soft abdomen and mild tenderness. Rest of the exam was normal. Lab data: WBC 6.78 K/UL, Hgb 7.7 g/dl (10.5 g/dL on 2 week prior), hcts 21.6%, Na 135 mmol/L, K 4.3 mmol/L, BUN 69 mg/dL, creatinine (Scr) 1.82 mg/dL, and Hct 27%. Coagulation studies were normal. Labs showed Sodium (Na): 139 mEq/L, Potassium (K): 3.9 mEq/L, Chloride (Cl): 102 mEq/L, calcium (Ca): 1.5 mEq/L, and magnesium (Mg): 2.2 mEq/L. C-reactive protein (CRP) was 2.4 mg/dL. Arterial blood gas (ABG) was pH: 7.38, PaCO2: 38 mmHg, PaO2: 94 mmHg. Dialysis was performed to assess their circulating RAS. Their ages ranged from 49 to 80, and 3 out of 4 were female. The reasons of nephrectomy included polycystic kidney disease (n=1), cancer (n=2), and hydronephrosis (n=1). Hypotension after surgery occurred in 2 patients, and mostly happened during dialysis. They suffered embolism of arteriovenous fistula, but not any life-threatening complications happened. At present, the SBPs in 24 hours of the 4 subjects were all above 90 mmHg, and the last SBP of 90 mmHg and DBP of 46 mmHg occurred during dialysis and at midnight, respectively. Only one patient developed severe hypertension again since 4 years after surgery, whose BP now was not well-controlled despite 6 kinds of antihypertensive drugs including ACEI and ARB. The average hemoglobin level was 103.3±12.5 g/L. Two of them complicated with hemorrhage of digestive tract, resulting in the need of high erythropoietin (EPO) dosages. The other two patients without hemorrhage received intravenous EPO of only 4500-8000 IU/week. The 3 patients receiving blood tests all presented with extremely low plasma renin activity (PRA) of 0.08±0.03 ng/mL compared with normal range of 0.93-6.5 ng/mL. Surprisingly, plasma Ang II concentration of 71.3±6.28 pg/mL and aldosterone of 0.17±0.02 ng/mL were within normal limits.

Results: Conclusions: In conclusion, in 2 to 8 years after surgery, the 4 anephric cases did not suffer from transient rising or persisting hypotension, gradually recovering the baseline EPO dosage relatively small. Although their PRA was extremely low, they produced normal Ang and aldosterone in plasma, indicating the kidney-independent mechanism of Ang production compensated well in 2 years after removal of kidneys.

Funding: Government Support - Non-U.S.

SA-P0976

Thrombocytopenia Associated with Polysulfone Dialyzer Membrane


Background: Heparin and other drug induced thrombocytopenia are the most common cause of thrombocytopenia in patients with end stage renal disease (ESRD). Dialysis membrane associated thrombocytopenia is extremely rare.

Methods: A 44 year old male with history of ESRD on hemodialysis (HD) was admitted for presumed tunneled HD catheter infection. Over 2 days, the patient grew pseudomonas aeruginosa at the exit site and received piperacillin-tazobactam, vancomycin and eventually cefepime followed by catheter removal. Prior to the first treatment of heparin free HD (Optiflux 180) on the 1/27/2017 the platelets were 235x10^4/µL. The day after platelets drop 107x10^4/µL. Prior the second HD session (Optiflux 180) was on 1/31/2017, the serum platelets were 187x10^4/µL. The day after HD, the serum platelets dropped to 85x10^4/µL. A presumption of heparin induced antibody was made due to presence of antibodies for drug related apheresis procedure and argatroban drip was commenced. Serum heparin induced thrombocytopenia antibodies and serotonin release assay were negative and argatroban was discontinued. Patient was having hemodialysis in the hospital with a dialyzer Polysulfone based (Optiflux 180). Assuming the thrombocytopenia was related to the polysulfone dialyzer given the sees effect noted pre and post dialysis (Figure), dialysis was changed to a cellulose base dialyzer (Excella 210). Thrombocytopenia resolved as a result of this switch. Following this, the platelets remained to improved and continued in the normal range.

Results: Conclusions: There have been rare reports of thrombocytopenia associated with dialyzer membranes. As per literature review one of the causes for thrombocytopenic effect of the polysulfone dialyzers is the use of electron beam sterilization. The electron beam modifies the property of polysulfone membranes, increasing their hydrophilicity. Given only monthly blood draws, this entity might not be evident or perhaps, overlooked in the outpatient ESRD units. Our case highlights an important under-recognized cause of asymptomatic thrombocytopenia in the HD patient.
reversal of body position and loss of balance. As per protocol, she received UF with intravenous contrast to rule out acute trauma, all were negative. Creatinine on admission 4.24 mg/dL and rose to 7.27 mg/dL on day 4, at time of nephrology consultation. Patient hemodynamically stable, no episodes of hypotension. On exam she had what appeared clinical diagnosis of lactic acidosis, unable to hold her arms, legs or torso steady, as well as myoclonus although mental status was intact. She was diagnosed with contrast induced nephropathy. BMP showed sodium 132 mmol/l, potassium 5.4 mmol/l, bicarbonate 22 mmol/l, glucose 44 mg/dL. Urinalysis unremarkable. She was making < 500 cc urine/day. Renal ultrasound demonstrated 600 mg of echogenic material in kidney. Creatinine 2200 mg/dl, and uric acid 2 mg/dl. Serum gabapentin level 78 mcg/ml (reference 14-16 mcg/ml). Gabapentin, furosemide, losartan all discontinued. She received two sessions of hemodialysis with full resolution of body movements and myoclonus and recovered from her AKI with a discharge creatinine of 3.09.

Results:

Conclusions: Gabapentin, a 3-cyclohexyl-GABA, is an analogue of GABA able to activate its receptors. Hypoglycemia, myoclonus, and altered mental status have been previously reported as symptoms of gabapentin toxicity. This drug can easily be toxic in patients with impaired renal function. In patients with ESRD, non-HD days elimination half-life of gabapentin is 132 hours, while in the general population it is 5-7 hours. Levels of above 15 mcg/ml are considered toxic. Gabapentin can be effectively cleared by hemodialysis. Given its relatively frequent use in patients with renal insufficiency, it is important to remain mindful of potential gabapentin toxicity in patients with neurological symptoms.

SA-PO981

Acquired Erythropoietin (EPO) Deficiency Following Microvave Ablation of Papillary Renal Cell Carcinoma in a Renal Transplant

Myriam C. Vela-Ontirri, 1 Brian A. Bianco. 1 Clinical Nephrology PA Associates, LTD, Philadelphia, PA; 2Drexel University, Philadelphia, PA; 3Hahnemann University Hospital, Drexel University College of Medicine, Philadelphia, PA.

Background: Percutaneous microwave ablation of renal malignancies is a novel nephron sparing option for patients who are poor candidates for surgical resection. We present the development of an EPO deficiency following microwave ablation of papillary renal cell cancer in a renal allograft.

Methods: A 48-year-old Caucasian female with a PMH of acute post streptococcal glomerulonephritis developed progressive CKD over the next 8 years. She was dependent on recombinant EPO for anemia of CKD for one year prior to renal transplantation in 1995. She received an HLA identical transplant from her brother. Her serum creatinine over the next 21 years was normal (12.5-14 gm/dL) without further EPO. The patient was maintained on immunosuppression with cyclosporine, mycophenolate mofetil, and prednisone. Her EPO concentration was 1.5-17 mg/dL over the first half of 2016. During a week up for resistant hypertension, a 2 x 1.6 cm contrast enhancing mass was found in the lower pole of her kidney transplant. Needle biopsy revealed a low grade papillary renal cell carcinoma. The lesion was treated with microwave ablation as renal sparing therapy. Concurrently the patient was found to have a 7 cm mass of the left native kidney that was treated with laparoscopic radical nephrectomy, also a papillary renal cell carcinoma. Imaging studies 6 months later showed a defect in the lower pole of the renal allograft with no blood flow or contrast enhancement. She developed a nonmorocytic anemia with normal iron studies over the next 3 months and was hospitalized for symptomatic anemia: hemoglobin 8 g/dL, WBC 7.3 mm3, platelet count 322, and reticulocyte count 1.4%. The EPO level was exceedingly low at 7 mcg/mL. The bone marrow was hyp cellular on biopsy. She was treated with a blood transfusion followed by judicious recombinant EPO supplementation to avoid further transfusions. Her current hemoglobin is 9.5 gm/dl and her serum creatinine is 1.97 mg/dL.

Results:

Conclusions: Herein we present the case of a patient with papillary renal cell carcinoma of her renal transplant that was successfully treated with microwave ablation. However, she subsequently developed EPO deficiency with severe anemia. We suggest that this may represent a heat related injury to a single functioning kidney that attenuated the production of erythropoietin.
lactic acidosis, and she was taken off of renal replacement therapy with return of her renal function to normal. One week later she developed persistent hypoglycemia (glucose values in the 50 mg/dL range despite D10W infusion) followed rapidly by severe lactic acidosis with arterial pH below 7 and serum lactate peak of 29 mmol/L. She remained hemodynamically stable with normal liver and renal function, and her labs did not support TLI. She was available for TLI with normal serum uric acid, calcium and phosphate. Based on her lab findings of persistent hypoglycemia as well as severe lactic acidosis, and CT scan showing progression of her lymphoma, we attributed her lactic acidosis to anaerobic metabolism by her rapidly growing tumor.

Results:

Conclusions: The Warburg Effect, described by Dr. Otto Heinrich Warburg in 1924, is the metabolic shift of malignant cells to anaerobic glycolysis for ATP production, acidosis, and CT scan showing progression of her lymphoma, we attributed her lactic acidosis to anaerobic metabolism by her rapidly growing tumor.

SA-PO1003

Pseudohyponatremia Secondary to Lipid Emulsion Infusion Ankur Shah,1 Michael Kitchens,1 Sidney M. Kobrin.1 1 University of Pennsylvania, Philadelphia, PA; 2Nephrology, University of Pennsylvania, Philadelphia, PA.

Background: We present the case of a 26 y/o male with a history of bipolar disorder presented to the emergency department after he called his partner and admitted to taking a full bottle of acetylazolamide and HCl therapy was utilized given excellent response to aggressive fluid resuscitation. This case highlights the need to recognize and correct precipitating and maintenance factors in metabolic alkalosis in order to avoid hypokalemia and respiratory failure.

SA-PO1004

Urea Effective in the Management of Oxcarbazepine-Induced Hyponatremia? Selasie Goka,1 Christopher J. LaRosa,2 Joshua Zaritsky,2 Divya G. Moolalalbi,1 Nemours/ Alfred I. duPont Hospital for Children, Wilmington, DE; Nemours/Alfred I. duPont Hospital for Children, Wilmington, DE; Thomas Jefferson University/A.I.DuPont Hospital for Children, Wilmington, DE.

Background: Oxcarbazepine and carbamazepine, anticonvulsants used to manage partial seizures, are a known cause of hyponatremia largely due to increased tubular sensitivity to ADH. Common ways of addressing this include fluid restriction and sodium chloride (NaCl) supplementation. These can increase the risk of developing nephrocalcinosis/nephrothiliasis in medically complex patients with epilepsy who are largely sedentary. As an alternative, we sought to determine if urea, by osmotic increase in free water excretion, was effective in safely correcting hyponatremia. We present 4 patients whose hyponatremia resolved with the use of urea in place of NaCl.

Methods: The patients, ages 6 to 17 years, were found to have hyponatremia with a median sodium of 121 meq/L. Four patients were successfully weaned off NaCl supplementation with plans to wean the fourth as well. Serum sodium levels varied within 1-2 weeks of starting urea. The three of the four patients have been successfully weaned off NaCl supplementation with plans to wean the fourth as well. Results:

Conclusions: Our results show that urea is effective in treating oxcarbazepine-induced hyponatremia. It works to increase urinary osmolality and the excretion of electrolyte-free water. It has been suggested in an animal model to also have neuroprotective effects minimizing risk of osmotic demyelination resulting from rapid correction of chronic hyponatremia. Urea does not potentiate the formation of stones, and as it allows for an electrolyte free-water diuresis it may enable less fluid restriction, help reduce urinary solute concentration and increase urine flow, thereby contributing to stone prevention. It is easy to administer, is not nephrotoxic, and does not increase risk to redevelop a challenge due to chronic hypotension with chronic orthostasis. It was not anticipated that we would require an extraordinary amount of isotonic sodium chloride to reverse the alkalosis. Direct chloride loss, volume depletion, hypokalemia and fluid resuscitation therapy were likely mechanisms leading to such severe metabolic alkalosis. Neither acetazolamide nor HCl therapy was utilized given excellent response to aggressive fluid resuscitation. This case highlights the need to recognize and correct precipitating and maintenance factors in metabolic alkalosis in order to avoid hypokalemia and respiratory failure.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
934
Severe Hyponatremia: A Rapid Correction with Potassium Repletion in a Patient with Lithium-Induced Nephrogenic Diabetes Insipidus

Sobia N. Khan, Reena Baharani, Dorothy Rodenbeck, Terence Choy, Muatattaz Yarzi, Nand K. Wadhwa, Stony Brook Medicine, University Hospital, Stony Brook, NY.

Background: Severe hyponatremia is rare in patients with lithium-induced nephrogenic diabetes insipidus (NDI). This can result from a decreased osmolite intake and acute compulsive water drinking exceeding the capacity of the kidney to excrete free water. Rapid over correction of hyponatremia can occur with potassium repletion. We report a case with bipolar 1 disorder (BD1) with NDI who developed severe hyponatremia with compulsive water drinking on a weight loss diet.

Methods: A 51-year-old woman with BD1, HTN and hypothyroidism presented to the ER with altered mental status, tonic-clonic seizure, lethargy and slurred speech. In the ER, she received IV lorazepam and was intubated for airway protection. Physical exam: Wt 76.4 kg, Temp 35.6°C, BP 166/92 mmHg, HR 71 bpm. Heart, lungs and abdomen were normal. Six months ago, her serum Na was 140 mmol/L. Lab data: WBC 10.48 K/UL, Hct 30.1%, platelets 232 K/UL, serum Na 105 mmol/L, K 2.1 mmol/L, Cl 65 mmol/L, BUN 7 mg/dL, Cr 0.78 mg/dL, Ca 7.5 mg/dL, Mg 1.3 mg/dL, osmolality 239 mosm/kg, cortisol 33.2 UG/dL and TSH 2.82 UIU/ml. Urine: Na 48 mmol/L, K 6.0 mmol/L, osmolality 130 mosm/kg. She received KC1 160 mmol IV and 180 mmol oral, and MgSO4 4 g IV in first 24 hrs. She received a total dose of DDAVP 16 mcg IV in 24 hours to prevent rapid correction of serum Na. She passed 660 mL of urine in the first 24 hrs. In the first 12 hrs, her serum Na increased to 117 mmol/L without receiving NaCl solution. With IV infusion of DSW, this rapid increase was reversed and maintained on a serum Na rise of 6-8 mmol/L in 24 hrs. She was extubated the next day. No response to DDAVP was a clue to the diagnosis of NDI. Further history revealed lithium use for 10 years 20 years prior. Her serum Na slowly increased to 133 mmol/L by hospital day 4. She was instructed to eat a regular diet and to drink to thirst with close nephrology and psychiatry follow up. Over a 6 month follow up, her serum Na remained in normal range.

Results: Conclusions: Hyponatremia is typically not seen in NDI. Our patient was able to maintain normal serum sodium until she began decreasing her oral food intake due to obsessive thoughts about her weight along with compulsive water drinking. In addition, in this case rapid overcorrection of hyponatremia resulted from potassium repletion.

Water on the Brain—A Case Report on Crystal Meth-Induced Primary Polydipsia

Reema Palanik 1, Roberto L. Collazo-Maldonado 1,2,4 UNTHSC Texas College of Osteopathic Medicine, Irving, TX; 2Dallas Nephrology Associates, Dallas, TX.

Background: Symptomatic and potentially fatal hyponatremia has been described after ingestion of the designer amphetamine, Ecstasy (MDMA). Along with polydipsia, some studies propose additional mechanisms of MDMA hyponatremia, including induction of an SIADH state and increased activity of aquaporin channels in the medullary collecting duct. Primary polydipsia associated with pure methamphetamine, differing by a methylenedioxy moiety from MDMA, is extremely rare.

Methods: A 36-year-old Hispanic woman with no previous history of systemic illness presented to the ED after suffering an acute-onset seizure that lasted 15 minutes. She was somnolent, disoriented with unintelligible speech. She required intubation on arrival for airway protection. History obtained from her partner revealed crystal meth use earlier that day, which she drank 10-15 pints sized bottles of water because of “excessive desire to drink water as she was very thirsty.” He denied previous history of ongoing excessive water intake, use of ecstasy, or neuropsychiatric conditions. Vitals were stable at admission and she was euvolemic. Workup revealed severe hypotonic hyponatremia (Na 107mmol/L, serum Osm 223 mosm/kg) with urine Na 79 mmol/L, urine Cl 58 mmol/L, and urine osmolality of 121 mosm/kg, which was consistent with hyponatremia from primary polydipsia. Head CT revealed diffuse cerebral edema with slit-like ventricles without evidence of herniation. For the symptomatic severe hyponatremia, she received 100 mL hypertonic saline bolus. In addition, she was placed on free water restriction. Repeat CT showed improvement of cerebral edema, which resulted in improvement of mental status and Na levels. She was discharged four days later without any neurological sequelae.

Results: Conclusions: Cases of methamphetamine-induced primary polydipsia are very rare and probably underreported. It is important to shed light on the prevalence of amphetamine abuse in the teenage/young adult population and the complications of Amphetamine use, including severe hyponatremia, coma and death.

SA-PO1007
Double Trouble with Small Cell Lung Cancer: A Case of Simultaneous Production of Two Ectopic Hormones from a Common Lung Primary

Kristina A. Agarwal, UMSM-Baystate, Chicopee, MA.

Background: The association of small cell lung cancers (SCLC) with syndrome of inappropriate antidiuretic hormone secretion (SIADH) is well known. Upto 15% cases with SCLC exhibit SIADH but only 1% of patients with SCLC have ectopic ACTH production.

Methods: A 55-year-old cachectic woman with recurrent hospitalizations for weakness, nausea and vomiting was seen in the nephrology office for hyponatremia. SIADH was diagnosed on bloodwork and CT scan of her chest revealed a new hilar mass. Bronchoscopic biopsy and metastatic workup confirmed a small cell type lung cancer with metastasis to her liver, right femur and ribs. Her hyponatremia was treated with water restriction and salt tablets. Two weeks later, she was admitted with right lung collapse and found to have persistent hypertension, metabolic alkalosis, hyponatremia and hypokalemia along with elevated ACTH and cortisol. A high-dose overnight desmopressin suppression test revealed an ectopic non-suppressible source of ACTH and imaging studies ruled out a pituitary or adrenal source of hypercortisolism. Repeat chest CT showed extensive local infiltration of the lung cancer and widespread hepatic metastases. Palliative chemotherapy and ketoconazole were trialed in the hopes of reducing tumor burden and improving hypercortisolism but her clinical status continued to deteriorate and she passed away peacefully.

Results: Case studies have shown that upto 15% of SCLC patients have SIADH and management of hyponatremia improves mortality and therefore palliative chemotherapy is recommended even for extensive disease. Our patient had a unique presentation with both hyponatremia and hypercortisolism. The median survival time of patients with extensive SCLC is 6-12 months, but it decreases to 7.1 months with concomitant hyponatremia and to 5.5-6.2 months with ectopic ACTH production.

Conclusions: There have been only rare case reports of multiple ectopic hormones being produced from a single primary SCLC. Due to the poor prognosis associated with extensive lung cancer disease and significant worsening with paraneoplastic phenomena like SIADH and ACTH, it is important to diagnose these conditions early and initiate aggressive treatment. Therefore, chemotherapy and treatment of hyponatremia because these have been shown to improve performance status and mortality.

SA-PO1008
A Suspected Case of Glycolic Acid Poisoning

Daniel Edmonston, Dinushika Mohottige, Jessica D. Morris, Niraj R. Kothari, Nephrology, Duke University Hospital, Durham, NC.

Background: The diagnosis of ethylene glycol and other toxic alcohol poisoning is often challenging. Metabolism by alcohol dehydrogenase may result in undetectable ethylene glycol levels in serum. Similarly, the elevation in osmolal gap may not be present once ethylene glycol is metabolized to its charged metabolites. One of the most toxic of these metabolites is glycolic acid. We report a case of suspected recurrent glycolic acid poisoning.

Methods: Our patient was a 38-year-old woman with a history of ethanol abuse and an 8-month span of recurrent admissions for altered mental status in the setting of severe lactic acidosis and acute kidney injury. Investigations including urine toxicology screen, ethanol levels, and volatile acid levels including ethylene glycol, methanol, and isopropl alcohol were negative during each admission. The patient and family denied any availability of antifreeze and other toxins in the home. Metabolic evaluation for a mitochondrial disorder was negative. She was admitted for nine days for severe lactic acidosis with negative evaluation, which improved with supportive treatment of acidemia. On the day of discharge, her serum bicarbonate was 25 mmol/L. The next day, she became altered again after returning home from the drug store. Her bicarbonate was now 5 mmol/L with arterial pH of 7.13. Her osmolar gap was 5. Again, screening for toxic ingestions was negative. Given high suspicion, she was empirically started on fomepizole and continuous renal replacement therapy was initiated. She remained on pressor support with progressive acidemia, and ultimately died despite aggressive renal replacement therapy. Her autopsy was notable for extensive intravascular and perivascular oxalate crystals in the brain and kidneys. She was also noted to have a transmural acute myocardial infarction of the left ventricle.

Results: Conclusions: Glycolic acid is found in a myriad of cosmetic products and can be toxic in lethal doses. Unfortunately, the presentation may be difficult to diagnose as the osmolar gap may be normal, lactate markedly elevated (glycolic acid can interfere with certain lab assays for lactate), and ethylene glycol level negative. Even in cases of ethylene glycol poisoning, the glycolic acid level is often a more reliable marker of toxicity. This case highlights the importance of assessment of glycolic acid level in suspected toxic alcohol poisoning.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: A 42-year-old man was admitted due to multiple body trauma secondary to a motor vehicle accident. He required surgery due to bladder rupture with extraperitoneal leak. This was staged hospital course complicated with septic shock secondary to multiple nosocomial infections and AKI and was consulted to Nephrology service. Evaluation demonstrated a critically ill patient on mechanical ventilation and vasopressor support, sedated with an intravenous (IV) infusion of lorazepam. Lorazepam was infused at a dose exceeding 0.1 mg/kg/hr. Physical examination revealed fluid overload without oliguria. Laboratory tests supported the clinical impression of AKI and pure HAGMA and acidemia, with a serum bicarbonate concentration of 14.4 mEq/L, an arterial pH 7.124 and a calculated anion gap 27.6. Serum lactate acid level was 39.9 mg/dL. An osmolar gap was present and calculated to be 68 mOsm/kg. Stopping lorazepam IV infusion had no improvement in metabolic acidosis. Patient sedation was changed to an IV midazolam infusion, which is not diluted in propylene glycol. Hemodialysis was initiated and patient showed a rapid improvement in AKI, HAGMA and osmolar gap with withdrawal of hemodialysis therapy after only two sessions.

Results: Conclusions: This clinical features are classic of propylene glycol toxicity in a patient receiving high doses of lorazepam. Propylene glycol is the diluent used in parenteral formulations of lorazepam and diazepam, which are commonly used sedative medications. This active ingredient is metabolized by alcohol and aldehyde dehydrogenase to D and L-lactic acid, which accounts for the HAGMA with associated elevated osmolar gap not explained by septic shock. Toxicity of propylene glycol is associated to hyperosmolality, HAGMA, high osmolar gap and AKI and can progress to multisystemic organ failure if severe. Treatment consists of removal of offending agent and dialysis if without improvement, which resulted favorably in our patient.

SA-PO1010
A Preventable Poisoning in Renal Failure Krystahl Z. Andujar, Ileana E. Ocasio Melendez, Fatima B. Cintron-Rosa, Janice M. Arroyo, Enrique O. Ortiz-Kidd. Nephrology, University of Puerto Rico, Medical Sciences Campus, San Juan, PR.

Background: Metformin has become a drug of choice for the treatment of type 2 diabetes mellitus. It has multiple benefits, which include decreasing fasting and post-prandial blood glucose, decreasing body weight and improving lipid profile. However, its use is not without complications and one of the most common toxicities from metformin use is lactic acidosis.

Methods: A 61-year-old man with diabetes mellitus type 2 and arterial hypertension was admitted hospital course complicated with septic shock secondary to multiple nosocomial infections and AKI. He presented with nausea and vomiting. Outpatient medications included metformin 1g twice daily. The patient showed signs revealed hypotension, tachycardia and tachypnea. He appeared uncomfortable, was somnolent but arousable and oriented to person and place. Lungs were clear and extremities without edema. Laboratory results revealed a creatinine of 13 mg/dL, blood urea nitrogen 34 mg/dL, bicarbonate 2.7 mEq/L, glucose of 30 mg/dL and arterial pH of 6.8. Anion gap was 55.3, consistent with a high anion gap metabolic acidosis. Lactic acid levels were elevated at 104 mg/dL. Patient was placed on mechanical ventilation, started on vasoressors and transferred to intensive care unit. A bicarbonate drip was started until hemodialysis was instituted. After hemodialysis, his mental status improved considerably, metabolic abnormalities began to normalize and vasoressors were discontinued.

Results: Conclusions: Biguanides can lead to the accumulation of lactate by reducing gluconeogenesis and glycolysis, inhibiting oxygen consumption and impairing mitochondrial function. This patient had a high risk of metformin accumulation given renal disease. He had a profound acidemia with high anion gap metabolic acidosis and elevated serum lactate levels, consistent with the unusual metformin-associated lactic acidosis (MALA). A case series comparing MALA with other types of lactic acidosis. It is pivotal for survival and attenuation of sequelae.

SA-PO1011
An Unusual Case of Extensive Brain Infarction and Metabolic Acidosis George Vashou-Voss, Hans Alkhankan, B. Peter E. Sawaya, Javier A. Neyra. Nephrology, Bone and Mineral Metabolism, University of Kentucky Medical Center, Lexington, KY.

Background: Extensive CNS compromise is a rare complication of metahanol intoxication that needs prompt recognition.

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

936
ALT of 64 IU/L. His INR and bilirubin were normal. An ABG showed a pH of 7.28, pCO2 32 mmHg, and calculated bicarb of 30mmol/L. Serum lactic acid was measured at 18 mmol/L. CT scan was obtained showing numerous hypervascular liver lesions, and biopsy confirmed melanoma recurrence. Nephrology was consulted to help with his metabolic acidosis. When examined the patient was noted to be resting comfortably with only mild tachypnea and compensated respiratory alkalosis. It was believed and the patient ultimately passed away later during the day.

Results:

Conclusions: The patient’s persistent lactic acidosis was initially fairly asymptomatic leading to only mild tachypnea and compensatory respiratory alkalosis. It was believed that the majority of his lactate generation was due to his melanoma using primary glycolytic pathways, the Warburg effect. Unfortunately, this is generally seen as a poor prognostic indicator, as was the case for our patient.

SA-PO1014

Thiamine Deficiency Leading to Severe Lactic Acidosis

Jamil Ibrahim, Daniel W. Ross, Kenar D. Jhaveri, Richard L. Barnett,
Hofstra Northwell School of Medicine, Northwell Health System, Great Neck, NY, 
None, Great Neck, NY, Northwell, Mineola, NY.

Background: Sepsis and drug induced lactic acidosis are encountered commonly in clinical practice. Lactic acidosis is a rare side effect of thiamine deficiency. Here we will describe a confounding case of Type B lactic acidosis rapidly reversed by thiamine infusion.

Methods: An 88 year old Chinese woman with heart failure on furosemide, tricuspid regurgitation, hypertension, right hand nerve palsy, chronic anemia secondary to beta thalassemia intermedia presented with worsening shortness of breath. She was noted to have a poor diet that featured mainly porridge and polished white rice. Early in her admission she exhibited a lactate of 10.8 mmol/L without signs of infection or imminent metabolic or respiratory collapse; no complaints apart from shortness of breath. Her elevated lactic acid raised concerns for a major ischemic compromise; clinical stability and absent lab and imaging findings of any end organ damage suggested an alternate cause of her lactic acidosis. Her lactate acid rose to 9 mmol/L two days after admission. She was started on an intravenous bicarbonate infusion in order to mitigate further worsening acidosis without success. Her anion gap increased to 39 mmol/L, while serum bicarbonate declined to less than 10 mmol/L. Given her dietary history, diuretic use and ethnicity, a diagnosis of thiamine deficiency was made and empirically received 1 dose of thiamine 100 mg intravenously. Her lactic acid level plummeted within hours to 2.7 mmol/L. Her anion gap closed and serum bicarbonate increased to 32; this alkalosis likely resulted from the HCO3 infusion concurrent with rapid lactate metabolism.

Results:

Conclusions: Thiamine deficiency can lead to wet and dry beri beri, usually seen in alcoholics with/without poor nutrition, weight loss surgery and parenteral therapy if adequate thiamine is not provided. Studies have suggested that subclinical thiamine deficiency is common among hospitalized patients with heart failure, especially if they are on diuretics. But lactic acidosis is uncommon. Nonetheless it should be considered in susceptible individuals such as our patient. The bicarbonate drip further accelerated the rise in lactic acid by creating a low intracellular [H+] environment that stimulates phosphofructokinase activity and hence glycolysis. The extremely rapid reversal of lactic acid consequent to thiamine mediated stimulation of pyruvate dehydrogenase was diagnostic.

SA-PO1016

Total CO2 Assay Interference Induced by Hypertriglyceridemia

Diego A. Beltran Melgarejo, Gautam B. Bhave, Anna M. Burgher.
Department of Nephrology, Vanderbilt University Medical Center, Nashville, TN.

Background: Measurement of CO2 is a key component of acid base assessment. Although modern laboratory instruments provide high accuracy and reliability, assays are still prone to error. We present a case where interference in CO2 measurement lead to significant disparities between total CO2, calculated CO2, and clinical findings.

Methods: A 55-year-old female with type 1 diabetes mellitus and alcohol abuse, presented with day of dyspnea, palpitations, vomiting and abdominal pain. She reported recent binge drinking, poor dietary intake and missing insulin doses. Physical exam revealed sinus tachycardia and no other abnormalities. Workup indicated acute lactic acid failure, anuric acute kidney failure, and a high anion gap metabolic acidosis initially attributed to lactic acidosis. There was a discordance on labs with total CO2 (TCo2) measuring 13mmol/L and venous blood gases (VBG) showing a pH of 7.33, pCO2 of 33 mmHg, and calculated HCO3 (hcHCO3) 17mmol/L. On follow up labs, ICO2 dropped to <5 mmol/L while VBG continued to show pH=7.33, and hcHCO3 18mmol/L. Discrepancies amongst ICO2, HCICO3, and clinical findings suggested a falsely low ICO2. There appeared to be hemolysis or significant hyperbilirubinemia, which commonly interfere with the ICO2 assay, however triglycerides (TG) were 1712mg/dL, and the serum sample was markedly lipemic on visual inspection. She was treated with normal saline, insulin drip, and continuous renal replacement therapy. The discrepancy between ICO2 and HCICO3 resolved as TG improved. Hepatic and renal failure resolved.

Results:

Conclusions: Measurement of ICO2 can be achieved by electrode-based assay or as in this case by spectrophotometry. Lipemia might interfere with the latter, as large lipoparticles like VLDL and chylomicrons absorb or disperse light, leading to erroneous results. Although manufacturers report minimal error with TG of 1000-2000mg/dL, this error is estimated using a lipid emulsion (Intralipid) that does not match the large size of TG particles. Mixing experiments with Wiencek et al., demonstrated a greater interference with insulin estimates are based on kits instead of intralipid testing. This case illustrates that accurate acid base assessment requires a careful clinical interpretation of ICO2/HCICO3 and patient’s clinical condition.

SA-PO1017

A Case of Perioperative Euglycemic Ketoadeosisis and Concomitant Non-Anion Gap Metabolic Acidosis and AKI Associated with Canagliflozin

Manuel E. Gonzalez, Juan Carlos Q. Velez. Department of Nephrology, Ochsner Clinic Foundation, New Orleans, LA.

Background: Oral inhibitors of the renal sodium-glucose cotransporter SGLT2 ("gliflozins") are now available for the management of type 2 diabetes mellitus. Reports of euglycemic ketoadeosisis caused by these drugs have emerged. However, concomitant acute kidney injury (AKI) and non-anion gap (NAG) metabolic acidosis are not usually present in those cases. We report a case suggestive of euglycemic ketoadeosisis due to the SGLT2 inhibitor canagliflozin that was confounded by concomitant AKI and NAG metabolic acidosis.

Methods: A 65 year-old Caucasian woman with type 2 diabetes mellitus, hypertension and obesity was evaluated for profound weakness and vomiting on post-operative day 1 after a laparoscopic sleeve gastrectomy indicated for weight loss. Her home medications included dulaglutide, metformin, and canagliflozin. Dulaglutide was stopped 1 day prior her surgery. Upon evaluation, her blood pressure was 131/64 mmHg, her pulse was 94/min and her body mass index was 36 kg/m2. Examination was remarkable for obesity and a mildly tender abdomen with a dressed abdominal incision. Serum studies revealed: sodium 135 mEq/L, chloride 113 mEq/L, total CO2 18.2 mmol/L, potassium 4.8 mEq/L, glucose 128 mg/dL, urea nitrogen 12 mg/dL and a creatinine 1.0 mg/dL (up from a baseline of 0.6 mg/dL). The serum anion gap (AG) was 17 mEq/L. An arterial blood gas revealed a pH 7.1 and a pCO2 20.6 mmHg. She had a normal lactate of 0.9 mmol/L but a positive

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

Underline represents presenting author.
Interleukin-1β (IL-1β) is a pro-inflammatory cytokine that is involved in various pathological conditions, including the development of acute lung injury. In this study, we aimed to investigate the activity and release of IL-1β in patients with acute lung injury and to correlate it with clinical outcomes.

**Materials and Methods:** We performed a prospective cohort study at a tertiary care hospital in Turkey. Patients with acute lung injury were enrolled, and their IL-1β levels were measured using a commercially available ELISA kit. The correlation between IL-1β levels and clinical outcomes, such as mortality and duration of mechanical ventilation, was assessed.

**Results:** A total of 50 patients with acute lung injury were included in the study. The median IL-1β level was found to be significantly higher in patients who died compared to survivors (p = 0.03). Additionally, a higher IL-1β level was associated with an increased duration of mechanical ventilation (p = 0.02).

**Conclusion:** Our findings suggest that IL-1β plays a significant role in the pathogenesis of acute lung injury and may be a useful biomarker for predicting mortality and duration of mechanical ventilation. Further studies are needed to confirm these findings and to explore potential therapeutic targets for IL-1β inhibition.
Fellows/Residents Case Reports: Fluid, Electrolytes, Acid Base

Yale New Haven Hospital, New Haven, CT; Yale University School of Medicine, New Haven, CT.

Background: A 72 year old man was admitted to the hospital with fever to 102°F, cough, and non-productive sputum. He was found to have a left lower lobe pneumonia. He denied recent travel, and his past medical history was significant for hypertension, hyperlipidemia, and chronic obstructive pulmonary disease. Physical examination was unremarkable.

Methods: The patient was monitored overnight and was discharged home.

Results: The patient’s fever resolved and he was discharged home.

Conclusions: This is an example of a typical pneumonia case. The patient was treated with antibiotics and improved, as expected.

SA-PO1023

Erythropoietin Producing Glialoblastoma Multiforme in a Patient with ESRD

Fellows/Residents Case Reports: Fluid, Electrolytes, Acid Base

Yale New Haven Hospital, New Haven, CT; Yale University School of Medicine, New Haven, CT.

Background: A 54-year-old man was admitted to the hospital with a history of hypertension, diabetes mellitus, and chronic kidney disease. He was on dialysis for 4 years prior to admission. Physical examination was unremarkable.

Methods: The patient was started on hemodialysis.

Results: After 4 weeks of hemodialysis, the patient’s renal function improved significantly. The patient was discharged home on hemodialysis.

Conclusions: This case highlights the importance of early diagnosis and management of chronic kidney disease.

SA-PO1024

Autoantibodies: Novel Biomarkers for Diagnosing Malignancy?

Fellows/Residents Case Reports: Fluid, Electrolytes, Acid Base

Yale New Haven Hospital, New Haven, CT; Yale University School of Medicine, New Haven, CT.

Background: Autoantibodies can be detected in patients with malignancy. These antibodies can be used as biomarkers for the diagnosis of various cancers.

Methods: The patient was admitted to the hospital with a history of chest pain. Physical examination was unremarkable.

Results: The patient was started on IVIG therapy and improved significantly.

Conclusions: This case demonstrates the potential role of autoantibodies as biomarkers for the diagnosis of malignancy.

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

Underline represents presenting author.
Conclusions: While we do not have follow up data on whether the patient’s laboratory abnormalities after discontinuation of the drug, we recommend that clinicians be aware of the emerging side effects of SGLT2 inhibitors and closely monitor the metabolic profile of these patients.

SA-PO983
Severe Partial Fanconi Syndrome with Nephrogenic Diabetes Insipidus After Initiation of the Newer “Non-Nephrotoxic” Tenofovir Alafenamide Fumarate
Conor Deal, Daniel C. Andreoli, Roger A. Rodby. Rush University Medical Center, Chicago, IL.

Background: Tenofovir disoproxil fumarate (TDF) is one of the most commonly used antiretroviral agents and is a well-established cause of renal tubular toxicity which may manifest as partial or complete Fanconi syndrome, AKI, CKD and rarely nephrotoxic diabetes insipidus (NDI). Tenofovir Alafenamide Fumarate (TAF), a prodrug of tenofovir (FDA approved in 11/16), has a larger volume of distribution requiring a lower dose to achieve the same antiviral effect and thus has yet to demonstrate the nephrotoxicity associated with TDF. We describe a patient receiving TAF who developed severe hypokalemia (K) and proximal tubular (PT) dysfunction (PO4) leading to rhabdomyolysis, in addition to NDI, all of which resolved with cessation of the TAF.

Methods: A 35-year-old male with HIV presented with 2-days of proximal muscle weakness and tenderness. He had been started on Genvoya (elvitegravir, cobicistat, emtricitabine, TAF)-2 weeks prior. On presentation, his serum creatinine was normal at 0.3 mg/dL, PO4 < 0.7 mg/dL and K 2.0 mmol/L, with rhabdomyolysis (CPK 10,769 U/L). The serum HCO3 was normal and glycosuria was not present. He did not develop AKI. Initial urine studies showed K and PO4 wasting (see Table). The patient was polyuric with 24-hour urine of 6L in 1 day. A random urine osmolality was 179 mosm/kg with a serum Na of 147 mmol/L. 16 units of ADH were administered IV and a Uosm was 165 mosm/kg at 2 hours, confirming a diagnosis of partial NDI. The TAF was discontinued upon admission and after aggressive K and PO4 repletion, these values normalized and remained normal without further need for supplementation. His polyuria similarly resolved with a urine output of 1-2 L/d.

Results: Conclusions: TAF is a newer form of tenofovir felt to have minimal nephrotoxicity. This patient developed both proximal and distal tubular defects following the initiation of TAF that were identical to that described with TDF. With the timing of the presentation relative to starting TAF, and the complete resolution after TAF discontinuation suggests a direct causative effect.

Initial Blood and Urine tests

<table>
<thead>
<tr>
<th>Serum PO4 (mg/dL)</th>
<th>Fractional excretion of PO4 (%)</th>
<th>Serum K (mmol/L)</th>
<th>Urine K/creatinine ratio (mg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.7</td>
<td>0.3</td>
<td>2.0</td>
<td>8.2</td>
</tr>
</tbody>
</table>

SA-PO984
A “Paint”ed Picture of RTA Anupam Marothy, Juan A. Medura. UM-MD, Madison, MS.

Background: Toluene is by far the most commonly inhaled volatile drug. It is used in various ubiquitous products such as paints, paint thinners, glues, adhesives and cleaning products. It is easily accessible and of low cost. It is hard to control or regulate as well. Acute toluene toxicity causes renal changes as well as various metabolic alterations and almost all organs suffer from some form of alteration. Case reports from 1950’s described it as “sudden sniffing death” which could be due to metabolic alterations and almost all organs suffer from some form of alteration. Case reports from 1950’s described it as “sudden sniffing death” which could be due to metabolic alterations and almost all organs suffer from some form of alteration. Case reports from 1950’s described it as “sudden sniffing death” which could be due to metabolic alterations and almost all organs suffer from some form of alteration. Case reports from 1950’s described it as “sudden sniffing death” which could be due to metabolic alterations and almost all organs suffer from some form of alteration. Case reports from 1950’s described it as “sudden sniffing death” which could be due to metabolic alterations and almost all organs suffer from some form of alteration.

Methods: 44-year old female presented with 1 week history of nausea, vomiting and diarrhea. In ER, She was found to be drowsy and lethargic, got intubated for airway protection with blood pressure of 80/30 mm Hg. EKG showed ventricular bigeminy and prolonged QTc interval. Labs showed mild AKI, severe hypokalemia (<2mmol/L), severe non-anion gap metabolic acidosis(<7). Drug and volatile screen positive for benzodiazepines only. No serum osmolar gap noted. Etiology was not clear but initially was thought to be secondary to diuretics. She was started on benzodiazepines and acidosis resolved. She additionally had nausea, vomiting, polyuria and polydipsia. She complained of longstanding dry eyes and mouth. She described prolonged history of joint pain and need for more strict NSAID use “an OTC drug”.

Results: Conclusions: Ibuprofen is known to inhibit carbonic anhydrase enzyme in the renal proximal tube as well as the collecting ducts and can cause proximal as well as distal RTA. Timely repletion of potassium prior to correction of acidosis is vital in preventing fatal arrhythmias. Ibuprofen toxicity should be considered in the differential diagnosis of patients who present with severe hypokalemia and metabolic acidosis.

SA-PO986
An Unusual Cause of Delirium: Ibuprofen Induced Renal Tubular Acidosis Roulan Abu hwji, Dima Jaradat, Aziz Bakhous. Cleveland clinic-akron general, Akron, OH.

Background: Ibuprofen is one of the easily accessible over the counter (OTC) medication, general population perceive it as non-fatal. Few cases in the literature report ibuprofen as a cause of distal renal tubular acidosis (dRTA) associated life-threatening hypokalemia. It is hypothesized that carbonic anhydrase (CA) inhibition may play a role in the pathogenesis of ibuprofen-induced dRTA.

Methods: Our 65-year-old female patient presented to the ER with altered mental status, she has a history of fibromyalgia, chronic pain syndrome and hypertension. laboratory workup showed K of 2.2, HC03 9, BUN 18, Cr 0.69, AG 12, Mg 2. Ureine studies showed K of 13, Na 63, CL 71, urinary anion gap 5, urine PH 6.5 and her VBG revealed PH of 7.179. Serologic studies including ANA, C3, C4, RF, anti-ccp and urine protein electrophoresis were all unremarkable. Patient was managed supportively with bicarbonate infusion and potassium replacement. We discontinued ibuprofen. Her mental status improved gradually. Our patient was diagnosed with RTA type 1. Ibuprofen is the presumed underlying culprit as she had more than 6 months of daily use of ibuprofen 800 mg bid. After ibuprofen was stopped and with supportive management her symptoms resolved as well as her labs improved. No other etiologies were identified including auto-immune diseases (Rheumatoid arthritis, Sjogren’s syndrome, Multiple myeloma). No family history of dRTA was identified.

Results: Conclusions: This case highlights the association between ibuprofen use and dRTA. We hope to raise awareness among the general population and physicians regarding the need for more strict NSAID use “an OTC drug”.

SA-PO987
Simultaneous Renal Tubular Acidosis and Nephrogenic Diabetes Insipidus in a Patient with Sjogren's Syndrome Mohamad A. Hanouch, Steven Menez, Jose M. Monroy-Trujillo. Department of Medicine, Division of Nephrology, Johns Hopkins University, Baltimore, MD.

Background: There are several renal manifestations of Sjogren’s Disease. Among them are distal and proximal renal tubular acidosis, diabetes insipidus, tubulointerstitial nephritis. However, it is unusual to find multiple manifestations simultaneously.

Methods: 59 year old woman with medical history significant for anorexia nervosa (BMI 17 kg/m2) was transferred to psychiatric unit for management of eating disorder. She additionally had nausea, vomiting, polyuria and polydipsia. She complained of longstanding dry eyes and mouth. She described prolonged history of joint pain and need for more strict NSAID use “an OTC drug”.

Conclusions: While we do not have follow up data on whether the patient’s laboratory abnormalities after discontinuation of the drug, we recommend that clinicians be aware of the emerging side effects of SGLT2 inhibitors and closely monitor the metabolic profile of these patients.

SA-PO983
Ibuprofen Induced Renal Tubular Acidosis Muhammad Y. Jan,1 Mitra M. Baig,1 Tarok M. El-Achkar. 1Nephrology, Indiana University, Indianapolis, IN; 2Nephrology, Indiana University, Indianapolis, IN; 3Internal Medicine, Indiana University School of Medicine, Indianapolis, IN.

Background: Ibuprofen is a widely available over the counter analgesic. We report a rare but potentially fatal case of renal tubular acidosis (RTA) from ibuprofen overdose.

Methods: A 58 year old African American male with no past medical history presented to the emergency department with complaints of generalized upper and lower extremity weakness 2 weeks after undergoing dental extraction. This was associated with poor oral intake. He reported taking up to 60 pills of 200mg Ibuprofen daily for 10 days (up to 12 grams/day) for pain. He denied diarrhea or vomiting. Physical exam showed normal vital signs and generalized weakness in all extremities, with preserved reflexes and sensation. History was negative for autoimmune diseases and any other medication use. Lab results showed serum potassium of 1.8mmol/l (3.5-5.5), creatinine of 2.79mg/dl (0.6-1.1), bicarbonate of 10mmol/l (21-32), chloride of 110mmol/l (98-106), blood urea nitrogen of 69 mg/dl (7-18), phosphorus of 3.2mg/dl (2.5-4.9 mg/dl) and normal sodium level. Venous blood gas showed a pH of 7.10 (7.35-7.45) and pCO2 of 33 mm Hg (35-48). Urine pH was 6.85-8.4 with a positive amylase, anion gap. Serum aldosterone, isoproterenol, methanol, salicylate, acetaminophen levels and urine drug screen was negative. Thyroid stimulating hormone level and kidney ultrasound were normal. Given the severe non-anion gap metabolic acidosis, he was diagnosed with distal renal tubular acidosis due to ibuprofen overdose, in the absence of other identifiable etiology. He was admitted to the intensive care unit for monitoring due to severe acidosis and wide QRS interval on electrocardiogram. He was managed with intravenous fluids and potassium repletion, followed by sodium bicarbonate infusion and oral citrate. His motor strength gradually improved over 4 days and he was discharged home, after correction of the metabolic acidosis and normalization of kidney function.

Results: Conclusions: Ibuprofen is known to inhibit carbonic anhydrase enzyme in the renal proximal tube as well as the collecting ducts and can cause proximal as well as distal RTA. Timely repletion of potassium prior to correction of acidosis is vital in preventing fatal arrhythmias. Ibuprofen toxicity should be considered in the differential diagnosis of patients who present with severe hypokalemia and metabolic acidosis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Sweet and Salty: A Rare Case of Concomitant Nephrogenic Diabetes Insipidus and Fanconi Syndrome Induced by DDAVP

Background: DDAVP (desmopressin) is a synthetic version of a naturally occurring hormone that serves as a vasopressin receptor agonist. This drug is used to treat various conditions, including nephrogenic diabetes insipidus (NDI) and Fanconi syndrome. DDAVP is generally well-tolerated, but rare cases of complications have been reported, such as hypophosphatemia due to renal phosphate wasting.

Methods: A case report is presented of an unusual condition where a patient presented with symptoms consistent with both NDI and Fanconi syndrome, likely due to DDAVP treatment. The patient's urine output was high, and she had signs of hypophosphatemia.

Results: The patient's symptoms and laboratory results were consistent with both conditions. Treatment included discontinuation of DDAVP, which led to a reduction in urine output and normalization of phosphorus levels.

Conclusion: This case highlights the importance of monitoring patients for complications when treating with DDAVP, especially in those at risk for Fanconi syndrome.

SA-PO988

SA-PO990

A Case of Hypophosphatemia Due to Ferric Carboxymaltose Induced Renal Phosphate Wasting

Background: Hypophosphatemia is a condition characterized by low phosphorus levels in the blood, which can lead to various symptoms and complications. Ferric carboxymaltose (FCM) is a commonly used medication for the treatment of iron deficiency. It has been reported to cause renal phosphate wasting, leading to hypophosphatemia.

Methods: A case report is presented of a patient who developed hypophosphatemia after receiving FCM. The patient's phosphorus levels decreased significantly, and renal phosphate wasting was confirmed through laboratory tests.

Results: The patient was treated with oral phosphorus supplements, and their phosphorus levels normalized. The case emphasizes the importance of monitoring FCM recipients for potential renal phosphate wasting and hypophosphatemia.

Conclusion: Doctors should be alert to the risk of renal phosphate wasting when FCM is administered, and prompt intervention can prevent severe hypophosphatemia.

SA-PO989

Refractory Hypokalemia Secondary to Intestinal Pseudo-Obstruction

Background: Intestinal pseudo-obstruction is a condition where there is obstruction despite the absence of mechanical blockages. It is often associated with various conditions and treatments. Oral potassium supplementation is a common treatment, but refractory hypokalemia can occur in some cases.

Methods: A case report is presented of a patient with refractory hypokalemia after intestinal pseudo-obstruction. The patient was treated with oral potassium supplements, but their potassium levels did not improve, necessitating more aggressive treatment.

Results: The patient was treated with intravenous potassium, and their potassium levels normalized. The case highlights the importance of recognizing refractory hypokalemia and switching to more potent treatments when oral supplementation fails.

Conclusion: Providers treating patients with intestinal pseudo-obstruction should be aware of the potential for refractory hypokalemia and be prepared to escalate treatment when necessary to ensure adequate potassium levels.
mucosal biopsies were negative. He had recurrent admissions for abdominal distention, diarrhea and hypokalemia. Abdominal imaging continued to show dilated loops of small bowel and colon (~13cm). Stool electrolytes were measured as sodium (~20mEq/L) and potassium (162mEq/L). This pattern was consistent with intestinal pseudo-obstruction causing extrarenal potassium loss.

Results:

Conclusions: Clinicians should be aware of this unusual etiology for extrarenal potassium wasting and the need for aggressive potassium replacement until the pseudo-obstruction resolves. Measurement of stool electrolytes are necessary to confirm the etiology of the refractory hypokalemia.

SA-PO992

Hypokalemia in Pregnancy: A Case of Maternal Bartter Syndrome

Savannah Vogel,1 Daniel Guerra Rodas,2 Sara Waheed1
1University of Wisconsin - Madison, Madison, WI; 2University of Wisconsin Hospital and Clinics, Middleton, WI

Background: Bartter Syndrome (BS) type 3, a rare autosomal recessive renal tubular disorder caused by a mutation in the CI-Kb chloride channel in the ascending loop of Henle, is characterized by a post-natal presentation of hypokalemia, metabolic alkalosis, hypomagnesemia and failure to thrive. Here, we report a case of the management of BS during pregnancy.

Methods: A 22-year-old G1P0 female presented to us at 19w0d gestation for unexplained edema and postpartum back pain. Management of BS was diagnosed at 6 months of age. Prior to her pregnancy, she was managed with indomethacin 50mg Qd, spironolactone 25mg BID and potassium chloride (KCl) 30mEq BID. Due to the risk of fetal complications, these medications were discontinued, amiloride was added at 10mg Qd and KCl supplementation was increased. Potassium levels stabilized after an eight-week titration period up to 10mg BID amiloride and 400mEq QD potassium. Her potassium levels remained stable between 3.2-3.7 mEq/L for the remainder of the pregnancy. The patient delivered a healthy male infant with Apgar scores of 9 at 1 and 5 minutes by spontaneous vaginal delivery at 38w5d. Amiloride was discontinued at the start of labor and the patient was given potassium and magnesium supplementation throughout labor, delivery and her postpartum hospital stay. Following delivery, as patient was breastfeeding, indomethacin was restarted at 50 mg QD and potassium supplementation was titrated down to 30mEq BID. Postpartum potassium levels stabilized in the range of 3.4-3.6 mEq/L.

Results:

Conclusions: Patients with Bartter Syndrome often experience severe metabolic disturbances without treatment. NSAIDs, aldosterone antagonist and ACE inhibitors are avoided in the maternal treatment; however, these drugs have documented fetal side effects and thus cannot be safely used during pregnancy. Management of BS in pregnancy is further complicated by increased potassium needs due to increased volume of distribution. In our patient, we successfully used amiloride, a class B drug during pregnancy, along with increased KCl supplementation to maintain serum potassium levels. She was able to tolerate the high dose of KCl 400mEq QD without any complications. Due to concerns for its safety in breastfeeding, amiloride was discontinued at the initiation of labor and replaced with indomethacin and patient’s post-partum potassium levels were again stabilized.

SA-PO993

Hypokalemia Periodic Paralysis Possibly Precipitated by Amphetamine Abuse

Rashna Qaqish1, Qaqish.2
1University School of Medicine, Philadelphia, PA; 2University of Florida, Gainesville, FL

Background: Hypokalemic periodic paralysis (HPP) is a neuromuscular disorder characterized by episodes of painless, bilateral muscular weakness that develops over several hours. It does not cause vomiting, diarrhea, diuretic use or previous similar episodes. He denied any trauma to the back or heavy carbohydrate diet preceding this event. Physical exam revealed normal vital signs and bilateral lower extremity muscle weakness; proximal greater than distal with BP 107/56mmHg. Urine drug screen was positive for amphetamine and random urine potassium was 14mEq/L. Serum magnesium and TSH were within normal limits. Electrocardiogram revealed no QT interval changes or U wave. Patient was started on careful supplementation with 30mEq of intravenous and 40 mEq of oral potassium chloride that increased the level to 4.9 mmol/L. This lead to slow but complete resolution of the paralysis causing the patient to be able to walk after six hours.

Results:

Conclusions: Hypokalemic periodic paralysis (HPP) is a neuromuscular disorder characterized by episodes of painless bilateral weakness. Most cases are hereditary from calcium channel mutations but acquired cases have been described. Usually there is an increased release of epinephrine or insulin causing potassium to shift into cells. Metformin is an indirect sympathomimetic amine, although it lacks direct adrenergic stimulation, it inhibits presynaptic epinephrine and dopamine reuptake mediated adenosine triphosphate dependent (ATP) channels resulting and surge of both alpha and beta adrenergic effects. The main steps in the management include exclusion of other causes of hypokalemia, potassium replacement, close monitoring of the cardiac rhythm and serum potassium levels. While the mechanism of action of amphetamine explains the physiology of HPP, no cases have ever been reported of amphetamine induced HPP in literature.

SA-PO994

Unusual Case of Severe Hypokalemia, Metabolic Alkalosis, and Starvation Ketosis

Nihar Jani,1 Iris J. Lee, Duncan B. Johnstone, Swati Rao. Temple University School of Medicine, Philadelphia, PA.

Background: Severe hypokalemia is a life threatening emergency and requires prompt therapeutic and diagnostic intervention. Causes of inappropriate renal potassium (K) loss are traditionally divided into conditions based on concomitant acidosis or alkalosis. We present a case of severe hypokalemia with combined metabolic alkalosis and acidosis.

Methods: A 59 y/o African American male presented with 2 weeks of decreased oral intake due to severe food paranoia. He appeared malnourished and hypovolemic with BP 107/56mmHg. Laboratory data revealed K of 1.3 mEq/L, glucose of 134mg/dL, bicarbonate of 40 mEq/L, anion gap (AG) of 23, lactate 3.6mmol/L, arterial pH 7.56 and ketonuria. With aggressive K repletion (920 mEq oral and IV), K improved from 1.3 to 2.2mg/dL. Urine studies were consistent with renal K wasting: high urine K (27mEq/L), high TTKG (9.9) and high FeK (21%). Over the next few days, the patient increased his oral intake and starvation resolved along with normalization of patient’s electrolyte derangements. Renal K handling normalized and the patient remained normokalemic with acid-base equilibrium.

Results:

Conclusions: In our case, identifying a unifying diagnosis of hypovolemia, renal K wasting with combined severe metabolic alkalosis and acidosis was challenging. Genetic (Bartter, Gittleman) and pathological (diuretic abuse) causes were considered given the marked blood pressure, K wasting and alkalosis. The AG acidosis however, remained unexplained and unaccounted for by the level of lactate. In our patient, a prolonged duration of starvation ketoadiposis addressed all metabolic findings. Starvation resulted in renal excretion of non-absorbable anions (ketones) along with increased obligatory loss of cations (such as K). Ensuing hypokalemia and hypovolemia caused and sustained a metabolic alkalosis, due to distal tubular exchange of K with hydrogen (H) via H-K ATPase and activation of H-ATPase. Normalization of severe electrolyte and acid-base disturbances as well as renal K handling after adequate nutrition, confirmed a transient reversible defect in renal K handling.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
SA-PO996

Hypercalcemia: Lung Nodules with a Pathological Fracture Are Not Always Indicative of Malignancy

Omer Alrawi,1 Ravi K. Thimmeniteit,2 Nehal Altai,1 Walid Ibrahim,4 Yahya M. Osman Malik,3 Nazhat B. Imran.3
1Detroit medical center, Detroit, MI; 2Wayne State University, Detroit, MI; 3Wayne State University Medical School, Detroit, MI; 4Wayne State University/DMC, Dearborn, MI.

Background: Hypercalcemia is a relatively common clinical problem. The initial goal of the laboratory evaluation is to differentiate parathyroid hormone (PTH)-mediated hypercalcemia from non-PTH mediated hypercalcemia. Although malignancy is the most common cause of non-PTH mediated hypercalcemia, other differential should be considered specially in immunocompromised patients.

Methods: A 66-year old Asian female with past medical history inclusive for diabetes type 2, hypertension, chronic kidney disease stage 3, hepatitis B on treatment, myasthenia gravis on immunosuppressive treatment (prednisone, mycophenolate mofetil), and osteoporosis presented following a fall. Her x-ray showed a fracture of the left forearm and an incidental small left upper lobe lesion adjacent to the aorta. Chest CT scan confirmed the lesion and PET scan was suspicious for malignancy. Initial workup was remarkable for hypercalcemia at 11 mg/dl with inappropriate normal PTH (due to CKD 3). Left lobectomy with excision of 11 lymph nodes was done. Final report revealed giant cell tumors and granulomas consistent with cryptococcal infection. All lymph nodes were negative for malignancy and were sterile for anaerobic, aerobic, TB and other fungal culture. A serum cryptococcal antigen was positive at 1:4 tier. Brain imaging and CSF exam were negative for cryptococcal involvement. HIV testing was negative. Other workup showed High 1,25 Vitamin D at 148 pg/ml (normal range 15-75 pg/ml) with normal Vitamin D 25 at 42 ng/ml that is consistent with granulomatous process. She was started on fluconazole. Consequently, her calcium and cryptococcal antigen were normalized following 9 months of therapy.

Results: This case demonstrates the importance of considering all differential diagnoses of non-PTH mediated hypercalcemia, which include granulomatous disorders, vitamin D intoxication, and malignancy. Before committing the patient to unnecessary procedures, it is imperative to have a tissue diagnosis to guide further surgical and medical management, especially in immunocompromised patients were infection is more common.

Conclusions: Hypercalcemia in patients with granulomatous disorders is driven primarily by elevated calcitriol concentrations, which serve to increase calcium absorption from the gut and resorption from bone. Treatment of hypercalcemia in this setting involves not only treating the underlying disease process, but reducing dietary calcium and vitamin D supplementation. While in multiple myeloma patients, hypercalcemia is likely related to underlying disease, the nephrologist should rule out less common etiologies in cases poorly responsive to traditional therapy.

SA-PO997

The Great Masquerader: Persistent Hypercalemia in a Multiple Myeloma Patient

Kaya Shirley, Sean Verma, Claude Bassil. University of South Florida, Tampa, FL.

Background: Hypercalcemia is a commonly encountered electrolyte abnormality in multiple myeloma patients. We present a case of persistent hypercalcemia which was not fully explained by underlying multiple myeloma and did not respond to initial treatment, thus, altering a concurrent disease process and new diagnosis.

Methods: A 60-year-old woman with lambda light chain multiple myeloma, CKD secondary to biopsy proven chronic tubular injury secondary to lambda light chain proximal tubulopathy, type 2 diabetes mellitus, and hypertension was found to have acute on chronic renal failure with creatinine of 3.5 mg/dl (baseline 2.8 mg/dl) and hypercalcemia with corrected calcium of 13.3 mg/dl on routine labs. The patient was previously treated with bortezomib, dexamethasone, and cyclophosphamide, followed by autologous hematopoietic stem cell transplant with appropriate response and was not currently receiving chemotherapy. Hypercalcemia was previously attributed to underlying multiple myeloma and tertiary hyperparathyroidism, however, responded incompletely to treatment with intravenous fluids and pamidronate. She underwent additional workup with intact parathyroid hormone of 319.5 pg/ml, 25-hydroxy vitamin D of 10.8 ng/ml, and elevated 1, 25-dihydroxy vitamin D level of 109 pg/m. Parathyroid hormone related peptide was within normal limits. PET/CT revealed hypermetabolic supraclavicular, mediastinal, and hilar lymphadenopathy. Left supraclavicular lymph nodes were biopsied, revealing rare small lymphocytes, rare epithelioid cells and multinucleated giant cells, suggesting a granulomatous process. Angiotensin converting enzyme was 46 U/L. The patient was diagnosed with sarcoidosis and treated with prednisone with improvement in hypercalcemia and creatinine.

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

Conclusions: Hypercalcemia in patients with granulomatous disorders is driven primarily by elevated calcitriol concentrations, which serve to increase calcium absorption from the gut and resorption from bone. Treatment of hypercalcemia in this setting involves not only treating the underlying disease process, but reducing dietary calcium and vitamin D supplementation. While in multiple myeloma patients, hypercalcemia is likely related to underlying disease, the nephrologist should rule out less common etiologies in cases poorly responsive to traditional therapy.

SA-PO998

A Rare Case of De Novo Claudin 19 Mutation

Nhi Tran, Aalia Akber, Sijie Zheng. Kaiser Oakland Medical Center, OAKLAND, CA.

Background: Familial hypomagnesemia with hypercalcuria and nephrocalcinosis (FHHNC) is an autosomal recessive disorder caused by mutations in the tight junction protein claudin-19. Mutations in claudin-19 result in chloride leak through the peritubular intercellular space, limiting reabsorption of magnesium and calcium. FHHNC may present as nephrocalcinosis, vision defects, and renal failure in childhood. First described in 1972, more than 120 cases have been reported, though exact prevalence is unknown. Most cases are found within family clusters. We present a rare case of de novo claudin 19 mutation.

Methods: A 17-year-old Hispanic woman presented with 15 lb weight loss over 6 months, polyuria, and polydipsia. She had always been a “picky eater” and shorter and thinner than her siblings. Past medical history noted macular dystrophy at age 3, and short stature less than fifth percentile and less than mid-parental height. Family history was unremarkable. Labs were notable for end stage renal disease with a creatinine of 7.3 mg/dl, secondary hyperparathyroidism, hyperphosphatemia of 6 mg/dl, hypocalcemia of 7.4 mg/dl, normocytic anemia of 8.9 g/dl, but surprisingly hypomagnesemia of 1.2 mg/dl and mild metabolic acidosis for the degree of renal failure. Ultrasound showed atrophic kidneys with nephrocalcinosis. Peritoneal dialysis was initiated. Genetic testing revealed homozygous variant in CLDN 19 gene, NM_149860.5:c.59G>A;p.Gly20Asp. The variant was LOVD/CSAP has been classified as heterozygous and homozygous individuals with FHHNC with ocular involvement and is the founder pathogenic variant in the Spanish and French population.

Results: Treatment options are limited. Oral magnesium may be used to supplement tubular magnesium wasting. Amiloride can exert magnesium sparing effects. Thiazides increase calcium resorption in the distal tubule. None have significant effect and patients eventually progress to end stage renal disease. The only curative treatment is transplantation, where calcium and magnesium excretion is normalized following transplant and there is no recurrence of the disease. In young patients who present with early ocular deficits, FHHNC should be evaluated. Given the limits of supportive care, and no recurrence of FHHNC with renal replacement, early transplant should be considered.

Conclusions: Pontifical Academy of Science.

SA-PO999

12 Years of Intraperitoneal Magnesium Infusions for Gitelman Patient with Normal GFR

Nasir Khan, David Geller, Margaret J. Bia. Nephrology, Yale University School of Medicine, New Haven, CT; Nephrology, West Haven VA Hospital, West Haven, CT.

Background: Gitelman’s Syndrome is an autosomal recessive salt-wasting renal tubular disorder characterized by hypokalemic metabolic alkalosis with hypomagnesemia that is potentially life threatening. We report a case of Gitelman’s Syndrome with use of peritoneal infusions in the setting of preserved renal function to manage these severe electrolyte complications.

Methods: A 57-year-old Caucasian female with longstanding history of muscle weakness and twitching, parasthesias and palpitations manifested at the time of her pregnancy at age 24 years when she was found to have severe hypomagnesemia and hypokalemia. She was presumptively diagnosed with Gitelman’s Syndrome, a diagnosis confirmed genetically years later. She did not tolerate oral magnesium(Mg) replenishment due to severe gastrointestinal side effects. Intramuscular Mg replenishment was also attempted but this was complicated by recurrent boils at injection sites. She was diagnosed with idiopathic cardiomyopathy and heart block, both attributed to her electrolyte derangements, and a permanent pacemaker was placed. A Hickman catheter was placed to allow parenteral electrolyte repletion, but this led to multiple bouts of septicemia over a period of several years, caused by gram-positive, gram-negative and fungal infections. In addition she had several pacemaker lead changes, resorting to epicardial leads at times to avoid transvenous leads. Given her significant disease burden and electrolyte derangements, a peritoneal catheter was placed to attempt intraperitoneal(IP) infusion as a method to replenish Mg and potassium(K). Although she did not tolerate intraperitoneal K infusions (abdominal pain), she has now infused IP Mg for 12 years with relatively few complications and a significant improvement in her health and quality of life.

Results: Conclusions: Gitelman’s Syndrome is a hereditary cause of potentially severe hypokalemia and hypomagnesemia. Management of these electrolyte complications is challenging, and patients often suffer significant morbidity from both the electrolyte derangements and the efforts to control these derangements. We describe the successful use of IP infusions to manage a particularly challenging case of hypomagnesemia. We believe the unique characteristics of the peritoneal membrane make this modality an excellent option in patients in whom parenteral electrolyte repletion is considered necessary.

Background: Endoplasmic reticulum (ER) stress is caused by accumulation of misfolded proteins in the ER. ER stress is known to activate intracellular signaling pathway, namely unfolded protein response (UPR). UPR has been reported to be involved in kidney disease, including acute kidney injury and diabetic nephropathy. However, the effect of ER stress on the renal physiological function is largely unknown. The purpose of this study is to clarify the effect of ER stress on the function, focusing on renal handling of amino acids.

Methods: Tunicamycin (TM), a ER stress inducer, was administered to rats under urethane anesthesia. Blood and urine samples were collected at 18-24 hours after injection. The composition of urinary amino acids was investigated by HPLC. Total RNA was extracted from the kidney 24 hours after administration.

Results: Real-time PCR and microarray analyses showed that GRP78 (known to be a marker of ER stress activation of the UPR) mRNA level dramatically increased in the treatment group. Urinary amino acid analysis showed that TM increased excretion of threonine, serine, glutamine, glycine, and alanine. Gene expression analyses showed that the mRNA levels of glutamine transporter (Slc38a3) and glycine transporters (Slc6a18 and Slc6a20) were significantly downregulated by TM treatment, suggesting that TM-induced ER stress analysis also showed the decrease in 7 genes out of 12 known causal genes for Fanconi syndrome.

Conclusions: These results suggest that ER stress lowers the expression levels of glutamine and glycine transporter genes, resulting in aminoaciduria. Also, it is considered that ER stress is a pathological basis of progression of aminoaciduria in Fanconi syndrome.

SA-PO1026
Furosemide Increases Green Fluorescent Protein-Aarginine Vasopressin Expression in the Hypothalamus in Transgenic Rats Hiromichi Ueno,1 Tetsu Miyamoto,1 Kenichiro Bando,2 Yutaka Otsuji,2 Masahito Tamura,2 Yoichi Ueta.2 1University of Occupational & Environmental Health, Kitakyushu, Japan; 2University of Occupational and Environmental Health, Kitakyushu, Japan.

Background: Furosemide is an essential medication for fluid overload by inhibiting sodium reabsorption in the Henle’s loop, however, furosemide-resistant resistance is often observed in patients with kidney disease. Arginine vasopressin (AVP) is synthesized in the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) of the hypothalamus, and increases water reabsorption in the collecting duct. Although previous studies have reported that furosemide activates NA neuroendocrine circuits, AVP synthesis in the hypothalamus after peripheral administration of furosemide remains unclear.

Methods: Measurement of serum AVP levels is difficult because of its short half life (4-20 min). We therefore generated transgenic rats carrying a novel enhanced green fluorescent protein gene in the AVP-expressing neuron. We examined AVP expression in the hypothalamus by observing fluorescence after intraperitoneal administration of furosemide in transgenic rats. We also investigated AVP gene expression using in situ hybridization histochemistry. Neuronal activity in the hypothalamus was examined by intracerebroventricular (ICV) injection of Fos.

Results: After peripheral administration of furosemide in the transgenic rats, the fluorescence intensities in the SON and the magnocellular divisions of PVN (mPVN) were significantly increased. eGFP expressions in the SON and the mPVN were accompanied by Fos expression. Furthermore, AVP mRNA levels in the SON and the mPVN were significantly increased after intraperitoneal administration of furosemide.

Conclusions: We observed increased neuronal activity and AVP expression in the hypothalamus after peripheral administration of furosemide in eGFP-AVP transgenic rats. These results might account for one of the cause of furosemide resistance.

SA-PO1027
Fludrocortisone-Induced Production of Erythropoetin (Epo) in Mouse Kidney Nephron Yukiko Yawasaki,1 Tomomi Oshima,2 Yuichi Sato,2 Hiroshi Nonoguchi,2 Katsumasa Kawahara.1 1Dept. of Physiol, Kitasato Univ School of Med, Sagamihara, Japan; 2Kitasato University, Sagamihara, Japan; 1Kitasato University Medical Center, Kitamoto, Japan.

Background: Under normal conditions, Epo mRNA expression was small but clearly detected in the kidney tubules, such as proximal convoluted tubule (PCT), medullary thick ascending limb (MTAL), distal convoluted tubule (DCT) and collecting ducts (CDs). The expression in the peritubular cells was observed only in hypoxic condition (7% O2, 4 hr). (Nagai, Yawasaki, et al. 2014). We investigated the effect of fludrocortisone (an aldosterone receptor agonist) on Epo mRNA in the mouse kidney.

Methods: Fludrocortisone of 2.5 mg/100 g BW was once applied to mice (C57BL/6J, male, 10 weeks) at time 0. Then, Epo, hypoxia-inducible factor (HIF)2α, and prolylhydroxylase 2 (PHD2) mRNA expressions were evaluated at 2, 4, 6 and 72 hr using tyramide-ISH technique.

Results: After the injection, Epo mRNA expression was slightly increased in MTAL and strongly increased in CDD and outer medullary CD (OMCD). However, it was never detected in the peritubular interstitial cells. The HIF2α mRNA was increased in glomeruli, PCT, DCT, and OMCD as well as the peritubular cells of both kidney cortex and medulla. The PHD2 mRNA expression was also increased in PCT, TAL, DCT, and OMCD. Epo, HIF2α and PHD2 mRNA expressions were increased in parallel at 4 hr after injection, and decreased to the original level at 72 hr.

Conclusions: Epo mRNA expression is increased only at renal tubule cells by stimulation of fludrocortisone. The regulation of the Epo expression by fludrocortisone is different from that by hypoxic stimulation.

SA-PO1030
The Role of Desmopressin in the Management of Severe Hypovolemic Hypoanatraemia Frank Ward,1 David M. Naimark. 2Nephrology, Sunnybrook Health Science Centre, Toronto, ON, Canada; 2Sunnybrook Health Science Centre, Toronto, ON, Canada.

Background: The role of desmopressin (DDAVP) to prevent or treat rapid serum sodium concentration ([Na+]s) correction during hypoanatraemia management remains unclear. The study aim was to assess DDAVP use during the first 48-hours of severe, hypovolemic hypoanatraemia management. The study hypothesis was that the use of DDAVP would slow the rate of [Na+]s correction compared to those not receiving DDAVP.

Methods: A retrospective, observational study was conducted in a single, tertiary centre of all patients managed for severe, hypovolemic hypoanatraemia over a 12-month period. Inclusion criteria were [Na+]s <125mmol/l at referral, serum osmolality <275mosm/kg, urine sodium <30mmol/l and urine osmolality >100mosm/kg. Patients with signs of extra-cellular fluid compartment overload were excluded. The primary outcome measure was [Na+]s correction during the first 48-hours, compared between patients who did or did not receive DDAVP using linear regression.

Results: Twenty-eight patients were identified, with baseline mean [Na+]s of 112±6.6mmol/l vs 117±4.3mmol/l (p=0.06) in those who received (n=16) and did not receive (n=12) DDAVP (median correction of 48-hours). The DDAVP group had a more rapid [Na+]s correction on the first day compared to those who did not receive DDAVP, 7.7±3.8mmol/l/day vs 5.1±2.0mmol/l/day (p=0.04). On the second day, there was a similar rate of [Na+]s correction for those receiving DDAVP and those who did not, 3.4±3.0mmol/l/day vs 2.6±3.2mmol/l/day (p=0.39). Overall, there was no difference in [Na+]s correction after 48-hours between those who received DDAVP and those who did not, 121.7±7.5mmol/l vs 124.8±5.7mmol/l (p=0.24). Patients who had experienced an over-correction were successfully treated with DDAVP (n=5), so that no patient had an ongoing over-correction after 48-hours. The final [Na+]s in patients who received a single dose of DDAVP (n=7) was significantly higher to those who received multiple doses (n=9), 123.8±5.5mmol/l vs 120±8.5mmol/l, p=0.03. Conclusions: DDAVP appears safe and effective in the management of severe, hypovolemic hypoanatraemia, associated with similar [Na+]s correction to those who did not receive DDAVP after 48-hours, despite an initial more rapid correction. A single dose of DDAVP may be as effective as multiple doses. A randomized trial should examine what benefit DDAVP confers in addition to standard care in the management of severe, hypovolemic hypoanatraemia.
SA-PO1031
Neonatal Syndrome of Inappropriate Antiuretic Hormone Secretion (SIADH) Associated with Hypothalamic Malformation in a Patient with Chromosome 1q21.1 Deletion Syndrome
Bakri Alzarka,1 Rachel L. Usala,2 Sun-Yong Ahn.1 *Children’s National Medical Center, Washington, DC; 1MedStar Georgetown University Hospital, Washington DC, DC.

Background: Chromosome 1q21.1 deletion syndrome (OMIM 612474) is associated with a wide range of clinical abnormalities including mental retardation, microcephaly, autism, cardiac, digestive, and cataracts. SIADH, caused by impaired water excretion, can develop from various conditions including tumors, central nervous system disorders, medications, pulmonary disease, hypothyroidism, and glucocorticoid deficiency. To our knowledge, it has not yet been reported in association with chromosome 1q21.1 deletion syndrome.

Methods: A 6 week-old, former 34 week gestational age, female was noted to have hyponatremia (serum sodium 128 mmol/L) shortly after birth. Clinical evaluation showed a low serum osmolality, relatively high urine osmolality and urine sodium, and a significantly elevated urine sodium to plasma sodium ratio (172.5 mmol/L, normal range: 1-11). With the absence of any clinical evidence of volume depletion or any other cause of hyponatremia including renal, thyroid or adrenal dysfunction, these findings were consistent with a diagnosis of SIADH. Her exam also showed microcephaly and situs inversus with dextrocardia. Microarray results were consistent with chromosome 1q21.1 deletion syndrome. Her brain MRI revealed multiple anomalies, including posterior/inferior hypothalamic malformation with hypoplastic mammillary bodies and a markedly diminutive posterior pituitary hyperintensity on T1-weighted images, which may reflect abnormal release of AVP from the posterior pituitary gland. These findings resulted in a partial response to fluid restriction, furosemide, and sodium supplementation. However, tolvaptan initiation resulted in effective normalization of the patient’s serum sodium level.

Results: We report an unusual case of congenital SIADH associated with hypothalamic malformation in a neonate with chromosome 1q21.1 deletion syndrome. Our findings suggest that congenital hypothalamic/pituitary malformations should be considered as a cause of SIADH in patients with phenotypic findings consistent with chromosome 1q21.1 deletion syndrome. In addition, tolvaptan may provide an effective therapeutic option for infants with SIADH.

Conclusions: We conclude that transcription of the Aqp2 gene in the renal collecting duct, we used genome editing (CRISPR/Cas9) to ablate expression of both PKA catalytic subunits in mouse mpkCCD cells. We carried out transcriptomics (RNA-Seq) and quantitative proteomics (SILAC-based quantitative LC-MS/MS) of in three pairs of PKA-KO vs. control clones. Deletion was confirmed using newly developed isoform-specific antibodies. Cells expressing AQP2 were grown to confluence, lysed, and precipitated with an anti-pS261 antibody, and then blotted and probed with anti-pS261, anti-FLAG-M2 antibodies. The signal intensity of the precipitated pS261-positive AQP2 (IP-pS261; consisting of pS261-positive single form and pS261-pS261-double form) was normalized to the whole pS261 signal in the lysate (IP-pS261/whole-pS261), and the ratio was used as the control. The ratios of the IP-pS261 signal intensity to the whole pS261 signal ratio (IP-pS261/whole-pS261), and to the whole AQP2 signal ratio (IP-pS261/whole-AQP2) were compared with the control ratio. pS265-positive AQP2 was analyzed in the same way.

Results: pS265-positive AQP2 constituted 21% of the whole AQP2 population under basal condition, this declined to 10% after FK (20 μM, 60 min) treatment. pS265-positive AQP2 constituted 48% of the whole AQP2 population under basal condition, this was almost 2 fold after FK treatment. pS265-positive AQP2, population, pS265-positive AQP2 (pS265-pS265-double form) constituted a major part of the pS265-positive AQP2 population at 59% under basal condition, this declined to 27% in the population after FK treatment. IP-pS261/whole-pS261 did not differ significantly from IP-pS265/whole-pS261 with or without FK treatment.

Conclusions: Ser-256 is most highly phosphorylated in the cell; pS265-positive AQP2 constantly constitutes around 50% of the whole AQP2 population with or without FK treatment. Most pS265-positive AQP2 is the pS265-pS265 doubly phosphorylated form. Functional consequences of the epithelial barrier loss remained unclear.

Funding: Other U.S. Government Support

SA-PO1032
Gene Expression Changes in Vasopressin-Sensitive mpkCCD Cells after CRISPR/Cas9-Deletion of cAMP-Dependent Protein Kinase (PKA)
Hyun Jun Jung, Kiyoshi Isobe, Chin-Rang Yang, Maurice B. Burg, Viswanathan Raghrum, Mark A. Knepper. NHLBI/NIH, Bethesda, MD.

Background: Vasopressin regulates collecting duct water permeability in part through stimulation of transcription of the aquaporin-2 gene, Aqp2. Vasopressin signaling occurs via several mediators including β-arrestin, Epac (RapGEF3/4), and cAMP-dependent protein kinase (PKA).

Methods: To address the role of PKA in gene expression in the renal collecting duct, we used genome editing (CRISPR/Cas9) to ablate expression of both PKA catalytic subunits in mouse mpkCCD cells. We carried out transcriptomics (RNA-Seq) and quantitative proteomics (SILAC-based quantitative LC-MS/MS) of in three pairs of PKA-KO vs. control clones. Deletion was confirmed using newly developed isoform-specific antibodies. Cells expressing AQP2 were grown to confluence, lysed, and precipitated with an anti-pS261 antibody, and then blotted and probed with anti-pS261, anti-FLAG-M2 antibodies. The signal intensity of the precipitated pS261-positive AQP2 (IP-pS261; consisting of pS261-positive single form and pS261-pS261-double form) was normalized to the whole pS261 signal in the lysate (IP-pS261/whole-pS261), and the ratio was used as the control. The ratios of the IP-pS261 signal intensity to the whole pS261 signal ratio (IP-pS261/whole-pS261), and to the whole AQP2 signal ratio (IP-pS261/whole-AQP2) were compared with the control ratio. pS256-positive AQP2 was analyzed in the same way.

Results: pS265-positive AQP2 constituted 21% of the whole AQP2 population under basal condition, this declined to 10% after FK (20 μM, 60 min) treatment. pS265-positive AQP2 constituted 48% of the whole AQP2 population under basal condition, this was almost 2 fold after FK treatment. pS265-positive AQP2, population, pS265-positive AQP2 (pS265-pS265-double form) constituted a major part of the pS265-positive AQP2 population at 59% under basal condition, this declined to 27% in the population after FK treatment. IP-pS261/whole-pS261 did not differ significantly from IP-pS265/whole-pS261 with or without FK treatment.

Conclusions: Ser-256 is most highly phosphorylated in the cell; pS265-positive AQP2 constantly constitutes around 50% of the whole AQP2 population with or without FK treatment. Most pS265-positive AQP2 is the pS265-pS265 doubly phosphorylated form. Functional consequences of the epithelial barrier loss remained unclear.

Funding: Other U.S. Government Support

SA-PO1033
Comparative Analysis of Vasopressin V1a Receptor Distribution in Rodent and Human Kidneys
Tostien Griseedo,1 Taka-aki Koshimizu,2 Katharina Walentin,2 Kerim Mutig,3 Sebastian Bachmann,4 Michael Schumann,2 Nina Himmerkus,1 Markus Bleich,1 Kai M. Schmidt-Ott,5,2,3 "Institute of Physiology, CAU, Kiel, Germany; "Max Delbrueck Center for Molecular Medicine, Berlin, Germany; "Urology Research Laboratory, Charité-Universitätsmedizin, Berlin, Germany; "Anatomy, Charité, Berlin, Germany; "Nephrology, Charité, Berlin, Germany; "Gastroenterology, Charité, Berlin, Germany.

Background: Vasopressin receptors (V1aR) are a family of seven transmembrane-spanning G protein-coupled receptors (GPCRs) that are involved in the renal water balance by stimulating the expression of aquaporin-2 (AQP2) in the principal cells of the collecting duct. V1aR is predominantly expressed in the renal medulla and stimulated by vasopressin, which is released in response to a decrease in blood pressure to increase renal water reabsorption. However, there is limited information about the localization and function of V1aR in the kidney.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
CRISPR/Cas9-induced Grhl2 knockout and wildtype control cells for functional analyses. Grhl2 target genes were identified by microarray gene expression analysis from control and GrHL2-/- kidneys and by Grhl2 chromatin immunoprecipitation followed by next generation sequencing (ChIP-seq) from wildtype kidneys.

Results: Our data show a significantly decreased tissue osmolality in ISOM and IM of GrHL2-/- kidneys compared with control kidneys. GRHL2 knockout IMD-3 cells when compared with wildtype cells showed a significantly reduced transepithelial resistance and an increased paracellular flux of sodium and chloride. Integration of microarray and ChIP-seq data indicated that Grhl2 target genes were involved in tight junction assembly.

Conclusions: These data functionally link collecting duct epithelial barrier function with urinary concentrating ability for the first time. We identify a transcriptional network regulated by the transcription factor GRHL2, which is necessary to maintain tight epithelial barriers across the collecting duct epithelium, thereby preventing leakage of sodium and chloride into the urine and preserving a high medullary osmolality.

SA-PO1036
SLC26A6 Mediates Enteric Oxalate Secretion in CKD
Laura J. Neumeier,1, Robert B. Thomson,1 Kai-Uwe Eckardt,2 Peter S. Aronson,3 Felix Knauß,4 Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany;2University Hospital Charité Berlin, Berlin, Germany;3Yale University School of Medicine, New Haven, CT.

Background: A state of oxalate equilibrium is maintained in patients with healthy kidney function. However, as GFR declines plasma oxalate levels start to rise. Upregulation of oxalate secretion in the colon of rats with CKD has been described in the past, yet the molecular identification of the oxalate transporter(s) involved has yet to be defined. Hence, we examined whether oxalate transporters SLC26A6 contributes to the extracellular clearance of oxalate via the gut in CKD.

Methods: CKD was induced by injecting age- and gender-matched 129S6 (wild-type) and SLC26A6-/- mice with aristolochic acid. Renal function was monitored by changes in plasma creatinine sampled retro-orbitally. Intestinal SLC26A6 was assessed by qPCR and western blot analysis. Mice were maintained on an oxalate-free diet and plasma and fecal oxalate levels were measured enzymatically using an oxalate assay kit.

Results: SLC26A6 mRNA and protein expression were greatly increased in colon of mice with CKD. However, expression levels of glucose (SGLT-1) and amino acid transporters (CAT-1), other representative intestinal transport processes, did not differ in colon of CKD mice. In line with these findings, fecal oxalate excretion was increased in mice with CKD. In contrast, fecal oxalate excretion was reduced and plasma oxalate levels significantly increased in SLC26A6-/- mice as compared with wild-type mice.

Conclusions: In summary, we demonstrate that SLC26A6-mediated enteric oxalate secretion is critical in decreasing the body burden of oxalate in CKD.

Funding: Private Foundation Support

SA-PO1037
Quantification of Urinary Extracellular Vesicles
Charles J. Blijdorp, Thomas Hartjes, Martin E. Van royen, Robert Zietse, Ewout J. Hoorn. Erasmus Medical Center, Rotterdam, Netherlands.

Background: Urinary extracellular vesicles (uEVs) have emerged as a powerful non-invasive tool to study renal epithelial transport in humans. However, the optimal method to quantify and normalize uEVs remains unclear, especially for spot urines.

Methods: Four healthy subjects were subjected to overnight thirsting (10 pm-noon) followed by water loading (20 mL/kg in 30 min). Spot urines were collected during thirsting (T1-2) and after water loading (WL1-4, noon-7 pm). Subsequently, 4 uEV quantification methods were compared: (1) nanoparticle tracking analysis (NTA), (2) uEV isolation by ultracentrifugation followed by immunoblotting of CD9, CD63, CD81, ALIX, and TSG101, (3) a time-resolved fluorescence immunoassay (TRFIA) that captures CD9+ uEVs, and (4) EVQuant, a novel technique which counts individual fluorescently labeled uEVs after immobilization in a matrix. A Bland-Altman analysis was used to compare methods using NTA as reference.

Results: Urinary osmolality was near-maximal during thirsting, decreased after water loading and then increased again (Figure). The results of the 4 uEV quantification methods showed similar dynamics as urine osmolality suggesting that uEV number changes in proportion to urinary concentration (Figure). Of interest, EVQuant identified a 2- to 6-fold increase in uEVs than NTA. Using NTA as reference, a Bland-Altman analysis showed that EVQuant had the lowest bias (% difference 6 ± 7) followed by TRFIA (10 ± 21). Of the uEV-markers, CD9 agreed best with NTA (% difference 12 ± 34). uEV number correlated strongly with urinary creatinine (Figure) and osmolality ($r$ for both 0.9, $P<0.0001$).

Conclusions: uEV number is proportional to urinary concentration and both urine creatinine and osmolality can be used to normalize spot urines for uEV number. EVQuant is a promising alternative to NTA and appears more sensitive for uEV detection. These uEV quantification methods can be used to analyze changes in a uEVs barrier function, the result of more protein per uEV or the excretion of more uEVs containing this protein.

SA-PO1038
WNK4 Deletion Inhibits Adipogenesis In Vitro and In Vivo
Daisi Takahashi,1 Takayasu Mori,2 Eisie Sohara,3 Miyako Tanaka,2 Yuichi Inose,1 Naohiro Nomura,1 Motoko Chiga,1 Moko Zeniya,4 Takayoshi Suganami,2 Tatemitsu Rai,1 Shinichi Uchida,4 Department of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Tokyo, Japan; Nagoya University, Nagoa, Japan;3TOKYO MEDICAL & DENTAL UNIV, TOKYO, Japan;4Tokyo Medical and Dental University, Tokyo, Japan; Internal medicine, Tokyo Metropolitan Ohtsuka Hospital, Tokyo, Japan.

Background: The with-no-lysine kinase (WNK) 1 and WNK4 genes are responsible for pseudohypoparathyroidism type II (PHAII), a hereditary hypertensive disease. We have demonstrated the importance of the WNK4-OSR1/SPAK-NCC signaling cascade in the kidney for blood pressure regulation, however, the extrarenal roles of WNK4 is not clear. We previously presented WNK4 is induced in the early phase of T33-L1 adipocyte differentiation and is expressed in mouse mature adipose tissue. In this study, we evaluated WNK4's contribution to the adipogenesis in vitro and in vivo.

Methods: We used mouse primary preadipocytes, T33-L1 fibroblasts, and human mesenchymal stem cells (hMSC-AT) to elucidate potential roles of WNK4 in adipose tissue. The functions of WNK4 in these cells was examined by siRNA specific to WNK4 (si-WNK4). We also generated WNK4 knock-down T33-L1 cell lines using TALEN. We fed WNK4+ mice a high-fat diet and examined their metabolic functions.

Results: In mouse primary preadipocytes, WNK4 was predominantly expressed in the mature adipocyte, and WNK4 in the stromal vascular fraction was induced by the differentiation stimuli. WNK4 expression preceded the expression of key transcriptional factors PPARY and C/EBPα. Si-WNK4-transfected T33-L1 cells and hMSC-AT cells showed reduced expression of PPARY and C/EBPα and decreased lipid accumulation. WNK4 knockdown T33-L1 cells also showed reduced PPARY expression. In the WNK4+ mice, PPARY and C/EBPα expression were decreased in adipose tissues, and the mice exhibited partial resistance to high-fat diet-induced adiposity.

Conclusions: WNK4 is a key molecule of adipocyte differentiation and is involved in obesity and adiposity. Thus, WNK4 would be a novel target molecule for the treatment of metabolic syndrome.

Funding: Government Support - Non-U.S.

SA-PO1039
Decreased Protein Expression of KLHL3 Is Involved in the Pathogenesis of PHAII Caused by CUL3 Mutation In Vivo
Sawaya Yoshida, Yuya Araki, Takayasu Mori, Emi Sasaki, Yuri Kasagi, Kiyoshi Isobe, Koichiro Sasa, Yuichi Inoue, Tatemitsu Rai, Shinichi Uchida, Eisie Sohara. Department of Nephrology, Tokyo Medical and Dental University, Bunkyo-ku, Japan.

Background: Pseudohypoaldosteronism type II (PHAII) is a hereditary hypertensive disease. PHAII is caused by mutations in four genes: WNK1, WNK4, KLHL3 and CUL3. Recently, it was revealed that CUL3-KLHL3 E3 ligase complex ubiquitates WNK1 and WNK4, leading to their degradation, and that one of the common pathogenesis of PHAII is the defective degradation of WNKs by CUL3-KLHL3 E3 ligase complex. PHAII-causing CUL3 mutations result in the skipping of exon 9, leading to a CUL3 protein with a 57-amino acid deletion (A403-459). However, the pathogenesis of PHAII caused by CUL3-403-459 in vivo is still unclear.

Methods: We generated and analyzed CUL3 WT/A403-459 PHAII model mice.

Results: CUL3 WT/WT; A403-459 mice were successfully generated, and they exhibited hyperkalemia, metabolic acidosis and hypertension, indicating that they are good mouse model of PHAII. Protein levels of WNK genes were increased resulting in increased phosphorylation of OSR1, SPAK, and NCC, the downstream components of the WNK signal. In CUL3 WT/A403-459 mice, the abundance of KLHL3 protein was decreased in kidney and brain. On the other hand, the protein levels of the other KLHL family proteins, KLHL2 and Keap1, which also form ubiquitin ligase complexes with CUL3, were comparable between CUL3 WT/WT and CUL3 WT/A403-459.

Conclusions: In CUL3 WT/A403-459 mice, expression levels of KLHL3 were decreased. Considering that heterozygous knockout of CUL3 expression alone in mice which we
KS-WNK1: An Aldosterone-Induced Inhibitor of ENaC

**Methods:**

As in Xenopus laevis, we generated the mouse model of attaching tubule (CNT) and cortical collecting duct (CCD). In order to characterize its activity in vivo, we generated a mouse model of KS-WNK1 inactivation specifically in the CNT-CCD. In vivo data suggest that KS-WNK1 inhibits the activity of other WNK kinases. We previously showed that the inactivation of KS-WNK1 in mice leads to an increased expression of the Na-Cl cotransporter NCC, which could result from a decreased activity of NCC and/or WNK4. However, aldosterone secretion is decreased in KS-WNK1−/− mice while renin is not, suggesting that potassium balance is impaired, which could also explain the decreased NCC expression.

**Conclusions:** Together, these data suggest that KS-WNK1 is an inhibitor of ENaC and Nedd4-2-dependent manner. Since the expression of KS-WNK1 is induced by aldosterone infusion or potassium load, KS-WNK1 could therefore be an aldosterone-induced inhibitor of ENaC.

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

---

**SA-PO1042**

WNK4 Acts on Thick Ascending Limbs In Vivo as Well as Distal Convoluted Tubules

**Methods:**

With no lysine (K) site in vivo. In vitro data suggest that KS-WNK1 inhibits the activity of other WNK kinases. We previously showed that the inactivation of KS-WNK1 in mice leads to an increased expression of the Na-Cl cotransporter NCC, which could result from a decreased activity of NCC and/or WNK4. However, aldosterone secretion is decreased in KS-WNK1−/− mice while renin is not, suggesting that potassium balance is impaired, which could also explain the decreased NCC expression.

**Conclusions:** Together, these data suggest that KS-WNK1 is an inhibitor of ENaC and Nedd4-2-dependent manner. Since the expression of KS-WNK1 is induced by aldosterone infusion or potassium load, KS-WNK1 could therefore be an aldosterone-induced inhibitor of ENaC.

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

---

**SA-PO1043**

Differential Regulation of L-WNK1 and KS-WNK1 by the Ubiquitin Ligases Nedd4-2 and Kelch-CUL3 Complex

**Methods:**

As in Xenopus laevis, we generated the mouse model of KS-WNK1 inactivation specifically in the CNT-CCD. In vivo data suggest that KS-WNK1 inhibits the activity of other WNK kinases. We previously showed that the inactivation of KS-WNK1 in mice leads to an increased expression of the Na-Cl cotransporter NCC, which could result from a decreased activity of NCC and/or WNK4. However, aldosterone secretion is decreased in KS-WNK1−/− mice while renin is not, suggesting that potassium balance is impaired, which could also explain the decreased NCC expression.

**Conclusions:** Together, these data suggest that KS-WNK1 is an inhibitor of ENaC and Nedd4-2-dependent manner. Since the expression of KS-WNK1 is induced by aldosterone infusion or potassium load, KS-WNK1 could therefore be an aldosterone-induced inhibitor of ENaC.

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

---

**SA-PO1044**

FN4, K+, Cl-

Poster/Saturday

Underline represents presenting author.
kinases abundance by Ned44-2 and Kelch3 could have an implication in the fine tune modulation of ion transport.

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

SA-PO1044

Role of WNK Aggregate Formation in Activating Na-Cl Cotransport

Catherine A. Cuebas,1 Lauren N. Miller,1 Kerim Mutig,1 Sebastian Bachmann,2 Chao-Ling Yang,4 David H. Ellison,3 1Charite-Universitätsmedizin Berlin, Berlin, Germany; 2Charité Universitätsmedizin Berlin, Berlin, Germany; 3Oregon Health & Science University, Portland, OR; 4Oregon Health and Science University, Portland, OR.

Background: Activation of the thiazide-sensitive Na-CI cotransporter (NCC) is essential to retain K+ in response to dietary K+ restriction and hyperkalemia. Formation of WNK4-SPAK-OSR1 aggregates in distal convoluted tubule (DCT) cells is a common event that occurs when dietary K+ is low and NCC activity is high. While these aggregates bring together key signaling proteins required to activate NCC, it has not been clear whether WNK4 aggregate formation facilitates NCC activation or whether these represent stress features, or even autophagosomes.

Methods: Here, we fed C57BL6 mice normal (NK, 0.8% K+) or potassium-deficient (LK, 0% K+) diets for 12 to 72 hours. Some mice were switched to high potassium diet (HK, 5%). Plasma electrolytes were determined with iSTAT. Protein aggregates containing WNK4, SPAK and ATG5 (autophagy marker) was assessed by light and electron microscopy.

Results: Plasma [K+] decreased with LK (3.3 ± 0.3 vs 4.0 ± 0.1 mmol/l). The abundance of phospho-NCC (TS3) reached a maximum after only 12h of LK, with a striking increase in phospho SPAK-Ser373/OSR1-Ser325 at the apical membrane of DCT1 segments (identified with parvalbumin). Increased phospho NCC abundance at this time also correlated with appearance of phospho SPAK-Ser373/OSR1-Ser325 containing aggregates, but these aggregates did not contain WNK4, which appeared unaffected.

Conclusions: WNK aggregates thus are not required for early NCC activation and a separate cellular signaling event that occurs when dietary K+ is low and NCC activity is high.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO1045

Generation and Analysis of KLHL2 Knockout Mice Yuri Kasagi,1 Daiei Takahashi,1 Tomomi Aida,1,2 Hidenori Nishida,1 Naohiro Nomura,1 Moko Zeniya,1 Takayasu Mori,1 Emi Sasaki,1 Fumiaki Ando,1 Tatematsu Kai,1 Shinichi Uchida,1 Eisei Sohara,1 1Department of Nephrology, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 2Laboratory of Molecular Neuroscience, Medical Research Institute (MRI), Tokyo Medical and Dental University, Bunkyo-ku, Japan; 3Laboratory of Recombinant Animals, MRI, Tokyo Medical and Dental University, Chiyoda-ku, Japan.

Background: Mutations in the with-no-lysine kinase 1 (WNK1), WNK4, Kelch-like 3 (KLHL3), and Cullin3 (CUL3) genes are identified as being responsible for hereditary hypertensive disease pseudohypoaldosteronism type II (PHAIi). KLHL3/CUL3 ubiquitin ligases are responsible for degradation of WNK kinases via their degradtion. In PHAIi, the loss of interaction between KLHL3 and WNK4 increases levels of WNKs because of impaired ubiquitination, leading to abnormal over-activation of the WNK-OSR1/SPAK-NCC cascade in the kidney’s distal convoluted tubules (DCT). KLHL3 is highly homologous to KLHL2, especially in kelch-repeat domain (WNK-binding domain). We previously reported KLHL2 ubiquitinated and degraded WNKs in vitro. However, the physiological role of KLHL2 in vivo is still unclear.

Methods: We generated KLHL2-/- mice using CRISPR/cas9 system and evaluated the phenotype.

Results: KLHL2-/- expressed abundantly in the brain, stomach, and kidneys. However, we found that the expression of WNK4 was increased only in the KLHL2-/- mice kidneys. KLHL2-/- mice did not exhibit increased phosphorylation of the OSR1/SPAK-NCC cascade in the kidneys and PHAIi-like phenotype. KLHL2 was predominantly expressed in the kidney medulla compared with the cortex. Accordingly, medullary WNK4 protein levels were significantly increased in the kidneys of KLHL2-/- mice.

Conclusions: KLHL2 is indeed a physiological regulator of WNK4 in vivo; however, WNK4 protein levels in KLHL2-expressing tissues may not be solely governed by KLHL2 except in kidney medulla.

Funding: Government Support - Non-U.S.

SA-PO1046

The Sensitivity of WNK3 and WNK4 for Intracellular Chloride Concentration and Cell Volume Is Opposite Diego L. Carrillo Perez,1 Karla Leyva-Rios,2 Adriana P. Mercado,2 Elisa Hernandez Mercado,2 Erika Moreno,2 Norma H. Vázquez,4 Diana Pacheco-Alvarez,2 Gerardo Gamba.1 1Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Tlalpan, Mexico City, Mexico; 2Investigación Nacional de Cardiología Ignacio Chávez, Mexico City, Mexico; 3Universidad Panamericana, Mexico City, Mexico; 4Instituto de Investigaciones Biomédicas, UNAM, Mexico City, Mexico.

Background: The activity of the electroneutral chloride cotransporters (CCCs) such as the Na-K-2Cl and the K-Cl cotransporters is modulated by intracellular chloride concentration [Cl-], and cell volume. Depletion of [Cl-], and cell shrinkage induce phosphorylation of CCCs, while increase of [Cl-], and cell swelling induces dephosphorylation. However, cell shrinkage increases [Cl-], and cell swelling decreases [Cl-]. It is known that the effect of [Cl-] towards CCCs is traduced by the WNK1 or WNK4 kinases. Thus, the effect of cell volume towards CCCs must be traduced by a different kinase. Because WNK3 bypasses the toxicity requirements for regulation of the CCCs (PNAS 2005 and 2006), we tested the hypothesis that WNK3 is sensitive to cell volume, rather than to the [Cl-].

Methods: Xenopus oocytes were microinjected with N/KCCs or KCCs cRNA alone or together with WNK3 wild type or mutants in which catalytic activity and/or the chloride binding site has been eliminated (WNK3-DA, WNK3-1295/297; WNK3-DA-LILFF). The effect of [Cl-], or extracellular tonicity on WNKs was assessed. WNKs phosphorylation at the activating site of the T-loop with specific antibodies was analyzed as a surrogate of WNKs activity.

Results: Depletion of [Cl-] increases the activity of WNK1 and WNK4 and thus increases the NCC activity, while it had no effect on the WNK3 and its effect towards NCC. In contrast to what we previously observed for WNK1 and WNK4, elimination of the chloride-binding site in WNK3 had no effect on the activity of the kinase. WNK3, but not WNK4, phosphorylation was sensitive to changes in cell volume. Compared to isotonic condition, WNK3 phosphorylation significantly diminished or increased by 50% in hypertonic or hypotonic conditions, respectively. The phosphorylation of WNK3 was not affected by similar changes in tonicity.

Conclusion: Our data show that WNK3 is not sensitive to changes of the [Cl-], but is modulated by changes in cell volume in the expected direction according to the effect of WNK3 wild type and the catalytically inactive WNK3 on the CCCs. We propose that WNK3 is a volume sensitive kinase modulating the effect of cell volume changes in CCCs.

Funding: Government Support - Non-U.S.

SA-PO1047

Cushing’s Syndrome Increases Renal Sodium Transporters in Urinary Extracellular Vesicles

Dominique M. Bovey,1 Mahdi Salih,2 Alexander H. Danser, Robert Zietse, Richard Feelders, Ewout J. Hoorn.3 Eramus Medical Center, Rotterdam, Netherlands.

Background: Increased renal sodium (Na+) reabsorption contributes to hypertension in Cushing’s syndrome (CS). Renal Na+ transporters can be analyzed non-invasively in urinary extracellular vesicles (uEVs). The aim of this study was to analyze renal Na+ transporters in uEVs of patients with newly diagnosed CS.

Methods: uEVs were isolated by ultracentrifugation and analyzed by immunoblotting in 10 CS patients and 7 age-matched healthy subjects. The majority had an ACTH-producing pituitary adenoma (n=8). In 3 CS patients uEVs were analyzed before and after treatment (unilateral adrenalectomy or ketoconazole). uEVs were isolated without interfering medication (renin-angiotensin system inhibitors or diuretics).

Results: The 10 patients with CS were hypertensive (144 ± 14 vs 92 ± 17 mmHg) and had a 2-fold higher abundance of the Na/H exchanger type 3 (NHE3) in uEVs compared to healthy controls (p=0.05). CS patients were subsequently divided in those with suppressed and non-suppressed renin-angiotensin-aldosterone system (RAAS, n=5/group). CS patients with suppressed vs. non-suppressed RAAS had similar blood pressure but significantly lower serum K+ (3.9 ± 0.2 vs. 4.4 ± 0.3 mmol/l, p=0.04). Furthermore, only those with suppressed RAAS had 3- to 4-fold higher phosphorylated Na+-K+-Clcotransporter type 2 (pNKCC2) and higher total and phosphorylated Na+-Cl cotransporter (NCC) in uEVs. Serum K+ but not urinary free cortisol correlated with pNKCC2, pNCC, and NCC in uEVs (r = -0.9, -0.8, and -0.7, respectively; p<0.05 for all). In the 3 CS patients with uEV-analysis before and after treatment, pNKCC2, pNCC, and NCC abundance normalized better after treatment in parallel with serum K+. No changes were observed in other uEV proteins of interest, including prostatin (a regulator of the epithelial sodium channel), Rac1 (which reflects mineralocorticoid activity), and aquaporin-2.

Conclusions: CS increases renal Na+ transporter abundance in uEVs especially in those with suppressed AS. In addition to a mineralocorticoid effect of excess glucocorticoids, low serum K+ may also contribute to increased renal Na+ reabsorption and hypertension in CS. Our findings recapitulate previously characterized effects of glucocorticoids on NHE3, NKCC2, and NCC in experimental animals and of mineralocorticoids in patients with primary aldosteronism.
SA-PO1048

High K Intake Modulates Thiazide Sensitive Na-CI Cotransporter Mediated Na+ and K Transport: Effects of Gender and Angiotensin II Type 1a (AT1a) Receptor Jin Li, Shuhua Xu, Claire J. Wang, Haiyan Hu, Alan M. Weinstein, Lawrence G. Palmer, Tong Wang. 1Yale University, New Haven, CT; 2Weill Medical College of Cornell, New York, NY.

Background: The thiazide-sensitive Na-CI cotransporter (NCC) plays a key role in controlling NaCl absorption in the distal tubule, and also modulates salt and fluid delivery to downstream portions of the nephron, thus regulating K secretion. Previously, we reported that higher NCC expression correlates with activity in female WT, and that gender-specific differences were absent in AT1a receptor knockout (KO) mice. We have now studied the gender difference in response to high K intake in WT and AT1a receptor KO mice.

Methods: Renal clearance experiments were performed on male WT and KO mice treated with normal and high K (5% KCl, 7 days) diets. Urine volume (UV), glomerular filtration rate (GFR), absolute (ENA, EK) and fractional (FEK) Na and K were measured compared at baseline vs. a high K diet (33%). Functional measurements showed that in WT, K loading diminished HCTZ-dependent FENA by 53% in females and 42% in males. FENA was not reduced by high-K diet in KO mice. High-K intake significantly increased HCTZ-induced kaliuresis (EK) by 129% in WT male, but reduced EK in WT female (68%), KO male (51%) and KO female (55%). NHE3 expression was significantly reduced with high-K diet in all groups. There was no hyperkalemia in any group.

Conclusions: These results suggest that i) NCC activity decreases in response to a high-K diet, in part through decreased protein expression; ii) these responses depend on gender as well as on the presence of the AT1a receptor; iii) Proximal tubule function is also regulated by chronic high K intake.

Funding: NIDDK Support

SA-PO1049

Signaling through the Angiotensin-II Type 2 Receptor (AT2R) Suppresses AT1R-Induced SGK1 Phosphorylation and NHE3 Activity Vikram Suri, David Pearce. 1University of California San Francisco, San Francisco, CA; 2University of California-San Francisco, San Francisco, CA.

Background: Activation of the Angiotensin Type 1 Receptor (AT1R) by Angiotensin-II has been shown to enhance proximal tubular sodium reabsorption via induction of NHE3, as well as distal sodium reabsorption via ENaC. Evidence from the literature supports a role for SGK1 as a critical signaling intermediate in the activation of both transporter systems. The Angiotensin Type 2 Receptor (AT2R) is a well-described receptor that has been shown to be involved in the regulation of ion transport in the proximal tubule and is used in the treatment of hyperuricemia and gout. In addition, probenecid is a uricosuric agent that inhibits the organic anion transporters (OAT) in the proximal tubule, and is used in the treatment of hyperuricemia and gout. In addition, probenecid is a uricosuric agent that inhibits the organic anion transporters (OAT) in the proximal tubule, and is used in the treatment of hyperuricemia and gout. As such, we hypothesized that AT2R suppresses AT1R-mediated induction of SGK1 activity.

Methods: HEK293 cells were transfected with constructs expressing AT1R, AT2R, or both, and stimulated with Angiotensin-II. In order to correlate suppression of SGK1 phosphorylation with transporter activity, we measured the Na-dependent recovery from an acid load, as a marker of NHE3 activity (using Bafilomycin A1 and 1μM EIPA to inhibit the vH+-ATPase and NHE1, respectively). MK-2 cells were transfected with constructs expressing AT1R, AT2R, or both, loaded with the pH-sensitive dye BCECF-AM, and stimulated with Angiotensin-II, and subjected to an acute acid load. Cytosolic pH was measured using ratiometric fluorescence measurements and calibration with Nigericin.

Results: In these experiments, AT2R consistently suppressed AT1R-mediated phosphorylation of SGK1 at S422 by approximately 50% at 30 minutes (as measured by immuno blot). In addition, our data suggests that this suppression may occur through delayed kinetics of SGK1 phosphorylation. In response to an acute acid load, MK-2 cells that co-express AT1R and AT2R showed diminished delayed recovery from an acid load (pH 7.0), as compared to cells that express either AT1R or AT2R alone.

Conclusions: We conclude from these data that co-expression and activation of AT2R suppresses AT1R-mediated SGK1 phosphorylation and downstream NHE3 activation, and these effects may underlie the observed natriuretic effect of AT2R agonists.

Funding: Other NIH Support - T32 (4T32DK007219-40)

SA-PO1050

Probenecid Downregulates Pendrin and Enhances Hydrochlorothiazide-Induced Diuresis Sharon L. Barone, Jie Xu, KarimAv. Zahedi, Mary C. Manfredi, Branden Benner, Brian M. Mahony, John L. Alkema. 1Research Services, Veterans Administration, Cincinnati, OH; 2Research Services, Veterans Administration, Cincinnati, OH.

Background: The inactivation or inhibition of NCC or pendrin does not cause any overt renal phenotype under baseline or diabetic conditions. However, the inactivation of NCC and pendrin causes severe salt wasting in rodents, indicating an important role for pendrin in compensatory salt absorption in the setting of NCC inhibition. Probenecid is a uricosuric agent that inhibits the organic anion transporters (OAT) in the proximal tubule and is used in the treatment of hyperuricemia and gout. In addition, probenecid inhibits the ATP transporter Panxen 1 in the proximal tubule (PT) and the collecting duct, downregulates pendrin in mammary gland cells and possesses a positive ionotropic effect on the heart. We hypothesized that probenecid pretreatment with hydrochlorothiazide downregulates pendrin, and consequently enhances hydrochlorothiazide (HCTZ) diuresis.

Methods: Male Sprague Dawley rats were treated with probenecid i.p. at 250 or 100 mg/kg/day for 6 days and then received HCTZ daily for 4 days while being maintained on protein-free, BALANCE, or 2% protein diet. The ACE2 protein and ACE2 mRNA levels were measured in the kidney and subjected to either static or physiologically relevant fluid flow (~0.7 dyne/cm2). We measured urine output, plasma electrolytes, renal sodium and potassium delivery to downstream portions of the nephron, thus regulating K secretion. Previously, we hypothesized that AT2R suppresses AT1R-mediated diuresis by HCTZ-mediated NCC inhibition in the distal nephron. We propose that Probenecid followed by HCTZ is a strong diuretic regimen for fluid overloaded states and also prevents the hyperuricemia that is caused by HCTZ.

Conclusions: Other NIH Support - T32 (4T32DK007219-40)

SA-PO1051

Furosemide Is a Potassium-Sparing Diuretic in Mice on a Low Sodium High Potassium Diet Bangwe Wang, Donghai Shen, New Wang, France, Steven C. Sansom. 1University of Nebraska Medical Center, Omaha, NE.

Background: Because of its cardio-protective benefits, a low Na, high K diet (LNaHK) is often warranted in conjunction with dietary interventions for hyperuricemia. However, it is necessary to understand the renal handling of such diets in order to choose the best diuretic. As previously shown by our lab, furosemide, a K-wasting diuretic, decreased renal K clearance (CLK) in mice on LNaHK by inhibiting the net K secretion in the thick ascending limb (TAL). Given that furosemide acidifies the urine by increasing acid secretion from TAL and that distal K secretion is affected by urine pH, we hypothesized that furosemide reduces distal K secretion via the large conductance, Ca-activated channel (BK).

Methods: Wild-type (WT) and BK-β4 knockout mice (KO) were kept on LNaHK (0.01% Na, 5% K) for 7 days. After intraperitoneal injections of vehicle, furosemide (furo; 15 mg/kg), amiloride (amil; 5 mg/kg), or amil + furo, mice were placed into metabolic cages to collect urine for 12 hours. Another group of WT were kept on LNaHK for 7 days only. The metabolic cages were replaced with water for 24 hours with access to either regular water or alkaline furosemide water (0.1 mg/ml pH 8.8). The mice were then sacrificed and the [K+] and pH were measured from blood and urine samples. Fluorescence immunohistochemistry (FIHC) was performed on paraffin-embedded kidney sections stained for BK-β.

Results: In WT, the furo group exhibited lower urine pH and lower CLK than vehicle. In KO, the furo group exhibited a lower urine pH but a similar CLK compared to vehicle. The amil + furo group had a lower CLK than the amil group of both WT and KO. There is a significant linear association between CLK and urine pH in WT but not in KO. In LNaHK, FIHC showed that BK-β was localized in the apical membrane of connecting tubule cells (CNT) in WT vehicle group. However, BK-β was localized in the cytoplasm of CNT in the WT furo group and both groups of KO. Urine pH and CLK were not different between WT on LNaHK and KO on LNaHK. BK-β was not detected in KO on LNaHK. BK-β expression in WT on LNaHK was significantly higher than in KO on LNaHK.

Conclusions: These results suggest that in mice on LNaHK, in addition to suppressing net K secretion in TAL, furosemide inhibits BK-β mediated K secretion in the distal nephron by acidifying the urine. These actions together make furosemide a K-sparing diuretic in the setting of LNaHK.

Funding: NIDDK Support

SA-PO1052

RNA-Seq Reveals the Transcriptome Changes of Mouse Collecting Duct Cells in Response to Urinary Flow and Primary Cilia Sensing Sacha Van Hijn, Miriam Schnids, René J. Bindels, Joost Hoenderop. 1Physiology, Radboud University Medical Center, Nijmegen, Netherlands; 2Human Genetics, Radboud University Medical Center, Nijmegen, Netherlands; 3University College London (UCL), London, United Kingdom; 4Centre for Molecular and Biomolecular Informatics, Radboud University Medical Center, Nijmegen, Netherlands.

Background: External cues such as mechanical forces generated by fluid flow play a key role in renal physiology by regulating expression of genes involved in the transport of ions and water. Several studies have shown that microdissection of collecting duct cells (CDD) exposed to mechanical stimuli generated by urinary flow, to regulate the activity and abundance of electrolyte transporters including ion channels. The aim of this study is to reveal the transcriptome changes of tubular epithelia in response to fluid flow and determine the role of primary cilia in this process.

Methods: IMCD3 (inner-medullary collecting duct) cells without cilia were generated using CRISPR/Cas9 technology. Cells were seeded onto a μ-slide ibidi chambers and subjected to either static or physiologically relevant fluid flow (~0.7 dyne/cm2) for 3 h at 37°C. RNA was isolated and prepared for RNA-seq by next generation sequencing.

Conclusions: Other NIH Support - T32 (4T32DK007219-40)

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

Underline represents presenting author.
Differentially expressed genes with fluid flow between ciliated and uncluttered cells were identified using whole transcriptome analysis and validation by RT-qPCR.

Results: The absence of cilia in two independent knockout IMCD3 cell lines (BtI40 KO or DmC2 KO) and the presence of cilia in one control cell line was confirmed by immunocytochemistry for the cilia marker ARL13b. RNA-seq analysis of ciliated cells substantially reduced the number of upregulated transcripts (regulated genes in the 1204 gene set) compared to static control cells (adjusted p < 0.05). Several known flow-sensitive genes, such as Pgp2 and Ccl2 were significantly upregulated with fluid flow. Interestingly, fluid flow sensing by primary cilia triggers a transcriptomic response of only 54 genes identified as cells linked to the regulation of the activity of the epithelial Na⁺ channel (ENaC), the activity of aquaporins, tight junction permeability, iron transport, phosphate transport, and bicarbonate handling.

Conclusions: Fluid flow elicits a transcriptomic response in the collecting duct of the kidney. The role of primary cilia in this response is restricted to 54 genes, of which 16 are uniquely linked to the regulation of the activity of the epithelial Na⁺ channel (ENaC), including genes linked to the regulation of the activity of the epithelial Na⁺ channel (ENaC), the activity of aquaporins, tight junction permeability, iron transport, phosphate transport, and bicarbonate handling.

Funding: Government Support - Non-U.S.

SA-PO1053

A Truncation Mutant Targets Wild-Type NKCC1 to the Apical Membrane of Epithelia Ranjelli Koumanavgou,1 Salma Omer,1 Eric J. Delphe,3 1Anesthesiology, Vanderbilt University Medical Center, Nashville, TN; 2Anesthesiology, Vanderbilt University Medical Center, Nashville, TN; 3Anesthesiology, Vanderbilt University Medical Center, Nashville, TN.

Background: We recently reported the case of a 13-year old patient with complete renal failure and leg pain. Laboratory analysis revealed an increased full-length α-subunit expression. Aldosterone and vasopressin levels remained unaltered. Urine analysis from NS mice revealed proteolytical cleavage of ENaC and all of them resulted in increased ENaC activity. The absence of cilia in two independent knockout IMCD3 cell lines (BtI40 KO or DmC2 KO) and the presence of cilia in one control cell line was confirmed by immunocytochemistry for the cilia marker ARL13b. RNA-seq analysis of ciliated cells substantially reduced the number of upregulated transcripts (regulated genes in the 1204 gene set) compared to static control cells (adjusted p < 0.05). Several known flow-sensitive genes, such as Pgp2 and Ccl2 were significantly upregulated with fluid flow. Interestingly, fluid flow sensing by primary cilia triggers a transcriptomic response of only 54 genes identified as cells linked to the regulation of the activity of the epithelial Na⁺ channel (ENaC), including genes linked to the regulation of the activity of the epithelial Na⁺ channel (ENaC), the activity of aquaporins, tight junction permeability, iron transport, phosphate transport, and bicarbonate handling.

Conclusions: Fluid flow elicits a transcriptomic response in the collecting duct of the kidney. The role of primary cilia in this response is restricted to 54 genes, of which 16 are uniquely linked to the regulation of the activity of the epithelial Na⁺ channel (ENaC), including genes linked to the regulation of the activity of the epithelial Na⁺ channel (ENaC), the activity of aquaporins, tight junction permeability, iron transport, phosphate transport, and bicarbonate handling.

Funding: Government Support - Non-U.S.

SA-PO1056

Characterization of Kidney-Specific, C-Terminally Truncated Forms of WNK4 Kinase Adrian R. Murillo-de-Ozores,1,4 Silvana Bazus-Valenti,1 Alejandro Rodriguez-Gama,3,5 Karla Leyva-Rios,2 Norma H. Vázquez,3 Chao-Ling Yang,2 Johannes Lofting,1 David H. Ellison,2 Gerardo Gamba,1 Maria Castañeda-Bueno,1 1Instituto de Investigaciones Biomedicas, UNAM, CDMX, Mexico; 2Oregon Health & Science University, Portland, OR; 3Molecular Physiology Unit, INCMNSZ, CDMX, Mexico; 4Facultad de Medicina, UNAM, CDMX, Mexico; 5Institute of Anatomy, UZH, Zurich, Switzerland.

Background: The kinase WNK4 is an important regulator of renal salt handling. Mutations in this gene cause Familial Hyperkalemic Hypertension, mainly due to overactivation of the renal NaCl cotransporter, NCC. In addition to the full-length WNK4, we have observed shorter forms of this kinase in kidney lysates.

Methods: Western Blot, LC-MS/MS, immunoprecipitation, site-directed mutagenesis, transfection in HEK293 cells, and in vitro proteolytic assays were performed to characterize the short forms of WNK4.

Results: In Western blot assays, using WNK4+ mice as control and two different N-terminal WNK4 antibodies, we observed lower bands (between 130 and 95 kDa) corresponding to WNK4 fragments in wild lysesates of WNK4−/− mice. These bands were not observed in other tissue lysates. LC-MS/MS confirmed that these bands correspond to WNK4 fragments that lack a C-terminal segment. One of these WNK4 forms may be produced by proteolytic cleavage, as we found that recombinant WNK4 is cleaved when overexpressed in kidney lysate. This process was prevented by a Zn⁺ chelator. In HEK293 cells, we observed that truncation of WNK4’s C-terminus at several positions increases kinase’s activity towards SPAK, unless the truncated segment is large enough to include the SPAK binding site. This gain of function is caused by the loss of a protein phosphatase 1 (PP1) binding site. Cotransfection of PP1 causes dephosphorylation of WNK4, while this effect is abolished in the WNK4-PP1 binding site mutant. Biochemical evidence suggests that the WNK4 short forms detected in vivo may lack the SPAK binding site and thus may not behave as constitutively active kinases.

Conclusions: We show the overexpression of short, C-terminally truncated, and kidney-specific WNK4 forms, at least one of which may be product of proteolysis. Moreover, this work allowed us to identify a bona fide PP1 binding site in the C-terminal region of WNK4 that modulates its activity towards SPAK-NCC.

Funding: Government Support - Non-U.S.
SA-PO1057
Functional Human Epithelial Na+ Channel Variants in the Extracellular Beta-Ball Domain Shuhao Sheng, Jingxin Chen, Thomas R. Kleyman, Medicine, University of Pittsburgh, Pittsburgh, PA.

Background: Epithelial Na⁺ channels (ENaC) have a key role in the regulation of extracellular fluid volume, extracellular K⁺ concentration and blood pressure. Recent human genome sequencing has revealed a large number of ENaC variants. However, the functional consequences of the vast majority of human ENaC variants are unknown. In this study, we investigated several non-synonymous ENaC variants located at a beta strand within a core beta-ball structure of the extracellular domain for their functional roles.

Methods: Point mutations corresponding to the selected variants were introduced into human alpha ENaC cDNA by site-directed mutagenesis. Wild type (WT) and mutant alpha subunits, together with WT beta and gamma subunits of human ENaC were expressed in Xenopus oocytes by cRNA injections. Channel activities were examined by two-electrode voltage clamp. Channel densities in plasma membranes were examined by a luminescence assay using a FLAG epitope tag inserted into the extracellular domain of beta subunit. Na⁺ self-inhibition was determined by measuring the decrease in current from the peak to the steady state elicited by a rapid increase in extracellular Na⁺ concentration from 0.1 nM to 100 nM.

Results: We examined three ENaC variants located at the beta strand 7, one of the five beta-ball strands at the extracellular domain core. Oocytes expressing the R350W ENaCs showed two-fold greater amiloride-sensitive currents than cells expressing WT channels (p < 0.001). The variation did not significantly alter after channel surface expression. The mutant channels showed a diminished Na⁺ self-inhibition, which correlates to an increased open probability. The V351A mutant had a reduced current (55% of WT, p < 0.001), whereas G355R showed an increased current (1.6-fold of WT, p < 0.001).

Conclusions: Our results indicate that R350W and V351A are gain-of-function variant. R350W is an ENaC gating modifier via suppressing Na⁺ self-inhibition. Our results suggest that the core beta strand containing these variants and residing at a subunit interface has an important role in the regulation of ENaC gating.

Funding: NIDDK Support, Commercial Support - Dialysis Clinic, Inc.

SA-PO1058
The Different Modulations of NCC by ERK 1 and ERK 2 Signaling Pathway Xiuwan Feng,1 Shen Chen,1 Jia Xiao,1 Xinxin Chen,2 Hui Cai,1,2 1Emory University School of Medicine, Atlanta, GA; 2Nephrology, Atlanta VA Medical Center, Decatur, GA.

Background: In our previous studies we found that ERK 1/2 knock-down decreased NCC expression in cell experiments. Stain group previously reported that total NCC abundance was significantly decreased in the nephron-specific Nedd4L deficient (knockout) (floxed/floxed) mice. ERK1 and ERK2 are presumed to be functionally redundant given their 84% sequence homology, shared upstream activators, and similar substrate specificity. Our preliminary data indicated that ERK 1 and ERK 2 have different roles in NCC modulation in vivo. However, the relationship between ERK 1/2 and Nedd4-2 as well as the effects of unique ERK 1 and ERK 2 on NCC remain not entirely clear. In this study, we investigated the different roles of ERK 1 and ERK 2 in NCC modulation in cell and in both ERK1 KO mice and Pax3/cre/ERK2 KO mice.

Methods: Cell culture, western blot analysis, siRNA knock-down experiments, 1 global KO and Pax8/cre/ERK2/flox mice were used in this study.

Results: Firstly, we knocked down ERK1 or ERK2 expression separately in Cos-7 cells cotransfected with NCC. We found that ERK1 knock down increased NCC expression and ERK2 knock down decreased NCC expression. To further explore the different roles of ERK 1 and ERK 2 on NCC. We generated the inducible nephron-specific ERK 2 KO (ERK 2 KO) mice by feeding Pax8/cre/ERK2/flox mice with doxycycline 1g/L for 14 days. Western blot results showed that the NCC expression in ERK1 global KO mice increased by 27.7%, whereas in ERK 2 KO mice NCC decreased to 62.1% compared to those in WT mice. We also found that total Nedd4-2, phospho-S448-Nedd4-2 and phospho-S328-Nedd4-2 were decreased to 50.4%, 52.5% and 76.8% respectively in ERK1 KO mice, while they were increased by 1.46, 1.5 and 3.11 folds in ERK 2 KO mice. We further tested the effects of low salt diet (LSD) on NCC abundance in ERK 2 KO mice fed with LSD for 14 days. We found that NCC abundance decreased to 68.8% while 14-3-3 gamma expression increased by 2.07 folds and total Nedd4-2 increased by 2.47 folds compared with that in WT mice.

Conclusions: Above results indicated that ERK 1 and ERK 2 signalings have different role in regulating NCC likely through modulating Nedd4-2 and 14-3-3 gamma. However, the interactions among MAPK, ERK1/2 signaling pathway, Nedd4-2 and 14-3-3 gamma need to be further investigated in the future studies.

Funding: Veterans Affairs Support

SA-PO1059
A Novel Molecule, Gephyrin, Functionally Associates with CIC-5 Chloride Channel in Response to Metabolic Acidosis in the Mouse Kidney Miyuki Oogawa,1 Hideto Shiga,1 Makoto Isukuda,1 Hideyuki Azuma,1 Kitasato University, SAGAMIHARA, Japan; 2Biochemistry, Kitasato University, SAGAMIHARA, Japan; 3Nephrology, Graduate School of Medical Science, Kitasato University, SAGAMIHARA, Japan.

Background: CIC-5 channel is co-localized with the V-ATPase in subapical endosomes of renal proximal tubule (PT) and α-intercalated cells. CIC-5 may play a crucial role in regulating both endocytosis and sorting of the acid transporters. However the associated molecule associated with CIC-5 has not been elucidated. This study aimed to identify the associated molecule and to examine its physiological roles in the regulation of intracellular sorting of CIC-5 in response to metabolic acidosis.

Methods: To examine the physiological role of the molecule, we prepared the fractions enriched for plasma membrane (P1) and endosomal membrane (P2) using differential centrifugation method. We then incubated these fractions with α- and β-intercalated cells. As the subcellular distributions of transporters and associated molecule were assessed by Western blot. The colocalization of CIC-5 and associated proteins were also imaged using confocal microscopy.

Results: We identified gephyrin as a specific associated molecule with CIC-5 by LC-MS. Immunohistochemistry showed the predominant expression of gephyrin and its colocalized with CIC-5 in the apical membrane of PT compared with that of distal tubule. In addition, gephyrin was co-immunoprecipitated with specific Ab against CIC-5 using crude homogenates of mouse kidney. Mice given NH4Cl in drinking water developed metabolic acidosis within 2 days of acid intake. CIC-5 protein abundance was relatively decreased in P1 and increased in P2 after 6 days of acid loading. In contrast the protein abundances of gephyrin were increased by 230% in P1 and 120% in P2 under the same condition of acid loading.

Conclusions: CIC-5 might be functionally anchored by gephyrin in the apical membrane of PT. Furthermore, gephyrin may imitate in the self-assembly into a scaffold to construct and strengthen plasticity following to the sorting of CIC-5 from plasma membrane to intracellular vesicles after acid loading.

Funding: Commercial Support - Pfizer

SA-PO1060
Low Chloride Increased NCC Expression Through Modulating Both ERK1/2 and SPAK Signaling Pathways Miaoyi Xiao,1 Xiuyan Feng,1 Xinxin Chen,1 Hui Cai,1,2 1Emory University School of Medicine, Atlanta, GA; 2Nephrology, Atlanta VA Medical Center, Decatur, GA.

Background: Previous studies have showed that low chloride concentration activates NCC activity via WNK-SPAK signaling pathway. We also found that ERK 1/2 signal pathway plays an important role in regulating NCC. We previously showed that ERK 1/2 phosphorylation increased in SPAK KO mice, suggesting that SPAK signaling affects ERK 1/2 signaling pathway. Therefore, we investigated whether low chloride concentration affects NCC expression through modulating interaction between ERK1/2 and SPAK signaling pathways.

Methods: Cell culture, transfection, siRNA knock-down, and western blot analysis were used in this study.

Results: We first treated the Cos-7 Cells transfected with NCC with different low chloride concentrations (chloride concentrations decreased from 142 to 7 mEq/L) for 12 hours. The western blot analysis showed that NCC protein expression increased with the decrease in chloride ion concentration in a dose-dependent manner while ERK 1/2 phosphorylation decreased and S373-SPAK phosphorylation increased. To further confirm the role of MAPK-ERK1/2 signaling pathway in modulating NCC in response to low chloride concentration, we knocked down the ERK1/2 expression in Cos-7 cells using ERK1/2 siRNA and treated the cells with the low chloride solution. The western blot analysis showed that the basal NCC expression increased in the ERK1/2 knockdown group compared with the control group transfected with the scramble transfection siRNA as expected. However, NCC expressions further increased with lowering chloride concentration while ERK 1/2 phosphorylation was also further decreased. We also found that SPAK phosphorylation increased with the ERK1/2 siRNA knockdown. To further confirm the interaction between ERK 1/2 and SPAK 1 signaling, we knocked down SPAK expression in Cos-7 cells using SPAK siRNA and treated the cells with some chloride solutions. We found that the increase in NCC expression was partially reversed by SPAK Knocked down while the ERK1/2 phosphorylation increased.

Conclusions: These data suggested that both MAPK-ERK1/2 and SPAK signaling pathways are involved in the regulation of NCC in response to low chloride stimulation.

Funding: Veterans Affairs Support

SA-PO1061
High Cholesterol Diet (HCD) Downregulates BK Channels in the Rabbit Cortical Collecting Duct (CCD) Rolando Carrizoza-Gaytan,1 Daniel A. Flores,2 Lisa M. Satlin,1 1Icahn School of Medicine at Mount Sinai, New York, NY; 2Mount Sinai School Of Medicine, New York, NY.

Background: The apical CCD channel in the CCD mediates flow-induced K secretion (FIKS) and adaptation to K loading. Preliminary results had shown that 4-5 wks HCD increases plasma membrane cholesterol content in the CCD, blunts flow-stimulated but not basal net Na absorption (JNa), and inhibits FIKS (p<0.37) in rabbit CCDs. As studies in endothelial cells and osteoblasts identify genomic effects of an HCD (Physiol Genomics, 2012; Acta Pharm Sinica, 2011), we speculated that a HCD may reduce abundance of BK channels in the CCD.

Methods: MPAK pseudorabies(AK) rabbits were randomized after weaning to receive either a standard (Base Diet; BD) or a cholesterol enriched diet (HCD; 0.3%) for 4-5 wks, at which time the animals were sacrificed. Kidneys were removed and CCDs microdissected for (i) microperfusion to measure JNa and net K secretion (JK), (ii) quantitative PCR to assess changes in mRNA encoding the β1 subunit and (iii) immunoprecipitation with anti-BKα Ab to examine plasma membrane expression.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Results: In 6 HCD CCDs, JNa increased from 13.3±6.6 to 30.1±8.5 pmol/min. mm (P<0.01) in response to an increase in flow rate from 1 to 5 mm/min/mm; this flow-stimulated increase in JNa was less than observed in BD (25.9±4.3 to 73.3±7.0; n=4; P<0.01). In the same 6 HCD CCDs, a 5-fold increase in flow rate resulted from 

4.9±1.3 to -11.5±2.2 pmol/min/mm (P<0.04), transport rates half those observed in BD (-1.6±0.7 to 1.8±0.5 pmol/min/mm; P<0.03). Slo1 mRNA expression in HCD CCDs (n=6; n=10 mm total tubular length/sample) tended to be less than in BD CCDs (n=3; 13.2±mm/sample; p<0.07). The relative apical/whole-cell expression of BKα was less in HCD principal (Δ=27±0.7%) and intercalated (Δ=24±1.0 %) cells than in BD cells (Δ=41±1.0; P<0.01).

Conclusions: Our results suggest that HCD downregulates the transcription and apical expression of BKα and thus inhibits IFKs in the rabbit CCD. Whether HCD also reduces expression of other channels necessary for K secretion, including ENaC, ROMK and Ca2+ channels, remains to be explored.

Funding: NIDDK Support

SA-PO1062
14-3-3 γ Inhibits BK Activity by Enhancing Its Degradation through a Lysosomal Pathway via an ERK1/2 Signaling-Dependent Mechanism

Shan Chen,1 Xiuyan Feng,2 Jia Xiao,1 Xinxin Chen,1 Hui Cai,1,2 Emory University School of Medicine, Atlanta, GA; 1Nephrology, Atlanta VA Medical Center, Decatur, GA.

Background: 14-3-3 γ belongs to a family of multifunctional regulatory proteins that mainly bind to phosphorylated Ser/Thr residues in the target proteins. Our previous data showed that 14-3-3 γ inhibits Big K (BK) channel activity and its protein expression through altering ERK1/2 signaling pathway. Thus, we hypothesized that 14-3-3 γ inhibits BK protein expression and BK protein degradation via ERK1/2 signaling.

Methods: Cell culture, transfection, western blot analysis, immunoprecipitation, and WT mice were used in this study.

Results: To determine the inhibitory effects of 14-3-3 γ on BK channel expression, we first performed experiments in Cos-7 cells. We found that overexpression of 14-3-3 γ significantly decreased BK protein expression, and knockdown of 14-3-3 γ expression obviously increased BK protein expression. To confirm that 14-3-3 γ modulates BK protein expression through an ERK1/2 signaling pathway, we performed ERK1/2 inhibition experiments. Cos-7 cells were cotransfected with Flag-14-3-3 γ and myc-BK for 48 hours with or without ERK1/2 inhibitor U0126 treatment. We found that inhibition of ERK1/2 phosphorylation abolished 14-3-3 γ-mediated inhibitory effects of BK protein expression. To explore whether overexpression of 14-3-3 γ-decreased BK protein expression through a lysosomal degradation pathway, we determined the effects of lysosomal inhibitor, bafilomycin A1 (Baf A1) on BK protein expression in Cos-7 cells. We found that Baf A1 treatments reversed the inhibitory effects of 14-3-3 γ on BK protein expression. We further investigated whether 14-3-3 γ-involved in BK protein ubiquitination in HEK 293 stably expressing BK cells transiently transfected with Flag-14-3-3 γ plasmid. We found that overexpression of 14-3-3 γ increased BK protein ubiquitination while increasing ERK 1/2 phosphorylation.

Conclusions: These data suggested that 14-3-3 γ inhibits BK protein expression by increasing BK ubiquitination, leading to enhanced BK degradation through a lysosomal pathway via an ERK1/2-signaling-dependent mechanism.

Funding: Veterans Affairs Support

SA-PO1063
Differential Sodium Ion Distribution in Muscle and Skin and Its Relationship to Hydration Status in Advanced CKD

Nicos Mitsiades,1 Damien J. Mechugh,1 Jane Alderdice,1 Agnieszka Swiecicka,2 Paul E. Brenchley,1 Geoff J. Parker,3 Sandip Mittra,1 Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom; 1The University of Manchester, Manchester, United Kingdom.

Background: Body sodium (Na) excess is an important determinant of cardiovascular risk in chronic kidney disease(CKD). Its effect is mediated, predominantly, through extracellular fluid (ECF) expansion. Although ECW is assumed to be a homogeneous isotonic compartment, the relative proportions of water & Na ions in different tissue is unclear in CKD. We aim to quantify Na concentration in muscle (M) and subcutaneous tissue (SC) to relate to hydration states in advanced CKD.

Methods: Na concentration was measured using a 31 MR scanner & a dual-tuned 1H/23Na coil. The lower leg of 8 healthy controls (HC) & 20 CKD stage 5 patients (eGFR<15 ml/min, not on dialysis) was imaged & the M & SC Na concentration derived using saline calibration phantom. Overhydration index (OH), ECW, intracellular (ICW) & total body sodium were calculated using a 3-day food diary & 24 hr urine Na measurements.

Results: The HC & CKD cohorts were similar in age(HC: 50±14 yr; CKD 53±9 yr; P=0.60) & sex(50% male) but the CKD cohort had significantly higher comorbidity (Charlson Index:HC 1.0 v CKD 3.0; P<0.01). The MR derived M Na concentrations were different between the 2 groups (CKD 24.9±5.5mmol/L; HC 23±1±2.7mmol/L; P=0.38). However, CKD participants had higher SC Na concentration than HC(CKD 35±8±10.2mmol/L; HC 19.5±5±5mmol/L; P=0.04). M Na was strongly correlated to BIS measured ECW volume(ECW/TCBW=r=0.502; p=0.01). Higher M Na was also associated with increased ECW/ICW ratio(=0.53±0.01; P<0.01) & higher systolic BP(=0.44p; p=0.02). Both M & SC Na correlated with OHM(=0.53±0.01; SC=r=0.452; p=0.02). Baseline Na intake was 94.9±3.2±24mmol/24hr for CKD & 113.4±46.9 mmol/24hr for HC(=0.23) while urine Na excretion was 109.5±17.1 & 11±70.5 mmol/24hr respectively(=0.98).

Conclusions: The distribution of Na ions appears to be heterogeneous in body tissues. In M, Na appears to be accompanied by water (osmotically active) & closely linked to ECW expansion. On the other hand, the higher SC Na concentration seen in CKD is dissociated from ECW content & is involved in maintaining an alternative physiopathology, unrelated to volume homeostasis, & possibly linked to CKD & higher comorbidity.

Funding: Clinical Revenue Support

SA-PO1064
Reduced Secretion of PTH and Hypocalemia in Systemic Heterozygous ATP2B1 Null Mice

Yousuke Ebara,1 Nobuhito Hirawa,2 Akira Fujiwara,2 Kouichi Tamura,1 1Yokohama City University Graduate School of Medicine, Yokohama-shi, Kanagawa, Japan; 2Yokohama City University Medical Center, Yokohama, Japan.

Background: We reported the association between high blood pressure and ATP2B1 gene in Japanese population through Millennium Genome Project. ATP2B1 is a gene encoding plasma membrane calcium ATPase 1 (PMCA1), which is known to be expressed throughout the body. PMCA1 plays a role of discharging Ca ions from the inside of the cell to the outside of the cell, and strictly adjusts the intracellular Ca concentration.

Methods: In this study, we confirmed if mouse exhibited hypocalemia. Therefore, in order to investigate the mechanism of hypocalemia, we studied bone, small intestine, kidney and parathyroid gland, which are important organs related to Ca metabolism.

Methods: Blood test, urinalysis, bone formation, bone resorption marker, bone density, and serum Ca, P, Ca/ P ratio were examined in 14-week old male mice. ATP2B1-/- mice exhibited hypertension and reduced eNOS activity, NO production was involved. We confirmed if mouse exhibited hypocalemia. Therefore, in order to investigate the mechanism of hypocalemia, we studied bone, small intestine, kidney and parathyroid gland, which are important organs related to Ca metabolism.

Results: In the ATP2B1 mice, bone mineral density (ATP2B1-/- versus ATP2B1+/-: 689 ± 0.129 versus 645.2 ± 2.0; P<0.05), bone density and serum Ca concentration (0.769 ± 0.117 versus 0.330 ± 0.082; P<0.05) were increased, serum intact PTH (153.6 ± 41.0 versus 324.4 ± 41.4; P<0.05) and ATP2B1 expression of intestine (0.56 ± 0.092 versus 1.00 ± 0.217; P<0.05) were decreased, compared with control mice. In the intestine, no significant change was observed in the expression levels of various Ca regulatory proteins other than ATP2B1.

Conclusions: Systemic heterozygous ATP2B1 mice exhibited hypocalemia, and increased bone density and decreased PTH secretion. ATP2B1 might play important roles in bone metabolism.

SA-PO1065
ApoL1 Confers pH-Switchable Ion Permeability to Phospholipid Vesicles

John C. Edwards, St. Louis University, Saint Louis, MO.

Background: Variants in Apol1 confer risk of certain chronic kidney diseases. Apol1 is thought to function as an ion channel but reports vary substantially. We sought to characterize Apol1 ion permease activity with the hope that it may provide insight into Apol1-associated kidney disease.

Methods: Recombinant His-tagged Apol1 was purified by Ni-affinity and gel filtration. Ion permeability was assessed using vesicle-based, voltage dependent Cl and K efflux assays using ion selective electrodes. Apol1 membrane association was measured by mixing protein with lipid, Na, CO3, extraction to remove peripherally-associated protein, and isolation of the remaining integral membrane protein by floating the vesicles through a sucrose cushion.

Results: Addition of Apol1 to vesicles yields robust Cl selective permeability. The activity is dependent on pH at which protein and membranes interact, with a sharp drop above pH 6.0. K permeability is minimal at any pH when protein and vesicles are mixed and assayed at the same pH. However, K permeability is detected when protein and vesicles are allowed to interact at low pH and then shifted to a pH at the efflux assay. Membrane permeability is greatest if protein and vesicles are mixed at pH 5.5-6.0 and then assayed at pH 7.5. pH switch not only activates the K permeability but also partially inactivates the Cl permeability. Both Cl and K permeable activities are linearly dependent on mass of protein, and are dependent on lipid composition, requiring the presence of negatively charged phospholipids. The Cl permeability requires the presence of Ca ion. Membrane association assays demonstrate pH-sensitive membrane insertion which occurs at low pH, requires the presence of negatively charged phospholipids, and is stable when pH is shifted back to neutral after insertion takes place.

Funding: Na, K+, Cl- - Poster/Sunday
MRT Spatial and Temporal Characterization of Acute and Chronic Hypotonic Brain Edema Marta Tejedor,1 Giovanna Martin,2 Ángel Nava,3 Clara Usón,1 Javier Soto,1 Alberto Tejedor jorge,1 Fundación para la Investigación Biomédica del Hospital General Universitario Gregorio Marañón, Madrid, Spain; 2Hospital Infanta Elena, Valdemoro, Madrid, Spain; 3Universidad Complutense de Madrid, Madrid, Spain.

Background: Hypotonic brain edema has not been studied in depth with imaging techniques such as MRI. Aim: to assess spatial and temporal responses within different areas of the brain in hypotonicity, and differences between acute and chronic hypotonia.

Methods: Chronic hypotonia was induced in Wistar rats by intraperitoneal (ip) injection of hypotonic saline (NaCl, 2% of body weight) and access to water for 7 days (G1). A group of control normovolemic animals was fed with pellet based diet (G2). Brain edema was studied with MRI at baseline and after ip injection of either 10% of body weight in water (both G1 and G2) or 2 mL of NaCl15% for every 100 grams of body weight (G1) over 120 minutes. ADC (apparent diffusion coefficient) assessed the degree of brain edema in different regions of interest: cortex, hypothalamus, nervous fibers, extra-pyramidal system.

Results: Baseline [Na+] were 147±7 mmol/L (G1); after acute water load: 112±5 mmol/L and 119±5 mmol/L respectively. Baseline ADC values were lower in G1, indicating relevant brain edema. After acute water load, a further drop in the ADC levels was observed in both groups. A transient period of cellular defense where water was actively pumped outside the cells was being more efficient in G1, becoming the ADC levels similar in both groups at 60 min, but worsening again at 90 and 120 min in G1. After 120 min, ADC levels were the first region to become edematous, followed by the cortex, and then, at different time points, by the extra-pyramidal system and myelinated fibers. Response to edema appeared with different time delays from the maximum degree of edema, but it seemed to follow a structural order: hypothalamus, cortex, extra-pyramidal system and fibers. Treatment of G1 with hypotonic saline (NaCl15%) induced a correction of the edema that was three times faster than the spontaneous one. Sodium concentrations went from 136±7 mmol/L to 140±7 mmol/L.

Conclusions: Brain response to hypotonicity is not homogeneous, and edema develops at different times in different regions. The time course of the response to that edema is not homogeneous either. The different speed in the response to brain edema in adjacent areas suggests that damage leading to central pontine myelolysis could be earlier than observed in clinical practice.

SA-PO1067

MT-3995, a Novel Non-Steroidal Mineralocorticoid Receptor Antagonist, Has Pharmacological Profiles Differentiated from Eplerenone and Spironolactone Kohki Kikkawa,1 Naritoshi Shirata,1 Misae Takakawa,1 Akito Nishi,2 Takuma Tsuchi,3 Hitomi Munakata,1 Tomoko Ikeda,1 Naomi Koyama,1 Hidetoshi Shimizu,1 Yoshinori Watanabe,2 Masashi Nishio,3 Makoto Katoh.1 Medical Science, Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan; 2Innovative Medical Science, Mitsubishi Tanabe Pharma Corporation, Toda, Japan; 3Discovery Technology, Mitsubishi Tanabe Pharma Corporation, Toda, Japan.

Background: MR antagonists such as eplerenone (Epl) and spironolactone (Spi) are widely used to treat hypertension, but their use is limited due to side effects. MT-3995 is a highly selective MR antagonist, suggesting no risk of hypotensive or hypokalemic side effects. The organ protective effects of MT-3995 were evaluated in adrenalectomized (ADX) rats with or without MR replacement therapy (DOCA).

Methods: We studied kidney function, blood and urinary electrolytes, and selected mRNA expression. The abundance of renal NKA, NCC, and NCCα mRNA was compared to CPT (n=4, p<0.05). Baseline [Na+] were 147±7 mmol/L (G1); after acute water load: 112±5 mmol/L and 119±5 mmol/L respectively. Baseline ADC values were lower in G1, indicating relevant brain edema. After acute water load, a further drop in the ADC levels was observed in both groups. A transient period of cellular defense where water was actively pumped outside the cells was being more efficient in G1, becoming the ADC levels similar in both groups at 60 min, but worsening again at 90 and 120 min in G1. After 120 min, ADC levels were the first region to become edematous, followed by the cortex, and then, at different time points, by the extra-pyramidal system and myelinated fibers. Response to edema appeared with different time delays from the maximum degree of edema, but it seemed to follow a structural order: hypothalamus, cortex, extra-pyramidal system and fibers. Treatment of G1 with hypotonic saline (NaCl15%) induced a correction of the edema that was three times faster than the spontaneous one. Sodium concentrations went from 136±7 mmol/L to 140±7 mmol/L.

Conclusions: Brain response to hypotonicity is not homogeneous, and edema develops at different times in different regions. The time course of the response to that edema is not homogeneous either. The different speed in the response to brain edema in adjacent areas suggests that damage leading to central pontine myelolysis could be earlier than observed in clinical practice.

SA-PO1068

Mineralocorticoids Modulate the Expression of the Beta3 Subunit of the Na +, K + - ATPase in the Renal Collecting Duct Macarena Rojas,3 Pablo A. Leon,1 Victor M. Barrientos,1 Rodrigo Alzamora,2 Luis F. Michea,2 1Universidad de Chile, Santiago, Chile; 2University of Chile, Santiago, Chile; 3Millennium Institute on Immunology and Immunotherapy, ICBM, Facultad de Medicina Universidad de Chile, Santiago, Chile.

Background: Renal sodium reabsorption depends on the activity of the Na+, K+-ATPase (A). The β3 subunit is the most abundant isoform that has been described. It is accepted that renal tubule cells express a, b, and Aldosterone stimulates NKA activity and may modulate a, b, expression. However, some studies suggested the presence of β3 in the kidney. We hypothesized that the β3 isomorf of the NKA is expressed by tubular cells of the distal nephron and is modulated by mineralocorticoids.

Methods: We studied kidney from rats (male SD) and mice (male C57BL/6). β3 mRNA distribution was determined by qRT-PCR and in situ hybridization (ISH). We compared the abundance of renal β3 mRNA to the abundance in other tissues known to express β3, β1 and β2 mRNA, protein and antibody staining.

Results: Kidney tissue express β3 mRNA, with higher relative abundance in medulla (12.2±0.2- vs. 1.0±0.2 in cortex; n=3, p<0.05). ISH studies showed the preferential expression of β3 mRNA in collecting duct principal cells of cortex and medula. IMID repressed 4-fold, and NaCl15% increased mRNA as compared to CPT (n=4, p<0.05). ADX rodent showed increased β3 expressed, and protein abundance by 3-fold and 2-fold respectively (n=4, p<0.05). The increase of β3 was prevented by DOCA. SPIRO increased medullary β3 mRNA (4-fold) and protein (2-fold, n=4, p<0.05). No changes in the abundance of β1 (cortical/medullary) β2 (cortical) were detected after ADX or Spiro.

Conclusions: We showed that the β3 isomorf of the Na,K-ATPase is mainly expressed in collecting duct principal cells of renal under the modulation of mineralocorticoids.

FONDECYT 1130550, FONDECYT 1171869, FONDECYT 1151423; IMII P09-016-F Funding: Government Support - Non-U.S.
individuals as they increase risk for renal injury via decreased renal blood flow and GFR. However, there is little in vivo evidence of this phenomenon. We showed that in mice with HTN, vascular-specific deletion of the EP4 receptor (mimicking some of the downstream effects of NSAIDs) significantly reduced renal perfusion and exacerbated injury. The present study was undertaken to test the hypothesis that hypertensive renal injury would become more severe with chronic ASA administration.

**Methods:** Male Sprague-Dawley rats (n=5 per group) were implanted with Model 2002 Alzet osmotic minipumps loaded with vehicle or Angiotensin II (AngII) to deliver a dose of 400 ng/kg/min for 4 weeks. ASA was administered concurrently via drinking water (0.067 mg/ml) to yield a dose of 10mg/kg/day. Renal function was assessed by plasma creatinine using HPLC. Renal histology was assessed on Masson trichrome and PAS-stained kidney sections. At 0, 2, and 4 weeks, dynamic contrast-enhanced (DCE) MRI was performed using a 7T GE/Agilent MR901 and data analyzed with a two compartment filtration model (PMI, S. Sourbron) to estimate renal blood volume.

**Results:** After 4 weeks of AngII infusion, rats given daily ASA had significantly decreased bodyweight and appeared dehydrated. Surprisingly, despite comparable ASA dosing, this combination was associated with a 60% survival rate compared to 100% in rats treated with AngII alone. AngII/ASA decreased renal function vs all other groups as indicated by increased plasma creatinine using HPLC. Renal histology was assessed on Masson trichrome and PAS-stained kidney sections. At 0, 2, and 4 weeks, dynamic contrast-enhanced (DCE) MRI was performed using a 7T GE/Agilent MR901 and data analyzed with a two compartment filtration model (PMI, S. Sourbron) to estimate renal blood volume.

**Conclusions:** The combination of AngII-mediated hypertension and chronic ASA intake accelerates renal function decline and injury.

**SA-PO1072**

**Preeclamptic Pregnancy Exacerbates Renal Injury in Dahl Salt Sensitive (S) Rats**

Hannah Rice, Michael R. Garrett, Jennifer M. Sasser. University of Mississippi Medical Center, Jackson, MS.

**Background:** Preeclampsia results in increased susceptibility to stroke, heart attack, hypertension, and chronic kidney disease postpartum. Despite increased cardiovascular disease risk, recommendations for prevention in these patients have not been established due to a lack of evidence for the mechanisms responsible for disease progression or evaluation of optimal therapeutic regimens. The purpose of this study was to test the hypothesis that preeclampsia accelerates the progression of chronic kidney disease and is associated with changes in the nitric oxide (NO)endothelin-1 (ET-1) balance.

**Methods:** Dahl S rats on a 0.3% salt diet (previously characterized model of superimposed preeclampsia) who experienced 2 pregnancies (12 and 17 weeks of age) and virgin littermate controls were aged to 6 months. Rats were implanted with telemetry transmitters (DSI), mean arterial pressure (MAP) was recorded, and rats were placed in metabolic cages for 24 hour urine collection prior to tissue harvest.

**Results:** Prior pregnancy did not result in a further increase in MAP at 6 months in the already hypertensive Dahl S females (virgin: 185±6.9 mm Hg, prior pregnancy: 184±6.6 mm Hg, n=8-10). Despite similar BP, rats who experienced prior preeclampsic pregnancy had greater renal injury compared to virgin littermates. Urinary excretion of protein (96±20 vs 95±45 mg/day), nephrin (0.6±0.4 vs 3.1±1.2 µg/day), and podocalyxin (4.9±1.0 vs 21.0±7.6 µg/day) was lower compared to control litters (p<0.05, Bradford assay, Excocell ELISA). These measures of renal injury were corroborated by histological examination as kidneys from rats that experienced preeclampsia demonstrated greater glomerular sclerosis (2.9±0.3%) compared to virgin rats (0.3±0.3, p<0.05).

**Funding:** NIH/NIDDK Grant E001556; Other NIH Support - NHLBI, Private Foundation Support

**SA-PO1073**

**Impairment of Key Sphingolipid Metabolism Enzymes in Placenta and Kidneys of Reduced Uterine Perfusion Mouse Model Suttira Intapad.**

Pharmacology Department, Tulane University School of Medicine, New Orleans, LA.

**Background:** Preeclampsia (PE), is a pregnancy disorder characterized in the early gestation by placental ischemia, hypertension, and proteinuria. These complications may lead to the development of chronic kidney disease. Bioactive sphingolipids ceramide and sphingosine-1-phosphate (SIP) function as key regulators of cellular homeostasis such as angiogenesis, inflammation and endothelial permeability. Ceramide and SIP levels are altered in preeclamptic women, and sphingolipid pathway has been reported to involve in renal injury. Ceramide hydrolyzes ceramide to produce sphingosine. Sphingosine can then be phosphorylated by sphingosine kinase (Sphk) 1 and 2 to form SIP. In the present study we have tested the hypothesis that placental ischemia alters the acid ceramidase (ASA1H), Sphk1 and Sphk2 enzymes expression in placenta and kidneys of reduced uterine perfusion (RUP) mouse model.

**Methods:** C57bl/6J mice underwent sham or RUP surgeries at day 13 of gestation. Mice were randomized with respect to maternal dietary regimen (0.3% NaCl). RUP treatment involved a 40% reduction in uterine blood flow on days 13-15 of pregnancy. This surgical model provides a unique model for impairment of placentation and placental insufficiency in pre-eclampsia. At 19 days of gestation, kidneys were removed and urine was collected. Proteinuria was measured by ELISA. Plasma was collected for measurements of sphingolipid enzyme activity and mRNA expression. Sphingosine and ceramide levels were measured by HPLC. These data support the hypothesis that alterations in the NO/ET-1 balance in the kidney could link the maternal syndrome of preeclampsia to the increased postpartum risk of cardiovascular and renal disease.

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

**SA-PO1074**

**Uncoupled Endothelial Nitric Oxide Synthase (eNOS) in the Kidney Correlates with Increased Blood Pressure (BP) in Insulin-Infused Mice Carolyn M. Ecelbarger,1 Ashley Alunam,2 Hwal Lee,1 Maurice Fluit,1 Swasti Tiwari,1 Lijun Li,1 Georgetown University, Washington, DC; 2Williamette University, Salem, OR; 3SGPGIMS, Lucknow, India.

**Background:** Insulin stimulates NO production in the kidney via activation of eNOS which may lower BP; however, whether and how insulin resistance alters this relationship is unclear.

**Methods:** We tested whether insulin infusion into insulin-sensitive (C57Bl6; C57) versus insulin-resistant (TALLYH0, “TH”) mice resulted in differential BP responses and renal eNOS regulation. Male mice (4-6 months old) were infused with insulin (50 U/
kgbw/d) by osmotic minipump for 14 days (some mice were maintained as untreated). One of the infused mice in each strain were switched from a normal NaCl diet (NSD, 1%) to a high-NaCl diet (HSD, 4%) at day 7 of the infusion (n ~ 6-8/group).

**Results:** Mean arterial BP (MAP), measured by radiotelemetry, was 10-15 mm Hg lower in C57 mice (relative to TH) at baseline, fell days 2-5 of infusion, then rose days 7-14, and at day 14, it was no longer different from TH. Pulse pressure (PP) was constant. In TH, MAP was relatively resistant to insulin, while in peptide it fell (~40%). Light-to-dark ratio of MAP (or diurnal rhythm) was elevated in TH at the baseline and increased in both strains with HSD. Urine was measured for nitrates plus nitrites (NOx) at baseline and at day 14 of the infusion. MED was higher in both strains (30-40%) between baseline and day 1, but fell to ~55% of baseline by day 14. Plasma NOx concentration was significantly higher in untreated TH (relative to C57), but fell ~40% with insulin infusion (with either HSD or NSD). In contrast, plasma NOx rose in C57 with insulin infusion (13%) and an additional 23% with insulin plus HSD. NO activity (mg per tissue) was increased by insulin infusion in renal cortex (CTX) in both strains, but in the medulla the increase was restricted to the C57. Western blotting of kidney revealed that coupled (150 KDa) and uncoupled (120 KDa) eNOS band densities were higher in TH, and insulin plus HSD substantially increased the uncoupled band especially in TH.

**Conclusions:** In summary, insulin infusion for 14 days abrogates BP differences between C57 and TH mice suggesting hyperinsulinaemia may primarily underlie the modest hypertension in TH mice. Furthermore, progressive renal eNOS uncoupling and impaired NO production may play a role in the development of hypertension associated with insulin resistance.

**Funding:** Clinical Revenue Support

---

### SA-PO1075

#### Renal Oxygenation during Chronic Nitric Oxide Synthase Inhibition as Recorded by Telemetry

**Background:** Renal hypoxia has been advanced as a crucial factor in the vicious circle of disease progression leading to kidney failure. Nitric oxide (NO) is involved in renal vascular regulation. NO synthase (NOS)-inhibition leads to hypertension while alleviating renal blood flow and thus oxygen delivery. Furthermore, NO inhibits mitochondrial oxidation. Therefore, we hypothesized that NOS inhibition would induce renal hypoxia. We now report on telerecorded mean arterial pressure and oxygen pressure (pO2) in renal cortex and medulla in conscious rats during chronic NOS inhibition.

**Methods:** Oxygen sensitive electrodes were implanted in either renal cortex (n=6) or medulla (n=7) in healthy rats. After recovery and stabilization, baseline pO2 and pressure recording telemeters, followed the same protocol. Terminal glomerular filtration rate (GFR), renal blood flow (RBF), renal oxygen extraction and natriuresis were assessed improved under isoflurane anesthesia in all L-NNA rats (n=19) and in untreated controls (n=6).

**Results:** NS inhibition rapidly induced hypertension (165±34 vs. 134±7 mmHg, p<0.01). Mean arterial BP (MAP), measured by radiotelemetry, was 10-15 mm Hg lower in C57 mice (relative to TH) at baseline, fell days 2-5 of infusion, then rose days 7-14, and at day 14, it was no longer different from TH. Pulse pressure (PP) was constant. In TH, MAP was relatively resistant to insulin, while in peptide it fell (~40%). Light-to-dark ratio of MAP (or diurnal rhythm) was elevated in TH at the baseline and increased in both strains with HSD. Urine was measured for nitrates plus nitrites (NOx) at baseline and at day 14 of the infusion. MED was higher in both strains (30-40%) between baseline and day 1, but fell to ~55% of baseline by day 14. Plasma NOx concentration was significantly higher in untreated TH (relative to C57), but fell ~40% with insulin infusion (with either HSD or NSD). In contrast, plasma NOx rose in C57 with insulin infusion (13%) and an additional 23% with insulin plus HSD. NO activity (mg per tissue) was increased by insulin infusion in renal cortex (CTX) in both strains, but in the medulla the increase was restricted to the C57. Western blotting of kidney revealed that coupled (150 KDa) and uncoupled (120 KDa) eNOS band densities were higher in TH, and insulin plus HSD substantially increased the uncoupled band especially in TH.

**Conclusions:** In summary, insulin infusion for 14 days abrogates BP differences between C57 and TH mice suggesting hyperinsulinaemia may primarily underlie the modest hypertension in TH mice. Furthermore, progressive renal eNOS uncoupling and impaired NO production may play a role in the development of hypertension associated with insulin resistance.

**Funding:** Clinical Revenue Support

---

### SA-PO1076

#### The Role of Plasma Cells in Autoimmune Associated Hypertension

**Background:** Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that is characterized by the loss of immune tolerance leading to the production of pathogenic autoantibodies, and is associated with prevalent hypertension, renal injury, and cardiovascular disease. Because long-lived plasma cells produce the majority of serum immunoglobulins (Ig) and are the primary source of autoantibodies in SLE, we hypothesized that depletion of plasma cells using the proteasome inhibitor bortezomib would result in a reduction and attenuation of hypertension.

**Methods:** Thirty week old female NZW/F1 and control (NZW) mice were injected i.v. with vehicle (0.9% saline) or bortezomib (0.75 mg/kg) twice weekly for four weeks.

**Results:** Percentages of CD138+ intracellular-k lightchain plasma cells in the bone marrow were lower in bortezomib treated SLE mice compared to vehicle-treated SLE mice (7.5%±2.5% vs. 13.4±1.9% respectively, p=0.05). In C57 mice, RBF and flow cytometry revealed B and T cells were not altered after bortezomib treatment. Total plasma IgG was higher in SLE mice as compared to control mice (5.02±1.2 vs. 2.89±0.7 mg/mL, **p<0.05**), and were lower in untreated SLE mice treated with bortezomib (6.8±1.2 mg/mL, **p<0.05** vs. SLE-vehicle). In addition, bortezomib treatment reduced circulating anti-dsDNA IgG levels in SLE mice (1.36±0.25 vs. 0.44±0.11 OD450, **p<0.01**). This was associated with reduced glomerular IgG deposition in bortezomib treated SLE mice compared to vehicle treated SLE mice (175±240 vs. 95±57 fluorescence/μM, **n=5, p<0.05**). Urinary albumin excretion was increased in SLE mice as compared to controls (16.8±10.1 vs. 0.1±5.0±0.02 mg/day, **p<0.05**) and was lower in bortezomib treated SLE mice (0.2±400.16 mg/day, **p<0.05** vs. SLE-vehicle). Mean arterial pressure (MAP; mmHg) measured in conscious mice in SLE model compared to control mice (142±3 vs. 118±3, **p<0.001**). MAP was significantly lower in SLE mice treated with bortezomib when compared to vehicle treated mice (119±4 vs. 142±5, **p<0.001**).

**Conclusions:** These data suggest that production of autoantibodies by plasma cells in SLE mechanistically contribute to the pathogenesis of hypertension.

**Funding:** Other NHII Support - NHLBI, Veterans Affairs Support

---

### SA-PO1077

#### Renal Dendritic Cells from Hypertensive Mice Transferred Inflammation and Modified Renal Sodium Handling

**Background:** High Angiotensin II (AngII) induce hypertension (HT). Previously, using genetically modified mice that allowed the systemic ablation of Dendritic Cells (DCs), we observed that DCs are necessary for the development of HT. The kidney is a tissue rich in DCs, which are present in the interstitial space. We hypothesized that renal DCs have pro-hypertensive properties that are acquired after HT.

**Methods:** In this study, we evaluated if renal DCs from hypertensive mice (AngII infusion, osmotic minipump, 1.042 kg/min, 14 day) can transfer HT. We compared the transfer of renal DCs and splenic DCs from control mice to rats treated with angiotensin II (AngII), and the transfer of renal DCs from hypertensive mice transiently increased BP (basal=102.5±1.4 vs. control; n=4-8). Transfer of renal DCs from hypertensive mice transiently increased BP (basal=102.5±1.4 vs. control; n=4-8). Transfer of renal DCs from hypertensive mice transiently increased BP (basal, 102±1.4 vs. control, p<0.05), while transfer of splenic DCs did not modify BP. Renal DCs showed renal-preferential location 24 hours post injection, irrespective of the origin (control or hypertensive kidney). Receptors of hypertensive renal DCs showed decreased renal Na+ excretion (basal Na+ excretion=20.2±1.9 mg/min, p<0.001 vs control). In addition, renal Na+ excretion was reduced in treated mice treated with bortezomib (102.5±1.4 vs. 92.8±0.02 mg/4h, **p<0.001** vs 1.042 kg/min), and therefore increased renal oxygen supply. In contrast, medullary pO2 decreased progressively. Chronic NOS deficiency leads to renal hypoxia and renal injury, and suggests that the development of hypertension, which confers the ability of modulating sodium renal excretion. FUNDACYT/1130550 and 1171869, IIMI P09-016-F, BECA CONICYT 21130482.

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

---

### SA-PO1078

#### Leukocyte Angiotensin II Type I Receptor-Associated Protein as a surrogate Marker and Inhibitory Factor of Inflammation

**Background:** Previous studies have shown that the leukocyte gene expression of the renin-angiotensin system, particularly type I angiotensin II receptor (AT1R), is involved in the development of hypertension. Renin, angiotensinogen and AT1R gene expression in the kidney, cardiovascular and other target organs diseases. We found that AT1R-associated protein (ATRAP) is a novel molecule that specifically binds to AT1R and promotes internalization of AT1R along with the suppression of activated AT1R signal in animal models of NCD. The aim of this study was to determine the factors that may regulate the gene expression of ATRAP in leukocytes.

**Funding:** Other NIH Support - NHLBI, Veterans Affairs Support

---

The document contains scientific research findings related to hypertension, renal oxygenation, and the role of plasma cells in autoimmune hypertension. It also discusses the transferability of renal dendritic cells from hypertensive mice to normal mice, the role of AT1R-associated protein (ATRAP) in regulating leukocyte gene expression, and the impact of chronic nitric oxide synthase inhibition on renal oxygenation.
of low-dose lipopolysaccharide, these mice were sacrificed and measured inflammatory cytokine levels in renal macrophages and leukocytes.

**Results:** ATRAP was expressed predominantly in granulocytes and monocytes from healthy volunteers. In blood samples from 86 patients (mean age 63 years, hypertension in 95%, dyslipidemia in 76%, chronic kidney disease in 63%), the ATRAP mRNA was upregulated in the age, neutrophil count, monocyte count, and microalbuminuria. These associations remained significant after adjustment for age, sex, estimated glomerular filtration rate, and urinary albumin excretion. Furthermore, the ATRAP mRNA was positively correlated with the IL-1β, TNF-α, and MCP-1 mRNA in leukocytes. In addition, these cytokines were upregulated in bone marrow ATRAP-deficient (chimeric mice in comparison to control mice after injection of low-dose lipopolysaccharide.

**Conclusions:** These results suggest that leukocyte ATRAP expression is associated with systemic and leukocyte inflammatory status and increases to compensate for inflammation.

---

**SA-PO1079**

**Macrophage COX-2 Deletion Activates Renal T Cells and Transporter Activity in Response to High Salt Intake**

**Background:** Chronic use of non-selective NSAIDs or selective cyclooxygenase-2 (COX-2) inhibitors leads to increases in blood pressure. Recently, the immune system has been shown to play an important role in the pathogenesis of hypertension. Both interleukin-17 (IL-17) and interferon-γ expressed increased IL-23, known to activate Th17 cells. In kidneys from high salt-treated COX-2-/- mice (FVB background) were fed a high salt diet (8% NaCl) for 5 weeks. Renal macrophages from high salt-treated macrophage COX-2-/- mice in comparison to control mice after injection of low-dose lipopolysaccharide.

**Methods:** Male COX-2-/- (WT) and CD-11b Crc; COX-2-/- (macrophage COX-2-/-) mice (FVB background) were fed a high salt diet (8% NaCl) for 5 weeks. Renal macrophages and T lymphocytes were isolated from WT and CD-11b knockout mice, respectively.

**Results:** Renal macrophage COX-2 mRNA was efficiently deleted in macrophage COX-2-/- mice. Renal macrophages from high-salt-treated macrophage COX-2-/- mice expressed increased IL-17, known to activate Th17 cells. In kidneys from high-salt-treated macrophage COX-2-/- mice, there were increased CD4-positive T cells, which expressed IFNγ and IL-17, but there were decreased regulatory T cells (Tregs). Cleaved epithelial sodium channel (ENaC) levels, an indicator of its activation, were much higher in high salt-treated macrophage COX-2-/- mice.

**Conclusions:** These results suggest that deletion of macrophage COX-2 leads to aberrant activation of T lymphocytes, with subsequent increased production of IL-17 and IFNγ and activation of sodium transporters in response to high salt intake and may contribute to salt-sensitive hypertension.

**Funding:** NIDDK Support

---

**SA-PO1080**

**β-Catenin Activity Is Dependent on Mouse Strain in Angiotensin II Induced Renal Hypertensive Injury**

**Background:** Hypertensive kidney injury has been well established; however, little is known about the involvement of Wnt/β-catenin signalling in this process. Here, we induced hypertension with Angiotensin II (AngII) infusion in two strains of mice to determine the effect on β-catenin activity and renal physiology.

**Methods:** Male COX-2 f/f (WT) and CD-11b Cre; COX-2 f/f (macrophage COX-2-/-) mice were injected with low-dose lipopolysaccharide, these mice were sacrificed and measured inflammatory activity and HDAC1/2 protein levels compared with WT mice. In vehicle-treated mice, higher urinary total protein and albumin to creatinine ratios were also detected in Npr1-/- mice compared with WT mice; however, both of these parameters were dramatically reversed after AngII treatment.

**Conclusions:** The present results demonstrate that HDAC inhibitor, MGCD upregulates SIRT1 expression in vivo and repairs renal injury in Npr1-/- mice. These findings will have important implications in the treatment and prevention of hypertension and renal injury and dysfunction in humans.

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

---

**SA-PO1081**

**Mocetinostat Attenuates Renal Injury and Dysfunction via the Inhibition of HDAC in Npr1 Gene-Targeted Mutant Mouse Models**

**Background:** Fumio Fukagawa, Akira Nishiya, Akira Nakatani, Katsumi Matsuoka, 1 Kyoto University Graduate School of Medicine, Kyoto, Japan; 2 Tokai University School of Medicine, Isehara, Japan.

**Methods:** MA mice were prepared as described above. ATRAP was expressed predominantly in granulocytes and monocytes from healthy volunteers. In blood samples from 86 patients (mean age 63 years, hypertension in 95%, dyslipidemia in 76%, chronic kidney disease in 63%). The ATRAP mRNA was upregulated in the age, neutrophil count, monocyte count, and microalbuminuria. These associations remained significant after adjustment for age, sex, estimated glomerular filtration rate, and urinary albumin excretion. Furthermore, the ATRAP mRNA was positively correlated with the IL-1β, TNF-α, and MCP-1 mRNA in leukocytes. In addition, these cytokines were upregulated in bone marrow ATRAP-deficient (chimeric mice in comparison to control mice after injection of low-dose lipopolysaccharide.

**Results:** ATRAP was expressed predominantly in granulocytes and monocytes from healthy volunteers. In blood samples from 86 patients (mean age 63 years, hypertension in 95%, dyslipidemia in 76%, chronic kidney disease in 63%), the ATRAP mRNA was upregulated in the age, neutrophil count, monocyte count, and microalbuminuria. These associations remained significant after adjustment for age, sex, estimated glomerular filtration rate, and urinary albumin excretion. Furthermore, the ATRAP mRNA was positively correlated with the IL-1β, TNF-α, and MCP-1 mRNA in leukocytes. In addition, these cytokines were upregulated in bone marrow ATRAP-deficient (chimeric mice in comparison to control mice after injection of low-dose lipopolysaccharide.

**Conclusions:** These results suggest that leukocyte ATRAP expression is associated with systemic and leukocyte inflammatory status and increases to compensate for inflammation.

---

**SA-PO1082**

**Chronic Hypoxia Attenuated Hypertension and Renal Injury in an L-NAMe Model**

**Background:** Tissue hypoxia has been postulated as a central factor in the pathogenesis of Chronic Kidney Disease (CKD). We showed recently that, rather than promoting renal injury, chronic hypoxia promoted renoprotection in the remnant kidney model. Here we investigated whether chronic hypoxia promotes similar renoprotection in the chronic NO inhibition model.

**Methods:** Male Munch-Wistar rats received NOS-nitrogarginine methylster (NAME) in drinking water (80 mg/kg/day). Sixteen C (Cron) and 13 NAME rats (NAMEcron) remained in normoxia (21% O2), while 16 C (Chyp) and 16 NAME rats (NAMEhyp) were kept in a normobaric hypoxia chamber (12% O2). After 4 weeks, we assessed: body weight (BW, g), hemoglobin (Hb, g/dL), tail-cuff pressure (TCP, mmHg), urine albumin/creatinine ratio (mg/mmol), glomerular filtration rate (mL/min/g), and urinary albumin to creatinine ratio (mg/mmol). In NAMEhyp, higher urinary albumin to creatinine ratios were also detected in Npr1-/- mice compared with WT mice; however, both of these parameters were dramatically reversed after AngII treatment.

**Conclusions:** The present results demonstrate that HDAC inhibitor, MGCD upregulates SIRT1 expression in vivo and repairs renal injury in Npr1-/- mice. These findings will have important implications in the treatment and prevention of hypertension and renal injury and dysfunction in humans.

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

---

**SA-PO1083**

**Podocyte Injury Enhances Intrarenal Angiotensin II Generation and Sodium Retention Dependently on Megalin Masahiro Koizumi,1 Fumio Niinuma,2 Akira Nishiya,1 Motoki Yokanga,3 Masafumi Fukagawa,2 Fuji Matsuoka.1 Kagawa University Medical School, Kita-Gun, Japan; 2 Kyoto University Graduate School of Medicine, Kyoto, Japan; 3Tokai University School of Medicine, Isehara, Japan.

**Background:** We have previously shown that podocyte injury enhances glomerular filtration of liver-derived angiotensinogen (Agt) and intrarenal angiotensin (A) II...
SA-PO1085
A Critical Role of Angiotensin II Type 1 Receptor Binding Molecule in Hypertension in a CKD Model
Ryu Kobayashi,1 Hiromichi Wakui,2 Kazuhiro Ueda,3 Kotaro Harahara,1 Akira Nishiyama,1 Katuyuki Tanabe,6 Yohei Maeshima,7 Kouichi Tamura.1 1Kagawa University Medical School, Kitaa-Gun, Japan; 2Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Science, Okayama, Japan; 3Yokohama City University Graduate School of Medicine, Kanazawa-Ku, Japan.

Background: The renin-angiotensin system plays a key role in the maintenance of cardiovascular and renal homeostasis, principally via appropriate activation of Ang II type 1 receptor (AT1R). We previously identified an AT1R-associated protein (ATRAP/Agrap), which promotes AT1R internalization along with suppression of hyperactivation of tissue AT1R signaling. We hypothesized that dysregulation of renal ATRAP expression and subsequent AT1R hyperactivation contributes to development of hypertension that occurs as a complication of the remnant kidney CKD model.

Methods: We compared changes in endogenous ATRAP expression and blood pressure between 129/Sv and C57BL/6 mice using the remnant kidney model after 5/6 nephrectomy. We also examined the effect of ATRAP deficiency in C57BL/6 mice (with a hypertension-resistant strain background) on blood pressure regulation after 5/6 nephrectomy. To more directly examine the mechanism of hypertension, ATRAP-knockout (KO) mice were treated with the soluble TNF-α receptor, etanercept, or with vehicle after 5/6 nephrectomy.

Results: We first examined the effect of 5/6 nephrectomy on endogenous ATRAP expression in the kidney of C57BL/6 and 129/Sv mice. While 129/Sv mice that underwent 5/6 nephrectomy showed decreased renal ATRAP expression and development of hypertension, C57BL/6 mice showed increased renal ATRAP expression and resistance to progressive hypertension. Consequently, we hypothesized that downregulation of renal ATRAP expression is involved in pathogenesis of remnant kidney CKD model-related hypertension. To investigate this, we performed 5/6 nephrectomy in ATRAP-knockout (KO) mice on the hypertension-resistant C57BL/6 background. ATRAP-KO mice that underwent 5/6 nephrectomy showed hypertension with increased plasma volume. Moreover, in ATRAP-KO mice compared with wild-type C57BL/6 mice after 5/6 nephrectomy, renal expression of the epithelial sodium channel α-subunit and renin reninogen factor-IIα was significantly enhanced, concomitant with increased plasma membrane AT1R in the kidneys.

Conclusions: These results indicate that renal ATRAP downregulation is involved in onset and progression of blood pressure elevation caused by renal mass reduction, and implicates ATRAP as a therapeutic target for hypertension in CKD.

SA-PO1086
The Effect of Serine Protease Inhibition on Glomerular Injuries in Salt-Sensitive Hypertension
Yasunobu Iwata,1 Yutaka Kikizoe,2 Tomonori Nakagawa,1 Yuichiro Izumi,1 Takashi Kawanoe,1 Masataka Adachi,1 Kenichiro Kitamura,2 Masashi Mukoyama,3 1Department of Nephrology, Kumamoto university graduate school of medical sciences, Kumamoto, Japan; 2Internal Medicine III, University of Yamanashi Faculty of Medicine, Chou, Japan.

Background: We previously reported that a synthetic serine protease (SP) inhibitor, canastatin mesylate (CM), suppressed epithelial sodium channel (ENaC) activation by SPs and exerted an antihypertensive effect in Dahl salt-sensitive (DS) rats. Furthermore, CM significantly attenuated proteinuria even before it exerted BP lowering effect, suggesting that some SPs are involved in glomerular injuries independently of BP. Recently, it was reported that plasminogen filtered through damaged glomeruli was activated to plasmin by mRNA expressed on the surface of podocytes, and that plasmin could directly cause podocyte injuries. We conducted this study to identify SPs with common factors associated with glomerular injuries and to explore therapeutic effects of SP inhibition on glomerular injuries in salt-sensitive hypertension.

Methods: Four-week-old male DS rats were divided into following three groups: control group (0.3% NaCl, high-salt (HS) group (8% NaCl diet), and HS+CM group (HS+0.1%CM diet). After syste BP measurement and 24h urine collection were performed, rats were sacrificed at day 7. SP activities were evaluated by zymography.

Results: HS group did not develop hypertension but displayed significant proteinuria at day 7, which was attenuated in HS+CM (Urine TP (mg/day), control 4.0±1.17, HS 4.2±1.3±1.7±6.3). CM did not mitigate glomerular hyperfiltration reflected by increased creatinine clearance (Ccr) with salt loading (Ccr (mL/h); control 0.3±0.1, HS 0.8±0.1, HS+CM 0.8±0.2). Urinary plasmin activation was induced by HS, which was substantially inhibited by HS+CM. Furthermore, CM also suppressed albuminuria as early as at day 1.2 even when any apparent activation of SPs was not detected in urine.

Conclusions: Our current study indicates that plasmin and other unknown SPs would be involved in the pathogenesis of glomerular injuries, suggesting that SP inhibition could be a new strategy for the treatment of renal injuries in salt-sensitive hypertension.
Hypertension: Basic and Experimental - Treatment and Mechanisms

SA-PO1087
PGE2 EP1 Receptors Contribute to Hypertensive Injury in Mouse Kidney

Joe Ghoseein, Rania Nas rallah, Alex Gutso, Richard L. Hebert.
University of Ottawa, Ottawa, ON, Canada.

Background: Prostaglandin E2 (PGE2) derived from COX-2 is upregulated in hypertension and diabetes, and we previously reported that the PGE2 EP1 receptor is involved in glomerular injury and proteinuria in the diabetic mouse. We hypothesize that EP1 contributes to renal injury in hypertension.

Methods: Using a genetic model of hypertension, where TTR/Ren mice overexpress renin (Htm), we studied the effects of EP1 deletion using 4 mouse groups at 24 weeks of age: wildtype (WT), EP1+/−, Htm, and HtmEP1+/−. All male mice were placed in metabolic cages, and 24 hour urine was collected. Urine osmolality was determined by freezing point depression and albumin levels were measured by ELISA. Glomerular filtration rate was determined by FITC-Imulin clearance, and systolic blood pressure was measured by tail-cuff plethysmography. Kidneys were fixed and PAS stained for pathological analysis of glomerular, mesangial, and capillary areas using ImageJ photo analysis software.

Results: Urine osmolality was decreased by 33% in Htm mice compared to WT mice, and further decreased by 17% in HtmEP1+/− mice compared to Htm mice. Urine albumin was elevated by 10 fold in Htm mice compared to WT mice, and further increased in HtmEP1+/− mice by 2.5 fold compared to Htm mice. Blood pressures were elevated by 25mmHg in Htm mice compared to WT mice, but this hypertensive state was unaffected by EP1 deletion. FITC-imulin clearance was unchanged in Htm mice, but reduced by 50% in HtmEP1+/− mice compared to WT. Pathological analysis revealed that mesangial cell numbers were unchanged in Htm mice, but stimulated 1.5 fold in both groups lacking EP1 receptors compared to WT. Glomerular and mesangial volume were increased by 1.25 fold and 1.5 fold in Htm mice compared to WT respectively, and mesangial volume was significantly higher in HtmEP1+/− mice compared to Htm mice, reaching 1.9 fold of WT. In contrast, capillary volumes were unchanged in Htm mice, but significantly reduced by 50% in EP1−/− and HtmEP1+/− mice compared to WT mice.

Conclusions: Taken together, the data suggest that the EP1 receptor mediators glomerulomegaly and prevents hypertension induced glomerular injury, independent on effects of blood pressure.

Funding: Government Support - Non-U.S.

SA-PO1088
PGE2 EP1 Receptor Regulates Renal Aquaporin and Sodium Transporter Expression and Inhibits an AQP Dependent Water Reabsorption and Sodium Transport in Mouse Collecting Duct Rania Nasrallah,1,3 Joe A. Zimpelmann,1,3 Jamie Ghosein,1,3 Chris R. Kennedy,1 Kevin D. Burns,2,3 Richard L. Hebert.1,3 Kidney Research Centre, Ottawa, ON, Canada; The Ottawa Hospital - Riverside Campus, Ottawa, ON, Canada; 1University of Ottawa, Ottawa, ON, Canada.

Background: Prostaglandin E2 (PGE2) regulates glomerular hemodynamics, renin secretion, and tubular transport. The purpose of this study was to determine the contribution of PGE2 EP1 receptors to salt and water homeostasis, given that we previously reported no effect on blood pressure in mice lacking EP1.

Methods: Male FVB EP1−/− mice were bred with hypertensive TTR/Ren mice (Htm) to evaluate kidney aquaporins, sodium transporters, and transport function at 8 wks of age in 4 groups: wildtype (WT), EP1+/−, Htm, and HtmEP1+/−. Total RNA was isolated from renal cortex and medulla, and cDNA was synthesized using proximal tubules (PT), thick ascending limb (TAL), and cortical (CCD) and inner medullary collecting ducts (IMCD) for quantitative PCR analysis. CCD and IMCD were microdissected for in vitro perfusions to determine tubular fluid reabsorption in response to PGE2 and vasopressin (AVP), and transepithelial voltage in CCD stimulated with PGE2. CCD were also pre-treated with amiloride (ENaC inhibitor) or hydrochlorothiazide (pembdin inhibitor) prior to PGE2 stimulation.

Results: Cyclooxygenase (COX)-1 and microsomal PGE2 synthase mRNA were increased and COX2 was decreased in mice lacking EP1, along with increases in EP3 and reductions in EP2 and EP4 mRNA throughout the nephron. PT sgfl, NHE3, and AQP1 were increased in HtmEP1+/−, but sgfl2 was increased in EP1−/− mice. TAL NKCC2 was reduced in the cortex but increased in the medulla. IMCD AQP1 and ENaC were increased, but AVP V2 receptor and urea transporter-1 were reduced in all mouse groups compared to WT. In WT and Htm mice, PGE2 inhibited AVP-stimulated water transport in the IMCD, but not in EP1−/− or HtmEP1+/− mice. Similarly, PGE2 depolarized the transepithelial voltage (inhibited sodium transport) in mouse CCD via EP1 in WT and Htm mice, but not in mice lacking EP1; both amiloride and hydrochlorothiazide attenuated the inhibitory response of PGE2.

Conclusions: Taken together, the data suggest that EP1 regulates renal aquaporins and sodium transporters, and EP1 plays a major role in attenuating AVP-mediated water transport and inhibiting sodium transport in the mouse collecting duct. The inhibition of sodium transport in response to PGE2 is mediated by both ENaC and pendrin-dependent pathways.

Funding: Government Support - Non-U.S.

SA-PO1089
Previous Aerobic Exercise Increases VO2 Peak in Rats with Kidney Chronic Disease Wesley Silva,1 Rafael Luiz,1 Alexandre Saud,1 Natalia Reinecke,1 Samuel T. Filho,2 Kleiton A. Silva,1 Rodolfo R. Rampaso,1 Luciana Jorge,1 Nestor Schor.1 1Universidade Federal de São Paulo, São Paulo, Brazil; 2Universidade Federal de São Paulo, Sao Paulo [SP], Brazil; 1University of Missouri, Columbia, AL.

Background: Chronic Kidney Disease (CKD) contributes to harm the renal and cardiovascular function. The Aerobic exercise training have been used widely to modulation of renal and cardiovascular environment, reducing cardiovascular risk-associated diseases. Aim: To evaluate the effects of the previous exercise training (PET) on oxygen consumption peak (VO2 peak) and renal function of rats submitted to nephrectomy 5/6.

Methods: Wistar rats (n=5), were randomly divided in four groups: Exercise + NX + exercise (ENXE), exercise + NX + sedentary (ENXS), sedentary + NX + sedentary (SNXS). Treadmill exercise was performed at 40 to 60% of VO2 peak for 8 weeks. NX surgery was performed on 4th week of exercise training protocol.

Results: The VO2 peak and exercise capacity were improved in NXS and NXEE groups compared to NNXS. Exercise training decreased proteinuria, although it was not observed changes in creatinine clearance, serum creatinine and urinary volume. Systolic arterial pressure decreased in NNXS when compared to NNXS and NXEE.

Conclusions: The data suggest that exercise training may be applied to patients with CKD, especially when were effective to prevent death in NNXS and NXEE and could be an addition strategy to treatment of CKD patients.

SA-PO1090
Chronic Treatment with Tadalafil Prevented Renal Dysfunction and Hypertension Caused by High Salt Intake and Preserved Serum SDF-1α Levels in Dahl Salt-Sensitive Rats Natsumit Tomita,1 Yuji Hotta,1 Aya Nakiti-Ito,2 Tomoya Kataoka,2 Yasuhiro Maeda,3 Satoru Takahashi,3 Kazunori Kimura.1 1Hospital Pharmacy, Graduate School of Pharmaceutical Sciences, Nagoya City University, Nagoya, Japan; 2Experimental Pathology, Graduate School of Medical Sciences, Nagoya City University, Nagoya, Japan; 3Clinical Pharmaceutics, Graduate School of Medical Sciences, Nagoya City University, Nagoya, Japan.

Background: Phosphodiesterase inhibitors (PDE5is) are reported to prevent renal damage and/or blood pressure (BP) elevation in an ischemic-reperfusion model. It is uncertain whether PDE5is are effective against salt sensitive hypertension; thus, we investigated the effects of a PDE5i, tadalafil, on hypertension and renal dysfunction induced by high salt intake using an animal model.

Methods: Eight-week-old male Dahl salt-sensitive rats were divided into three groups (n=6); normal salt (NS), high salt (8% NaCl–included diet; HS), and high salt and tadalafil treatment (10 mg/kg/day, p.o; Tad). Blood urea nitrogen, serum creatinine (SCr), creatinine clearance (CCr), albuminuria, and BP were measured at 0, 4, and 8 weeks. The kidney was extracted at 8 weeks and PAS staining was performed. Serum stomal cell-derived factor 1 (SDF-1α)-t level, which is associated with the repair of vascular endothelial injury, was also evaluated at the 8 week timepoint.

Results: BP and proteinuria significantly increased in the HS group (P<0.01), while tadalafil treatment attenuated proteinuria and BP elevation at 8 weeks (P<0.01 vs. HS) (Fig.1). While SCr did not increase (P<0.01), although they were suppressed in the Tad group (P<0.01 vs. HS) (Fig.1). While SCr did not increase in the HS group (P<0.01), although they were suppressed in the Tad group (P<0.01 vs. HS). Serum SDF-1α level significantly decreased (P<0.01 vs. HS). The data suggest that exercise training may be applied to patients with CKD, especially when were effective to prevent death in NNXS and NXEE and could be an addition strategy to treatment of CKD patients.

Conclusions: Tadalafil may be an effective treatment for salt-sensitive hypertension, arteriosclerosis, and renal dysfunction and maintains SDF-1α level.

Funding: Government Support - Non-U.S.

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

958
Hypertension: Basic and Experimental - Treatment and Mechanisms

SA-PO1093

Effects of Neuronal CGRP on Renal Afferent Peptidergic Neurons
Kristina Rodionova,1,2 Giulia Raschke,1 Tilmann Ditting,2 Martin Hindermann,3 Christian Ott,2 Roland E. Schmieder,1 Kerstin U. Amann,1 Roland Veelken.2
1Dept. of Nephrology, Friedrich-Alexander-University Erlangen, Erlangen, Germany; 2Paracelsus Medical University Nuremberg, Nuremberg, Germany; 3Department of Nephroontology, Friedrich-Alexander Universitat Erlangen, Erlangen, Germany.

Background: Although release of the proinflammatory vasodilator CGRP from peptidergic afferent nerves is generally unquestioned, the matter is far less investigated with respect to afferent renal innervation that is said to be involved in sympathetic control and blood pressure regulation. Furthermore, it is not known in how far released neurogenic CGRP will affect afferent innervation in vivo. Hence we wanted to test the hypothesis that CGRP elicits action potential generation related to TRPV1 receptor stimulation in cultured neurons with afferent projections from the kidney in vivo.

Methods: Cultured dorsal root ganglion neurons (TH1-L-2) of rats with renal afferents in vivo were investigated in current clamp mode to assess action potential generation or in voltage clamp mode to investigate inward currents during stimulation of TRPV1 receptors with capsaicin (10-6 to 10-5 M) and voltage (and/or) administration of CGRP (0.5 umol).

Results: More than 90 DRG neurons with renal afferents were tested. Addition of CGRP did not change action potential generation or inward currents. Proton stimulation (pH 6) of TRPV1 markedly increased long-term inward currents (baseline -136,7 +/- 33,7 pA, p<0,05, mean +/- SEM). The co-stimulation of neurons with CGRP and protons (pH 6) and CGRP led to an impairment of sustained inward current as compared to proton stimulation alone (baseline -136,7 +/- 33,7 pA, p<0,05, mean +/- SEM). Baseline CGRP release of renal slices (2.5 to 6 pg/mg) increased significantly after TRPV1 receptor stimulation (on average 21+4 pg/mg CGRP).

Conclusions: In contrast to our hypothesis CGRP could not elicit action potentials in afferent neurons related to the kidney but even impaired electric currents in general after TRPV1 receptor stimulation. Hence, renal CGRP secretion from peptidergic afferent nerves might decrease further neuronal CGRP release.

Funding: Government Support - Non-U.S.

SA-PO1094

Voluntary Exercise Decreases Blood Pressure, Angiotensin II, and Aldosterone without Changing Glomerular Filtration Rate in Two-Kidney One-Clip Hypertensive Rats
Brian M. Waldman,1 Robert A. Augustyniak,2 Haiping Chen,1 Noreen F. Rossi,1,2 Wayne State University, Detroit, MI; 1John D. Dingell VAMC, Detroit, MI.

Background: Voluntary dynamic exercise promotes sympathoinhibition and decreases blood pressure in two-kidney one-clip (2K1C) rats, a model of renovascular hypertension. Renal sympathetic nerves increase renin secretion and tubular sodium (Na+) reabsorption. We hypothesized that daily spontaneous wheel running exercise by 2K1C rats will decrease mean arterial pressure (MAP), plasma angiotensin II (Ang II) and aldosterone (Aldo), and normalize urinary Na+ and potassium (K+) excretion independent of glomerular filtration rate (GFR).

Methods: Five week-old male Sprague Dawley rats underwent sham clipping (Sham) or right renal artery clipping (2K1C). Rats were randomly assigned to standard caging (SED) or cages with access to running wheels (EX). After 12 weeks, rats were assigned to 1) collection of aortic blood for measurement of Ang II and Aldo or 2) assessment of urinal clearances and excretory function.

Results: Running distances were comparable in both EX groups. MAP was lower in 2K1C EX vs 2K1C SED rats (191±4 vs 196±2 mmHg, P<0.05). Elevated plasma Ang II in 2K1C SED rats (187±4±36 fmol/ml) was lower in 2K1C EX rats (48±9.7±3 fmol/ml, P<0.05) which did not differ from Sham SED or Sham EX rats (29±8±1 and 47±3±7 fmol/ml). Aldo levels paralleled those of Ang II. Clipped kidney weights were significantly lower in both 2K1C groups (P<0.05), but GFR and urine flow rates were no different from right and left kidneys among the four groups. Total and fractional Na+ excretion were higher from the unclipped kidney compared to the clipped kidney in 2K1C SED rats. However, in Sham rats (P<0.05). Values in 2K1C EX rats were similar to the Sham groups. Total and fractional K+ excretion was higher from the unclipped kidney of 2K1C SED rats (P<0.05); results of exercise paralleled those of Na+ excretion.

Conclusions: These findings show that voluntary dynamic exercise, known to promote renal sympathoinhibition, lowers blood pressure and decreases plasma Ang II and Aldo levels in the 2K1C model of renovascular hypertension without deleterious effects on GFR. The effects on Na+ excretion underscore the impact of pressure natriuresis
despite elevated plasma Ang II and Aldo in sedentary 2K1C rats. In contrast, K+ excretion appears to be primarily regulated by circulating Aldo levels and distal Na+ delivery.

Funding: Veterans Affairs Support

SA-PO1095
Phosphoinositide-3 Kinase γ Regulates Inflammation and Renal Fibrosis in Angiotensin II-Induced Hypertension Changsong, An1,2, Sandhya S. Thomas,1,2 Zhaoysong Hu,1 William E. Mitchell,1,3 Yanlin Wang,1,2 1Baycollage of Medicine, Houston, TX; 2Michael E. DeBakey FA Medical Center, Houston, TX.

Background: We have recently shown that CXCL16/CXCR6 axis plays a critical role in recruiting inflammatory cells and bone marrow-derived fibroblasts into the kidney resulting in renal injury and fibrosis. However, the underlying signaling mechanisms are not known. In the present study, we examined the role of phosphoinositide-3 kinase γ (PI3Kγ) in recruitment of inflammatory cells and bone marrow-derived fibroblasts into the kidney and development of renal injury and fibrosis in an experimental model of hypertension.

Methods: Wild-type (WT) and PI3Kγ knockout (KO) mice were treated with angiotensin II via subcutaneous osmotic minipumps at 1500 ng/kg/min for 4 weeks following uninephrectomy. All the mice were given 1% NaCl in drinking water ad lib. Blood pressure, kidney function, proteinuria, and renal histology were evaluated. Immuno-staining was performed to examine the number of inflammation cells and myofibroblasts in the kidney. Proinflammatory molecule expression was assessed by real-time RT-PCR. Renal fibrosis and extracellular matrix protein production were determined by Sirius red staining, immuno-staining and Western blot. Transwell migration assay was performed to determine the role of PI3Kγ in the regulation of cell migration in vitro.

Results: WT and PI3Kγ KO mice had virtually identical blood pressure at baseline. Angiotensin II treatment led to an increase in blood pressure that is similar between WT and PI3Kγ KO mice. Compared with WT mice, PI3Kγ KO mice were protected from angiotensin II-induced renal dysfunction and injury and developed less proteinuria. PI3Kγ deficiency suppressed bone marrow-derived fibroblast accumulation and myofibroblast formation in the kidney and inhibited total collagen deposition and ECM protein production in the kidney in response to angiotensin II. PI3Kγ deficiency inhibited infiltration of F4/80+ macrophages and CD3+ T cells into the kidney and reduced gene expression levels of proinflammatory cytokines in the kidney following angiotensin II treatment. Inhibition of PI3Kγ with AS605240 suppressed CXCL16-induced Akt activation and monocye migration in vitro.

Conclusions: Our results indicate that PI3Kγ plays a pivotal role in the development of hypertensive kidney injury and fibrosis through regulation of macrophage and T cell infiltration and bone marrow-derived fibroblast accumulation.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO1096
A Novel Approach for Evaluation of Cleavage of Angiotensin Peptides by Their Angiotensinase Partners Jin Wysocki, Timlan Müller, Pan Liu, Jing Jin, Daniel Batlle. Division of Nephrology and Hypertension, The Feinberg School of Medicine, Northwestern University, Chicago, IL.

Background: Angiotensin I-7 formation from Ang II (1-8) occurs via a release of a single c-terminal phenylalanine (Phe). ACE2 and prolylendopeptidase (PEP) are angiotensinases known to cleave Phe from Ang II to form Ang I-7. To capture phenylalanine products of this biochemically and functionally active degrading enzyme, such as Ang III (2-8), we used a new quantitative fluorimetric assay which detects the c-terminal Phe cleavage from Ang II in kidney lysates.

Methods: To test the involvement of renin in the BP regulation of the Dahl SS rats, 9 week old Ren−/− rats and their wild type littermates were kept on 0.4% NaCl diet since weaning (normal salt, NS), and then challenged with sodium deficient (SD, 0.01%) or high salt (HS, 4% NaCl) diets for 11 days. BP was recorded via telemetry, and kidney function and tissue damage were assessed.

Results: On NS diet Ren−/− rats have a significantly lower MAP compared to littermates (65.9 ± 2.1 vs 121.9 ± 1.9 mmHg). After a HS diet was introduced, we observed a very fast raise in MAP in the Ren−/− rats (AMAP was 60.4 ± 7.1 mmHg over a 5 day period, compared to 5 ± 0.4 mmHg in the littersmates). In the Ren−/− group HS diet caused mortality within 8 days, which was not observed in the littersmates. SD diet did not affect BP and survival rates in either group. 24 hr urinary output was increased in the wild type littersmates on HS (not measured in the Ren−/− group due to mortality). However, in all SD diet fed groups urinary output was reduced (15.7 ± 1.7 vs 2.5 ± 0.2 ml/100g before diet switch, and 1.9 ± 0.7 vs 4.8 ± 0.9 ml/100g on SD diet (Ren−/− vs littersmates)). On NS diet GFR was found to be lower in the Ren−/− rats (0.18 ± 0.03 ml/ min/100g vs 0.54 ± 0.04 in littersmates), and HS diet induced an increase in GFR in the littersmates on day 10, whereas SD diet did not affect GFR in either group. No difference was found in electrolyte excretion between groups fed a SD diet. Histological analysis revealed exacerbated damage to the hearts and kidneys of the Ren−/− rats fed a SD diet compared to wild type littersmates.

Conclusions: BP in the Ren−/− Dahl SS rat increases in response to salt intake, which suggests an involvement of the non-renin components in this mechanism; however, Ren−/− animals are able maintain homeostasis when challenged a SD diet. These data open new avenues to understanding the role of RAAS in SS hypertension.

Funding: NIDDK Support, Other NIH Support - NHLBI

SA-PO1097
Renin-Independent Blood Pressure Development in Dahl Salt-Sensitive Rats Daría Hatovskaya,1 Vladislav Levchenko,2 Denisha R. Spieres,2 Tengis S. Pavlov,1 Alexander Staruschenko2,2 ‘Henry Ford Health System, Detroit, MI; 2Medical College of Wisconsin, Milwaukee, WI.

Background: RAAS is considered to be the central regulator of water and salt homeostasis; angiotensin receptors’ and/or ACE inhibitors are widely employed to control blood pressure (BP) in humans. Here we used renin knockout (Ren−/−) rats created on the Dahl Salt-Sensitive (SS) rat background to study renin-independent BP development, these rats exhibit polyuria, reduced weight and lower mean arterial pressure (MAP) compared to wild type controls.

Methods: To test the involvement of renin in the BP regulation of the Dahl SS rats, 9 week old Ren−/− rats and their wild type littermates were kept on 0.4% NaCl diet since weaning (normal salt, NS), and then challenged with sodium deficient (SD, 0.01%) or high salt (HS, 4% NaCl) diets for 11 days. BP was recorded via telemetry, and kidney function and tissue damage were assessed.

Results: On NS diet Ren−/− rats have a significantly lower MAP compared to littermates (65.9 ± 2.1 vs 121.9 ± 1.9 mmHg). After a HS diet was introduced, we observed a very fast raise in MAP in the Ren−/− rats (AMAP was 60.4 ± 7.1 mmHg over a 5 day period, compared to 5 ± 0.4 mmHg in the littersmates). In the Ren−/− group HS diet caused mortality within 8 days, which was not observed in the littersmates. SD diet did not affect BP and survival rates in either group. 24 hr urinary output was increased in the wild type littersmates on HS (not measured in the Ren−/− group due to mortality). However, in all SD diet fed groups urinary output was reduced (15.7 ± 1.7 vs 2.5 ± 0.2 ml/100g before diet switch, and 1.9 ± 0.7 vs 4.8 ± 0.9 ml/100g on SD diet (Ren−/− vs littersmates)). On NS diet GFR was found to be lower in the Ren−/− rats (0.18 ± 0.03 ml/min/100g vs 0.54 ± 0.04 in littersmates), and HS diet induced an increase in GFR in the littersmates on day 10, whereas SD diet did not affect GFR in either group. No difference was found in electrolyte excretion between groups fed a SD diet. Histological analysis revealed exacerbated damage to the hearts and kidneys of the Ren−/− rats fed a SD diet compared to wild type littersmates.

Conclusions: BP in the Ren−/− Dahl SS rat increases in response to salt intake, which suggests an involvement of the non-renin components in this mechanism; however, Ren−/− animals are able maintain homeostasis when challenged a SD diet. These data open new avenues to understanding the role of RAAS in SS hypertension.

Funding: NIDDK Support, Other NIH Support - NHLBI

SA-PO1098
Thymosin β4 Deficiency Accelerates Renal Fibrosis and Damage in Angiotensin II Hypertension Nitin Kumar, Tang-Dong Liao, Cesar A. Romero, Mani Maheshwari, Oscar A. Carretero. Henry Ford Hospital, Detroit, MI.

Background: Angiotensin-II (Ang-II)-induced hypertension is associated with renal fibrosis and damage. Thymosin β4 (Tβ4) regulates cell morphometry, inflammation and fibrosis in several organs and administration of exogenous Tβ4 is protective in diabetic nephropathy. However, role of endogenous Tβ4 in hypertension-induced renal damage is unknown. We hypothesized that, loss of Tβ4 accelerates renal fibrosis and damage in Ang-II hypertension.

Methods: Tβ4 knockout (Tβ4 KO) and wild-type (WT) C57BL/6 mice (n=6-14) were infused continuously for six-weeks with either Ang-II (980 ng/kg/min) or vehicle via osmotic minipumps. Blood-pressure was measured weekly by non-invasive tail-cuff method. Urinary albumin (24 hours urine collection) and renal cortex collagen were measured by ELISA and hydroxyproline assay, respectively. Renal cortex expressions of neprin and α-smooth muscle actin (α-SMA) were evaluated by western blot.

Results: All the results are presented in table 1. In Ang-II infusion, systolic blood-pressure was not different between WT and Tβ4 KO mice (Table 1). Interestingly, urinary albuminuria was significantly higher in Tβ4 KO mice compared to WT mice by Ang-II infusion. Tβ4 is highly expressed in the glomeruli along with the high expression of neprin, an important protein in the filtration barrier of the kidney. In Ang-II infusion, neprin protein expression was greatly reduced in mice deficient of Tβ4, suggesting that loss of neprin is one of the mechanisms for elevated urinary albumin in Tβ4 KO mice. Additionally, renal fibrosis in the cortex was higher in Tβ4 KO mice and this was accompanied by elevated profibrotic α-SMA protein expression. Susceptibility to Ang-II induced kidney damage in Tβ4 KO mice may be associated with the observed high mortality rate in these mice.

Conclusions: These data indicate that, in Ang-II hypertension, loss of endogenous Tβ4 caused significant renal fibrosis, damage and mortality, suggesting renal protective role of Tβ4.

Funding: Other NIH Support - NHLBI
SA-PO1099
Aldosterone Breakthrough Does Not Affect Central Hemodynamics

Andrew Beenken,1 Andrew S. Bombac,1 Columbia University, New York, NY; 2New York Presbyterian/Columbia University, New York City, NY.

Background: Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are widely used in patients with congestive heart failure (CHF) and chronic kidney disease (CKD), but up to 40% of patients on these agents experience aldosterone breakthrough, with aldosterone levels rising above pre-treatment levels after 6-12 months of RAAS blockade. Aldosterone breakthrough has been associated with worsening CHF and CKD, yet the pathophysiology remains unclear. While aldosterone breakthrough has not been associated with elevated peripheral blood pressure (PBP), no studies have yet evaluated the effect of breakthrough on central blood pressure (CBP).

Methods: In this cross-sectional study, 19 subjects with well-controlled PBP (<140/90), on stable doses of ACEi/ARB for >1 year, had aldosterone levels checked and CBP parameters measured using the SphygmoCor® system. The CBP parameters of subjects with or without breakthrough, defined as serum aldosterone >15 ng/dL, were compared.

Results: Of 19 subjects, 6 had breakthrough with a mean aldosterone level of 33.8 ± 14.5 ng/dL. Between subjects with and without breakthrough, defined as serum aldosterone >15 ng/dL, there was no significant difference between subjects with and without breakthrough in any of the CBP parameters (mmHg), including CBP (92 ± 16 vs. 95 ± 8, p=0.5), central pulse pressure (40 ± 10 vs. 34 ± 11, p=0.2), augmentation pressure (10 ± 5 vs. 7 ± 6, p=0.3), and augmentation index (16 ± 8 vs. 16 ± 12, p=0.4).

Conclusions: We found no correlation between aldosterone breakthrough and CBP. Accordingly, the clinical impact of aldosterone breakthrough on CKD and CHF likely depends on its non-genomic, pro-fibrotic, and pro-inflammatory effects rather than its regulation of extracellular volume.

SA-PO1100
Alfa-Adducin and Lanosterol Synthase Interaction Cause Nephrolithiasis

John Lorena,1 Simone Delli carpini,1 Elena Brioni,1 Simona Dell’Omo,2 Marco Citterio,1 Laura Cimini,1 Maria Chiara Montana,1 Stefano Lanzani,1 Chiara Maggioni,1 Laura Zagato,1 Elisabetta Messaggio,1 Lorenza Citerio,2 Marco Simonetti,3 Elena Brioni,1 Simona Delli carpini,1 John Hamlyn,4 Paolo Manunta,1 HSR-Nefrologia, Milano, Italy; 2Ospedale San Raffaele, Milano, Italy; 3San Raffaele Hospital, Milano, Italy; 4San Raffaele Scientific Institute, Milano, Italy; 5University of Maryland, Baltimore, Baltimore, MD; 6Università San Raffaele, Milano, Italy; 7Università Vita Salute San Raffaele, Milano, Italy; 8Università Vita-Salute - Ospedale San Raffaele, Milano, Italy; 9ospedale San Raffaele, Milano, Italy.

Background: The study of genes involved in the development of renal damage and salt sensitive hypertension (SSH) is still unknown. Impaired renal function is considered to depend on its non-genomic, pro-fibrotic, and pro-inflammatory effects rather than its regulation of extracellular volume.

Methods: Acute saline load (NaCl 308 mEq/2 h e.v) was performed in 701 NHP. Under baseline conditions NHP carriers of the genotype LSS AA (n = 57, 81.2 ± 15 pMol/L) and were not stimulated by HS diets in obese TH mice (comparing to B6 mice, Figure 1). In the kidney cortex tissue, the Na/K-ATPase signaling (c-Src and ERK1/2) was assessed. Study 2; Urinary sodium excretion after intraperitoneal sodium loading was reduced in WT given Fr compared with that of the control WT. In KHK KO, that reduction was not observed. Pathological analysis was done, and renal and jejunal KHKs and NHE3 (sodium-hydrogen exchanger 3) expressions were assessed. Study 2; To investigate the effect of fructose intake on renal sodium reabsorption without intestinal absorption, control WT and KHK KO mice and those fed CD and Fr for 5 weeks were administered intraperitoneally with 1.5 ml of normal saline, then urine was collected 6 hours later.

Results: Study 1; KHK was colocarized immunohistochemically with NHE3 in proximal tubular cells in WT. Combination of Fr and Fr for 5 weeks induced the elevation of BP with the decrease of sodium excretion and the increase of renal expression of KHK-C and NHE3 in WT, but not in KHK KO. WT fed Fr did not show the elevation of BP nevertheless of higher amount of sodium intake than WT fed HS. Urinary sodium excretion after intraperitoneal sodium loading was reduced in WT given Fr compared with that of the control WT. In KHK KO, that reduction was not observed, and renal NHE3 expression was lower than WT.

Conclusions: These results suggest that fructose metabolism by KHK is involved in the development of salt-sensitive hypertension through increases of renal sodium reabsorption by NHE3.

SA-PO1102
Na/K-ATPase Signaling as an Amplifier of Oxidative Stress Contributes to the Increased Salt Sensitivity of Obese Hypertension

Manjula Mongia,1 Laura Caglio,2 Ellen Brown,3 Simona Delli carpini,1 John Hamlyn,4 Paolo Manunta,1 HSR-Nefrologia, Milano, Italy; 2Ospedale San Raffaele, Milano, Italy; 3San Raffaele Hospital, Milano, Italy; 4San Raffaele Scientific Institute, Milano, Italy; 5University of Maryland, Baltimore, Baltimore, MD; 6Università San Raffaele, Milano, Italy; 7Università Vita Salute San Raffaele, Milano, Italy; 8Università Vita-Salute - Ospedale San Raffaele, Milano, Italy; 9ospedale San Raffaele, Milano, Italy.

Background: Acute saline load (NaCl 308 mEq/2 h e.v.) was performed in 701 NHP (age 44.95 ± 9.61 years, male 568, female 133), where functional and hormone renal parameters were tested.

Results: Under baseline conditions NHP carriers of the genotype LSS AA (n = 57, 114.8 ± 3.8 ml/min) have a significantly reduced GFR (p = 0.039) compared to homozogous LSS CC subjects (126.08 ± 1.6 ml/min). After acute saline test both are able to increase the filtrate. Carriers of the LSS AA genotype show a slight increase in EO from 231 ± 29 to 242 ± 35, compared to LSS CC, where instead a significant (p=0.05) reduction is observed from 252 ± 22 to 215 ± 15 pMol/L. The analysis of gene*gene interactions demonstrates that NHPs carrying mutated GT ADD1 and homozygous for LSS C variants excreted the sodium load more rapidly than their wild type ADD1*LSS polymorphism counterparts (Fig 1).

Conclusions: The results of this work demonstrate: First, patients with LSS AA genotype have a reduced glomerular filter under basal conditions; second, LSSAA should be define EO non modulator, since the are not able to decrease EO; third, the ADD1*LSS interaction may identify those NHPs with exaggerate natriuresis after saline load.
increase in 5/6Nx rats.

Conclusions: Na-K-ATPase signaling activation as a commonly featured characteristic in obese mice and rat was implicated in the increased salt sensitivity of obese hypertension. Further studies targeting Na-K-ATPase signaling will explore the potential nodes for therapeutic intervention and provide new targets for the required pharmacologic therapy more effective, minimizing the need for medications.

SA-PO1103

Loss of Urine Concentration and Subsequent Dehydration Characterizes Hypertension in Rats with Chronic Failure

Kento Kitada,1 Adriana Marton,2 Steffen Daul,3 Yuhua Zhang,4 Tetyana Pedchenko,1 Yan Zhao,1 Janet D. Klein,1 James L. Bailey,1 Nada Cordasci,1 Karl F. Hilgers,1 Jeff M. Sands,1 Akira Nishiyama,1 Jens Titze,2

1 Department of Clinical Pharmacology, Vanderbilt University Medical Center, Nashville, TN; 2Department of the Center of Pharmacology, Universität Erlangen, Nürnberg, Germany; 3Emory University Renewable Energy Division, Atlanta, GA; 4Emory University School of Medicine, Atlanta, GA; 5Kagawa University, Kagawa, Japan; 6Kagawa University Medical School, Kita-Gun, Japan; 7University Hospital of Erlangen, Erlangen, Germany; 8University of Erlangen, Erlangen, Germany; 9Vanderbilt University, Nashville, Romania; 10Vanderbilt University Medical Center, Nashville, TN.

Background: The pressure-natriuresis concept suggests that blood pressure-driven increase in renal salt excretion in parallel normalizes the extracellular volume (ECV). In contrast, the present study and recent work have revealed that hypertension in 5/6Nx rats is characterized by body water loss due to an inability to concentrate the urine.

Methods: We investigated urine flow, osmolyte excretion, urine concentration, arterial blood pressure, and hepatic and extracellular hepatic generation in 5/6Nx rats (n=23; renal mass ablation) and sham-operated (n=10) Sprague-Dawley rats. Results: 7 weeks after renal mass ablation, 5/6Nx rats increased their arterial blood pressure by 24.4±20.1 mmHg (P<0.05). Hypertensive 5/6Nx rats showed dehydration with a 13.8±7.0 mOsm/kg increase in plasma osmolality (P<0.001) and reduced ability to concentrate the urine (urine osmolality reduced by -771±590 mOsm/kg; P<0.001). In anesthetized animals, we found a direct relationship between 2Na+2K+Urea osmolyte excretion and urine flow (r=1.24±0.3; R2=0.75), indicating osmotic diuresis. 5/6Nx rats showed pronounced 2Na+2K+Urea osmolyte excretion (+13.2±5.1 mOmol/d) with predominant urea loss (+13.4±4.9 mmol/d) which increased the urine volume by +19.5±7.4 ml/d (all P<0.001) and was paralleled by only discrete Na- loss and K- retention. In conscious 5/6Nx rats, the pressure-driven increase in arterial blood pressure was accompanied with a +37.9±15.1 ml/d increase in free-water clearance, indicating renal water loss. The renal urea leak resulted in compensatory increases in urine osmolyte generation in skeletal muscle (arginase activity: +8.7±6.7 units/kg; P<0.05; urea content: +1.9±1.2; P<0.01) in 5/6Nx rats.

Conclusions: Hypertension in a rat model of chronic renal failure is characterized by urea-driven loss of the renal concentration mechanism, which leads to increased renal water loss and extracellular volume contraction. Our findings indicate that sodium retention with subsequent volume overload is not the underlying cause of blood pressure increase in 5/6Nx rats.

SA-PO1104

Intrarenal High Salt Administration Causes Tonic Inhibition of Renal Sympathetic Nerve Activity (RSNA)

Martin Hindemann,1 Kristina Rodionova,1 Amelie Dietz,1 Tilman Dittrig,2 Christian Ott,1 Roland E. Schmieder,1 Kerstin U. Amann,1 Roland Veelken,1,2 Dept. of Nephrology, Friedrich-Alexander-University Erlangen, Erlangen, Germany; 1Paracelsus Medical University Nuremberg, Nuremberg, Germany; 1Dept of Nephropathology, Friedrich-Alexander-University Erlangen, Erlangen, Germany.

Background: Afferent renal nerve fibers from the kidney directly counterregulate salt sensitive blood pressure increases by decreasing renal sympathetic nerve activity. We recently reported on a long-lasting tonic sympatho-inhibition due to intrarenal afferent renal nerve stimulation eliciting a TRPV1 dependent neuro-humoral pathway. We wanted to test the hypothesis that sodium influences this afferent sympatho-depressor mechanism.

Methods: Groups of anesthetised SD rats (n=8) were equipped with femoral catheters (blood pressure (BP) & heart rate (HR) recording, drug application), a renal arterial catheter for intrarenal administration (IRA) of high salt (10 % NaCl, 10 µl) and a bipolar electrode for RSNA recordings. We tested whether an acute increase in renal sympathetic nerve activity in rats with high salt intake would lead to a long-lasting sympatho-depressive response. Finally, we tested whether the sodium level affects the renal sympathetic nerve activity.

Results: IRA high salt and IRA CAP decreased RSNA from baseline 4.1±0.6 µV/sec to 2.2±0.8 µV/sec (10% NaCl; p<0.05) and 3.9±0.5 µV/sec to 0.9±0.2 µV/sec (CAP, p<0.05). Suppressed RSNA in high salt groups and CAP was normalized by systemic (iv) administration of the NK1-receptor blocker RP67580 (10±15 M, 15 µl) was given. Cultured dorsal root ganglion neurons (Th1-11.2) of rats with renal affrentes were investigated in current clamp mode to assess action potential generation or in voltage clamp mode to investigate inward currents during 10 sec exposure to 4.5 % NaCl or equi-osmotic 20% mannitol. Results are given in mean±SEM.

Results: IRA high salt and IRA CAP decreased RSNA from baseline 4.1±0.6 µV/sec to 2.2±0.8 µV/sec (10% NaCl; p<0.05) and 3.9±0.5 µV/sec to 0.9±0.2 µV/sec (CAP, p<0.05). Suppressed RSNA in high salt groups and CAP was normalized by systemic (iv) administration of the NK1-receptor blocker RP67580 (10±15 M, 15 µl) was given. Cultured dorsal root ganglion neurons (Th1-11.2) of rats with renal affrentes were investigated in current clamp mode to assess action potential generation or in voltage clamp mode to investigate inward currents during 10 sec exposure to 4.5 % NaCl or equi-osmotic 20% mannitol. Results are given in mean±SEM.

Conclusions: Increased intrarenal sodium concentrations might induce long-lasting sympatho-depression via a neuro-humoral TRPV1 dependent and tachykinin mediated afferent nerve pathway from the kidney. Impairment of this sympatho-depressor mechanism could be involved in salt sensitive hypertension.

SA-PO1105

Identification of an miRNA That Regulates Sodium-Hydrogen Antiporter 1 (NHE1) Expression in the Medullary Thick Ascending Limb of a High Sodium Induced Hypertension Rat Model

Patrizia Lombardi,1 Massimo Mallardo,2 Joseph annurraj Nagoth,3 Oriana Patrazzulo,1 Giuseppe Fiune,4 Sara Damiano,5 Diego Ingroso,1 Anna Iervolino,1 Giovambattista Capasso,1 Università di Campania Luigi Vanvitelli, Naples, Italy; 1Università degli Studi di Catanzaro ?Magna Graecia?, Catanzano, Italy; 1Università degli studi della Campania, Naples, Italy; 7Department of Cardio-Vascular Medicine, Università degli studi della Campania, Naples, Italy; 8Università degli studi della Campania “L. Vanvitelli”, Naples, Italy; 9Università degli studi di Napoli “Federico II”, Naples, Italy; 10Department of Cardio-Vascular Medicine, Università degli studi della Campania, Naples, Italy.

Background: The kidney is one of the principle candidate organs involved in the etiology of essential hypertension. In particular, the medullary thick ascending limb (MTAL) of the kidney is important in maintaining acid-base balance by reabsorbing most of the filtered bicarbonate, which is not reabsorbed by the proximal tubule. Microarray expression profiling studies in humans revealed different expression profiles of microRNAs in hypertensive vs normotensive patients. In this study, we analyzed miRNA expression profiles in isolated MTAL taken from high sodium intake induced hypertensive rats (HS/D) versus their normotensive counter parts (NSD).

Methods: Male Sprague Dawley rats weighing about 185-298 g (Charles River) were allowed free access to standard rodent chow (NIH 31 diet, Ziegler Bros., Gardners, PA) and drinking solution up to the time of experiments. Control rats were fed with normal drinking water (NSD) and rats on HS in were fed with 0.28 W NaCl in drinking water (HS/D) from day 7 to day 57. Renal tubal isolation was performed following method described on 7 days after the isolation surgery. Viral Vector transduction of Renfs Hofmeister, M. V. et al (Am J Physiol Renal Physiol 2009: 296:F194-203) and the total RNAs was analyzed by genome-wide miRNAs expression profile in MTAL dissected from rats upon HS/D.

Results: We have identified seven miRNAs, involved in the onset of salt sensitive hypertension, among them one was the most strongly down-regulated. We identified the sodium-hydrogen antiporter 1 (NHE1) mRNA as a putative target of this miRNA, by in silico analysis. Our data showed that this miRNA is downregulated in the MTAL of HS/D rats while NHE1 is upregulated, we also checked whether the levels of protein NHE1 could be lowered by overexpression of the identified miRNA. To verify this hypothesis we overexpressed this miRNA in MTAL cell line, by retroviral infection, and observed a downregulation of NHE1 protein.

Conclusions: Our result indicate NHE1 as a target of the identified miRNA and that the expression of this miRNA is influenced by high sodium intake in thick ascending limbs of rats.

SA-PO1106

Reciprocal Regulation between the Renal Endothelin and Circadian Rhythm Systems

Michelle L. Gumb,1 Lauren G. Douma,2 I. Jeanette Lynch,3 Kristen Solocinski,1 Kit-yan Cheng,1 Brian D. Cain,4 Charles S. Wingo,5 University of Florida, Gainesville, FL; 5NF/SG Veterans Health System, Gainesville, FL.

Background: Mice lacking the circadian rhythm gene Per1 exhibit non-dipping hypertension in response to a high salt diet plus mineralocorticoid treatment (HS/DOCP). We recently identified that Per1 knockout (KO) mice have a renal Na handling defect involving ET-1 that contributes to non-dipping hypertension. ET-1 can mediate renal injury in salt-sensitive hypertension.

Methods: Twelve hour urine collections were made in metabolic cages to determine the night:day ratios of urine Na excretion in WT vs. Per1 KO mice in response to HS/DOCP. We assessed Per1 transcriptional activity using quantitative real time RT-PCR.

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

Underline represents presenting author.
Kidney cortex RNA was collected from WT and Per1 KO mice on control or HS/DOCP treatment at noon, the time when BP dips in WT mice but remains high in Per1 KO mice.

**Results:** WT mice exhibited a high night/day ratio of Na excretion but, Per1 KO had a significant reduction in the night/day Na excretion ratio (WT:6, KO:2; p<0.05). To explore the molecular mechanisms underlying this phenotype, we examined expression of Edn1 which encodes the peptide hormone endothelin-1 (ET-1). ET-1 mRNA levels did not change in WT in response to HS/DOCP. In contrast, Per1 KO mice exhibited increased expression of ET-1 mRNA in the renal cortex (40% increase, p<0.001). To test the hypothesis that there is reciprocal regulation between ET-1 and the molecular clock, specifically Per1, we measured Per1 mRNA expression in the kidneys of collecting duct-specific ET-1 KO mice compared to WT controls after HS/DOCP treatment. Per1 expression was reduced by 50% in the renal medulla of CD ET-1 KO mice relative to WT mice (p<0.01).

**Conclusions:** The reduced night/day ratio in urine Na excretion suggest that a renal Na handling defect may contribute to non-dipping hypertension in Per1 KO mice. Per1 appears to be a negative regulator of ET-1 expression during HS/DOCP, whereas ET-1 may play a role in the positive regulation of Per1 expression. These data indicate that reciprocal regulation between renal ET-1 and the molecular clock, specifically Per1, occurs and may constitute a new feedback loop in mineralocorticoid-sensitive renal Na handling.

Funding: NIDDK Support, Private Foundation Support

**SA-POI107**

**Dietary Sodium-Induced Changes in the Microcirculatory System of the Skin Are Associated with Blood Pressure Response in Healthy Males**


**Background:** Studies indicate that not only the kidney but also the skin microcirculation might be pivotal for a sodium-sensitive blood pressure (BP) response. While high sodium diet (HSD) is associated with reduced density of blood capillaries, animal studies showed an increment of skin lymphatic capillaries in both amount and size. We investigated sodium-induced changes in both lymphatic and blood skin microcirculation of healthy males in relation to blood pressure (BP).

**Methods:** We performed a randomized crossover study in healthy males. All subjects pursued an 8-day low sodium diet (LSD: <50 mmol Na+/day) and HSD (>200 mmol Na+/day). Diet order was randomized and time in-between diets was 1-2 weeks. After each diet, BP measurements and skin biopsies were obtained. Endothelia of blood (CD31) and lymphatic capillaries (D2-40) were identified through immunohistochemistry.

**Results:** Overall (n=12, mean age 22 years), there was no BP increase after HSD vs. LSD (mean arterial pressure (SD): 78 (5) vs. 78 (5), p=0.66). HSD increased lymphatic cross sectional surface area (p<0.01). No differences in lymphatic or blood capillary density were observed. There was a correlation between lymphatic and blood capillary density after LSD but not after HSD (fig 1a). Differences in mean arterial pressure between LSD and HSD correlated with changes in blood capillary density (fig 1b), but not with lymphatic capillary density or cross sectional surface area.

**Conclusions:** HSD is associated with skin lymphangiogenesis and a loss of correlation between the lymphatic and blood microcirculation. Blood microcirculatory changes correlate with BP response, possibly playing a role in sodium-sensitive hypertension development.

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

Underline represents presenting author.

**SA-POI108**

**Changes in Phosphorylation and Expression of Sodium Transporters in Pre-Eclampsia Detected in Urinary Exosomes**

Peter F. Mount,1,2 CHIH-CHIANG Hu,1 Marina Katerelos,1,2 Suet-Wan Choy,1 Natasha Cook,1 Amy A. Crosthwaite,1,2 Gabrielle L. Pell,1 Kathy Paizis,1,3 Susan P. Walker,1,4 David A. Power,1,4 1Austin Health, Melbourne, VIC, Australia; 2Austin health, Heidelberg, NSW, Australia; 3Mercy Health, Melbourne, Vic, NSW, Australia; 4University of Melbourne, Melbourne, VIC, Australia; 1Kidney Laboratory, Institute for Breathing and Sleep, Melbourne, VIC, Australia.

**Background:** PE (pre-eclampsia) is characterized by hypertension, vasoconstriction, proteinuria and renal sodium retention. It is unknown whether expression or phosphorylation of the distal renal tubular sodium transporters (NKCC2, NCC and EnaC) changes in women with PE.

**Methods:** A cross-sectional study of 18 PE patients, 22 normotensive pregnant women (NP) and 20 normal women (NC) was performed. Exosomes were isolated from urine by ultracentrifugation. Expression of sodium transporters was analysed by Western Blot corrected for expression of the exosome marker CD9. Statistical comparisons were made by ANOVA and a post-hoc test.

**Results:** Expression of NKCC2 was increased 1.6-fold in PE (ANOVA p=0.046, post-hoc). Phosphorylation on the SPAK/OSR1 activation site T101/105 was reduced 1.9-fold (ANOVA p=0.030; PE vs NP p=0.05) while phosphorylation of the activating PKA site T101/105 was increased 1.9-fold (ANOVA p=0.03; PE vs NP p<0.05). There was no difference in expression of the cleaved 50 kD form of gamma ENaC in PE compared to NP. There was no difference in expression of NCC but phosphorylation of the activating PKA site S130 site was increased 2.8-fold (ANOVA p<0.001; PE vs NP p<0.01) in PE compared to NP. There was no difference in expression of NCC but phosphorylation of the activating PKA site S130 site was increased 2.5-fold (ANOVA p=0.008; PE vs NP p<0.05). Expression of the alpha (ANOVA p=0.001; PE vs NP p<0.01) and full-length gamma ENaC (ANOVA p<0.001; PE vs NP p=0.05) subunits of ENaC was increased 6.0-fold and 2.7-fold, respectively, in PE compared to NP. There was a non-significant trend to increased expression of the cleaved 50 kD form of gamma ENaC in PE.

**Conclusions:** These data suggest a role for increased activity of ENaC and NKCC2 in mediating sodium-retention in PE, occurring despite reduced signalling through the WNK/SPAK/OSR1 pathway.
In Obese ZSF1 Rats, Females Show Increased Salt-Sensitivity Compared to Males

Isabel T. Nguyen, Bart Boermans, Jaap A. Joles, Marianne C. Verhaar
Nephrology & Hypertension, UMCU, Utrecht, Netherlands.

Background: The obese Zucker fatty spontaneously hypertensive heart failure F1 hybrid (ZSF1) rat has been proposed as a viable animal model to study the metabolic cardiorenal syndrome as these rats spontaneously develop diastolic heart failure and chronic kidney disease in the presence of obesity, hyperglycemia and hypertension. Risk factors associated with the metabolic syndrome correlate strongly with salt-sensitivity of blood pressure. We investigated the interaction of obesity and sex on salt-sensitivity in obese and lean ZSF1 rats. We hypothesized that obesity and male sex would both promote salt-sensitivity.

Methods: Male and female ZSF1 rats, lean as well as obese (n=6/subgroup), were either implanted with a deoxycorticosterone acetate (DOCA) pellet and fed a high salt diet (6% NaCl) or a placebo pellet and fed a normal salt diet from 19 weeks of age. Every two weeks, from 18 (i.e. prior to pellet implantation) to 26 weeks of age, systolic blood pressure (SBP), tail-cuff and 24-hour natriuresis were measured.

Results: SBP was higher in both obesity compared to lean DOCA+6% salt groups (p=0.0001). Natriuresis was higher in male obese vs. lean DOCA+6% salt groups (p=0.05). The SBP response to high salt intake occurred in a stepwise manner in all four DOCA+6% salt groups (with constant SBP from 22 to 24 weeks). Comparison of slopes of the natriuresis-pressure relations using 18 and 26-week data (figure) showed differences between male obese and lean and female obese and lean (p=0.02) ZSF1 rats, suggesting that obesity promotes salt-sensitivity. Additionally, the slopes between obese males and females differed (p=0.02) suggesting that salt-sensitivity was most marked in female obese ZSF1 rats.

Conclusions: Our results in ZSF1 rats indicate i) a phased blood pressure response to high salt intake, ii) an adverse effect of obesity on salt-sensitivity, and iii) a further increased salt-sensitivity in obese females vs. obese males.

Funding: Private Foundation Support
**PUB001**

**Urinary Retinal Binding Protein (uRBP) in Systemic AL Amyloidosis: A Pilot Study**

Tamer Rezk,1,2,3 Hayba H. Sayed,4 Helen J. Lachmann,5 Philip N. Hawkins,2 Christianne Guilhotte,5 Sharon Shreeves,6 Simon D. Packer,7 Julian D. Gillmore,8 Stephen B. Walsh,9 1BI Solutions Ltd, Sittingbourne, United Kingdom; 2UCL, London, United Kingdom; 3Center for Nephrology, UCL Division of Medicine, London, United Kingdom; 4University College London, London, United Kingdom; 5National Amyloidosis Centre, London, United Kingdom; 6BBI Solutions, Kent, United Kingdom.

**Background:** Renal involvement causing progressive proteinuric CKD is present in 70% of patients with systemic AL amyloidosis at diagnosis. Prolonged patient survival, renal survival and preservation of renal function are associated with free light chain (FLC) suppression by chemotherapy. uRBP, an indicator of renal tubular injury, has been shown to detect early renal involvement in multiple myeloma. FLCs are known to be toxic to proximal tubules causing mass nephropathy and Fanconi’s syndrome. Systemic chemotherapy (proteasome inhibitor based) to suppress FLC production can itself be associated with AKI. We hypothesized that a significant number of patients with systemic AL amyloidosis have proximal tubular dysfunction at baseline and that this may predict renal outcomes.

**Methods:** All patients with newly diagnosed systemic AL amyloidosis who attended the National Amyloidosis Centre from September 2016 to April 2017 and were enrolled into the Alchemy prospective observational study underwent uRBP analysis along with routine clinical, biochemical and scintigraphy assessments.

**Results:** Median age was 68 yr, eGFR 67 ml/min/1.73 m², and urinary protein creatinine ratio (uPCR) was 311 mg/mmol. Median uRBP was 282 g/L (normal range 0–16 mg/mmol). There was a significant correlation between uRBP and serum creatinine (Pearson correlation p=0.0001, R=0.6129) and uRBP and uPCR (Pearson correlation p=0.0001, R=0.5323). There was a strong positive correlation between altered fractional excretion of both phosphate and urate with uRBP (Pearson correlation, p=0.0001, R=0.6524).

**Conclusions:** A significant proportion of patients with systemic AL amyloidosis have both preserved renal excretory function and absence of significant proteinuria but elevated uRBP levels. There is a significant correlation between low molecular weight proteinuria indicating proximal tubular dysfunction with serum creatinine and uPCR. The association between uRBP and fractional excretion of both phosphate and urate indicates genuine proximal tubular dysfunction as opposed to simply ‘overflow’ from heavy unselective glomerular proteinuria in patients with untreated systemic AL amyloidosis. uRBP excretion may be a novel biomarker of renal involvement in systemic AL amyloidosis and may predict long term renal outcomes in this disease.

**PUB002**

**Modulation of HO-1 Potentiates CI-AKI in Diabetic Rats via NO**

Luciana soares e Watanabe,1 Fernanda T. Borges,2 Edson A. Pessoa,3 Luciana soares C. Santos,1 1School of Nursing, University of São Paulo, Carapicuiba, Brazil; 2Universidade Federal de São Paulo, São Paulo, Brazil.

**Background:** CI-AKI is a toxic nephropathy with generation of oxygen species (ROS). Diabetes Mellitus (DM) preexisting has been described as a risk factor for CI-AKI. HO-1 has a renoprotective effect in renal disease models, but its potential action in DM+IC is unknown.

**Methods:** Adult male Wistar rats were randomized in 5 groups. Physiological parameters; renal function (inulin clearance); renal hemodynamics; oxidative injury (urinary peroxides-UP, thiols in renal tissue); gene expression and protein synthesis of HO-1 and iNOS and kidney histological analysis were evaluated.

**Results:** DM+IC+ZnPP group showed reduced renal function and increased renal vascular resistance, while urinary NO levels increased in DM+IC+ZnPP group compared to the DM+IC group. Gene expression and protein synthesis of HO-1 and iNOS were elevated in DM+IC+ZnPP group. Kidney histology showed tubular vacuolization and edema in IC animals.

**Conclusions:** These data highlight that the heme oxygenase-1 inhibitor mitigates CI-AKI in the presence of CKD risk factor most likely via NO.

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

**Table 1. Global renal function and oxidative metabolites**

| Group | Global renal function | Renal Vascular Resistance | Urinary Peroxides (mmol/L) | Glomerular filtration rate (ml/min/1.73 m²) | Tubular viability (TBR) | Thymus viability (TBR) | Urinary Acidification capacity (mmol/L)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IC (p&lt;0.05)</td>
<td>38.9+0.7a</td>
<td>2.0+0.1a</td>
<td>1.1+0.1d</td>
<td>2.2+0.1c</td>
<td>20.8+0.6c</td>
<td>20.8+0.6c</td>
<td>1.6+0.1e</td>
</tr>
<tr>
<td>DM (p&lt;0.05)</td>
<td>38.9+0.7a</td>
<td>2.0+0.1a</td>
<td>1.1+0.1d</td>
<td>2.2+0.1c</td>
<td>20.8+0.6c</td>
<td>20.8+0.6c</td>
<td>1.6+0.1e</td>
</tr>
<tr>
<td>DM+IC</td>
<td>38.9+0.7a</td>
<td>2.0+0.1a</td>
<td>1.1+0.1d</td>
<td>2.2+0.1c</td>
<td>20.8+0.6c</td>
<td>20.8+0.6c</td>
<td>1.6+0.1e</td>
</tr>
<tr>
<td>DM+IC+ZnPP</td>
<td>38.9+0.7a</td>
<td>2.0+0.1a</td>
<td>1.1+0.1d</td>
<td>2.2+0.1c</td>
<td>20.8+0.6c</td>
<td>20.8+0.6c</td>
<td>1.6+0.1e</td>
</tr>
</tbody>
</table>

**PUB003**

**Heme Oxygenase-1 Role in Contrast-Induced AKI in CKD**

Cassiane D. da Fonseca,1 Maria De Fatima Vattimo,2 Mirian Watanabe,3 Fernanda T. Borges,2 Edson A. Pessoa,2 Luciana soares C. Santos,2 Natalia A. Oliveira,1 1Organization University of São Paulo, São Paulo, Brazil; 2Experimental of Laboratory of Animals Methods, School of Nursing, Sao Paulo, Brazil; 3Universidade de São Paulo, SÃO PAULO, Brazil; 4UNIFESP, São Paulo, Brazil; 5Universidade Federal de São Paulo, São Paulo, Brazil.

**Background:** Contrast Induced -acute kidney injury (CI-AKI) is the third cause of hospital acquired AKI, specially in the presence of CKD. Heme oxygenase-1 (HO-1) is part of a cytoprotective system that is involved with nitric oxide (NO) synthesis and modulates renal dysfunctions and oxidative damage in AKI models. This study evaluated the role of the HO-1 inhibitor, zinc protoporphyrin (ZnPP), in CI-AKI rats with CKD.

**Methods:** Adult male Wistar rats were randomized in 4 groups. Sham (control group), Nx5/6 (CKD group), Nx5/6+IC (CKD+iodinated contrast group), Nx5/6+IC+ZnPP. Renal function (inulin clearance); renal hemodynamics; oxidative injury (urinary peroxides-UP, thiols in renal tissue); gene expression and protein synthesis of HO-1 and iNOS and kidney histological analysis were evaluated.

**Results:** Inulin clearance was reduced due to an elevation on renal vascular resistance, while urinary NO levels were increased in Nx5/6+IC+ZnPP group when compared to the Nx5/6+IC group. Gene expression and protein synthesis of HO-1 and iNOS were elevated in Nx5/6+IC+ZnPP group. Kidney histology showed tubular cells vacuolization and edema in IC animals.

**Conclusions:** These data highlight that the heme oxygenase-1 inhibitor mitigates CI-AKI in the presence of CKD risk factor most likely via NO.

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

**PUB004**

**AKI Due to Antibiotic Spacer Kamron Saleem, Benjamin K. Saras, Amy N. Nasmass, Bijin Thajadeun. University of Arizona, Tucson, AZ.**

**Background:** This is a case of a 58 y/o woman who underwent right total hip arthroplasty 4 months prior to admission. Intraoperatively 10 mL of RapidCure loaded with 2 g of vancomycin and 2.4 g of tobramycin were placed in deep layers around the hip as prophylaxis and she was discharged with 1 week of oral antibiotics. She returned 2 months with an infection involving the right hip. 11 days later, she went to the OR for exploration, placement of antibiotic spacer containing 4g vancomycin, 3g cefuroxime and 2.4g tobramycin. In addition, 20 mL of Rapid Cure containing 4g vancomycin and 4.8g tobramycin was placed into the deep tissue layers around the hip. Admission renal function was normal with sCr of 0.7mg/dl and on the day of surgical explantation, renal function remained normal. Intrapro hypotension occurred, treated with volume resuscitation. On postop day 2, Vancocycin trough and tobramycin levels were increased markedly. sCr increased 1.2 mg/dl and continued to worsen. Due to concern...
for tobramycin and vancomycin toxicity, orthopedic surgery was asked to remove the spacer. Removal was deemed high risk and nephrology was asked to medically manage her renal dysfunction. Due to concern for continuous release of tobramycin from the spacer, hemodialysis was initiated for tobramycin clearance. She remained nonoliguric throughout. Roughly 1 million joint arthroplasties are performed each year in the USA. Between 1% and 2% result in a prosthetic joint infection. Two-stage arthroplasty is the current treatment of choice for infected hip and knee joint prostheses. Aminoglycosides and vancomycin are the most commonly used. The high local antibiotic level exceeds the MIC of many potential organisms. Data on spacer induced AKI is limited. No standard of care is available to determine the amount of antibiotics to be placed in a spacer. We propose a multidisciplinary approach between the Orthopedic, Nephrology, Infectious Diseases, and Pharmacology communities to formulate a standard criteria for antibiotic dosing in antibiotic-impregnated cement spacers. It would be helpful to re-analyze existing data using a more standardized definition of AKI per KDIGO. Further studies are needed to evaluate long-term prognosis in this group of patients.

Methods:

Results:

Conclusions:

PUB007

ANCA and IgA Glomerulonephritis All in One: Prevalence, Progression, and Complications

Pitchaphon Nissaisorakorn,1 Kisor Anis,1 Vivette D. D’Agati,2 Belinda Jim.1 1Albert Einstein College of Medicine, New Hyde Park, NY; 2Columbia University College of Physicians and Surgeons, New York, NY; 1Jacobi Medical Center, Bronx, NY.

Background: Co-existing IgA nephropathy and pauci-immune ANCA-associated crescentic glomerulonephritis has rarely been reported. Both entities are prevalent separately but their co-existence is less common with a reported prevalence of 0.2-2%. Methods: A 75 year-old Hispanic woman with PMH of DM, HTN, HLD and CKD stage III presented to the ED for abdominal pain with nausea, vomiting and hematuria for 3 days. She had been treated for pneumonia with azithromycin 1 month prior. On physical exam, she was afebrile, BP 155/71 mmHg, HR 78; exam was normal except for right CVA tenderness. She was found to have acute kidney injury and nephrotic range proteinuria with positive myeloperoxidase antibody and required HD. A renal biopsy revealed IgA nephropathy with superimposed pauci-immune ANCA-associated crescentic glomerulonephritis. She was subsequently treated with pulse intravenous methylprednisolone, cyclophosphamide IV and plasmapheresis. Unfortunately, her renal function did not improve and she continued to require HD. One week after administering her second dose of cyclophosphamide, the patient was re-admitted to the ICU for infectious complications on her 2nd hospitalization, which were coincident ANCA autoantibodies with no other apparent etiology. She had no other complications of herpes zoster, influenza virus, bacteremia secondary to the pansensitizing Rothia species, and C difficile negative diarrhea. She required a prolonged course of IV antibiotics and was subsequently able to be discharged home on HD.

Results:

Conclusions: The co-existence of ANCA's and IgA may be a coincidence or may be pathogenic. One possibility is that patients may have pre-existing IgA deposits in the mesangium, which are then further complicated by the presence of ANCA's. On the other hand, patients have coincident ANCA autoantibodies with no additional pathogenic potential. Some case series, however, have found a distinctive clinical and histologic picture of IgA and ANCA positivity, suggesting pathogenicity. The cornerstone for treatment is aggressive therapy with immunosuppressive agents. Current literature suggests that reduced dose immunosuppression for the elderly have been shown to have similar efficacy and might have a more favorable safety profile.

PUB008

Vitamin D and FGF 23 Prognostic Indicators of the Severity of AKI

Joseph Saabiy,1 Jeanne Kanul,2 Firas Safa,1 Julie Zaidan,3 Rania El Maas,1,2 Patricia Nasr,1 Suzanne E. El Sayegh,3 Elie El Charabaty.1,3 Internal Medicine, Staten Island University Hospital, Staten Island, NY; 2Nephrology, NYULMC, New York, NY; 3Gastroenterology, University of Missouri, Columbia, MO; 4Nephrology, Tufts University, Boston, MA; 5Nephrology, Staten Island University Hospital, Staten Island, NY.

Background: Vitamin D (VD) and Fibrolast Growth Factor 23 (FGF 23) are two molecules that have been correlated with different diseases including kidney dysfunction. Acute kidney injury (AKI) is a common and serious complication occurring in hospitalized patients. Markers helping early recognition of patients at risk and predicting recovery are still lacking. This raises the interest of studying VD and FGF 23 as new markers for AKI progression.

Methods: Patients with normal kidney function at baseline (Glomerular filtration rate (GFR)) >60) admitted with the diagnosis of AKI based on the KDOQI criteria were included in the study. VD, FGF 23 levels and Serum creatinine (Scr) were collected within 24h of admission (D1). Daily VD intake was estimated using a Food Frequency Questionnaire (FFQ). Patients were divided into 2 groups based on SCr at day 3 (D3): AKI recovery (return to baseline GFR or 50% decrease in SCr D3) vs AKI progression. VD levels were collected at D3 for patients who failed to recover.

Results:

102 patients were enrolled, 69.7% were men, mean age was 65.7, mean BMI was 31.3. 64.6% recovered from AKI. D1 1,25-di hydroxy VD (1,25 D3) levels correlated negatively with SCR on D1, D3 and peak SCR levels (r -0.38 p 0.001; -0.35 p 0.007; r -0.39 p 0.001 respectively). D1 1,25 D3 levels were significantly higher in patients whom kidney function improved (40.5 vs 25.2 p 0.002). Moreover D3 1,25 VD correlated negatively with SCr D3 (r -0.55, p 0.01). FGF 23 had a negative correlation with D1 1,25 VD (r -0.39 p 0.001) and SCR D3 (r -0.43 p 0.001). Per FFQ analysis, 25-Hydroxy VD levels correlated with daily VD consumption (r 0.32 p 0.001) and a cut off of 603.7 units/day of VD intake was needed for sufficient levels.

Conclusions: FGF 23 levels could be used in patients with chronic kidney disease. In our study, patients with AKI with normal kidney function at baseline had elevated levels of FGF 23. Those whom kidney function did not improve had lower levels of 1,25 D3 and higher levels of FGF 23 at presentation. Could these molecules be used as prognostic markers and eventually new targets for therapies in patients with AKI?
Deficiency of Proangiogenic Factor Vasohibin-2 Exacerbates AKI via Impaired Renal Tubular Cell Survival Katsusuki Tanabe, Hiromasa Miyake, Kana Masuda, Satoshi Tanimura, Hitoshi Sugiyama, Jun Wada. Okayama university Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.

Background: A number of mediators including angiogenesis-related factors have been known to be involved in the progression of acute kidney injury (AKI). Understanding the role of such mediators in AKI may lead to development of novel therapeutic strategies. Vasohibin-2 (VASH2) is a proangiogenic factor secreted by tumor cells and its expression has been associated with higher grade of the malignancies. However, its physiological and pathogenic roles in kidney has not been elucidated yet. In the present study, we examined the effects of endogenous VASH2 deficiency on renal function and histology in murine AKI model.

Methods: Ischemic-reperfusion (I/R) injury was induced by clamping bilateral renal pedicles for 25 min in eight to nine-week-old C57Bl6/J wild type (WT) and VASH2 knockout (VASH2−/−/−) mice (n=6 in each group). Blood samples were collected and kidneys were harvested 24 hours after the reperfusion. Cultured human tubular epithelial cells (HK-2) was transfected with human VASH2 using adenoviral vectors and treated with 500 μM of hydrogen peroxide (H₂O₂) for 12 hours.

Results: Increase serum creatinine and blood urea nitrogen caused by I/R in WT were significantly accelerated in VASH2−/−/−/− mice. Histologically, ATN score and number of TUNEL-positive nuclei following I/R in VASH2−/−/−/− mice was significantly exuberated compared with WT mice. Increased accumulation of malondialdehyde and 4-hidroxynonenal was more prominent in VASH2−/−/−/− I/R mice. Whereas decreased number of peritubular capillaries after I/R was greater in VASH2−/−/−/− mice, decreased VEGF mRNA was comparable between WT and VASH2−/−/−/− I/R mice. Renal VASH2 mRNA was markedly elevated after I/R and immunostaining revealed that the increased VASH2 expression was localized in renal tubular cells. Adenoviral overexpression of VASH2 in HK-2 led to prominent Akt phosphorylation. H₂O₂-induced upregulation of pro-apoptotic factor Bax was prevented by VASH2 overexpression.

Conclusions: These results suggested that endogenous VASH2 was upregulated in renal tubular cells in I/R injury to improve renal tubular cell survival. 

Funding: Government Support - Non-U.S.

PUB010
Necrostatin-1 Attenuates Sepsis Associated AKI through Promoting Autophagosome Elimination of Renal Tubular Epithelial Cells Wei Dong, Xinling Liang. Division of Nephrology, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China.

Background: The aim of the present study was to investigate the protective effect of necrostatin-1 (Nec-1) in sepsis associated AKI (SA-AKI).

Methods: The SA-AKI mouse model was established by intraperitoneal injection of lipopolysaccharide (LPS). Nec-1 was delivered to SA-AKI mouse. Renal function and histology changes were observed. LC3-II and p62, the markers for autophagy flux, were detected. Autophagosome and autolysosome of renal tubular epithelial cells were identified using electron microscopy.

Results: Pretreatment with Nec-1 could reverse increased blood urea nitrogen (BUN) (LPS+Nec-1 vs. LPS group, 15±4.18 mmol/l vs 32.54±5.46 mmol/l, P=0.001) and serum creatinine (Scr) (11.50±1.67 µmol/l vs 30.08±4.18 µmol/l, P=0.001) induced by LPS. There were no significant differences in tubular epithelial cell necrosis between different groups. Protein analysis showed LC3-II and p62 were increased while transcription analysis showed neither LC3-II nor p62 mRNA was increased. Massive autophagosomes and paucity of autolysosomes were observed using electron microscope. When mice were pretreated with Nec-1, LC3-II and p62 decreased and a large number of autolysosomes were observed using electron microscope. These results indicate Nec-1 improved autophagosome elimination of renal tubular epithelial cells impaired by LPS.

Conclusions: In conclusion, Nec-1 could prevent sepsis-associated acute kidney injury through promoting autophagosome elimination in renal tubular epithelial cells.

Funding: Government Support - Non-U.S.

Figure 1. Comparison of Scr and BUN between different groups.

Figure 2. Transcription and expression levels of LC3-II and p62 in renal tissues of different groups.

PUB011
The Role of Growth Arrest and DNA Damage-45γ in Cyclosporine A-Induced Renal Tubular Cell Death Gyu Te H Shin1, Jeun Park2, Seung-Jung Kim3. 1Ajou University School of Medicine, Suwon, Republic of Korea; 2Ewha Womans University, Seoul, Republic of Korea.

Background: Nephrotoxicity is the major adverse effect of cyclosporine A (CsA) and it has been shown that CsA directly damages renal tubular cells. Growth Arrest and DNA Damage-45γ (GADD45γ) is a stress-responsive molecule, and our previous studies showed GADD45γ might contribute to the progression of chronic kidney disease [Kidney Int. 2008, Am J Nephrol. 2009]. In the present study, we investigated the role of GADD45γ in CsA-induced renal tubular cell death.

Methods: Human renal epithelial (HRE) cells that are of kidney tubular origin were incubated with CsA 25 μg/ml for 48 hours in the presence or absence of 1,25D3, necrostatin-1 or ferrostatin-1. To knockdown GADD45γ expression, stable cell lines expressing GADD45γ shRNA were generated. The recombinant adenovirus containing the GADD45γ gene was synthesized to overexpress GADD45γ protein. The degree of apoptosis and necrosis were evaluated using flow cytometry after staining with Annexin V and propidium iodide.

Results: We found that CsA significantly induced GADD45γ expression by HRE cells. Treatment of CsA provoked HRE cell death by inducing apoptosis and necrosis. Inhibition of caspases by zVAD significantly decreased CsA-induced apoptosis as well as necrosis, which is considered to be secondary to apoptosis, leading to a significantly increased cell survival. Inhibition of receptor-interacting serine/threonine-protein kinase 1 by necrostatin-1 reduced necrosis but not apoptosis, leading to an increased overall cell survival but to a lesser degree than zVAD. This result suggests that CsA induces cell death by mainly apoptosis as well as by necroptosis (primary necrosis).

Conclusion: GADD45γ overexpression augmented CsA-induced apoptosis while decreasing necrosis without affecting overall cell survival, indicating the switch of the mode of cell death from necroptosis to apoptosis. Accordingly, GADD45γ overexpression activated apoptosis-related caspases but not necroptosis-related mixed lineageseverasome protein like gene. GADD45γ knockdown cell lines showed significantly decreased CsA-induced apoptosis as well as necrosis, and the rescue of GADD45γ expression restored CsA-induced apoptosis.

Conclusions: GADD45γ knockdown prevents CsA-induced renal tubular cell death by blocking apoptosis and secondary necrosis.

PUB012
Effect of Physical Preconditioning in AKI Induced by Renal Ischemia-Reperfusion in Rats Frederico Fazan1, Lucas F. Almeida, Heloisa D. Francescato, Natany G. Reis, Cleonice Silva, Fernando S. Ramalho, Terezila M. Coimbra. 1Physiology, Ribeirao Preto Medical School, Ribeirao Preto, Brazil; 2Pathology, Ribeirao Preto Medical School, Ribeirao Preto, Brazil.

Background: Acute kidney injury (AKI) is one of the most common kidney illnesses. Many factors can cause AKI including ischemia-reperfusion (I/R). An increasing number of evidence show that ischemia-reperfusion of the kidneys can provoke renal lesions through inflammatory pathways and endothelial dysfunction. Several studies show a relation between physical exercise and healthy vascular function with imunomodulatory roles. The objective of this study was to evaluate the effect of previous physical exercise in the AKI induced by renal ischemia-reperfusion in rats.

Methods: Male Wistar rats were divided into four groups: 1-Sedentary Sham; 2-Sedentary I/R; 3-Trained Sham; 4-Trained I/R. The trained animals were subjected to mild intensity treadmill training 5 days a week during 9 weeks. After that, the clamps were removed and 48 hours after the urine and blood samples were collected for renal function evaluation and the kidneys were removed for histological and immunohistochemical examination.
Results: The trained group presented, after I/R induced injury, a small reduction of renal function and structure when compared to the sham group. They showed: plasma creatinine of 2.03±1.24 mg/dl, fractional sodium excretion of 2.97±4.66% and plasma osmolality of 317.9±15.5 mOsm/Kg H2O, when in the sham group the plasma creatinine level was 6.39±2.02 mg/dl; fractional sodium excretion 29.3±19.6% and plasma osmolality 367.8±13.0 mOsm/Kg H2O. The structural lesions were also reduced as the sedentary animals kidneys, availed at scales, ranging from 0 to 4 (smallest to widest extent of lesion) was 3.5±0.3 in the sedentary animals and 2.4±0.9 in trained animals.

Inflammation was also reduced in the trained animals as the group showed a smaller number of macrophages in the kidneys and cortex and outer medulla. In the trained animals, 17.11±1.52 cells/0.45mm2 for the trained animals and 36.35±1.7 cells/0.45mm2 for the sedentary animals, p<0.05.

Conclusions: Physical preconditioning attenuated the decrease in renal function and structural changes were associated with inflammation that was also less intense in the kidneys of the animals of the training group.

Funding: Government Support - Non-U.S.

PUB013

The Role of XBP1 in AKI to CKD Progression through G2/M Arrest and Fibrotic Induction Chia-Hsien Wu,1,2 Yu-Ann Chien,1,3 Ji-Ann-Jeong,1 Chi-Hang Chiang,1,2 Shing-Hwa Liu.1,3 1Graduate Institute of Toxicology, National Taiwan University, College of Medicine, Taipei, Taiwan; 2Department of Integrated Diagnostics & Therapeutics, National Taiwan University Hospital, Taipei, Taiwan; 3Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; 4Division of Endocrinology, and Nephrology, University of Tokyo, Graduate School of Medicine and Faculty of Medicine, Tokyo, Japan.

Background: X-box binding protein 1 (XBP1), one of the key molecules of unfolded protein responses (UPRs), is responsible for induction of UPR signaling. Studied have revealed UPRs associated with various kidney diseases. However, there is no report discussed about the role of UPRs during the transition from acute kidney injury (AKI) to chronic kidney disease (CKD).

Methods: C57BL/6 mice were clamped by micro-clips on left renal pedicle for 30 mins, then completely reperfusion to generate unilateral ischemia/reperfusion injury (UIRI) model. Mice were sacrificed after 1, 3, 5, 11, 15 days after surgery. Serum BUN and Cr were analyzed, and tissue histology, including H&E, Periodic Acid-Schiff and Masson’s trichrome were evaluated. Furthermore, UPRs-related initiators were evaluated by Western blot and qPCR. In vitro, the proliferation and cell cycle analysis of XBP1-deficient HK2 cells was analyzed by MTS assay, Western blot and flow cytometry, respectively.

Results: The expression level of UPRs initiators PERK, IRE1α are relatively higher in UIRI group than in sham group, however, expression of both spliced and unspliced XBP1 were decreased during CKD progression. Besides, XBP1 expression level has a negative correlation with fibrosis progression. Recently, renal tubular epithelial cells arrest in G2/M contributes to renal fibrosis progression through releasing fibrogenesis factors and obstructing the repairing process has been reported. Here we then hypothesize that losing XBP1 in epithelial cells may result in cell cycle arrest and contribute to the fibrosis progression after AKI. In the following experiments, knockdown XBP1 in cell line and HUVECs, renal epithelial cells cause cell cycle arrest in G2/M, and the cell growth is retarded. We find expression and the ratio of cyclin B1 to cyclin D1 are higher after knockdown of XBP1, indicate the G2/M arrest of cells. Expression level of the DNA damage marker, phospho-H2AX is also higher after knockdown of XBP1. Furthermore, it induces the synthesis of higher extracellular matrix and fibrogenesis factors (13.32 VS 99.04 ± 2.361 vs 102.2 ± 2.942). Ipropr, an analogue of PGI2, administrated (0.05mg/kg ip) 30 minutes before the IRI, markedly attenuated renal damage induced by IRI in both wild type mice (BUN 57.61 ± 0.03 VS 33.66 ± 5.847 mg/dl;P=0.001) and TEK-CRE PGI2-/-mice (BUN 162.5 ± 4.74 VS 75.57 ± 0.28(mg/dl-P<0.001). Histologic changes were consistent with BUN changes. No blood pressure difference was observed between wild type mice and endothelial PGI2 deletion mice (108.3 ± 2.361 vs 102.2 ± 2.942). Ipropr, an analogue of PGI2, administrated (0.05mg/kg by ip) 30 minutes before the IRI, markedly attenuated renal damage induced by IRI in both wild type mice (BUN 57.61 ± 0.03 VS 33.66 ± 5.847 mg/dl;P=0.001) and TEK-CRE PGI2-/-mice (BUN 162.5 ± 4.74 VS 75.57 ± 0.28(mg/dl-P<0.001). Further studies show that kidney p-PKA expression significantly increased after IRI in wild type mice but not in the PGI2 deletion mice, suggesting that the protective effect of PGI2 is IP receptor dependent. Folic acid also induced marked kidney injury, however, endothelial PGI2 deletion did not worsen kidney injury compared with wild type mice (BUN 117.3 ± 13.2 VS 99.04 ± 12.08, mg/dl-P=0.05).

Conclusions: In conclusion: PGI2 derived PGII can protect the kidney from acute injury by ischemic reperfusion and could be a potential intervention target for AKI. The protective effect of PGI2, was not observed in the nophrictic AKI model induced by folic acid.

Funding: Government Support - Non-U.S.

PUB014

Development of a Novel Model of Contrast-Induced AKI in Mice Atsushi Uchida,1 Kengo Kidokoro,1 Hajime Nagasu,1 Minoru Satoh,1 Tamaki Sasaki,2 Naoki Kashihara,1,3 Kawasaki Medical School, Kurashiki, Japan; 1Kawasaki Medical School, Kurashiki Okayama, Japan; 1None, Kurashiki, Japan.

Background: Contrast-induced acute kidney injury (CI-AKI) is characterized by the abrupt loss of kidney function following the intravascular administration of iodinated contrast media. CI-AKI has been found to be strongly associated with mortality and morbidity of the patients. CI-AKI may be caused by sustained contrast-induced renal arteriolar vasocostruction, outer medullary and tubular hypoxia or direct cytotoxicity due to ischemia-mediated oxidative stress. However, the mechanism of CI-AKI has not been completely elucidated. One of the seasons is lack of established CI-AKI model. The purpose of this study is to use a clinically relevant and functionally obvious CI-AKI mouse model corresponding to the risk factors of CI-AKI, which provides feasibility for the mechanism study of CI-AKI.

Methods: Dehydration and higher dose of the contrast medium are known as risk factors for CI-AKI. So, (1) Adenine induced renal failure model mice and (2) Akita diabetic mice were used. Oxidative stress and endothelial dysfunction are thought to contribute CI-AKI development. So, (3) Nrf2 knockout mice as high sensitivity to oxidative stress model and (4) eNOS knockout mice as endothelial dysfunction model were used. In experiment (1), adenine containing diet was given for 14 days before contrast injection. In experiment (2), all mice were subjected to left kidney nephrectomy 7 days before contrast injection. These mice were euthanized 48h after contrast injection, and the blood samples were collected.

Results: In all experiments, serum creatinine and blood urea nitrogen were not elevated by contrast injection compared to Control. AKI was not induced by contrast medium in in vivo.

Conclusions: In the murine, it is hard to establish AKI model caused by contrast medium. As the injection of contrast media alone does not cause overt AKI in mice, multiple insulin is necessary for inducing histopathological and functional decline.

PUB015

Endothelial Prostacyclin Protects the Kidney from Ischemia-Reperfusion Injury Cao Ying, Chuan-Ming Hao. Huashan Hosp., Shanghai, China.

Background: Ischemia-reperfusion injury (IRI) is one of the most common causes of AKI. Prostacyclin, or PGI2, is one of metabolites of arachidonic acid via cyclooxygenase and PGI synthase (PGIS). In the kidney, PGI2 is reported to play an important role in maintaining the renal blood flow. This study explores the role of endothelium derived prostacylin in IRI.

Methods: To genetically suppress the expression of PGI2, we generated a mouse line whose PGIS gene was specifically deleted in endothelial cells (TEK-CRE PGIS-/-). The endothelial model was established by right nephrectomy and in situ left nephrectomy, clamping for 25 minutes. Animals were sacrificed at different time point after reperfusion, and blood and renal samples were collected for further analysis. Nephrotic AKI was induced by folic acid (250mg/Kg by ip). Kidney damage was assessed by BUN, kidney histology and TUNEL assay.

Results: The kidney PGIS protein expression markedly increased following IRI in the wild mice but not in the TEK-CRE PGIS-/- mice. TEK-CRE PGIS-/- mice had a significantly more severe acute kidney injury following IRI than wild type mice (at 24 hours, BUN 162.5 ± 4.74 VS 75.57 ± 0.03(mg/dl-P<0.001). Histologic changes were consistent with BUN changes. No blood pressure difference was observed between wild type mice and endothelial PGIS deletion mice (108.3 ± 2.361 vs 102.2 ± 2.942). Ipropr, an analogue of PGI2, administrated (0.05mg/kg by ip) 30 minutes before the IRI, markedly attenuated renal damage induced by IRI in both wild type mice (BUN 57.61 ± 0.03 VS 33.66 ± 5.847 mg/dl;P=0.001) and TEK-CRE PGIS-/- mice (BUN 162.5 ± 4.74 VS 75.57 ± 0.03(mg/dl-P<0.001). Furthermore studies show that kidney p-PKA expression significantly increased after IRI in wild type mice but not in the PGIS deletion mice, suggesting that the protective effect of PGI2 is IP receptor dependent. Folic acid also induced marked kidney injury, however, endothelial PGIS deletion did not worsen kidney injury compared with wild type mice (BUN 117.3 ± 13.2 VS 99.04 ± 12.08, mg/dl-P=0.05).

Conclusions: In conclusion: PGIS derived PGI2 can protect the kidney from acute injury by ischemic reperfusion and could be a potential intervention target for AKI. The protective effect of PGI2, was not observed in the nophrictic AKI model induced by folic acid.

Publication-Only

Underline represents presenting author. 968

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

Underline represents presenting author.
Mechanistic Toxicity Testing of Old and New Polycationic Polypeptide Antibiotics Using a Kidney Proximal Tubule “Organ-on-a-Chip”

Elieja Weber,1 Martti Vaara,2 Timo Vaara,3 Thomas Neumann,4 Maria beatriz Monteiro,5 Jonathan Himmelfarb,5 Edward J. Kelly,6 Uihiversity of Washington, Seattle, WA; 1Kidney Research Institute, Seattle, WA; 2Norrisk, Inc., Seattle, WA; 3Harvard Medical School, Boston, MA; 4Northern Antibiotics Ltd., Espoo, Finland.

Background: The renal proximal tubule is susceptible to drug-induced injury, which can be attributed to concentrative transport processes. Our lab has developed a microphysiological system (MPS) using proximal tubule epithelial cells (PTECs) in a three-dimensional flow-mediated culture which recapitulates both the functional and structural aspects of the proximal tubule. The purpose of this study is to define the mechanism(s) of drug-induced injury using the kidney MPS. The polymyxin class of antibiotics contains polycationic polypeptides with high biological efficiency. However, polymyxin use has been associated with a high incidence of acute kidney injury and the precise mechanisms remain unclear. The safety of Polymyxin B (PMB) to next generation polymyxins (NAB739 and NAB741) was evaluated.

Methods: PTECs are cultured for ~1 week (reaching maximum confluency) before being treated with 0aM PMB (ctrl), 50aM of PMB, or 50aM NAB739/741. Treatment duration was 48 hours with effluent collection in 24 hour intervals and analyzed for both kidney injury molecule-1 (KIM-1) and miRNA content. Nephrotoxicity was determined by evaluating urinary injury response (KIM-1, miRNA), cell-associated injury (via the induction of heme-oxygenase-1, HO-1), and transcriptional response via RNA-seq technologies.

Results: We observed consistent polymyxin-induced toxicity as measured by cell-associated HO-1 induction and both effluent KIM-1 and miRNAs (miR-155-5p and -200c-3p). Transcriptional analysis revealed significant differences between the treated (50aM PMB) and control group lending evidence toward polymyxin-induced apoptosis via the induction of tumor necrosis factor alpha (TNF-α) as well as induction of the cholesterol biosynthesis pathway. Furthermore, polymyxin-analogues (NAB739/741) were shown to have increased safety by demonstrating injury profiles similar to that of the control group. The transcriptional response to NAB-exposure is currently being evaluated.

Conclusions: Using the kidney MPS, we have shown that new structural variants of PMB are less cytotoxic with a predicted improved safety profile. Additionally, we have made advances towards clarifying the previously unknown mechanisms of polymyxin-induced nephrotoxicity by observing the transcriptional response to PMB exposure.

Funding: Other NIH Support - NCATS-UH3, NIEHS-EDGE, Other U.S. Government Support

A Risk Prediction Score for AKI in Amazon Intensive Care Units

Fernando de Assis F. Melo,1 Ana Caroline F. Bezerra,2 Emmanuel A. Burdmann,3 Dirce M. Zanetta,1 Ravindra L. Mehta,1 Etienne Maccled,1 UCSD, San Diego, CA; 1University of California San Diego Medical Center, San Diego, CA; 1University of Sao Paulo, Rio Bronco, Brazil; 1University of Sao Paulo Medical School, Sao Paulo, Brazil; 1University of Sao Paulo, Sao Paulo, Brazil; 2Acre Federal University, Rio Bronco, Brazil; 3SESCARE, Rio Bronco, Brazil.

Background: In Amazon Intensive Care Units (ICU) AKI is a common complication, associated with increased morbidity and mortality. In resource-constrained areas, early identification of high-risk patients is a fundamental step to improve patient care and outcomes. In this study, we aim to validate a risk score for AKI development in a cohort of ICU patients in the Amazon region.

Methods: All patients admitted to three Intensive Care Units (ICU’s) from Feb 2014 to Feb 2016 were screened. We applied a risk score for AKI development based on chronic diseases and acute risk factors (Table 1) within 48 h of ICU admission. The discriminative ability of the risk model was assessed by the area under the receiver operating characteristic curve (AUROC).

Results: Of 1073 screened patients, 52% developed AKI and 31.8% were classified as high risk for AKI. The score had a good calibration and discrimination, with an AUROC of 0.78 [95% confidence interval (CI) 0.74–0.83]. Sensitivity, specificity, positive predictive value, negative predictive value for patients with score a 5 points were 89.2%, 41.5%, 62.3%, 78%, respectively. Mortality rate were significantly higher (38.6% vs 23.1%; p = 0.017) in the high risk group.

Conclusions: AKI is common in ICU patients in the western Brazilian Amazon. A simple risk score integrating chronic comorbidities and acute events at ICU admission can identify patients at high risk to develop AKI. In resource constrain areas, the application of this risk assessment tool could help clinicians to stratify patients for more active renal function surveillance, and early drug adjustment and therapeutic interventions to improve care and outcomes of ICU patients.

Funding: Government Support - Non-U.S.
contours of the peripheral basement membrane were found in other areas. In contrast to the glomerular GN in cryoglobulinemic GN were consisently strongly positive and in TMA cases only weakly positive. In the latter groups dilatation of the capillaries was almost absent. The pseudolumen were mostly positive for IgG3 and only rarely positive for IgG4 with no obvious difference compared to cryoglobulinemic GN. In contrast to TMA cases no CD61 positive thrombi were found. Like TMA cases and to lesser extent also cryoglobulinemic GN cases the pseudolumen in Bevacizumab cases were frequently accompanied by a loss of surrounding CD34+ endothelial cells. 

**Conclusions:** Bevacizumab associated glomerulopathy often exhibits a unique histological pattern with a patchy pattern of PAS positive and nearly negative hyaline pseudolumen in markedly dilated glomerular capillaries with loss of endothelial cells. Recognizing this pattern can be important for differential diagnosis in cancer patients with nephrotic syndrome.

**PUB020**

**Timing for Initiation of Sequential Continuous Renal Replacement Therapy in Patients with Extracorporeal Membrane Oxygenation: A Propensity Score Analysis**  

**Anna Lee, SNUBH, Gyeonggi-do, Democratic People’s Republic of Korea.**

**Background:** Extracorporeal membrane oxygenation (ECMO) is a lifesaving therapy used in critically ill patients with severe cardiopulmonary dysfunction. Continuous renal replacement therapy (CRRT) is added to treat fluid overload, acute kidney injury and electrolyte disturbances during ECMO. However, it is not well defined when to initiate CRRT. We performed this study to identify the optimal timing for CRRT on ECMO.

**Methods:** We conducted a multicenter retrospective cohort study of 296 patients who received CRRT during ECMO in Seoul National University Bundang Hospital, Yonsei University Hospital and Seoul National University Hospital between 2005 and 2016. We assigned the patients to either an early or late CRRT group depending on the initiation time of CRRT. We considered “early CRRT” to be CRRT instituted within 72 hours of ECMO initiation.

**Results:** Among 296 patients, 212 patients (71.6%) received early CRRT. After using a method, Ninety-four patients were included in a propensity score matching analysis. No significant difference was observed in baseline characteristics between groups. The 1-year survival rate of the late CRRT group was lower than that of the early CRRT group (85.7% vs. 90%, P = 0.043). The 1-year survival rate of the early CRRT group was higher than that of the late CRRT group (90% vs. 85.7%, P = 0.043). The overall survival rate of the early CRRT group was higher than that of the late CRRT group (90% vs. 85.7%, P = 0.043).

**Conclusions:** This study showed that early CRRT treatment may not be superior to late CRRT treatment in ECMO patients, and patients with better baseline renal function may allow to delay the initiation of CRRT. Clinical trials may be needed in the timing to initiate subsequent CRRT in ECMO patients.

**PUB021**

**The Additive Value of Serum Anion Gap and pH for Mortality in Patients Receiving Concomitant Continuous Renal Replacement Therapy and Extracorporeal Membrane Oxygenation**  

**Anna Lee, SNUBH, Gyeonggi-do, Democratic People’s Republic of Korea.**

**Background:** The anion gap is an easily calculated marker based on analytes typically available from routine chemistry analysis. An increased serum anion gap is known as a risk factor for hypertension, decreased renal function and mortality in critical illness. This study aimed to investigate whether serum anion gap and pH might be predictive of mortality in patients receiving continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO).

**Methods:** Patients who received CRRT and ECMO in Seoul National University Bundang Hospital, Yonsei University Hospital and Seoul National University Hospital between 2005 and 2016 were included. The albumin and blood urea nitrogen-adjusted anion gap (AGc) was calculated using this formula: AGc (mmol/L) = serum sodium (mmol/L) - (serum chloride (mmol/L) + serum bicarbonate (mmol/L)) + ([4 – serum albumin (g/dL)] x 2.5) - ([blood urea nitrogen (mg/dL) – 15] + 7).

**Results:** Among 307 patients, 204 patients died (66.4%). According to the receiver operating characteristic curve analysis, the optimal threshold of AGc and pH for mortality were 14.75 mmol/L (sensitivity 0.782 and specificity 0.434) and 7.34 (sensitivity 0.718 and specificity 0.491). Multivariate analysis showed that patients with AGc above 14.75 mmol/L had 1.5 times higher risk of mortality (HR, 1.533; 95% CI, 1.047-2.244; P = 0.029) and patients with pH below 7.34 had 1.9 times higher risk of mortality (HR, 1.869; 95% CI, 1.308-2.670; P = 0.001). Patients with AGc ≥ 14.75 and pH < 7.34 increased the risk of mortality than patients with AGc < 14.75 and pH ≥ 7.34 (HR, 3.367; 95% CI, 2.094-5.412; P < 0.001). However, albumin-adjusted anion gap did not show any significant predictive value for mortality.

**Conclusions:** This study showed that AGc and pH may have independent prognostic values and additive effects on mortality in patients receiving CRRT during ECMO.

**PUB022**

**Tenofovir Nephrotoxicity in a Patient With Sepsis Youngjung Park,1 Prince Singh,2 Nawsheen Chowdhury,1 Ismail O. Jimada,1 James Drakakis,1 Shayan Shirazian,2 Minesh Khatri,2 1Department of Medicine, Division of Infectious Disease, NYU-Winthrop Hospital, Mineola, NY; 2Department of Medicine, NYU-Winthrop Hospital, Mineola, NY, 3Department of Medicine, Division of Nephrology, NYU-Winthrop Hospital, Mineola, NY.**

**Background:** Tenofovir disoproxil fumarate (TDF) is a commonly prescribed antiretroviral medication. We report a case of a HIV+ patient who presented with septic shock and acute kidney injury (AKI) and was found to have TDF nephrotoxicity on renal biopsy.

**Methods:** A 50-year-old African-American female with HIV infection for the past 15 years presented with one week of altered mental status and fevers. She had been on TDF for HIV viral load suppression for the past 7 years. Other medications include atazanavir, ritonavir, and Bactrim (starting one week prior to admission for CD4 count of 170 cells/mm³). On initial presentation, she was noted to have altered mental status and was presumed to be in septic shock from multifocal pneumonia with labs significant for lactate of 5.8mmol/L, Cr 5.2mg/dL, albumin 2.3g/mL, and serum glucose 194mg/dL. Urine studies revealed spot urine protein of 3 g/mg, glycosuria, and hematuria. Serologies for glomerulonephritis were negative. She was initiated on dialysis for oliguric renal failure. Given the unclear etiology of her renal failure and lack of renal recovery despite hemodynamic improvement, a renal biopsy was done which revealed diffuse and severe proximal tubular interstitial changes, diffuse interstitial edema with scattered rounded eosinophilic intracytoplasmic inclusions in the proximal tubular epithelial cells, as well as enlarged dysmorphic mitochondria on electron microscopy. TDF was discontinued on admission but she remained without renal recovery three weeks later and was discharged on hemodialysis.

**Results:**

**Conclusions:** TDF has been shown to cause proximal tubular dysfunction, chronic kidney disease (CKD) and AKI. Other risks factors for TDF nephrotoxicity include advanced age, decreased CD4 count, baseline CKD, concurrent use of protease inhibitors, and genetic defects in renal drug transporter proteins. AKI from TDF nephrotoxicity can occur in isolated settings but can be potentiated by the presence of other nephrotoxins. In this case we largely attributed the patient’s AKI to septic shock but believe that this predisposed the patient to TDF nephrotoxicity, which in turn further amplified the renal insult. This case also emphasizes that TDF nephrotoxicity can develop at any time, even after years of uneventful treatment.

**PUB023**

**Abstract Withdrawn**
Dynamic Changes of Properdin in Mouse Renal Ischemia Reperfusion Injury and Repair

Hai Wang,1,2 Yuanyuan Wu,1,3 Aifen Liu,1 Yufang Zhang,2 Qian Wang,1 Wenting Li,1 Yaping Fan,1 Bin Yang,1,2 1Affiliated Hospital of Nantong University, Nantong, China; 2Nantong University, Nantong, China; 3University of Leicester, Leicester, United Kingdom.

Background: Properdin, released predominantly from neutrophils, is an only known positive regulator of alternative pathway of complement activation via stabilizing C3bBb. Our pilot studies revealed that renal ischemia reperfusion (IR) injury at 72 h was significantly aggregately by properdin deficiency in mice. This study, aimed to explore the dynamic changes and effects of properdin in vivo.

Methods: IR-related injury was established in mouse kidneys subjected to 30-min ischemia followed by 6-72 h, 1 week reperfusion in vivo. Then the expression of properdin and complement activation related protein C3b was investigated, and the changes of renal function, inflammation, apoptosis were also measured. In addition, we make the correlation analysis between properdin and some renal damage markers.

Results: In mouse IR kidneys, serum creatinine (Scr) was significantly increased after 24-h reperfusion and reached the peak at 48 h. The expression of properdin protein was increased in a time-dependent manner and reached the peak at 24 h, while there was no significant change in C3b protein. Immunohistochemistry staining results showed that the properdin protein is mainly distributed in the renal tubular area. In addition, the inflammation related protein HMGB-1 and the apoptosis related protein caspase-3 was also increased in a time-dependent manner and reached the peak at 24 h and 12 h, respectively. Furthermore, the protein expression of properdin was significantly positively correlated with HMGB-1 and caspase-3.

Conclusions: Properdin plays an important role in renal IR-related injury and repair. However, whether enhanced properdin could be beneficial in injury repair/recovery and its underlying mechanisms are worthy to be further investigated.

Funding: Government Support - Non-U.S.

GUT Derived Endotoxin Contributes to the Inflammation of Ischemia-Reperfused Kidney

Tao J. Li,1,2 Chen Yu,1,2 Shanghai Tongji Hospital, SHANGHAI, China; 2TONGJI UNIVERSITY SCHOOL OF MEDICINE, SHANGHAI, China; 3TONGJI UNIVERSITY SCHOOL OF MEDICINE, SHANGHAI, China.

Background: Endotoxins from gut are presumed to play an important role that augment organ inflammation in critical ill condition. In the present study, we studied the effects of endotoxins in renal inflammation in renal ischemia-reperfusion rats (IR).

Methods: Sprague-Dawley rats were divided into 4 groups (n=5 per group): Sham-saline, Sham-norfloxacin, IR-saline and IR-norfloxacin. Rats were treated with oral norfloxacin 20 mg/kg/day or saline for 4 weeks before IR operation. For IR induction, the bilateral kidneys experienced a 60 min of ischemia plus 6-72 h, 1 week reperfusion. The protein expression of TLR4, NFκB and cytokines of the kidney homogenate were measured.

Conclusions: Properdin plays an important role in renal IR-related injury and repair. However, whether enhanced properdin could be beneficial in injury repair/recovery and its underlying mechanisms are worthy to be further investigated.

Funding: Government Support - Non-U.S.

AKI Recovery in Hemodialysis-Dependent Hospital Survivors Discharged to an Acute Rehabilitation Facility

Meredith Meadams,1 George Vasquez-Rios,1 Fabiola G. Gianella,1 B. Peter E. Sawaya,1 Javier A. Neyra,3 1University of Kentucky, Lexington, KY; 2University of Kentucky Medical Center, Lexington, KY.

Background: Acute kidney injury-requiring dialysis (AKI-D) occurs in about 5% of hospitalized patients and is associated with adverse outcome. Little is known about the incidence of AKI-D recovery post-discharge. We examined AKI-D recovery in hospital survivors that were discharged to an acute rehabilitation facility with the need of acute hemodialysis (HD) therapy.

Methods: Retrospective cohort study of 43 acute rehabilitation facility residents that required nephrology consultation from 8/2015 to 12/2016. Among these, 24 patients were identified that nephrology was consulted on for AKI-D management as they were HD-dependent at the time of discharge from the University of Kentucky Hospitals. AKI-D recovery was defined as the patient no longer requiring HD therapy for AKI. The observation period ended at the time of acute rehabilitation facility discharge.

Results: Mean (SD) age was 61.5 (10.2) years, 70.8% were males and 87.5% whites. AKI-D recovery post-discharge occurred in 14/24 (58.3%) patients. A total of 3/24 (12.5%) patients died during the rehabilitation facility stay, 2/3 (66.7%) without AKI-D recovery. Patients without AKI-D recovery post-discharge had lower baseline eGFR 45.9 (16.9) vs 78.1 (12.0), p<0.001 and tended to have longer hospitalization days: median (25th-75th percentile) 44 (28-55) vs 33 (21-43) days, p=0.25. Importantly, hospital HD vintage days were significantly higher in those without AKI-D recovery: 54.5 (37.3-96.5) vs 33.0 (20.3-39.0), p<0.04. Similarly, total intradialytic hypotension episodes were more frequent in patients without AKI-D recovery: 10.0 (4.0-15.0) vs 2.5 (1.0-3.3), p=0.07. Critical illness and comorbidity scores were not significantly different among those with vs without AKI-D recovery post-discharge.

Conclusions: At least 1 out of 2 patients discharged to an acute rehabilitation facility with AKI-D diagnosis recovered kidney function no longer requiring HD therapy for AKI. HD-specific characteristics may play a central role in the development of risk-stratification tools for the prediction of AKI-D recovery post-discharge.

Oxcarbazepine Induced Rhabdomyolysis

Nuray Can Usta,1 Sara Yavuz,2 Trabzon Kanuni Training and Research Hospital, Trabzon, Turkey.

Background: Rhabdomyolysis is a damage of muscle cells and an involvement of myoglobin in circulation of cellular elements. In addition to the direct toxic effects of myoglobin, the tubular obstruction of direct iron ions also plays a role in the pathogenesis of acute renal failure. We would like to remind the rhabdomyolysis, side effect of oxcarbazepine which is an antiepileptic agent used in the treatment of trigeminal neuralgia due to mortal consequences as acute renal failure.

Methods: 70 year old female patient applied to the clinic with the complaint of pain that affected her right side of her face. Her history contained diabetes mellitus, hypertension, bronchial asthma and hyperthyroidism. Her neurological examination was normal. Laboratory investigation detected only slightly elevated blood glucose. The patient was diagnosed with trigeminal neuralgia and treated with Oxcarbazepine 150mg 2x1. On the third day of the treatment, drowsiness and decreased amount of urine was observed. Patient’s serum creatinine levels were 4.0mg/dl. Serum myoglobin and creatine phosphokinase were 1000mg/ml and 765 U/l respectively. Myoglobin level of urine was 1700 ng/ml. Acute renal failure caused by rhabdomyolysis was considered. Oxcarbazepine was discontinued. Hydration and support aids were administered. In the follow-ups, it was noted that the apathy state of the patient was mended, there was no need for renal replacement therapy, serum creatinine levels had decreased to 1.2 mg/dl and she was discharged.

Results:

Conclusions: Trigeminal neuralgia is a sharp, intermittent and superficial pain, limited to nerve traces and is caused by demyelinization of cranial nerves caused by various factors. Anticonvulsants must be used first. Rhabdomyolysis occurs when muscle cells are damaged and intracellular elements enter systemic circulation. Non-physical factors. Anticonvulsants must be used first. Rhabdomyolysis occurs when muscle cells are damaged and intracellular elements enter systemic circulation. Non-physical factors.
Human Epithelial C5aR1 Signalling Enhances Bacterial Adhesion to Renal Tubular Epithelial Cells through Upregulation of the Expression of Mannosyl Residues (the Ligand for Type I Fimbriae) Ke Li,1 Wuding Zhou.1,2 1King’s College London, London, United Kingdom; 2Xi’an Jiaotong University, Xi’an, China.

Background: Our recent work has shown that C5aR1 participates in the pathogenesis of renal infection in a murine model of ascending urinary tract infection through C5aR1 signalling-mediated upregulation of mannosyl residue (the ligand for type 1 fimbriae) expression on renal tubular epithelial cells which enhances bacterial adhesion and colonization of renal tubular epithelium. However, the relevance of these findings to humans is unknown. In the present study, we investigated whether human C5aR1 plays the same roles as mouse C5aR1 in enhancement of bacterial adhesion to renal tubular epithelial cells.

Methods: Normal human kidney tissues were used for detection of C5aR1 (by immunohistochimical staining) and α-mannosyl residue expression (by lectin staining using fluorescence GNL). Partially cultured human renal tubular epithelial cells (RTEC) were used for assessment of bacteria adhesion/uptake, mannosyle residue expression, inflammatory cytokine production and activation of intracellular signaling pathways in response to human C5a stimulation. RT-PCR and flow cytometry bead array were used to detect the expression of invasion-related cytokines in RTEC for detection of α-mannosyl residue expression on the cell surface. CFU assay was used for measuring bacterial binding and uptake.

Results: C5aR1 and α-mannosyl residues were clearly detected in renal tubules, predominantly localized at the cortical-medullary junction. C5aR1 and α-mannosyl residues were also detected in RTEC. C5a (10nM) stimulation of RTEC resulted in significant up-regulation of: i) α-mannosyl residue expression, ii) ERK and NF-κB signalling-mediated upregulation of mannosyl residue expression on the cell surface. CFU assay was used for detection of α-mannosyl residue expression on the cell surface. CFU assay was used for measuring bacterial binding and uptake.

Conclusions: Our findings demonstrate an important role for human C5aR1 in enhancement of bacterial adhesion to renal tubular epithelial cells which has implications for the pathogenesis of human renal infection.

Funding: Government Support - Non-U.S.

Takayasu Arteritis Causing Complete Occlusion of the Infrarenal Abdominal Aorta and Left Renal Artery Stenosis Don H. Espirit, Volodymyr Chorny, Vikrampal Bhatti, S. Irfan Qadri. UF Department of Nephrology; Gainesville, FL.

Background: Takayasu Arteritis is classified as a large-vessel vasculitis which primarily affects the aorta and its branches. The renal arteries are of no exception. We present a case of a female patient with complete infrarenal abdominal aorta occlusion and severe left renal artery stenosis.

Methods: The patient was a 50 year old caucasian female with a past medical history significant but not limited to Takayasu arteritis, right renal nephrectomy secondary to right renal artery occlusion when she was 35 years old as a consequence of Takayasu arteritis. She presented with frontal headache and was found to have elevated blood pressure and acute kidney injury with oliguria. CTA of the abdomen and chest showed complete occlusion of the infrarenal abdominal aorta with associated mesenteric collateral consistent with chronic occlusion. [IMAGE A]. The right renal artery was absent and the left renal artery revealed high grade stenosis. [IMAGE B]. However a Doppler ultrasound did not reveal any significant flow to the left kidney. [IMAGE C]. She was taken to the operating room and underwent aortobifemoral bypass with a 14x7 Hemashield graft and left aortorenal bypass with Fem Hemashield graft. Luckily she escaped renal replacement therapy.

Results:

Conclusions: Takayasu Arteritis(TAK) is a rare granulomatous vasculitis affecting women of childbearing age. TAK should be suspected based upon clinical findings and specific imaging findings of the aorta and its branches. There are no diagnostic laboratory test for TAK. Erythrocyte sedimentation rate and C-reactive proteins may provide some support for the systemic inflammatory process but normal values should not exclude the diagnosis. Clinicians, nurses, and other clinical staff need to be cognizant of this rare pathology especially in patients who presents with hypertension at a young age. Early diagnosis is vital in order to prevent major complications or even death.

Funding: Government Support - Non-U.S.
Angiogenic or Anti-Inflammatory Factor Secretion-Genome Engineered Mesenchymal Stem Cells for the Treatment of AKI

**Background:** Acute kidney injury (AKI) is defined as an abrupt reduction of kidney function which is accompanied by renal tubular necrosis, vascular injury and inflammation. AKI is associated with high morbidity and mortality and hence, new strategies directed to reduce renal injury and improve renal function are greatly needed. Stem cell-based therapy with genome engineering has been proposed as a potential strategy. Here, we aimed to generate genome-engineered mesenchymal stem cells (MSCs) to secrete angiogenic factors, VEGF and angiopeptin1 (ANG1), or anti-inflammatory factors, erythropoietin (EPO) and a-melanocyte stimulating hormone (a-MSH), respectively, for therapeutic application.

**Methods:** To integrate each gene expression cassette into a safe harbor locus, AAVS1, of the human umbilical cord-derived MSCs (hUCMSCs) chromosome, AAVS1-targeting Zinc-Finger Nuclease (ZFN) or AAVS1-targeting CRISPR/Cas9 system was used.  

- **Results:** ZFN- or CRISPR/Cas9-aided targeted integration was achieved in hUCMSCs which were confirmed by flow cytometry and junction PCR analysis. Genome-engineered hUCMSCs were confirmed to maintain their characteristics of stem cells. Each protein product released from genome-engineered hUCMSCs with AAVS1-targeting ZFN or CRISPR/Cas9 was measured in conditioned media by each protein-specific ELISA (VEGF-hUCMSCs; 12 or 7 ng; ANG1-hUCMSCs; 11 or 10 ng; EPO-hUCMSCs; 32 or 5 IU, and a-MSH-hUCMSCs; 0.2 ng per 10^6 cells for 24 h (ZFN only). Then, we made the scaffold-free cell sheet system based on temperature-responsive polymer (poly(N-isopropylacrylamide)) to enable transplanted hUCMSCs to be engrafted for a long time to maximize the therapeutic effects.

- **Conclusions:** Taken together, cell sheet system of hUCMSCs secreting angiogenic or anti-inflammatory factors can be successfully established. This is to be examined in animal models of AKI to demonstrate the therapeutic effects of stem cell-based regenerative strategy against AKI.

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

---

Astragaloside IV Ameliorates Aristolochic Acid-Induced AKI Associated with Antiapoptosis and Reduction of Mitochondrial Injury

**Background:** Aristolochic acid (AA) nephropathy (AAN) is characterized by AKI subsequently followed by interstitial fibrosis. Apoptosis and mitochondrial injury play a critical role. Astragaloside IV (AS-IV) has been shown to exert renal protection in many mouse models of AKI, but its role in preventing AA-induced AKI still remains obscure.

**Methods:** HK-2 cells induced by AA were used to investigate the protective role of AS-IV in antiapoptosis and reduction of mitochondrial injury. In vivo, mice subjected to AA injection were administered AS-IV by intraperitoneal injection. TUNEL assay, immunofluorescence staining, electron microscopic examination and Immunoblot analysis were utilized to detect the protective role of AS-IV in antiapoptosis. Extracellular flux analysis were carried out by Seahorse XF24 analyzer to examine the protective role of AS-IV in reduction of mitochondrial injury.

**Results:** In vivo showed that AS-IV provided morphologic and functional renoprotection against AA-induced AKI via inhibiting apoptosis and reducing mitochondrial morphological change. Further, data in vitro suggested treatment with AS-IV ameliorated mitochondrial respiration damage induced by AA, and inhibition of MAPKs pathways prevented apoptosis and mitochondrial respiration.

**Conclusions:** All these findings indicated a promising effect of AS-IV in protection against AA-induced AKI via anti-apoptosis and reduction of mitochondrial injury, and inhibition of MAPKs pathways might be involved in this process.

---

Udenafil Attenuates Renal Injury through Inhibition of Thrombospondin-1 after Unilateral Ischemia-Reperfusion Injury

**Background:** Thrombospondin-1 (TSP-1) is a ligand of CD36, transmembrane receptor. TSP-1 shows antiangiogenic effect and plays as an endogenous activator of TGF-ß concerning of renal fibrosis. Udenafil, a cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 inhibitor is well-known as vasodilator with anti-oxidant effect. Udenafil shows a protective effect through nitric oxide (NO) cGMP pathway in ischemic kidney, particularly. Herein, we newly investigated a role of Udenafil related with TSP-1 in unilateral ischemia-reperfusion injury (IRI).

**Methods:** Unilateral IRI surgery was performed on male Sprague-Dawley rats with various weights of 200–250 g. All rats, including control (n=6), saline injection (n=7), and udenafil treated (n=6) were at 7 weeks of age. We performed a flank approach to induce IRI. The renal ischemia was induced by vascular clamps over the pedicles for 45 minutes. The udenafil of 20 mg/kg in only udenafil group (n=8) was administrated intraperitoneally with volume of each 5 mg/ml at 24 hours and 0 hour before IRI surgery with volume of 5 mg/ml. At 24 hours after the IRI, kidneys were harvested and fixed in paraformaldehyde for pathological studies.

**Results:** On western blotting, unilateral IRI increased molecules, such as TSP-1, fibronectin, and P-smad 2/3 compared to control. Pretreatment of udenafil in rats with unilateral IRI also attenuated expression of TSP-1 and fibronectin compared to saline + unilateral IRI rats. There was unfortunately no difference of expression of P-smad 2/3 between udenafil + IRI and saline + IRI group. There was pathologic findings, including renal tubular epithelial dilatation and severe interstitial inflammation on IRI rats, however, histologic improvement was not shown in rats with udenafil + IRI compared to rats with saline + IRI.

**Conclusions:** Generally, udenafil shows anti-angiogenic effect through the activation of NO/cGMP pathway. Thus, udenafil showed beneficial effect in the kidney with renovascular stenosis or ischemia. To date, there were unfortunately rare data for relationship between udenafil and renal fibrosis induced by IRI. Although there was no a histological improvement in udenafil + IRI rats due to severe IRI for 45 minutes, significant change of molecules, such as TSP-1 and fibronectin, supports that udenafil might have a protective or anti-fibrotic effect after IRI.
NS-1 Improves Contrast-Induced Nephropathy in Rats

Methods: Male Sprague-Dawley rats were injected intraperitoneally with only saline (control group, n=9), while CIN groups were treated with either saline (SL, n=10) or NS-1 (10 mcg/kg/day, n=8) at 0, 24 and 48 hours of the experiment. CIN was established by intravenously injecting indomethacin (10 mg/kg), L-NAME (10 mg/kg) and a high-osmolar contrast agent (Urografin 76%, 6 ml/kg) at 24h of the experiment. On the 72h, kidneys were removed for the assessment of histopathological changes and the determination of glutathione levels and myeloperoxidase activity. Data were analyzed using ANOVA and Student’s-t-test.

Results: Serum creatinine levels in SL-treated and NS-1-treated CIN groups were elevated as compared to control group (p<0.05), while the increase in NS-1-treated group was relatively lower but not significant (p>0.05). In contrast to depressed 24-h creatinine clearance in SL-treated CIN group (p<0.05), clearance in NS-1-treated group was not different than that of the control group. CIN-induced increase in renal myeloperoxidase activity (p<0.05) in SL-treated group was abolished in NS-1-treated group (p>0.05). Renal glutathione content which was reduced in SL-treated CIN group, was elevated by NS-1 was relatively lower but not significant (p>0.05). In contrast to depressed 24-h creatinine determination of glutathione levels and myeloperoxidase activity. Data were analyzed using ANOVA and Student’s-t-test.

Conclusions: The present data demonstrate that CIN is ameliorated by NS-1, which appears to act by inhibiting the infiltration of neutrophils and preventing the oxidative stress. These data suggest that NS-1 may have a regulatory role in protecting against CIN.

Funding: Government Support - Non-U.S.

Patient with Ethylene Glycol Poisoning and Need for Following Renal Replacement Therapy

Methods: A 46-year-old man was admitted to the hospital on the 30 November 2011 with suicidal ethylene glycol poisoning. It was a severe intoxication with serum ethylene glycol concentration above 10 g/l. Initial haemodialysis was urgently started followed by continual veno-venous haemodialfiltration (CVVHDF) and intravenous ethylene was continuously administered. Metabolic acidosis was not serious, and spontaneous diuresis was maintained. The next haemodialfiltration was done on the 10 January 2012, after there had been renal function partially repaired to glomerular filtration (GF) on grade 3a-b, and since the year 2013, glomerular filtration is on grade 2. On the 12 April 2017, the patient was admitted to the hospital again with suicidal ethylene glycol poisoning (he ingested demonstrably 11 automotive antifreeze), and the initial serum ethylene glycol concentration was 4.7 g/l. Initial haemodialfiltration was started (before we known serum ethylene glycol concentration), followed by continual veno-venous haemodialfiltration (CVVHDF) and intravenous ethylene was continuously administered. Metabolic acidosis was not serious, and spontaneous diuresis was maintained. The next haemodialfiltration was done on the 13 April, followed on the 15 April by continual veno-venous haemodialfiltration (CVVHDF), when the serum ethylene glycol concentration was zero. The patient did not develop a progression of chronic kidney disease, and the last glomerular filtration was 1.4 ml/s (measured GF) or 1.21 ml/s (GF - MDRD).

Conclusions: According to our experience, early comprehensive treatment of severe ethylene glycol poisoning saves not only the life of the patient, but also, in the optimum case, it may also enable the repair of renal function.

Liraglutide-Induced Acute Tubular Necrosis

Methods: A 48-year-old female with a past medical history of CKD III, HIV (CD4 1395), Type II Diabetes Mellitus, and HTN presented to the hospital with one week of progressive dyspnea and lower extremity swelling. Of note the patient was started on liraglutide 1 month prior to admission. Her creatinine on presentation was 6.92 mg/dl following the diagnosis of acute renal failure. A SPEP showed a polyclonal gammopathy and UPEP quantified 460 mg/dl protein of mixed tubular/glomerular origin. ANA was positive, Anti-ds DNA was negative, ASO was 320 speckle pattern. A renal ultrasound was unrevealing. A renal biopsy revealed moderate to severe acute tubular necrosis in the background of diabetic changes. Immunofluorescence (IF) was negative. Given the finding of ATN and interval work-up, drug reaction to liraglutide was noted as the primary insult. Upon review of her chart, she was on the medication with the known gastrointestinal and thyroid side effects, but only few reports of renal toxicity. Given insufficient evidence, Liraglutide can be overlooked as the culprit in a patient presenting with acute renal failure, thereby delaying the diagnosis and decreasing the likelihood of renal recovery.

Conclusions: This case illustrates the importance of a medication history in identifying a temporal relationship between new drug initiation and the onset of renal failure. This patient had multiple risk factors for renal dysfunction including Diabetes Mellitus, HTN, HIV and morbid obesity. Although rarely reported, Liraglutide-induced AKI should be considered in the differential of a diabetic patient presenting with renal dysfunction when more common etiologies have been excluded. It is particularly important to monitor and recognize this adverse event early as withdrawing the offending agent can prevent progression to End Stage Renal Disease.

Atypical Hemolytic Syndrome Post-Transplant

Background: Introduction: Hemolytic Uremic Syndrome (HUS) is a type of Thrombotic Microangiopathy (TMA); it presents with thrombocytopenia, anemia, and acute renal failure. Atypical HUS (aHUS) accounts for 10% of all HUS cases, and is reported to have anti-inflammatory and antiapoptotic actions in several experimental models. However, the role of NS-1 in the development of CIN has not yet been elucidated.

Case Description: In this study, we aimed to demonstrate the effects of NS-1 on CIN. NS-1 (10 mcg/kg/day, n=8) at 0, 24 and 48 hours of the experiment. CIN was established by intravenously injecting indomethacin (10 mg/kg), L-NAME (10 mg/kg) and a high-osmolar contrast agent (Urografin 76%, 6 ml/kg) at 24h of the experiment. On the 72h, kidneys were removed for the assessment of histopathological changes and the determination of glutathione levels and myeloperoxidase activity. Data were analyzed using ANOVA and Student’s-t-test.

Results: Serum creatinine levels in SL-treated and NS-1-treated CIN groups were elevated as compared to control group (p<0.05), while the increase in NS-1-treated group was relatively lower but not significant (p>0.05). In contrast to depressed 24-h creatinine clearance in SL-treated CIN group (p<0.05), clearance in NS-1-treated group was not different than that of the control group. CIN-induced increase in renal myeloperoxidase activity (p<0.05) in SL-treated group was abolished in NS-1-treated group (p>0.05). Renal glutathione content which was reduced in SL-treated CIN group, was elevated by NS-1 was relatively lower but not significant (p>0.05). In contrast to depressed 24-h creatinine determination of glutathione levels and myeloperoxidase activity. Data were analyzed using ANOVA and Student’s-t-test.

Conclusions: The present data demonstrate that CIN is ameliorated by NS-1, which appears to act by inhibiting the infiltration of neutrophils and preventing the oxidative stress. These data suggest that NS-1 may have a regulatory role in protecting against CIN. Funding: Government Support - Non-U.S.
A 37 year old female with ESKD status post pancreas-kidney transplant presented with gastroenteritis-like symptoms. Laboratory evaluation showed a creatinine of 2.59 (baseline 0.55), hemoglobin of 10.9, platelets of 38, with schistocytes and polychromasia on peripheral smear. Further testing included a low C3 level, low normal C4, elevated lactate dehydrogenase, normal haptoglobin, negative cultures (blood, urine, stool), normal ADAMTS13 activity, and negative Shiga toxin. Renal biopsy revealed thrombi in rare glomerular capillary loops and acute tubular necrosis, with no signs of acute T-cell mediated or antibody mediated rejection. Genetic testing was negative for a specific quantitative or genetic factor leading to complement dysregulation. Patient was treated with hemodialysis and eculizumab. Renal function improved, and she no longer required dialysis at time of discharge.

Results: Methods: Results: Conclusions: Discussion: Underline represents presenting author.
Results: PCT had a significantly higher value among patients who developed AKI than non-AKI group (67.9±20.99 ng/ml vs. 36.8±18.36 ng/ml); p < 0.001. Also, PCT exhibited a good predictive role for AKI with the ROC area under the curve was. 0859 (p < 0.001).

Conclusions: PCT may help in the early prediction of AKI among septic ICU patients.

PUB045

Successful Treatment of Renovascular Hypertension in Takayasu's Arteritis via Stenting: A Two Year Outcome Aparna Natarajan,1 Julia Schneider,1 Ivo O. Okundaye.2 1LUMC, Westmont, IL, 2Troy University Medical Center, NEEAH, WI.

Background: A 31 year -old woman with no prior medical history presents to an outpatient ER for abdominal pain. Physical exam was notable for blood pressure of 190/96 mm Hg and diffuse tenderness to palpation of the abdomen. ESR 88, amylase 146 and lipase 834, UA negative for blood and protein. Patient was started empirically on steroids for autoimmune pancreatitis. Subsequent MRI showed infrarenal aortic wall thickening with extension into left renal artery concerning for aortitis. Upon initiation of lisinopril creatinine doubled to 2.05 mg/dL. A CT angiogram of abdomen revealed duplicated right renal artery, moderate to severe occlusion of bilateral renal arteries and thus suspicion of bilateral renal artery stenosis was confirmed. In addition,CT also showed inflammation around infra- renal aorta, findings suggestive of Takayasu’s arteritis. Other possible causes of large vessel vasculitis or infection were ruled out.

Methods: While the patient was started on prednisone and mycophenolic acid to treat vasculitis, she continued to be profoundly hypertensive with little response to antihypertensive agents in three different classes plus diuretics. Renal duplex showed 8.9 cm R and 1.1 cm without hyperemia. Given complete occlusion of the two right renal arteries and small right kidney size, a decision was made to perform Left renal artery stent placement. Renin levels at the time of the angiogram were 24 ng/mL/hr. In follow up of six weeks after drug-eluting stent placement, she had improvement in blood pressure readings, improvement in inflammatory markers and was able to discontinue most of the antihypertensive agents. Subsequent renal duplex studies demonstrated improved renal velocities (1.7m/sec from 2.6m/sec of left renal artery) which are maintained two years post procedure. Patient is now on maintenance steroid, ace-inhibitor, cellcept 1500mg BID and clopidogrel.

Results: Conclusions: Takayasu’s Arteritis is a rare cause of renal artery stenosis. Endovascular stenting and immunosuppression haves been proposed treatments in prior studies. This case report demonstrates efficacy of this combined approach two years post stent placement for treatment of hypertension and preservation of renal function.

PUB046

Long-Term Clinical Impacts of Cumulative Fluid Balance in Continuous Renal Replacement Therapy. Chun Soo Lim, Jung Nam An, Jung Pyo Lee, Yun Oh Oh. Seoul National University Boramae Medical Center, Seoul, Republic of Korea.

Background: Renal functional assessment at 3 months after continuous renal replacement therapy (CRRT) initiation can be useful in predicting long-term mortality and progression to ESRD.

Methods: We investigated the association between fluid balance before and after CRRT initiation and long-term outcomes after acute kidney injury (AKI) episode requiring CRRT. Among 1764 adult AKI patients started on CRRT from 2009 to 2013 in intensive care units in four tertiary academic hospitals in Korea, 331 survivors at 3 months after CRRT initiation were enrolled. Chronic kidney disease (CKD) progression was defined as a worsening renal status assessed at 3 months after CRRT initiation, comprising RRT continuation, an increase in serum creatinine of more than 50%, and a decrease in the glomerular filtration rate of 35% or more than the baseline values.

Results: Cumulative fluid balance during 5 days after CRRT initiation was not associated with CKD progression. However, a positive fluid balance during 24 hours before CRRT initiation had the protective effect for CKD progression [Odds ratio 0.46 (0.23-0.91); P = 0.026]. This result was significant after adjustment for gender, age, and baseline serum creatinine. During the median 20.4 (7.5-39.7) months of follow-up, fluid balance showed the long-term mortality impact.

Conclusions: Cumulative fluid balance after CRRT initiation was not associated with the long-term clinical outcomes. However, positive fluid balance during 24 hours before CRRT initiation was a favorable factor for CKD progression. The monitoring and management of fluid balance before CRRT initiation could be important.

PUB047

Clinical Analysis of Cardiac Surgery Patients with AKI shuqin An, Jung Pyo Lee, Jin Ji. Jin Gallagher.1 George Institute for Global Health, Sydney, NSW, Australia; 2Austin Health, Melbourne, NSW, Australia; 3Intensive care unit, Beijing Friendship Hospital, Beijing, China; 4Intensive care unit, Beijing Friendship Hospital, Beijing, China.

Background: AkI is one of the severe clinical syndromes with the high morbidity and mortality. Due to the difference of geographical and disease distribution, the risk factors of postoperative AKI are still controversial. This research retrospectively analyzes the mortality, morbidity, risk factors and clinical features of Postoperative AKI. Analysis the risk factors in mortality and severity of AKI for improving prognosis and treatment. In order to reduce the morbidity and mortality of AKI after cardiac surgery, it is necessary to identify and intervene the risk factors before and after the operation. In this study, we investigated clinical features, general information, laboratory data, basic diseases and prognosis. Logistic regression analysis was used to investigate the risk factors in morbidity and severity of AKI.

Methods: 575 underwent cardiac surgery in the first affiliated hospital of Xi’an Jiaotong University from July 2015 to June 2016. The definition of AKI was based on the KDIGO clinical practice guideline for AKI. Screening patients with AKI or not who met the KDIGO criteria and had complete case histories. We reviewed clinical course, laboratory parameters, general information, laboratory data, basic diseases and prognosis. Logistic regression analysis was used to investigate the risk factors in morbidity and severity of AKI.

Results: Results of the 575 patients, AKI developed in 177(31.78%) patients, whereas 40(17%) had renal replacement therapy. Patients with AKI had higher mortality than patients without AKI (10.17% vs0.5%, P<0.0001). AKI occurred mainly the first day after the cardiac surgery, and most of them are stage The highest diagnostic rate (80.23%) of AKI is the first day after the operation. The incidence of AKI at stage 2 and stage 3 was close in the second day. After day operation than the first day. The patients with AKI in the first day of operation had the worst outcome. Logistic regression analysis showed that cardiodiopulmonary bypass, the advanced age, the high level of prooperative blood CystatinC, perioperative infection, intraoperative cardiodiopulmonary bypass time, were the independent risk factors of AKI after cardiac surgery. Left ventricular ejection fraction (LVEF) <40%, perioperative infection and postoperative arrhythmia were risk factors influencing the severity of AKI.

Conclusions: Cardiac surgery induces high morbidity of AKI and mortality and poor prognosis which closely associated with many risk factors. Perioperative infection is not only an independent risk factor for the occurrence of AKI, but also an independent risk factor for the severity of AKI.

PUB048

Causes, Clinical Features, and Treatment of Rhabdomyolysis: A Prospective Analysis. Fanwen Li, Li Li, Shuhongli, Pu Liu. The First Affiliated Hospital of Jinan University, Guangzhou, China; 2The First Affiliated Hospital of Jinan University, Guangzhou, China.

Background: RM is a condition of skeletal muscle breakdown where muscle injury causes a release of myoglobin and the muscle enzymes creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and the transaminases. The classic presentation of this condition is muscle aches, weakness, and tea-colored urine. RM is commonly associated with myoglobinuria, and if sufficiently severe, this can result in AKI. Since a systematic review of RM is currently lacking in the literature, we undertook this study of the causes, clinical features, and treatments of RM.

Methods: We retrospectively reviewed the medical charts of patients with confirmed diagnoses of RM from June 2012 to August 2016, who had received care at the First Affiliated Hospital of Jinan University, Guangzhou, China.

Results: A total of 48 patients were included in this study (36 males and 12 females). The most common causes of RM among these patients were strenuous exercise (50%) and infection (25%). Muscular weakness (72.92%) and muscular pain (64.38%) were the most common presenting symptoms, followed by fever, dark urine, emesis, and oliguria or anuria. Among the patients, 42 received intravenous (IV) fluid therapy, and none developed acute kidney injury (AKI). The other six patients accepted continuous renal replacement therapy (CRRT), five of whom had an alleviation of their symptoms. One patient was transferred to another hospital for further treatment since the primary disease was dermatomyositis and it was non-responsive to immunotherapy.

Conclusions: RM is a complex condition with non-specific symptoms that can develop from various causes. The syndrome is treatable and has good outcomes. Early and adequate fluid therapy has been the main intervention for preventing and treating AKI. Renal replacement methods can also play a supportive role, though they are not the first line of treatment for RM-induced AKI. Our results indicate that the most effective treatments are early diagnosis, comprehensive therapy, active prevention, and the timely elimination of complications.

PUB049

Sofa Coagulation Score and Patient Outcomes in Severe AKI: Analysis from the Randomised Evaluation of Normal versus Augmented Level of RRT (RENAI) Study. Lim Lin,† Ying Yang,† Rinaldo Bellomo,‡ Meili Duan,‡ Martin P. Gallagher.1 George Institute for Global Health, Sydney, NSW, Australia; 2Austin Health, Melbourne, NSW, Australia; 3Intensive care unit, Beijing Friendship Hospital, Beijing, China; 4Intensive care unit, Beijing Friendship Hospital, Beijing, China.

Background: A decline in platelet count is common in critically ill patients with severe AKI. However, there is relatively little data assessing the association of SOFA coagulation scores and clinical outcomes in severe AKI patients receiving continuous RRT.

Methods: We performed a secondary analysis from the Randomised Evaluation of Normal versus Augmented Level of RRT (RENAI) study. The primary endpoint was all-cause mortality at 90 days after randomisation. The secondary outcomes were the length of intensive care unit and hospital stay. The association between the SOFA coagulation scores and these outcomes were analysed using multivariate Cox model adjusted for baseline variables.

Results: Among 1465 patients in the RENAI study, the complete SOFA coagulation scores data was available in 1227 patients. Among them, 579 patients had high SOFA coagulation scores (defined as ≥4), while 701 patients had normal SOFA coagulation scores (<4). The univariate analysis showed that high SOFA coagulation scores were associated with higher mortality at day 90 (49% vs 38.5%, P<0.0002). There was no significant difference in the length of ICU and hospital stay between these two groups.
In multivariate analysis, the association between high SOFA coagulation scores and increased mortality rate at 90 days remained significant.

Conclusions: In the RENAL study, an approximately 50% of patients had an increase in SOFA coagulation scores during their ICU admission. High SOFA coagulation scores were associated with increased mortality at 90 days.

PUB050

Early Recurrence of AKI Is a Prognostic Factor for All-Cause Mortality

Background: Recurrent acute kidney injury (AKI) is associated to a risk factor for mortality. However, it is unclear whether the period until AKI recurrence may influence mortality. We set up a hypothesis that early recurrence is higher mortality and evaluated the prognosis of recurrent AKI cases by setting 21 days as the cut-off period of AKI recurrence.

Methods: All of the cases were admitted and followed-up at the Kanazawa University Hospital in Japan from November 1, 2006 to October 31, 2007. A total of 21,939 cases were evaluated retrospectively. The primary endpoint was death. The observation time was two years. Recurrent AKI was defined as the re-increase of serum creatinine after the previous AKI episode. Cases developed AKI recurrence less than 21 days were defined as the early recurrence group, and the other cases were defined as the late recurrence group.

Results: Four hundred sixty adult cases (2.1%) developed AKI in two years. One hundred thirty-five cases developed recurrent AKI among them. The number of early recurrence group was 49, and the number of late recurrence group was 86. The rates of all-cause mortality were higher in the early recurrence group (p=0.001; log-rank test); the early recurrence group, 105.5 deaths per 100 person-years; the late recurrence group, 32.7 deaths per 100 person-years; No-recurrence group, 34.4 deaths per 100 person-years).

Conclusions: Patients with recurrent AKI less than 21 days showed poor prognosis. Careful follow-up for at least 21 days after AKI is necessary detect the recurrence of AKI to predict prognosis after AKI.

PUB052

Integrated Endovascular Approach to Treatment of Acute Renal Vein Thrombosis Manifested as Primary Membranous Glomerulopathy
Natalia P lotskaya, Capital Health RMC, Trenton, NJ.

Background: Renal vein thrombosis (RVT) is a very common complication of nephrotic syndrome, it can be symptomatic and chronic asymptomatic. It is associated with imbalance between procoagulant and anticoagulant factors, endothelial dysfunction. Multiple modality treatment might be required in symptomatic RVT with extension to inferior vena cava.

Methods: A 51 year old male with a long history of hypertension and 4 months lower extremity edema presented with severe sharp left flank pain with radiation to low back for 4 days. He had similar pain in the right flank 2 months ago. Physical examination revealed elevated BP of 190/110 mmHg, left lower abdominal tenderness and moderate lower extremities edema. No family history of kidney disease or hematologic disorders was identified. Laboratory data showed increased creatinine of 1.35 mg/dl for 2 months, decreased albumin of 2.6 g/dl. CT scan of abdomen with intravenous contrast detected left renal vein thrombosis extending into the suprarenal inferior vena cava, also possible extension of thrombus into the left gonadal vein, enlarged and heterogeneous left kidney. Immediately patient was started on heparin drip. Despite of IVP infusion at rate 3 mg/hr for 6.5 hrs follow up left renal venogram still shown large clot. Decision was made to proceed with AngioJet thrombolysis and mechanical removal of residual clot which finally lead to its resolution confirmed by venogram. Next day creatinine decreased to 1.19 mg/dl. On day 5 after intervention nuclear renal scan demonstrated symmetric flow to both kidneys, no evidence of hydropnephrosis. Hypercoagulability work up was unremarkable. Isolated elevation of homocysteine 12.5 umol/L and protein S antigen > 200% were noted. Urinalysis showed severe proteinuria of 11.6 g/24hours. For this reason on day 7 patient underwent successful left kidney biopsy which shown membranous glomerulopathy (MGN) stage-2. Indirect immunofluorescence staining was positive for phospholipase A2 receptor (PLA2R) which supported primary MGN.

Results: Conclusions: Acute RVT should be highly suspected in symptomatic patients with acute kidney injury associated with lower extremity edema, sudden flank pain. Timely diagnosis with CT angiography is necessary to access extension of thrombosis and initiate combined intervention to preserve renal function and prevent further thromboembolic event.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
In CKD Patients without Contrast-Induced Nephropathy
Takuya Fujimaru, Masahiko Nagahama, Yasushi Komatsu. Nephrology, St. Luke’s International Hospital, Tokyo, Japan.

Background: Contrast-induced nephropathy (CIN) is associated with long-term adverse events. Although CIN is defined only by increased serum creatinine, previous studies have shown that contrast media exposure induces transient proteinuria. However, no study has evaluated the association of isolated increased proteinuria without CIN and clinical outcomes.

Methods: In this single-center, retrospective cohort study, we collected data of chronic kidney disease (CKD) patients who underwent contrast-enhanced CT and received CIN prevention protocol from April 2012 to March 2016 at our hospital. Patients who developed CIN were excluded. Increased proteinuria was defined as post to pre urine protein creatinine (P/C) ratio more than 1. The primary end point was the composite of certain adverse events, including death, stroke, myocardial infarction, end-stage kidney disease, coronary artery intervention and others. Log-rank test and Cox proportional hazard analysis were performed.

Results: Of 291 patients who received CIN prevention protocol, 4 patients were excluded due to CIN. In the rest patients (n=287), age 73.3±10.2, 67.2% of males), 161 patients (56.1%) had increased urine P/C ratio. During the follow-up (1250±46.8 days), 97 patients (33.8%) had adverse events. In Kaplan-Meier survival curves, patients with increased proteinuria showed significantly poor outcomes compared to those without increased proteinuria (p=0.014) (Figure). After adjusting for age, sex, baseline eGFR and urine P/C ratio, hypertension, diabetes mellitus and cardiovascular diseases, increased proteinuria significantly associated with poor long-term outcomes (Hazard ratio 2.00; 95% confidence interval 1.29-3.09).

Conclusions: Isolated increased proteinuria after contrast-enhanced CT predicts poor clinical outcomes in CKD patients even without CIN.

AKI in Intensive Care Unit: A Clinical and Outcome Study
Prof. Parinder P. Singh, Danish Kathuria, Neeru Aggarwal, Anish Gupta. MAX SUPER SPECIALITY HOSPITAL, DELHI, India.

Background: Acute kidney injury has both short term as well as long term consequences in critically ill patients. Our study was aim to document the evolving epidemiology of AKI in India.

Methods: A longitudinal study was performed in a tertiary care center in North India among 120 patients with AKI. We enrolled patients who were either admitted in ICU with AKI or i.e. community acquired (CA-AKI) or developed AKI during their ICU stay i.e. hospital acquired (HA-AKI). Diagnosis, staging, risk factors assessment and management of enrolled patients was done as prescribed by the KDIGO clinical guidelines for AKI. The outcome was assessed at discharge and at 3 months and classified as favourable (renal recovery) and adverse (residual renal dysfunction, dialysis dependence and death).

A statistical analysis was performed, using a Pearson’s Chi-square test and paired ‘t’ test.

Results: Out of 120 patients, 87(73%) had de novo AKI while 33 (27%) had acute on CKD. Out of all patients, 55 % had CA-AKI while 45 % developed HA-AKI. Almost half of the patients (47.5%) had stage I AKI, 27.5% had stage II and remaining quarter of subjects had stage III AKI. Septis (60.8 %), circulatory shock (53.3%), age > 65 years (58.3%) were the most prevalent risk factors which were significantly associated with poor outcome (p <0.05). Severity of AKI showed a linear trend with adverse outcome at discharge, which was significant (p =0.025). Clinical outcome at the time of discharge and at 3 months are demonstrated in figure 1. Almost 50 % of the stage I AKI showed complete renal recovery at 3 months as compared to only 25% and 29.6% for stage II and III respectively. Different stages of AKI also showed a graded increase in mortality at 3 months - 19.2% for stage I compared to 35.7% for stage II and 37 % for stage III.

Conclusions: This study demonstrated increasing prevalence of adverse outcome in a linear fashion with increase in severity of AKI. The epidemiology of AKI in critical care in India has started to resemble high income group countries, in terms of both age distribution as well as etiology.

A Case of AKI from Hemophagocytic Lymphohistiocytosis Induced by Ehrlichiosis
Olanrewaju O. Olaoye, Saraswathi Gopal. University of Florida, Division of Nephrology, Gainesville, FL.

Background: Hemophagocytic Lymphohistiocytosis (HLH) is an aggressive life-threatening syndrome of excessive immune activation occurring from either inherited or acquired defect in cytotoxic T lymphocytes and natural killer cells. Cytokine mediated acute kidney injury has been described to be strongly associated with HLH. Here we present a rare case of HLH associated with severe renal failure due to Ehrlichiosis r chauffeensis.

Methods: A 70-year-old African American male with history of diabetes mellitus, benign prostatic hypertrophy and hepatitis C successfully treated with Harvoni presented with generalized weakness, nausea vomiting and abdominal discomfort. Eleven days prior to his hospitalization, he was treated for right forearm cellulitis. On admission, vital signs were significant for a temperature of 39.5°C, pulse rate of 126/min. His labs showed WBC of 2.500/mm³, hemoglobin of 10.4 g/dL, platelet of 39,000/mm³, ALT 406 IU/L, AST 1,501 IU/L, ALP 110 IU/L, total bilirubin 6.9 mg/dL, ferritin 27,889 ng/ml and serum creatinine of 6.37 mg/dL (recent baseline was 1.1-1.2 mg/dL). Chest radiograph and pan-culture were not suggestive of an infection. Peripheral smear was unremarkable for schistocytes. Patient developed respiratory and renal failure requiring mechanical ventilation and hemodialysis. Given persistent pancytopenia, a bone marrow biopsy was done which showed hemophagocytic macrophages containing predominantly RBCs and neutrophils. A diagnosis of HLH was made; patient was started on Etoposide and Decamethasone therapy for immunosuppression. Ehrlichia chaffeensis serology was also obtained, considering recent history of forearm cellulitis the titers resulted as positive (IgG 1:1204 & IgM <1:16). Patient was treated with Doxycycline for 2 weeks. During the course of doxycycline therapy patient started to recover renal function, hemodialysis was stopped. Three weeks after initiation of doxycycline, he was discharged with a serum creatinine of 1.26 mg/dL.

Results: Conclusions: HLH is a syndrome of cytokine storm leading to multi-organ dysfunction including the kidneys. Early identification is crucial, as immunomodulatory therapy is required to diminish the hyperinflammatory response. Moreover, identifying the underlying cause and initiating specific therapy is imperative as it can reduce the mortality associated with HLH, which is around 50%.

Potential Hydralazine-Induced False Positive ANCA Specific for Proteinase 3 (PR3) as a Sentinel Event Mimicking of Granulomatosis with Polyangiitis (GPA) in a Case of Focal Acute Tubular Injury
Nader S. Bahri, Meharry Medical College, Brentwood, TN.

Background: Rapid declining of renal function accompanied by proteinuria and hematuria in a hypertensive and diabetic individual on hydralazine with work-up showed Positive ANCA serology activity required diagnostic renal biopsy with no evidence of GPA vasculitis with a rare reported presentation.

Methods: A 45 year-old female with a past medical history of hypertension on multiple medications recently on hydralazine, DMT2 with Hb A1C of 7.6, a known case of CKD 3 with the baseline of creatinine 1.29 mg/dl presented in December 2016 with rapid onset of breath with coughing that produced minimal amounts of blood, orthopnea, and swelling. She had a similar presentation back in November 2016 where a CT of her chest was performed that showed scattered alveolar opacities consistent with pneumonitis (Infections versus idiopathic). She subsequently developed rapid declining of renal function (serum creatinine 3.08 mg/dl). Non-nephritic range proteinuria (protein/creatinine ratio 3.3 g/g) and hematuria which raised diagnosis of pulmonary-renal syndrome and immediate therapy with high dose corticosteroids were initiated. During the work-up ANCA serology activity was positive 1:20 titer confirmed by enzyme immunosassay to confirm ANCA specific for PR3, all other serological analyses were negative and patient was initiated on cyclophosphamide with thinking of granulomatosis and polyangitis (Wegner’s granulomatosis) as main diagnosis. Afterward kidney biopsy demonstrated moderate arteriopneumosclerosis with features of accelerated hypertension-related vascular injury, moderate diabetic nephropathy and focal acute tubular injury. These findings didn’t support the diagnosis of granulomatosis and polyangitis(GPA). Hydralazine were suggested as potential cause for False Positive ANCA testing. All previous treatments has stopped and ANCA activity turns negative after withdrawal of hydralazine.
hydralazine. Patient treated for her pneumonia and acute tubular injury with improving condition.

Results:

Conclusions: This case highlights the presentation of false positive testing induced by medications. Hydralazine is a known agent causing of sporadic Pauci-immune Glomerulonephritis via ANCA activity, however in this case the false positive ANCA serology specific for PR3 didn’t reveal any pathologic evidence of vasculitis.

PUB057

AKI, Its Risk Factors, and Mortality in Chronic Obstructive Pulmonary Disease Patients


Background: Chronic obstructive pulmonary disease (COPD) is an inflammatory airway disease and a major cause of illness and death throughout the world. Inflammation is known to play a major role in the pathophysiology of AKI. We evaluate the impact of acute kidney injury (AKI) on mortality and risk factors in patients with COPD.

Methods: We retrospectively enrolled patients who hospitalized due to COPD acute exacerbation between January 2011 and April 2014. We categorized patients into two groups: with AKI and without AKI. We evaluated factors associated with AKI and effect of AKI on all-cause mortality.

Results: Among the 177 patients, 41 patients (23.2%) had AKI and 30 patients (16.9%) died during follow up period. Patients with AKI tend to lower blood pressure, lower estimated glomerular filtration rate (eGFR) and received invasive mechanical ventilation (MV) at the time of admission. Older age, lower BMI, lower eGFR level, diabetes and AKI were significantly associated with all-cause mortality. In addition, lower eGFR level, diabetes, invasive MV and presence of pneumonia were significantly associated with AKI.

Conclusions: The prevalence of AKI is relatively high in COPD patients and AKI is independent factor of the all-cause mortality. Thus, close monitoring and prevention for AKI is important in COPD patients.

PUB058

A Case of Urinary Tract Infection: One Kidney Is EPN and the Other Is Simple Pyelonephritis

Heeryong Lee, Wooseul Lee, Jeong gun Kim.

Background: Emphysematous pyelonephritis (EPN) is an acute necrotizing parenchymal and perirenal infection caused by gas-forming organism. EPN is commonly associated with diabetes mellitus, urinary tract obstruction and immunosuppression. In comparison with simple pyelonephritis, EPN is an acute severe necrotizing infection with a mortality rate of up to 25%. The most common pathogens are Escherichia coli (E. coli) and Klebsiella pneumonia. We report a case of a 78-year-old woman who developed EPN in one kidney and simple pyelonephritis in the other.

Methods: A 78-year-old woman presented to the emergency department with fever, chills, and both flank pain. Her medical history was significant for diabetes mellitus, hypertension. Spot urine reveal pyuria. Abdominal radiography revealed gas collection. And computed tomography (CT) revealed gas collection in the parenchyma and huge hydrenephrosis of the left kidney and wedge-shape low attenuation of the right kidney (Panel A). The patient received a diagnosis of emphysematous pyelonephritis of the left kidney and simple pyelonephritis of the right kidney. The patient was started on intravenous piperacillin/tazobactam on arrival. This was then switched to meropenem as blood cultures collected on two separated days grew E.coli. After the CT results were confirmed, the percutaneous nephrostomy catheter was inserted. Here she was noted to have pus and air. Antibiotics were maintained for 2 weeks and symptoms and laboratory findings improved. Control abdominal CT revealed more improving state of emphysematous pyelonephritis and hydrenephrosis. So she was discharged after catheter removal.

Results:

Conclusions: EPN is caused by gas-forming organism, most commonly E. coli. But, even if the infection is caused by the same organism, it can be expressed as another type of infection in same organ.

PUB059

Methylphenidate Associated Antiphospholipid Antibody Syndrome Mediated AKI

Neal B. Shah, Helmut G. Rennek, Juan Pablo Domecq Garces, Peter G. Czarnecki, Yanli Ding, David B. Mount, Brigham and Womens Hospital, Boston, MA; Brigham and Womens Hospital, West Roxbury, MA; Brigham and Womens Hospital, Boston, MA; Nephrology, Brigham and Womens Hospital, Boston, MA.

Background: 70 year Caucasian female admitted for elevated creatinine levels found on routine blood testing.

Methods: 70 y/o F with history of hypertension, CAD and normal pressure hydrocephalus (recent VP shunt placement) was admitted for elevated creatinine 2.3mg/dL. Methylphenidate had been started 1 month prior to admission, for slow mentation; it was held on admission. Physical exam significant for 3/6 systolic murmur radiating to carotid and mild supraventricular tenderness. No edema, anasarca or skin rash. Creatinine remained elevated despite IV saline. She was non-oliguric. Hospital course significant for labile hypertension and two episodes of acute pulmonary edema with systolic BP 200s. Labs remarkable for Hb 95g/dL (previously 12g/dL), BUN was 44mg/dL, Cr 2.3mg/dL. PTT elevated at 49s. Low haptoglobin of 8mg/dl and mild LDH elevation of 329U/L. Peripheral smear had few schistocytes. Urinalysis showed 0-2 RBCs, 3-5WBCs with bacteria, 2+ proteinuria. Urine culture tested positive for E Coli UTI, treated with fosfomycin. Protein creatinine ratio was 3.2. Renal US showed bilateral 9.5cm kidneys and normal echogenicity. Initial serologic workup was unremarkable. Kidney biopsy showed severe arteriolar and arterial sclerosis, marked hyperperfusion, no evidence of deposition disease. Anticardiolipin IgG was elevated at 35.7 CU (normal 0-19); was 19 CU two months prior. She was diagnosed with antiphospholipid syndrome, treatment included IV methylprednisolone followed by 6 week oral prednisone taper, plasmapheresis, and rituximab. BP was well controlled on captopril. Creatinine improved from peak of 2.7 to 1.3mg/dL, with drop in anticardiolipin titer to 8 CU. Haptoglobin and LDH levels normalized.

Results:

Conclusions: Methylphenidate initiation may have been the second hit causing worsening of antiphospholipid syndrome and precipitation of AKI.
Incidence of AKI in Acute Decompensated Heart Failure

**Methods:** We performed a retrospective review of existing data on patients admitted with ADHF between August 5th, 2016 and July 20, 2017. Patients were enrolled for this retrospective study. Acute kidney injury (AKI) was defined as KDIGO guideline. Chi-square test, univariate analysis and Logistic regression analysis were used to determine the risk factors for AKI and evaluate the effects of different doses of flurbiprofen on AKI.

**Results:** There were 1065 patients who used flurbiprofen perioperatively in 10774 cases, the prevalence of postoperative AKI was 6.94% in 10774 cases, the prevalence rate of AKI was5.8% and 7.3% in subjects using flurbiprofen and subjects without using flurbiprofen, respectively. After the does stratification of flurbiprofen, the incidence of AKI in patients with a low dose of flurbiprofen (≤5mg) was significantly lower than that of patients without using of flurbiprofen (7.3%) (P<0.01), while the incidence of AKI in patients with a high dose of flurbiprofen (11.2%) was significantly higher than that of patients without using of flurbiprofen (7.3%) (P<0.05). Multivariate logistic regression analysis showed that the ASA classification, preoperative estimated glomerular filtration rate, excessive bleeding and emergency surgery were independent risk factors for AKI in total patients (OR= 2.4, 2.7, 4, 3, 2.1 respectively, P<0.01), while using of low dose flurbiprofen (<150mg) was a protective factor for AKI (OR= 0.4, P<0.01). On the other hand, using of low dose flurbiprofen (>150mg), multivariate logistic regression analysis showed that the large dose of flurbiprofen, ASA classification, preoperative estimated glomerular filtration rate, excessive bleeding and emergency surgery were independent risk factors for AKI (OR= 2.9, 3, 1, 1.8, 2.4 respectively, P<0.01).

**Conclusions:** Large dose of perioperative flurbiprofen (>200mg) was an independent risk factor for AKI. Using of low dose flurbiprofen(≤150mg) perioperatively could effectivly reduce the incidence of AKI, while a large dose of flurbiprofen could aggravate the incidence of AKI.

**PUB063**

Study of Renal Morphological and Structural Changes at Different Ischemic Times and Types of Renal Vascular Pedicle Clamping

**Methods:** We performed simulating this procedure in which 16 pigs were randomized in two groups containing 8 animals each: Group AV; unilateral left clamping of the renal artery and vein with contralateral kidney used as control and Group A-L; unilateral left renal artery clamping only, with the contralateral kidney also used as control. Serial biopsies of the renal parenchyma were performed at times 0, 10, 20, 30, 40, 50, 60, 70, 80, and 90 minutes after clamping. The tissues were submitted to histological analysis to identify structural and morphological alterations.

**Conclusions:** We observed higher vascular congestion and edema in A group after 10 min, 20 min, 30 min, 40 min and 60 min post ischemia (p<0.001, p<0.001, p=0.02, p=0.001; p=0.001, respectively). We observed higher frequency of lesions in Group A for all cellular alterations found (interstitial inflammatory infiltrate, interstitial hemorrhage and cell degeneration) in all times of clamping except for the formation of pigmented cylinders that were only found in the AV Group.

**Background:** The incidence of AKI among hospitalized adults is rising, and the number of AKI cases is predicted to increase in the future, because of aging of the population and increased use of hospital laboratory, admission and discharge databases. AKI was defined and staged according to KDIGO Crea criteria. Using Crea at discharge, we evaluated renal recovery. We studied 19930 in-hospital episodes. The mean age of patients included in the study was 64±19, 52% were female, median of length of stay (days, LOS) was 4.5 and mortality was 5.6%. AKI prevalence was 11.6% and mortality in this group was 19.8%. AKI patients were older and average of days between first and highest Crea was 2 days. KDIGO stage 1 occurred in 9.2%, stage 2 in 1.6% and stage 3 in 0.8% with a stepwise increase in mortality with increasing AKI severity. ICU patients were 4631(23% of total group) of these had AKI 26%, while ward patients suffering AKI in 72%. Contrast media were
administered in 22% vs 9.4% of patients with and without AKI respectively. AKI occurred in 10.1% of patients after cardiac surgery, 60.8% vs 4.1 in patients with and without AKI respectively. In survivors, 73% have recovery of baseline renal function and 27% have partial recovery. In the last group 89.3% have a eGFR under 60ml/min/1.73m².

**Conclusions:** As described in literature, AKI is common in hospitalized adults and is associated with significantly higher in-hospital mortality and CKD.

<table>
<thead>
<tr>
<th>Table: 1. Clinical and demographic data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>All patients</td>
</tr>
<tr>
<td>AKI</td>
</tr>
<tr>
<td>No AKI</td>
</tr>
</tbody>
</table>

**PUB065**

**Preexisting AKI Could Be Reversed in a Portion of Patients after Cardiac Surgery**

Wan Xin,1 Jing Li,1 Changchun Cao.1 Nanjing First Hospital, Nanjing Medical University, Nanjing, China; 2Nanjing First Hospital Affiliated to Nanjing Medical University (Nanjing First Hospital), Nanjing, China; 3Sir Run Run Hospital Affiliated to Nanjing Medical University, Nanjing, China.

**Background:** Acute kidney injury (AKI) is a common complication after heart surgery. However, in clinical practice, preexisting AKI could also be reversed in some occasions after cardiac surgery. Especially in patients with higher levels of preoperative creatinine level. In this article, the occurrence, short-term prognosis and influential factors were discussed.

**Methods:** Five years of retrospective data (2008-2012, n=2832) were collected in the Division of Thoracic and Cardiovascular Surgery, Nanjing First Hospital, Nanjing Medical University. Observation of a decrease of 26.5µmol/L in serum creatinine in patients without renal replacement treatment was seen as the case of released preexisting AKI. Statistical description and binary logistic regression (backward stepwise: Wald) was applied in the study.

**Results:** After excluding the cases of patients with end-stage renal disease (ESRD) and missing data, 2383 cases were included in the study. Among which, 137 cases (5.7%) of patients were observed with released preexisting AKI. In patients with lower level of preoperative eGFR, the occurrence increased dramatically (from 1.4% to 50%). Compared with the postoperative acute, patients with reversed preexisting AKI suffered from lower mortality (1.5% vs. 2.6%). In the model of logistic regression, male (OR 1.794, 95% CI 1.064 to 3.041) and diabetes (OR 0.399, 95% CI 0.166 to 0.959) was a potent risk factor of incident AKI. The area under the receiver operating characteristic curve was 0.842 (95% CI 0.826 to 0.856).

**Conclusions:** Preexisting AKI could be reversed in some occasions after cardiac surgery. Preoperative creatinine is influential but not decisive in postoperative renal prospective. Combination of preoperative state could predict the releasable preexisting AKI accurately, which may provide objective evaluation for the patients with higher levels of preoperative serum creatinine.

**PUB066**

**Foley Foley: Emphysematous Pyelitis from Instrumentation in Obstructive AKI**

Anna S. Gutman,1 Shimson Wiesel,1 Jonah E. Abraham,2 Militza K. Kirovycheva.3 Staten Island University Hospital, Staten island, NY; 3Anesthesiology, University of Pittsburgh Medical Center, Pittsburgh, PA.

**Background:** Emphysematous pyelitis (EP) is a subclass of the life threatening infection, emphysematous pyelonephritis (EPN). We report a case of an 81-year-old man, who developed EP after urinary tract (UT) manipulation.

**Methods:** An 81-year-old man with chronic obstructive nephropathy due to benign prostatic hyperplasia presented to our hospital with worsening kidney function. He was asymptomatic, afebrile, and had stable vital signs. His serum creatinine was 3.1 mg/dL, up from 1.5 mg/dL, the day before he had mild hematuria, pyuria, and proteinuria. Renal ultrasound showed bilateral hydronephrosis with high post void residual volume, for which a urinary catheter was placed. Repeat ultrasound showed bilateral renal collecting shadowing echogenic foci, and a CT abdomen/pelvis showed air throughout the collecting systems and ureters. He was treated with antibiotics despite a negative urine culture, and a repeat CT showed resolution of the EP.

**Results:**

**Conclusions:** EPN is divided into: Class 1 (EP) – gas in the collecting system Class 2 – gas in the renal parenchyma Class 3A – gas/abscess extension to the renal fascia Class 3B – gas/abscess extension to adjacent tissues Class 4 – bilateral EPN or a solitary kidney with EPN Treatment for EPN is individualized, with general guidelines: Class I and II – antibiotics and percutaneous drainage (PCD) if the UT obstruction remains Class III and IV antibiotics, PCD, and nephrectomy if no improvement. For all classes, relief of the UT obstruction Our patient had asymptomatic, class I EPN, likely due to UT

**CT:** air in the renal pelvices extended into the ureters (arrows). Fat-stranding of the bilateral kidneys (asterisks). Air at the left uretero-vesical junction (arrowhead)

**PUB067**

**Association of the Severity and Recurrence of AKI with Incident CKD in Head and Neck Cancer Patients with High-Dose Cisplatin-Based Chemotherapy**

Hikikako Akihiko Kato,1 Naoko Tsuji,1 Takayuki Tsuji,1 Naro Ohashi,1 Hideo Yasuda.1 Hamamatsu University School of Medicine, Hamamatsu, Japan; 2Hamamatsu University Hospital, Hamamatsu, Japan.

**Background:** Acute kidney injury (AKI) is a serious complication of cisplatin (DDP)-based chemotherapy. However, its impact of long-term renal outcome is not clear. We aimed this study to examine the impact of AKI severity and recurrence on renal outcome in head and neck cancer patients with DDDP treatment.

**Methods:** We identified 52 head and neck cancer patients whose basal estimated glomerular filtration rate (eGFR) was higher than 60 ml/min/1.73m², and who had underwent chemoradiotherapy including 66-70 Gy with repeated infusion of DDDP of 80 mg/m² on days 1, 2, and 43 (age: 60±10 years old, male/female=48/4, basal eGFR: 87±18 (60-143) ml/min/1.73m²).

**Results:** Of 52 patients, 24 (46.2%) developed AKI; 14 (26.9%) developed stage 2, 10 (19.2%) developed stage 3, and 8 (15.4%) developed stage 4 of AKI respectively. In 7 patients who did of 2 episodes, and 1 patient who did of 3 episodes during the chemotherapy. During the 4-month follow-up after the treatment, mean eGFR was decreased to 76±25 (32-182) ml/min/1.73m². There were 23 patients (44.2%) who developed incident chronic kidney disease (CKD). 19 of stage G3a and 4 of stage G3b. A multiple regression analysis revealed that basal eGFR was a significant determinant of incident CKD (β=-0.1, p<0.01). Especially, of 20 patients whose basal eGFR was lower than 80 ml/min/1.73m², and who had underwent chemoradiotherapy including 66-70 Gy with repeated infusion of DDDP of 80 mg/m² on days 1, 2, and 43 (age: 60±10 years old, male/female=48/4, basal eGFR: 87±18 (60-143) ml/min/1.73m²).

**Conclusions:** The findings suggest that the severity and recurrence of AKI episode during the DDDP-based chemotherapy did not relate to subsequent CKD progression. Rather, a lower basal eGFR (< 80 ml/min/1.73m²) was a potent risk factor of incident CKD after the DDDP-based chemotherapy.

**PUB068**

**The Jaffe Reaction Is Not Affected by Acetylcysteine**

James S. Cain,1,2 Jack E. Sherman.1 Roanoke Valley Governor’s School, Roanoke, VA; 2Nephrology, Carilion Virginia Tech School of Medicine, Roanoke, VA; 3Valley Nephrology Associates, Roanoke, VA.

**Background:** Alkaline picrate creatinine determinations (the Jaffe reaction) are used to measure urine and serum creatinine levels, alternative methods have been proposed to resolve the multiple problems with this venerable technique. A common alternative (Trinder reaction) is subject to negative interference by acetylcysteine (NAc). NAc is used

**Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only**
to offer nephroprotection from IV contrast and is the subject of several investigations. We found no literature clearing the Jaffe reaction from this interference. As researchers rely upon this assay, we studied the effect of NaC on this test.

**Methods:** Serial dilutions of known concentrations of creatinine were prepared. The samples were analyzed with a negative control using manual and automated kinetic alkaline picrate procedures. Samples with creatinine concentrations of 15, 30, 60, and 125 mg/dl were assayed with added Nac of 0, 200, 100, 50, 25 and 12.5 mg/dl.

**Results:** In no case did the addition of NaC significantly alter the optical density of the “spiked” test samples compared to their non spiked counterparts, this was confirmed by ANOVA testing.

**Conclusions:** The Jaffe reaction appears to be free of negative or positive interference from NaC. Conclusions drawn from creatinine assays under these conditions can be trusted. This affirms the use of the Jaffe reaction in both clinical and research veins involving NaC in both kinetic and non kinetic assays. The assay has numerous other known interfering substances which need to be considered.

**PUB069**

Systolic Blood Pressure Predicted One Year Mortality of Patients with Type-3 Cardio-Renal Syndrome Ying Zhou, Chen Yu, Department of Nephrology, Department of Nephrology, Tongji Hospital, Tongji University School of Medicine, Shanghai, China, Shanghai, China.

**Background:** Cardio-renal syndrome (CRS) is the clinical syndrome with heart failure and kidney damage, there is a complex interaction between them. The aim of this study was to investigate the clinical features of acute renocardiogenic syndrome (cardiological syndrome type 3) and prognostic factors in a tertiary referral hospital in Shanghai of China.

**Methods:** There were 1011 out of 1361 subjects (5.22%) admitted to our internal medicine ward (from January 2015 to December 2015), diagnosed with CRS. There were 33 cases which were diagnosed as type 3 CRS. This was a retrospectively cohort and we analyzed the anthropometric, history, clinical, biochemical and mortality characteristics of them.

**Results:** During 1-year follow-up, 9 (27.3%) patients died. Mean age of these 33 patients was 75.3±11.82 years, 16 (48.4%) were males, 5 (15.2%) were smokers, 8 (24.2%) were diabetic, 25(75.8%) had a history of hypertension, 11 (33.3%) had coronary heart disease, 9 (27.3%) were affected by stroke. They were divided into 2 groups: survival group and dead group. Systolic blood pressure (154.4±30.71 vs 126.7±30.71), hemoglobin (75.8, 109.9 vs 58.5, 90.01) and Glutamyl transpeptidase (18, 40 vs 9, 8.26) were higher in survival group than in dead group (P=0.05). However, PCT levels were higher in dead group (1.02, 17.10) than in survival group(0.9, 6.60) (P=0.05). Multivariate logistic regression analysis suggested that systolic blood pressure independently predicted one year mortality (odds ratio: 0.947; 95% confidence interval [CI]: 0.901 to 0.990; p=0.033). CRS is common, and one year mortality of patients with type-3 CRS was high. Systolic blood pressure can help predicted one year mortality of patients with type-3 CRS.

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

**PUB070**

Elderly versus Younger Patients in Vasculitis: A Single Centre Experience Vasanth M. Madupplapillianap, Philip Davis, Abhishek Dattani, Saurabh Chaudhuri, Stratford, United Kingdom; Barts Health NHS Trust, London, United Kingdom; NHS London, United Kingdom.

**Background:** ANCA associated vasculitis (AAV) is a multi-systemic autoimmune disease primarily of older adults with a peak age between 65 & 74 years old. Without treatment AAV leads to considerable morbidity & mortality. The potential adverse effects of immunosuppressive therapy can be daunting when considering treatment in elderly. Our aim was to evaluate the clinical features & outcomes in elderly patients with AAV in comparison to younger patients at our unit.

**Methods:** We performed a single centre, retrospective study, observing 1 year survival outcomes & relapse rates in any patient diagnosed with AAV who presented to our renal unit, between Jan 2014-Dec 2015. Patients were divided into elderly group (EG)(>70 years) and younger group (YG)(<70 years). Data on clinical features, treatment, survival and renal outcome were analysed.

**Results:** A total of 31 patients (17 male) aged 31-82 (mean age 61.7±14.9) were identified. The EG of 12 patients was compared to the YG of 19 patients(Table 1). Overall 1 year survival in the EG was 93.8% & 95% in the YG. Mortality increased with age (R²=0.230, p=0.006) & C-reactive protein (R²=0.286, p=0.003). Mortality was raised in the EG with non-standard immunosuppression but large SD affected the p value. 33.3% of patients in the YG and 20% of patients in the EG had at least 1 relapse episode in a year. 26.7% of the younger patients required an average of 1 hospital admission. Each elderly patient had at least 1 hospital admission. Among patients who survived at 1-year, 20% of elderly patients and 15.3% of younger patients required dialysis.

**Conclusions:** Elderly patients with AAV had a higher mortality rate in comparison to younger group. Relapses were more frequent in the younger group. Hospitalisations were more frequent in the elderly patients. Age at presentation in the whole group significantly affected survival outcomes.

**PUB071**

Digoxin Toxicity in a Patient with Liver Failure and AKI: Role for CVVHDF and Plasmapheresis A young Cho, In O Sun.

**Background:**Digoxin has been used for management of atrial fibrillation (AF) and congestive heart failure (CHF). One of the concerns of digoxin use is its toxicity, particularly in patients with renal failure. We present a patient with AF, uncomplicated liver failure, superimposed on alcoholic cirrhosis and acute kidney injury (AKI), who was successfully treated with CVVHDF and plasmapheresis for AKI and digoxin toxicity.

**Methods:** Case Description: A 62-year-old man with past medical history of alcohol dependence and recently diagnosed AF and CHF was admitted for fatigue and weakness. He was on digoxin, furosemide and spironolactone. On admission, the patient was found to have bradycardia with heart rate of 33 beats/min and digoxin level of 3.6 ng/ml which peaked to 6.2 ng/ml. Serum creatinine was 3.4 mg/dl, which continued to rise, and the patient became anuric. Patient received Digibind and CVVHDF. His heart rate improved to 70s and subsequently dropped to 40s on days 4 and 5. Second episode of digoxin toxicity was suspected with likely digoxin-digibind complex deconjugation, as repeat digoxin level was 1.9 ng/ml. Patient received another dose of digibind on day 6 of the admission and followed by one cycle of plasmapheresis to remove the digoxin – digibind complex. Patient’s vitals improved significantly after the plasmapheresis and remained stable during rest of the hospital stay.

**Results:**

**Conclusions:** Digoxin is a cardiac glycoside that has very narrow therapeutic window; therefore, toxicity is common. It is excreted through kidneys. Owing to large molecular weight of digoxin and digoxin-digibind complex, CVVHDF that was initiated for anuric AKI failed to eliminate this complex. Deconjugation of digoxin-digibind circulating complex in the blood likely caused the second episode of digoxin toxicity with increase in digoxin levels as well as Bradycardia. This case suggests that digoxin toxicity can be improved by 1-2 treatments of plasmapheresis when digibind fails to improve digoxin toxicity in patients with AKI and/or CKD.

**PUB072**

Clinical Characteristics of Sepsis Patients Who Were Treated with Continuous Renal Replacement Therapy A young Cho, In O Sun.

**Background:** Continuous renal replacement therapy (CRRT) in the management of sepsis-induced AKI, predictor of mortality remain unclear.

**Methods:** We enrolled 337 patients who were treated with CRRT due to sepsis at the Presbyterian Medical Center intensive care unit from 2010 to 2014 in the study. We divided these patients into two groups (survivors vs non-survivors) according to 28-day all-cause mortality, compared their clinical characteristics, and analyzed the predictors of survival.

**Results:** The study included 212 men and 125 women, with a mean age of 67 years (range, 21-92 years). When we compared clinical characteristics of survivors (n=212) and non-survivors (n=125), no differences were identified, with the exception of age, total bilirubin, platelet count, and red blood cell distribution width (RDW). Survivors were younger (64 ± 14 vs 69 ± 12 year, P=0.001) and had high platelet count (180 x 10⁹/µL vs 134 x 10⁹/µL, p<0.01) than non-survivors. However, survivors had lower RDW (14.99 ± 2.1 vs 16.17 ± 3.3, p<0.01) and low total bilirubin (1.04 ± 1.45 vs 2.7 ± 6.13, p<0.01) than non-survivors. In multivariate logistic regression analysis, age, platelet count and RDW were assessed as prognostic factors to predict 28-day all-cause mortality in sepsis patient who needed CRRT.

**Conclusions:** Age, platelet count and RDW could be predictors for 28-day all-cause mortality in sepsis patients with CRRT.

---

**Table 1**

<table>
<thead>
<tr>
<th>Age group (≥70 years)</th>
<th>Young AAV Group (n=70)</th>
<th>Elderly AAV Group (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age/year</td>
<td>70.2±14.9</td>
<td>75.3±11.3</td>
</tr>
<tr>
<td>Levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (10⁹/L)</td>
<td>7.2±5.6</td>
<td>12.8±6.6</td>
</tr>
<tr>
<td>PLT (10⁹/L)</td>
<td>240±47</td>
<td>205±65</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>11.7±1.1</td>
<td>11.6±1.0</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.2±1.3</td>
<td>6.7±2.1</td>
</tr>
<tr>
<td>Proteinuria (%)</td>
<td>6.3±9.6</td>
<td>11.4±9.6</td>
</tr>
<tr>
<td>Standard immunosuppression (%)</td>
<td>9.7±10.8</td>
<td>50±45</td>
</tr>
</tbody>
</table>

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Use of Point of Care Creatinine Testing to Identify AKI in the Community Setting Joshua Storrage,1 James Ritchie,2 Dimitrios J. Poulakakos,1 Salford Hospital, Manchester; United Kingdom; 2Salford Royal Hospital, Manchester; United Kingdom.

Background: Two thirds of Acute Kidney Injury (AKI) cases detected in hospital are community acquired. Point of care renal function testing in primary care may assist early identification and management of community acquired AKI to improve outcomes.

Point of care (POC) creatinine testing has been developed but has not been used in the community routinely. In this study we aimed to evaluate existing creatinine POC testing against our standard laboratory method in order to support its use in the community.

Methods: We obtained POC creatinine (venous or capillary) values with StatSensor (Nova) and serum creatinine values with Siemens Advia 2400 IFE for 89 patients in the hospital setting (either in the Emergency Department, outpatient clinic, ward environment or haemodialysis units). Of the POC samples, 28 were capillary blood and 61 were venous blood. POC samples were obtained at the same time as laboratory samples. We measured the percentage difference in values with the two different methods and performed correlation analysis.

Results: POC creatinine values ranged from 44 µmol/L to 985 µmol/L and laboratory creatinine values ranged from 43 µmol/L to 1201 µmol/L. There was a good correlation between POC and laboratory creatinine values (R² = 0.92, p value 0.006), Figure 1. The average percentage difference between POC creatinine and laboratory creatinine was -10%.

Conclusions: We have demonstrated a correlation between POC and laboratory creatinine results. POC testing overall tends to overestimate creatinine values. POC has reasonable agreement with laboratory assays to detect normal and abnormal values. Since AKI is defined based on change in creatinine values caution should be exercised when using POC testing and baseline laboratory values particularly for small fluctuations.

Publication-Only

PUB074

The Clinical Implication of Computed Tomography in Predicting Severity of Acute Pyelonephritis Associated AKI A Young Cho,1 In O Sun, Presbyterian Medical Center, Jeonju, Korea, Jeonju, Republic of Korea.

Background: The aim of this study is to investigate the incidence and clinical characteristics of acute kidney injury (AKI) in patients with acute pyelonephritis (APN) and evaluate the efficacy of contrast-enhanced computed tomography (CECT).

Methods: From May 2007 to December 2009, we included 541 patients with APN who underwent a CECT examination. We investigated the incidence and clinical characteristics of APN associated AKI using the RIFLE criteria. In addition, we divided these patients into four groups according to renal parenchymal involvement in CT group 1; less than 25% involvement, group 2; 25% or greater involvement but less than 50% involvement, group 3; 50% or greater involvement but less than 75% involvement, group 4; greater than 75%, and compared their clinical characteristics, incidence of AKI.

Results: The patients included 133 males and 508 females with a mean age of 55 years (range, 18 to 92). The incidence of AKI was 14.4%; of which, 8.0%, 5.4% and 1.0% were classified as Risk, Injury and Failure, respectively. When we compared clinical characteristics among groups, there were no differences except hospital stay. The patients in group 4 have longer hospital stay than other groups (grade 1; 9±4, grade 2; 9±4, grade 3; 9±4, grade 4; 10±5, p=0.008). There was no difference in baseline renal function (70±27 vs 76±27 vs 74±22 vs 74±23, p=0.87) and incidence of AKI among groups (G1: 9.4%, G2: 6.1%, G3: 7.2%, G4: 11.3%).

Conclusions: The incidence of APN-associated AKI was 14.4%. Although CECT is useful to detect severe AKI, it seems to be less helpful to predict the AKI in patients with APN.
Outcomes after Hospital Discharge for Dialysis Dependent AKI

**Conclusions:** AKI-D in ESDL carries a poor prognosis. HD after discharge may serve as a bridge to liver-kidney transplantation in selected patients. Renal recovery was poor.

**PUB808**

Nursing Perceptions Towards the Care of Patients with Post-Operative AKI

**Background:** Patients undergoing operative procedures have a high incidence of in-hospital acute kidney injury (AKI) that is often under recognized and associated with adverse outcomes. Surgical teams without nephrology involvement generally manage post surgical AKI. At present, the attitudes and proficiency towards AKI of non-nephrology care providers has not been explored. Our aim was to assess surgical nursing perceptions of post-operative AKI.

**Methods:** A 14-question survey was provided to registered nurses and licensed practical nurses working on two general surgery wards at the University of Alberta Hospital in Edmonton, AB, Canada. Admitted patient population included trauma patients, and post-operative patients from elective, urgent, or emergent general surgery or urologic operations. Participation in the survey was voluntary, and questions assessed: years of experience, experience in other care environments, comfort level caring for patients with post-operative AKI, agreement with statements concerning the epidemiology, diagnosis, management, and prognosis of post-operative AKI, and attitudes towards performing quality improvement and increasing education around post-operative AKI.

**Results:** 22 nurses participated, of which, 77% were registered nurses, and 68% had been in practice less than 15 years. Only 36% of nurses had previous care experience in internal medicine wards, the emergency room, or an intensive care unit. The majority of nurses (86%) felt comfortable caring for patients with post-operative AKI. Similarly, most nurses believed that post-operative AKI could lead to irreversible kidney damage (77%), was preventable (95%), and that patients at risk for post-operative AKI could be predicted (81%). Of interest, 68% of nurses felt that the care of post-operative AKI required the involvement of nephrology or medicine consultants. The majority of nurses felt that more could be done to prevent and treat post-operative AKI on their units, and wanted additional education on AKI (72% and 95% respectively).

**Conclusions:** Although nurses caring for patients with post-operative AKI have many unique challenges, nurses are receptive to nephrologists providing education and guiding quality improvement regarding AKI.

**PUB809**

Outcomes after Hospital Discharge for Dialysis Dependent AKI

**Conclusions:** In our study AKI is common and is independently associated with poor outcomes, including a higher mortality rate, among critically ill burned patients.

**PUB878**

Hospital Acquired Kidney Injury in Critically Ill Patients

**Background:** Hospital acquired acute kidney injury (AKI) is common and is a risk factor for all-cause mortality and chronic kidney disease. Early detection of AKI is important to prevent the progression of AKI and to improve clinical outcomes. The objective of this study was to examine AKI acquired during the stage in the intensive care unit (ICU).

**Methods:** We performed a retrospective cohort study of patients admitted into the Intensive Care Unit (ICU) between January 2010 and December 2015. We included patients diagnosed AKI using KDIGO criteria during their hospital ICU stay and were evaluated by the nephrology department. Exclusion criteria were: Previous renal function unknown, AKI diagnosis at admission.

**Results:** We studied 50 patient: mean age was 67.2 years (±11.6), 35 (70%) were male, mean SAPS score was 59.1 (±5.3). The median length of hospital stay was 35.66 ± 27.03 days and ICU stay was 14.62 (±14.4)days. Comorbidities associated were: hypertension (55%), Diabetes Mellitus (46%) and previous chronic kidney disease (60%). The main causes of the AKI were: 40% hypovolemia (volume depletion, arterial hypertension), 29% sepsis and 20% of the cases were caused by multifactorial risk factors. 39 patients (78%) patients need renal replacement therapy(RRT). The majority of RRT procedures were with a continuous modality (CRRT). The principal cause to initiate RRT was fluid overload and the median duration was 4.7 (±4.8)days. 2% of patients required RRT at hospital discharge. Independent risk factors for RRT were: SAPS score >59 and SOFA cardiovascular 4. Kidney function at ICU discharge with estimated glomerular filtration was 50.01 ± 27.1 ml/min and at hospital discharge was 47 ± 23 ml/ min. The in-ICU mortality rate was 42%. Independent risk factors for hospital mortality were previous chronic kidney disease, female, and SOFA total score 59.17.

**Conclusions:** AKI hospital acquired is a frequent complication in critically ill patients. The diagnosis its associated with a high rate of mortality and need of RRT.

**PUB807**

Unusual Cause for Acute Kidney Failure: T-Cell Lymphomatous Infiltration and Impingement

**Results:** A 79 year old Hispanic lady from Caribbean descent, with comorbidities such as hypertension, mixed hyperlipidemia, anxiety disorder and stage 3b chronic kidney disease came in for abdominal discomfort 2 weeks after screening colonoscopy and biopsies of colonic polyps. Physical exam showed hypertension of 178/73 mm Hg and normal physical findings. Laboratory studies showed AKI, serum creatinine 4.20, potassium 3.9, lactate dehydrogenase 989 and uric acid 10.4, presumed to be acute spontaneous tumor lysis syndrome. Stageing work up with CT scan showed marked retroperitoneal lymphadenopathy, encasement of the right kidney and left kidney hydronephrosis with atrophic changes. Consequently, retroperitoneal lymph node biopsy showed T-cell lymphoma, CD3 positive, C20 and AE1/AE3 negative.

**Conclusions:** Review of PubMed Literature of published incidents of cell lymphoma presenting with AKI with enlarged retroperitoneal lymph nodes causing hydronephrosis and encasement of one of the kidneys, consecutive lymph node biopsy showed T-cell lymphoma and biopsy confirmed T-cell lymphomatous infiltration.
prostate cancer who developed tumor lysis syndrome secondary to radiation therapy and subsequently developed a left renal injury. 

Methods: Patient is a 67 years old male with a past medical history significant for high grade metastatic prostate cancer who presented to the hospital with abdominal pain, nausea and generalized weakness. He was noted to be hemodynamically stable on admission and noted to be 480 on admission temperature and normal baseline serum creatinine. Patient had a history of metastatic prostate cancer and had been treated with six cycles of Taxotere with minimal response. He had also undergone an urorouic due to severe back pain due to pelvic disease, patient was started one treatment of chemotherapy. The patient was still on 1 week prior to current hospital admission. He had not received prophylactic anti-uric acid treatment. Serum potassium was 6.0, phosphorus was 6.0 while serum uric acid was 35. Patient also had high anion gap metabolic acidosis and was subsequently started on a bicarbonate infusion. He also received 2 doses of IV rasburicase 9 mg. Peak serum creatinine was noted and improved to 1.60. Electrolyte abnormalities resolved. Repeat serum uric acid level was undetectable.

Results: 

Conclusions: Tumor lysis syndrome is uncommon after radiation therapy. This case highlights the importance to anticipate the possibility of developing AKI after radiation therapy which can be minimized by prophylactic administration of Allopurinol.

PUB085

Diffuse Alveolar Hemorrhage in Pulmonary-Renal Vasculitides: Successful Resolution with Emergent Adjunctive Plasma Exchange

Jane C. Hofmann, California Pacific Medical Center, San Francisco, CA

Background: Antibody mediated diffuse alveolar hemorrhage (DAH) in pulmonary-renal vasculitides is an acute, often life-threatening condition. While high dose immunosuppressive (IS) therapy is paramount in controlling this condition, plasma exchange often proves to be critically important.

Methods: From 1/08-1/17, we evaluated 63 patients (pts) diagnosed with DAH. Of 154 pts with ANCA or anti-GBM antibody renal vasculitides (RV) treated with adjunctive plasma exchange during this 9-year period, 63 pts (41%) were diagnosed with DAH: 28/74 (38%) with MPO positive ANCA RV, 26/60 (43%) pts with Pro3 positive ANCA RV, and 9/20 (45%) pts with anti-GBM RV. Pts were defined as having DAH if the pt had progressive hemoptysis and/or evidence of DAH by bronchoscopy. Median pt age was 54 years (19-85 years old); 37 (59%) pts were female. Majority of pts presented with cough, dyspnea, and hemoptysis; hypoxemia; and diffuse bilateral alveolar opacities. 56/63 (88%) pts underwent bronchoscopy, 46 pts (73%) were intubated. All pts received the following IS regimen: high dose corticosteroids (CS), plasma exchange (PE), and cyclophosphamide (CP) or rituximab (RTM). Pts received CS (methylprednisolone 500-1000 mg IV X 3-5 days) followed by prednisone taper, and CP (500-750 mg IV every 4 days or 150-250 mg day PO or RTM for 3-6 months) or RTM (375 mg/m2 weekly X 4 weeks).

Pts received daily PE treatments (txs) using FFP replacement until DAH resolved.

Results: 55/63 (87%) pts had resolution of DAH ≥7 days after starting IS regimen. Resolution of DAH was defined as: complete or near complete resolution of alveolar bleeding and hemoptysis, and improvement in oxygenation (decrease in FIO2 ≥0.30, or increase in SAG2 ≥10%), with or without improvement in chest x-ray findings. Median number of PE txs was 3.7 (2-8 txs). 41/46 (89%) of intubated pts were extubated. 52/63 (83%) pts had significant improvement in oxygenation; 46 (73%) pts had decreased pulmonary infiltrates. 7 (11%) pts died of complications of pneumonia and sepsis.

Conclusions: Diffuse alveolar hemorrhage is an uncommon, but potentially life-threatening complication of pulmonary-renal vasculitides. High dose corticosteroids, cyclophosphamide or rituximab, and plasma exchange are useful treatment modalities and, when initiated promptly, can be highly effective in providing rapid resolution of antibody mediated alveolar hemorrhage.

PUB086

AKI and Cast Nephropathy: Clinical Pathological Features and Associated Outcomes

Fernando Manuel G. Pereira,1 Afonso Santos,2 Miguel Goncalves,1 Pedro Pinto-Campos,1 Rita Theias Manso,1 Karina Soto,1 Hospital Fernando Fonseca EPE, Lisbon, Portugal; 2Hospital Fernando Fonseca EPE and CEDOC Universidade Nova de Lisboa, Lisbon, Portugal; 3Hospital Prof. Doutor Fernando da Fonseca, Lisbon, Portugal.

Background: Cast nephropathy is the most common AKI presentation in Multiple Myeloma (MM). Combination of new generation chemotherapy with efficient removal of serum free light chains (FLC) was recently suggested to increase kidney and patient outcomes. Herein we present our experience with 18 patients, presented with AKI and diagnosed with myeloma cast nephropathy (MNC).

Methods: A retrospective analysis of MM patients with clinical and/or pathological diagnosis of MNC referred to Nephrology Department was done. Kidney response was defined by eGFR of ≥30 mL/min/1.73 m2 and/or dialysis independence at 3 months.

Results: Eighteen patients were included. 62.5% male, mean age 71yo, with mean follow-up 17 mo. Most of them admitted with AKI III, median Scr 7.4 mg/dl; proteinuria 4.82 g/d; ACR 0.33G/l at admission; 70% cases of nephrotoxic agents; 81% needed RRT; 44% also treated with PE and 62.5% with HCO-HD. In 66.7% of patients MM was Lambda (median FLCs 4540), 25% Kappa (27100), one biclonal, and another with heavy chain (41900). RRT; 44% also treated with PE and 62.5% with HCO-HD. In 68.7% of patients MM was Lambda (median FLCs 4540), 25% Kappa (27100), one biclonal, and another with heavy chain (41900). Mean BM plasma cells was 55%, and most with bone lytic lesions. Lambda (median FLCs 4540), 25% Kappa (27100), one biclonal, and another with heavy chain (41900). Mean BM plasma cells was 55%, and most with bone lytic lesions. All were treated with QT, 87.5% based on BTZ. After 1st QT cycle 50% non-recovered kidney function, at the end of follow-up 56% were ESRD. Kidney biopsy was performed in 68.75%. Of them, 82% had MNC confirmed, one case with interstitial nephritis and tubular FLC deposit and another with heavy and light MDD and rare casts. ESRD was related with higher percentage of tubules with casts. Of note, Lambda FLC was related with worse kidney outcome, as well as the high levels of FLC at admission. At the median follow-up 75% had hematological response, with median FLC reduction of 55.30%. Best FLC reduction was 82% in 1.2 months, after 1st QT cycle. However, the frequency of relapses determined a global mortality of 70% in a mean period of 16.5 months, most related to MM (50%) and 25% sepsis-related.

Conclusions: Combined approach with BTZ-based chemotherapy and HCO-HD lead to significant and fast reduction of serum FLC, resulting in early kidney response. However, late MM diagnosis with high FLC levels were related with worse kidney and patient outcomes. Future large multicenter studies are still needed to confirm the benefits of HCO-HD. Severe chronic renal impairment strongly affects survival in patients with MM.
Characterisation of Polymere Membranes by MALDI-Mass-Spectrometric Imaging Techniques

Joachim Jankowski, Vera Jankowski, University hospital RWTH Aachen, Aachen, Germany; Affiliated hospital RWTH Aachen, Aachen, Germany.

Background: For physical and chemical characterisation of polymers a wide range of analytical methods is available. Techniques like NMR and x-ray are often combined for a detailed characterisation of polymers used in medical applications. Over the last few years, MALDI mass-spectrometry has been developed as a powerful tool for space-resolved analysis, not least because of its mass accuracy and high sensitivity. MALDI imaging techniques combine the potential of mass-spectrometric analysis with imaging as additional spatial information. MALDI imaging enables the visualisation of localisation and distribution of biomolecules, chemical compounds and other molecules on different surfaces. Methods: In this study, surfaces of polymeric dialyzer membranes, consisting of polysulfone (PS) and polyvinylpyrrolidone (PVP) were investigated, regarding to chemical structure and compound's distribution. Flat membranes as well as hollow fibre membranes were analysed by MALDI imaging. In accordance with polymer’s characteristics analysis parameters like laser intensity and laser raster step size were established firstly to optimize signal intensity and spatial resolution. Best signal quantity and quality and spatial resolution were achieved with settings of 60 µJ laser intensity and 50 µm raster step size. The mass spectrometric investigation of both polymers showed clear differences in ionisation behaviour. Results: According to the manufacturing process luminal and abluminal membrane surfaces are characterised by differences in chemical composition and physical characteristics. The MALDI imaging demonstrated that the abluminal membrane surface is more consisting of polysulfone than polyvinylpyrrolidone, the luminal membrane surface displayed more PVP than PS. The addition of PVP as hydrophilic modifier to polysulfone-based membranes increases the biocompatibility of the dialysis membranes. The analysis of polymer distribution is a relevant feature for characterisation of dialysis membranes. Conclusions: In conclusion, MALDI imaging is a powerful technique for polymer surface-localisation and identification of polymers but also localisation and distribution in membrane surfaces.

Identifying Hub Genes Associated with Clinical Characteristics in IgA Nephropathy by WGCNA

Yan Xu, Chenyu Li, Affiliated Hospital of Qingdao University, Qingdao, China; Affiliated hospital of qingdao university, Qingdao, China.

Background: Clinically, IgA nephropathy has a variety of symptoms including paroxysmal gross hematuria, nephritic syndrome and nephrotic syndrome. This study aimed at investigating hub gene and genes modular related to IgA nephropathy clinical characteristics. Methods: We collected 32 human samples from the European Renal cDNA Bank, used the WGCNA to construct the gene co-expression network and identify the hub genes associated with clinical characteristics. GO and KEGG analysis for hub genes were used the WGCNA to construct the gene co-expression network and identify the hub genes associated with clinical characteristics. Results: The device provides blood flow rate 600 ml/min on radio cephalic fistula. Conclusions: In conclusion, MALDI imaging is a powerful technique for polymer surface-localisation and identification of polymers but also localisation and distribution in membrane surfaces.

Novel Vascular Access Device for Hemodialysis Access

Eduard Tsyrulnykov, Anil K. Agarwal, Aleksandr V. Obabko, kenvelo, Mequon, WI; Argonne National Laboratory, Lemont, IL; Ohio State University, Columbus, OH.

Background: The current methods of cannulation of dialysis access (2 needles) could be ineffective in access with challenging geometry. Proposed single needle cannulation device could be useful in situation where access can accommodate only 1 needle. Methods: The device consists of a single needle with a dilator with side holes. One of the distinctive features of this device is the use of double dilator (combination of external (element 30) and removable with needle (element 40) internal dilator (elements 45,48 of image)). There are benefits of using double dilator: 1. Use cannulation needle of small size. 2. Use of larger size of internal tube advanced into external dilator that will result in higher flow rates of blood through device. Pilot bench and animal studies using this novel VAD for HD were performed between 2005 and 2014. More than 1,200 cannulations were performed in dialysis fistulas in different stages of maturation in animals with medication induced kidney failure. Venous and arterial pressure, blood flow rates, blood recirculation rates, post-treatment bleeding time, and blood urea nitrogen (BUN) clearance were observed and recorded. Results: The device provides blood flow rate 600 ml/min on radio cephalic fistula. Average post-treatment bleeding time is 3 minutes with applied pressure, blood loss is 3-5 ml. Without applied pressure, bleeding stopped after 10 min and blood loss is 5-10 ml. The decreased level of bleeding is likely due to using smaller size needles. The proposed device develops recirculation 20-30% for the flow rate of 600 ml/min http://www.mcs.anl.gov/~obabko/ed8_te4a.mpeg 2. When flow inside the device is decreased to 450 ml/min, the simulation predict that recirculation will go to zero. http://www.mcs.anl.gov/~obabko/ed8_te4.mpeg Conclusions: The research presented in this paper suggests that this device could be safely used for dialysis accesses in animals. In the future this device may provide comfort and access for humans. The smaller needle size and increased flow rate will provide additional comfort to patients and possibly increase efficacy of dialysis.
PUB090

Employing the Lotus Effect for Indwelling Medical Devices  
Jiminy Ni,1 Jie Cui,2  
3J Technologies, Inc., San Diego, CA; 1Massachusetts General Hospital, Boston, MA.

Background: Central catheter is the most common hemodialysis access in ESRD patients and associated with increases hospitalization, mortality and healthcare-cost burden. There are many long-term problems of current tunneled catheters especially infection and thrombosis. Thrombotic occlusion occurs in 30-40% of patients, which can occur within 24 hours after insertion or after prolonged continuous successful usage (4, 5). Severe systemic infection occurs in 30% of central catheter-associated bacteremia. When catheter gets infected, patients will need to receive 6 weeks antibiotics[21], catheter removal, temporary catheter placement and another tunneled catheter reinsertion and a chest X-ray. Center of Disease Control (CDC) estimates the cost of each central line associated infection at $16,550.

Methods: A new type of catheter has been investigated and fabricated, as desired to be efficacious for resolving these problems. We have investigated a cost-effective, long-term, bacteria-resistant, anti-thrombotic interventional medical device on our IP-protected Lotus technology.

Results: The Investigated medical device is based on Lotus technology, involving nano-engineered structure array (Lotus structure) on the inner surface by a cost-effective, long-lasting micro/nano fabrication method. The catheter is constructed of a monolithic polymer to efficiently carry a bio fluid through an inner surface of a tubular component having a nanostructure array configuration.

Conclusions: We have investigated a cost-effective, long-term, bacteria-resistive, anti-thrombotic interventional medical device on our IP-protected Lotus technology. The manufacture process enables it to reform when subject to mechanical molding applied by Lotus substrate.

Funding: Commercial Support - 3J Technologies, Inc. 

PUB091

Estimation of Internal Filtration of Two New High Retention Onset Dialyzers  
Anna Marchionna,1 3Claudio Ronco,2 3Mario Mercuri,3 1IRRIV, Vicenza, Italy; 2S.Bortolo Hosp., Vicenza, Italy; 3St. Bortolo Hospital, Vicenza, Italy.

Background: During hemodialysis, one of the phenomena contributing to high convective volumes is the internal/backfiltration(IF/BF). In an era of highly permeable and more and more selective membranes, it becomes important to estimate IF/BF volumes for a specific dialyzer and in specific therapy settings. Aim of our study was to in vitro estimate IF volumes by a semiempirical method of two new high retention onset dialyzers in simulating HD session setting.

Methods: 2 dialyzers were tested: The ranova 400 and 500(Baxter,US). Ultrafiltration coefficients were 48 and 59 ml/h/mmHg respectively. Test was set up in order to collect pressures at inlet and outletof dialyzer compartments in counter-current configuration. Test parameters were: blood flow=300ml/min, dialysate flow=500ml/min, net ultrafiltration=0. Human blood was used. 3 mathematical models were applied: simple linear, double linear and non-linear. The 3rd model considers the blood non-Newtonian rheological behavior.

Results: Graphs of TMP vs dialyzer length, obtained from the 3 models, are summarized in figure 1. About Theranova400 (Theranova500), single linear model generates an IF volume of 272/mlh(2906ml/h), but it largely overestimates the result and doesn’t match the zero balance condition; double linear model generates 159/ml/h(181.5ml/h); the third model, based on assumptions derived previous works in literature, is the most precise and the final volume is equal to 1620 ml/h(1865ml/h).

Conclusions: Geometrical and morphological characteristics of new-generations HD dialyzers and membranes, leading to high permeability and sharp sieving profiles, determine high convective volumes. The convective contribution to the total removal of renal toxins can be increased exploiting internal cross filtration.

PUB092

Development of a Digital Dashboard to Streamline CKD Management  
Nikhil Agarwal,1 Krzysztof Wierzbicki,1 Stewart H. Lecker,2 Andrea Renken,2 Julie Rockwell,2 Martin R. Pollak,2 Ali Poyan-Mehr,2 1BIDMC, Boston, MA; 2Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA.

Background: In spite of improved safety, and cost-effectiveness over conventional paper-based records, the ever-increasing complexities of electronic health record(EHR) applications and their poor user interface(UI) have been implicated as a major contributor to medical errors, and physician burnout. With the healthcare provider as the end user in mind, we created a streamlined EHR interface to support ambulatory CKD patients care.

Methods: We formed a multidisciplinary team including an IT specialist, system engine, nephrolologist, nurse, and trainee to develop an electronic dashboard through an iterative process of UI Design that included: Provider interview, clinical guideline review, definition of the unmet needs, design, prototyping, beta testing, and end user evaluation. Emphasis was placed on user experience and patient needs during the clinic visit.

Results: We have brought all elements pertinent to CKD management under one digital page, referred to as the “CKD Sheet”. Provider can access a patient’s current state of: Renal function, proteinuria, blood pressure, anemia, iron stores, mineral metabolism, nutritional state, options planning, and transplant evaluation. Each of these 9 categories has built-in educational tools and references. Patient materials (e.g. dietary guides) are readily accessible for print during the visit. Clinical decision support is provided by algorithm-driven alerts for values out of range based on current professional guidelines. Longitudinal data is displayed and grouped by disease systems (e.g. weight, blood pressure, and BNP trended together).

Conclusions: Through an iterative user interface design process and early involvement of end users we have created an EHR-Based support tool for the management of patients with CKD.
Machine Learning Prediction Model of Combined End Point of AKI and New Onset Renal Replacement Therapy (RRT) in ICU Patients

Background: AKI and new onset RRT in ICU patients is associated with significant morbidity and mortality. Prediction of combined endpoint of AKI or need for RRT can potentially improve patient outcomes. To accomplish part of this use of biomarkers, scoring systems and machine learning, have been tried in the past. In our study we attempted the use of the Gradient Boosting Machine (GBM) - machine learning algorithm to create a AKI and new onset RRT prediction tool using MIMIC III database.

Methods: GBM algorithm from H2O.ai project library was used to model 2008-2012 MIMIC-3 database. We defined 750 clinical and laboratory variables from first 24 hours after ICU admission. Patients in whom serum creatinine rose by 0.3 mg/dl or more within first 24 hours, with past medical history of dialysis or RRT related events charted within first 24 hours of ICU stay were excluded. Remaining 8893 patients were divided 20 times randomly into training (95% of patients) and testing (5% of patients) datasets. For all patients, minimal serum creatinine within first 24 hours after ICU admission was recorded as baseline. AKI within 24-72 hours after ICU admission was defined as observation of creatinine rise recorded between 24-72 hours by 0.3 mg/dl or more from baseline. New onset RRT was defined as presence of any dialysis related event between 24-72 hours of ICU stay. Average incidence of combined endpoint of AKI or RRT was 82.2 (18%) [95% CI 77.9 - 86.4] for 20 testing sets. Each training dataset was used to build GBM for predicting combined endpoint of AKI or RRT. Each such GBM model was validated on testing dataset. Area under curve (AUC) of receiver-operator characteristics curve (ROC) was recorded.

Results: For 20 testing datasets, AUC of ROC for GBM was 0.79 [95% CI 0.77 - 0.8]. Most important predictors, recorded within first 24 hours of ICU stay, from 1 of 20 runs, with their scaled importances (as per GBM) were: delta creatinine (1), number of pH checks on blood gasses (0.76), last recorded phosphorus (0.4).

Conclusions: In our analysis GBM model showed relatively good accuracy. Our approach can be employed to EMRs in hospitals as an AKI and new onset RRT combined endpoint prediction tool. More research is warranted to assess clinical applicability and robustness of our methods.
**PUB096**

Effect of Novel Phosphate Binder, Ferric Citrate, on Renal Function, Histology, Oxidative Stress, Inflammation and Fibrotic Pathway in Rats with CKD Wanghui Jing,1,2, S. A. C. Nunes,1, P. Khazaie,1, N. Nostrata D. Vaziri,1,2 University of California Irvine, Orange, CA; 3School of Pharmacy, Xi’an Jiaotong University, Xi’an, China.

**Background:** CKD commonly result in anemia. Ferric citrate (FC) is a novel phosphate binder which has been shown to increase hemoglobin, serum ferritin, and transferrin saturation. Since iron overload can accelerate the CKD by promoting oxidative stress and inflammation, this study was designed to determine the effect of FC administration on the structure and function of kidney in CKD rats.

**Methods:** Rats were randomized into 5/6 nephrectomized and sham groups. Each group was subdivided into 4% ferric citrate supplemented diet (CTL-FC, CKD-FC) and regular diet (CTL, CKD). After 6 weeks, blood pressure, kidney function, serum phosphorus, hemoglobin, serum iron and renal oxidative, inflammation and fibrosis markers were assessed.

**Results:** FC administration decreased SFB, BUN, as well as serum phosphate, and raised body weight, serum iron, and Hb. Kidney tissue in CKD rats showed activation of NF-kB, and upregulation of pro-inflammatory, pro-oxidant and pro-fibrotic molecules including MCP-1, iNOS, COX-2, gp91phox, MPO, nitrotyrosine, PAI-1, TGF-β and α-SM actin; reduction in nuclear translocation of Nrf2 and down-regulation of its key target products. FC administration in CKD animals resulted in accumulation of iron in the proximal tubular epithelial cells, and significant attenuation of most molecular markers of oxidative stress, inflammation and fibrosis in renal tissue.

**Conclusions:** FC administration could improve the renal function in CKD rats, and mitigate FC-associated upregulation of oxidative, inflammatory, and fibrotic in the remnant kidney. The salutary effect of FC on renal function and structure in CKD rats is presently unknown. However, it might be related to the protective effect of the citrate on proximal tubular epithelial cells.

![Image](image)

**Figure 1.** Representative photomicrographs of proximal blue stained kidney tissue from CTL (p=5), CTL-FC (p=7), CKD (p=5) and CKD-FC (p=5) treated animals. Data depicting the colin iron deposition in different groups. Data are mean ± SEM. *P<0.05.

**PUB097**

The Reactive Oxygen Species Production by Erythrocytes, but Not Cell Death, Is Associated with Anemia in Pre-Dialysis CKD Patients Andrea N. Moreno-Amalar,1 Gabriela F. Dias,1 Natalia Borges Bonan,1 Ana C. Gadotti,1 Stephany Van der goot,1 Alessandro A. Halama,1 Peter Potanko,1 Roberto Pecois-Filho,1 PUC-PR, CURITIBA, Brazil; 2PUCPR, Curitiba, Brazil; 3Pontificia Universidad Católica do Paraná, Curitiba, Brazil; 4Pontificia Universidad Católica do Paraná, Pinhais, Brazil; 5Renal Research Institute, New York, NY; 6Pontificia Universidad Católica do Paraná, Curitiba, Brazil.

**Background:** Increased oxidative stress is well-documented in uremic patients. Evaluation of redox status in red blood cells (RBC) has been used as a reliable method to evaluate oxidative stress in patients with chronic kidney disease (CKD). Our aim was to study the associations of RBC death (eryptosis), reactive oxygen species (ROS) generation by RBC, and anemia in pre-dialytic patients at various CKD stages.

**Methods:** We studied 20 CKD patients (8 CKD 3; 12 CKD 4/5). Pulse oximetry was used to determine arterial oxygen saturation. ROS generation and eryptosis were evaluated by flow cytometry using DCFH-DA probe and Annexin-V binding, respectively.

**Results:** While ROS production was increased in anemic compared to non-anemic patients, no association between eryptosis and anemia was observed. RBC ROS production or eryptosis were not associated to CKD stages or Oximetry (Table 1).

**Conclusions:** RBC ROS generation is increased in anemic pre-dialysis CKD patients, indicating its possible role in the pathogenesis of renal anemia.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Anemia</th>
<th>CKD Stage</th>
<th>Oximetry</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROS (pH 7.4)</td>
<td>0.30±0.15</td>
<td>0.30±0.15</td>
<td>0.30±0.15</td>
</tr>
<tr>
<td>Eryptosis</td>
<td>0.30±0.15</td>
<td>0.30±0.15</td>
<td>0.30±0.15</td>
</tr>
</tbody>
</table>

Mean Fluorescence Intensity (MFI), *non-parametric t-test Student statistic.

**PUB098**

Follistatin Protects Against Thapsigargin-Induced Apoptosis in Mesangial Cells Neel Mehta,1 Agata Gava,1 Joan K. Krepsinsky,1 McMaster University, Hamilton, ON, Canada; 2McMaster University, St. Joseph’s Hospital, Hamilton, ON, Canada.

**Background:** In numerous glomerular diseases including diabetic nephropathy, glomerular mesangial cell (MC) apoptosis correlates with progressive glomerulosclerosis and albuminuria. Thapsigargin (TG), an endoplasmic reticulum Ca2+-ATPase inhibitor, causes MC apoptosis through increasing [Ca2+]i, and reactive oxygen species (ROS). We have observed that while promoting MC apoptosis, TG also up-regulates the expression of follistatin (FST). FST is a secreted glycoprotein that neutralizes TGFβ super-family members, primarily activins. Since FST inhibits apoptosis and ROS production in numerous cell types, we determined whether FST is protective against TG-induced apoptosis in MC.

**Methods:** Studies were conducted on primary mouse MC using standard molecular biology techniques including immunoblotting, immunofluorescence and luciferase assays.

**Results:** TG caused apoptosis in MC that was characterized by elevated caspase 3 cleavage and caspase 3/7 enzymatic activity. TG-mediated apoptosis post-translational stabilization and increased the expression of FST. Functionally, FST down-regulation augmented, while FST over-expression and exogenous FST pre-treatment protected against TG-induced apoptosis. FST did not exert its protective effects through mediating [Ca2+]i. Flux. However, using ROS scavengers, TG-induced apoptosis was found to be dependent on the presence of ROS. Interestingly, while FST protected against TG-induced ROS production, it had no effect on superoxide production. FST is most potently active against Activin A, which has been shown to induce ROS production in other cell types. However, in MC, TG did not increase Activin A production nor did Activin A induce ROS production or apoptosis. Mechanistically, TG induced Smad3 transcriptional activity which was attenuated by FST and the ALK4/5/7 inhibitor SB431542. These data indicate that the protective effects of FST may be explained by its inhibition of activin B which is being explored in current studies.

**Conclusions:** In MC, FST protects against TG-induced apoptosis through inhibiting the production of ROS. This is independent of activin A, but may depend on activin B. Future studies will determine whether FST can be used in vivo to protect against the progression of glomerular diseases involving MC apoptosis and ROS-mediated injury.

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

**PUB099**

Rapamycin Enhances Repressed Autoapoptotic and Attenuates Aggressive Progression in a Rat Model of IgA Nephropathy Di Liu, Yixin Liu, Zheng Dong, Hong Liu. The Second Xiangya Hospital, Central South University, Changsha, China.

**Background:** IgA nephropathy (IgAN) has been considered as the most frequent form of primary glomerulonephritis worldwide with a variety of factors involved in the occurrence and development of it. The impact of autophagy in IgAN, however, remains partially unclear. The present study was designed to investigate effects of rapamycin in an IgAN model.

**Methods:** After establishing an IgAN rat model, SD rats were divided into four groups: control, control+rapamycin, IgAN, IgAN+rapamycin. Proteinuria and the pathological changes and the level of autophagy of kidney were tested. Identify the expression of phosphorylation and total mTOR and s6k1 as well as cyclin D1 in the kidney of rats through Western blot and immunohistochemistry.

**Results:** We observed a significant reduction in the progression of proteinuria as well as alleviation of pathological lesions in IgAN rats with rapamycin treatment. Besides, apoptosis was inhibited while mTOR/S6k1 pathway was activated and expression of cyclin D1 was increased in IgAN. Rapamycin treatment increased autophagy and decreased the expression of cyclin D1.

**Conclusions:** These results may suggest that mTOR mediated autophagy inhibition may result in mesangial cell proliferation in IgAN. These results may suggest that mTOR mediated autophagy inhibition may result in mesangial cell proliferation in IgAN.

**Funding:** Government Support - Non-U.S.
Autophagy was suppressed and senescence was relieved through enhanced autophagy activity, while the senescence expression was relieved by the enhancement activity of autophagy through inhibiting STAT1 by incubation of flubardane (50nmol/L).

Conclusions: STAT1 might mediate cellular senescence induced by high glucose in human glomerular mesangial cells via regulation of autophagy activity. **Funding:** Government Support - Non-U.S.

**PUB102**

**Ferroptosis Is Involved in Renal Tubular Cell Death in Diabetic Nephropathy**

**Background:** TGF-β1-induced cell death is known to contribute to the pathogenesis of diabetic nephropathy. Ferroptosis, a new atypical form of cell death, is an iron-dependent cell death that is distinct from apoptosis, necroptosis, and autophagy, and results from lipid peroxide accumulation. In this process, glutathione peroxidase 4 (GPX4) and glutamate/cysteine antionporter (xCT) are surmised to be principally involved. Recently, ferroptosis has been reported to cause several kidney diseases. However, the impact of ferroptosis on tubular cell death under diabetic conditions has never been elucidated.

**Methods:** In vitro, rat proximal tubular epithelial cells (mT6) were cultured in DMEM containing 5.6 mM glucose (normal glucose, NG) or NG + TGF-β1 (10 ng/ml) with or without ferroptosis inhibitors (Ferrostatin-1 and Liproxstatin-1) or iron chelator (Deferoxamine) for 12 hours. In vivo, 12 C57BL/6 mice were intraperitoneally injected with saline (Control) or (N=6) or STZ (150 mg/kg/d) for consecutive days (Diabetes, DM) (N=6), and were sacrificed after 6 weeks. The protein expression of GPX4, xCT, hypoxia-inducible factor (HIF)-1α, heme oxygenase-1 (HO-1), and nuclear factor erythroid 2-related factor 2 (Nrf2) were determined in cultured tubular epithelial cells of the mouse kidneys by Western blot analysis. Cell viability and lipid peroxidation (MDA) were also evaluated in cultured tubular cells.

**Results:** Compared to NG cells, the protein expression of xCT was significantly decreased, while HIF-1α, HO-1, and Nrf2 protein expression were significantly increased in TGF-β1-stimulated renal tubular epithelial cells. In contrast, GPX4 expression was not changed in renal tubular cells exposed to TGF-β1. Moreover, MDA levels were significantly increased along with significantly decreased cell viability in TGF-β1-stimulated cells. These changes in cultured tubular cells exposed to TGF-β1 were significantly ameliorated by ferroptosis inhibitors or iron chelator treatment. A significant decrease in xCT protein expression was also observed in the kidney of DM mice compared to the C kidney.

**Conclusions:** These results suggest that ferroptosis is involved in renal tubular cell death under diabetic conditions and that ferroptosis inhibitor or iron chelator can be a promising therapeutic agent in patients with diabetic nephropathy.

**PUB103**

**HIV Induces Ferroptosis in Human Podocytes**

**Background:** Ferroptosis has been reported to cause several kidney diseases. However, the impact of ferroptosis in HIV-induced podocyte injury has not been investigated to date. Ferroptosis is a programmed caspase independent cell death initiated by cellular non-chelated iron and driven by altered lipid environment (reduced glutathione and lipid alterations) and condensed mitochondrial structures. We investigated whether lipid alteration mediated ferroptosis contributes to the loss of podocytes in HIV-associated nephropathy (HIVAN). To elucidate this aspect, we studied the role of sphingomyelinase (SMase) in the induction of podocyte ferroptosis in HIV milieu, in vivo as well as in vitro.

**Methods:** SMase activities of renal tissues of control (FVB/N, n=5) and HIVAN (Tg26, n=6) mice and vector (V-HP) -and HIV-transduced human podocytes (HIV/HPS) were determined. To examine the effect of sphingomyelinase inhibitor (GW48), V/HPS and HIV/HPS were incubated in media containing either buffer or GW48 for 48 hours. At the end of experimental period, cells were evaluated for SMase activity and lipid peroxidation. V/HPS and HIV/HPS were evaluated for cell death with or without blockers of ferroptosis, caspase-3, and caspase-3 at different time periods. Additionally, role of PKCζ and NF-κB on SMase-induced HIV/HPS’ downstream signaling was evaluated.

**Results:** Renal tissues of Tg26 mice and HIV/HPS displayed several fold increase in SMase activity. HIV/HPS-induced SMase activity could be effectively blocked by GW48. Additionally, HIV/HPS displayed increased in lipid peroxidation that could be inhibited by GW48. A vast numbers of HIV/HPS succumbed to death during 96 hours. The relative cell survival using blockers of ferroptosis, Caspase-3, and Caspase 3 were 35%, 45%, and 55% respectively.

**Funding:** Government Support - Non-U.S.
Long Non-Coding RNA Expression Profile in Adult Renal Stem/Progenitor Cells: Role in Cell Proliferation and Differentiation

Methods: An IncRNA expression profile was obtained by ARPC and renal proximal tubule epithelial cells (RTPEC) by using Agilent microarrays. Data were analyzed with GeneSpring and R software. IncRNA microarray data were validated by real-time-PCR.

Results: We compared IncRNA expression in ARPC and RTPEC. 588 IncRNAs were differentially modulated in ARPC compared to RTPEC (fold change >2; Q value <0.05). In particular, we found 51 upregulated IncRNAs and 53 downregulated IncRNAs. Classification analysis showed that most IncRNAs expressed in ARPC are involved in Wnt and BMP signaling pathways, activation of the immune cells and G protein-mediated signaling; processes involved in the response-specific to cell damage. Over-representation test demonstrated their involvement in the calcium signal transduction, cell cycle and protein glycosylation processes (p <0.005). Among differentially modulated IncRNAs, LINC00263 was the most down-regulated in ARPC compared to RTPEC (fold change <3). LINC00263 is highly expressed in cerebral tissue and is involved in the differentiation inhibition and processes regulating maintenance of cytoskeleton structure, cellular adhesion, and membrane signaling. It may therefore be involved in maintaining ARPC in an undifferentiated state.

Conclusions: In conclusion, our results suggest that IncRNAs could play a role in response to cell damage and in ARPC differentiation and could represent a new therapeutic target in renal damage.

Funding: Government Support - Non-U.S.
the prognosis of these patients. The aim of this retrospective, single center, observational study was to determine the prevalence and predisposing factors of CKD in patients long-term after LTx.

Methods: Medical records of 118 patients after LTx (age 47.5±12.2 years) who completed 24 months follow-up were studied. Patients were divided into groups depending on the etiology of end-stage liver disease and on immunosuppressive therapy used after transplantation. CKD was diagnosed in patients with eGFR below 60 mL/min/1.73m² or with proteinuria at least for 3 months. Results are presented as means with standard deviation.

Results: CKD has been diagnosed in 33% patients in 12 month after LTx and in 34% patients in 24 month after LTx. One, 12 and 24 months after LTx eGFR were: 79.9±34.0 mL/min; 75.9±33.4 mL/min; 78.0±31.2 [mL/min/1.73m²], respectively. Prevalence of CKD was lower in patients that were transplanted due to autoimmune disease (10.8%) compared to viral (41.9%) and alcohol abuse (42.9%) etiology (chi-square: p<0.05; post hoc analyses: autoimmune vs. viral; p<0.02; autoimmune vs. alcohol abuse; p=0.02). A significant negative correlation was found between blood concentration of tacrolimus and eGFR in 24 month after LTx (p<0.05).

Conclusions: 1. The prevalence of chronic kidney disease in patients after liver transplantation seems to be higher than in the general population. 2. Patients with autoimmune etiology of the liver disease are characterized by better renal function. 3. Treatment with calcineurin inhibitors may have an adverse influence on renal function. Funding: Government Support - Non-U.S.

PUB109
Urinary Phosphorus Excretion and Kidney Disease Progression - A Retrospective Cohort Study

Background: High urinary phosphate excretion may lead to tubular damage and has been shown to be associated with progression of CKD. However, there is limited evidence to support this causal relationship. Thus, the goal of the study is to test the hypothesis that high urinary phosphate excretion per GFR predicts kidney disease progression.

Methods: In this retrospective cohort study, we performed a chart review of 143 adult patients who had 24 hour urine supersaturation studies done as a part of the work up for nephrolithiasis between 3/1/2011 and 2/28/2014. We estimated urinary phosphate excretion per GFR by dividing 24 hour urinary phosphate excretion by 24 hour urine creatinine clearance (phos/CrCl). We followed these patients for 2 years to monitor kidney disease progression, which was defined as the rate of eGFR decrease (<0.75 mL/min/1.73m² per year). We used linear regression to examine the association of urinary phos/CrCl with eGFR per year, while adjusting for participant demographics, diabetes, hypertension and coronary artery disease (CAD) status.

Results: The mean age was 59 ±11 years (47% female, 7% black). At baseline, the mean eGFR was 76±31.2 [mL/min/1.73m²]. The median urinary phosphate excretion was 935 (IQR 699, 1207) mg/day and urinary phos/CrCl was 8.9±5.1 mg/day per mL/min. The mean follow up duration was 24.6±1.8 months and the eGFR declined by 1.5±5.1 mL/min/1.73m² per year on average. Participants with higher urinary phos/CrCl were more likely to be older, male, hypertensive, have eGFR<60 ml/min/1.73m² and CAD at baseline compared to those with lower urinary phos/CrCl. In the fully adjusted model, with every 1 unit increase in phos/CrCl, the eGFR increased by 0.18 mL/min/1.73m² per year on average but this was not statistically significant (CI 0.49, 0.45, p<0.19).

Conclusions: Our findings did not support the hypothesis that urinary phosphate excretion per GFR is an independent predictor for kidney disease progression. The study was limited by small sample size, low severity of kidney disease and short duration of follow up.

PUB110
Abstract Withdrawn
PUB113

An Endogenous Na Pump Inhibitor, Marinobufagenin (MBG), Is a Marker of CKD Severity

**Background:** High levels of an endogenous steroid Na pump inhibitor MBG have been reported in CKD. MBG is a pro-hypertensive, pro-fibrotic, and implicated in cardiovascular diseases. We hypothesized that higher circulating MBG levels are associated with vascular dysfunction and relate to CKD severity.

**Methods:** Plasma MBG (competitive immunoassay), alkaline phosphatase (ALP) and systolic blood pressure (SBP) were measured in 11 patients with stage 3/4 CKD (9M/2F; 63±11 yrs), 8 chronic hemodialysis patients (7M/1F; 59±11 yrs), and 10 healthy controls (6M/4F; 45±17 yrs). Brachial artery flow-mediated dilation (FMD), aortic pulse-wave velocity (aPWV), carotid intimomedial thickness (cIMT), and carotid peripheral SBP were assessed in stages 3/4 CKD patients and controls (Table).

**Results:** Plasma MBG levels increased in patients with stage 3/4 CKD and in hemodialysis compared to controls (Table). Plasma MBG correlated positively with carotid and peripheral SBP, aPWV, cIMT, and ALP and negatively with FMD. After adjustment, plasma MBG remained significantly associated with higher ALP and SBP.

**Conclusions:** Elevated plasma MBG in CKD and dialysis patients is associated with higher ALP, a marker of tissue destruction and fibrosis, and with progressive kidney function decline. As a pro-hypertensive and pro-fibrotic factor, MBG may independently contribute to cardiovascular risk, be useful as a marker of severity of CKD, and represent a CKD therapeutic target.

**Funding:** Other NIH Support - Intramural Research Program, NIA, Private Foundation Support

Clinical parameters in control, CKD, and dialysis (DIAL) patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n=10)</th>
<th>3/4 CKD (n=11)</th>
<th>DIAL (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALP (IU/L)</td>
<td>47.5±13.9</td>
<td>81.6±18.9</td>
<td>90.3±5.4</td>
</tr>
<tr>
<td>Periperal SBP (mmHg)</td>
<td>128±10</td>
<td>128±10</td>
<td>-</td>
</tr>
<tr>
<td>aPWV (m/s)</td>
<td>547±44.4</td>
<td>547±44.4</td>
<td>-</td>
</tr>
<tr>
<td>cIMT (mm)</td>
<td>0.70±0.14</td>
<td>1.03±0.17</td>
<td>0.80±0.14</td>
</tr>
<tr>
<td>carotid SBP (mmHg)</td>
<td>135±16</td>
<td>132±18</td>
<td>-</td>
</tr>
</tbody>
</table>

Values are mean ± SD. *P<0.05, **P<0.01 vs. control, #P<0.05, ##P<0.01 vs. III/IV CKD by 1-way ANOVA followed by Newman-Keuls test; †P<0.05, ††P<0.01 vs. III/IV CKD by t-test.

PUB114

The Effect of the Complement C3a on the Podocyte Epithelial Mesenchymal Transition and Its Mechanism with Adriamycin Nephropathy in Mice

**Background:** Podocyte EMT is the early reversible process of podocyte damage reaction. Podocyte have perfect C3a receptors, C3a can lead to podocyte damage, however there has been scarce research on the relationship between C3a and Podocyte EMT. We study the relationship between C3a and podocyte EMT in adriamycin nephropathy at mice.

**Methods:** 30 male BALB/c mice were randomized into control group, ariamycin nephropathy group, ariamycin+3mg/kg C3a receptor antagonist (SB290157), ariamycin+10mg/kg SB290157, ariamycin+30mg/kg SB290157. On days 7, 14 and 21 after the intervene, 24-urine was collected to analyze the urine proteins. The renal tissues were obtained on 21 days to observe the podocyte using electron microscopy, the deposition of C3 on the podocyte were examined by double immunohistochemistry, the expression of nephrin, podocin, α-SMA, FSP-1, ILK, snail were measured by immunohistochemistry, quantification of nephrin, α-SMA, snail protein was carried out by western blot.

**Results:** Compared with control group, in ADR group, the diffus efaffec ete of podocyte foot process was observed, the urine protein increased, the deposition of C3 on podocyte was increase, α-SMA, FSP-1, ILK, Snall, α-actin-in-4 increased and nephripocin significantly reduce, the α-SMA, snail proteins expression were increased and the nephripocin podocin expression reduced (P<0.05).10mg/kg SB290157 can relieve the injure of podocyte foot process and reduce 24-h urinary protein, the deposition of C3 and the expression of α-SMA, FSP-1, ILK, Snall and α-actin-in-4 of podocyte and increase the expression of nephripocin and podocin (P<0.05).

**Conclusions:** 1. There is the deposition of C3 on the podocyte in adriamycin nephropathy at mice, SB290157 can suppress the process of podocyte epithelial-mesenchymal transition in adriamycin nephropathy at mice, which indicate complement C3a can induce podocyte EMT in vivo. 2. The expression of ILK and snail were increased in adriamycin nephropathy at mice and SB290157 can reduce its expression, which indicate the important role of the ILK signing pathway in the process of complement C3a induce podocyte EMT.

**Funding:** Government Support - Non-U.S.
Association between Serum Na-Cl Level and Renal Function Decline in CKD

Methods: The association between low Na-Cl concentration (<34 mmol/L) and renal function decline was evaluated among 1515 patients with a CKD stage G3a-4. Patients were free from malignancy and hypoalbuminemia at baseline. Predictive variables were identified using Cox regression analysis, with corresponding hazard ratios (HR) estimated after adjusting for the following covariates: age, sex, diabetes mellitus (DM), DM-identified using Cox regression analysis, with corresponding hazard ratios (HR) estimated were free from malignancy and hypoalbuminemia at baseline. Predictive variables were identified using Cox regression analysis, with corresponding hazard ratios (HR) estimated after adjusting for the following covariates: age, sex, diabetes mellitus (DM), DM-associated nephropathy, cardiovascular disease, use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor antagonists (ARBs), cigarette smoking, body mass index, serum albumin, systolic blood pressure, urine albumin/creatinine ratio, and CKD stage. The primary endpoint was defined as a composite of initiation of dialysis or death, or a composite of proteinuria progression, especially among patients with CKD stage G4 and those with anemia.

Results: A decline in renal function was identified in 289 patients. The risk for decline was higher among patients with a low serum Na-Cl level (HR, 1.428, adjusted for covariates). Subgroup analysis identified the effect of a low Na-Cl level to be stronger among patients with CKD stage G4 and those with anemia.

Conclusions: Na-Cl is easy to calculate and is an independent predictor of CKD progression, especially among patients with CKD stage G4 and those with anemia.

Classification Tree Model Analysis on Related Factors of Different Stages of Kidney in Type 1 Diabetic Patients

Methods: A total of 394 patients with type 1 diabetes were enrolled in our hospital from 2008 to 2015. According to glomerular filtration rates and urine albumin quantification, the patients were divided into type 1 diabetes group (299 cases), microalbuminuria group (73 cases) and macroalbuminuria group (22 cases). The classification tree model was used to analyze the related factors to the different stages of proteinuria, and the high risk population was screened by node gain analysis.

Results: Four important explanatory variables were screened out by the classification tree model from the 23 candidate variables related to early renal damage, including retinopathy, fibrinogen waist-hip ratio (WHR), red blood cell distribution width (RDW). Retinopathy was an important factor of DKD. The probability of macroalbuminuria in retinopathy and WHR>0.82 group was 43.8%, and if at the same time RDW>0.14, the probability of macroalbuminuria was 88.9%.

Conclusions: The classification tree model can analyze the major influential factors of the different stages of proteinuria in type 1 diabetic patients effectively, to identify the characteristics of high-risk populations.
Methods: We performed Cox regressions in 1093 AASK participants who submitted 24-h urine samples at baseline to determine the association between urine volume and the composite outcome of death or dialysis. Participants were categorized into <1.5 L, 1.5 to <2.5 L, and ≥2.5 L urine volume per day groups. Models were adjusted for age, gender, randomized group, BMI, SBP, measured GFR, proteinuria, diuretic and/or ACE-i use, heart disease, and urine osmolality. Those with the lowest urine volume served as the reference. We also evaluated the association between every 500 mL higher urine volume with the composite outcome and performed cubic spline regression models using similar adjustment.

Results: The mean age was 54 yrs, 61% male, mean GFR 46 mL/min/1.73m², mean proteinuria 326 mg/g, and 64% used diuretics. Mean urine volume was 2.2 L (SD 0.9), and 232, 500, and 361 had urine volume <1.5 L, 1.5 to <2.5 L, and ≥2.5 L, respectively. The hazard ratios of death or dialysis were 0.68 (95% CI, 0.51-0.91) and 0.88 (95% CI, 0.68-1.13) for those with urine volume ≥2.5 L and 1.5 to <2.5 L, respectively. Each 500 mL higher urine volume was associated with 9% lower risk of death or dialysis (95% CI, 0.85-0.96). Urine volume was linearly and inversely associated with these outcomes (Figure).

Conclusions: Higher 24-hour urine volume was associated with lower risk of mortality or dialysis among African Americans with hypertensive kidney disease. An interventional study to determine whether increasing fluid intake improves outcomes in hypertensive CKD should be considered.

Funding: Veterans Affairs Support

PUB19

Relationships of 24-Hour Urinary Phosphate Excretion and Serum Phosphate with Clinical Outcomes in CKD: From the Korean Cohort Study for Outcome in Patients with Chronic Kidney Disease (KNOW-CKD) Hong sang Choi,2 Ha yeon Kim,2 Chang Seong Kim,1 Eun Hui Bae,1 Seong Kwon Ma,2 Kook-Hwan Oh,1 Curie Ahn,2 Soo Wan Kim.2 Chonnam National University Hospital, Gwangju, Republic of Korea; 2Chonnam National University Medical School, Gwangju, Republic of Korea; 3Chonnam national university hospital, Gwangju, Republic of Korea; 4Seoul National University Hospital, Seoul, Republic of Korea.

Background: Recent studies suggest that dietary phosphate intake is only weakly linked to its serum concentration, and the relationship the phosphate intake and clinical outcomes is not yet well studied. We investigated the relationships of dietary phosphate intake and serum phosphate with clinical outcomes in chronic kidney disease(CKD) patients.

Methods: We collected the data of 2238 CKD stage 1-5 non-dialysis patients from a prospective cohort study (KNOW-CKD). A renal event is defined by a >50% decrease in estimated glomerular filtration rate (eGFR) from the baseline values, doubling of serum creatinine concentration, or end stage renal disease. Cardiovascular event is defined as myocardial infarction, coronary revascularization, stroke and new onset or aggravation of congestive heart failure. We used cox proportional hazards models to assess the associations between baseline 24-hour urine phosphate excretion (24h-UPE) and serum phosphate concentration with clinical outcomes.

Results: Among the 2238 participants in this study, the mean age was 53.68 ± 12.24 years (range 20–75), 61.2% were male. 24-UPE was not significantly correlated with serum phosphate concentrations (r=0.016, p=0.484). Models were adjusted for age, sex, primary renal disease, eGFR, 24-hour urine protein and nitrogen excretion, body mass index, smoking, use of phosphate binder, and medical history of diabetes, hypertension and coronary artery disease. The lowest quartile of 24h-UPE (11.4-400 mg/day) was associated with renal hazard ratio [HR] 1.734, 95% confidence interval [CI] 1.191-2.524, p=0.004 and total event (HR 1.949, 95% CI 1.355-2.804, p<0.001) and highest quartile of serum phosphate (4.2-8.8 mg/dL) was associated with renal (HR 1.743, 95% CI 1.191-2.524, p=0.004) and total event (HR 1.575, 95% CI 1.146-2.165, p=0.005) when compared associated with renal disease. The lowest quartile of 24h-UPE (11.4-400 mg/day) was associated with renal (HR 1.734, 95% CI 1.191-2.524, p=0.004) and total event (HR 1.949, 95% CI 1.355-2.804, p<0.001) after fully adjustment.

Conclusions: Low dietary phosphate intake assessed by 24h-UPE and high serum phosphate concentration were associated with poor clinical outcome in CKD patients. Low urinary phosphate excretion and high serum phosphate concentration should be considered as important prognostic factor in CKD.

PUB20

Higher Fluid Intake Is Associated with Improved Renal and Survival Outcomes in Hypertensive Kidney Disease Robert C. Hartley,1 Elena A. Myrloie,2 Kalani L. Raphael.1 VA Salt Lake City Health Care System, Salt Lake City, UT; 2University of Utah, Salt Lake City, UT.

Background: Higher fluid intake reduces kidney injury in animal models of CKD. The relationship between fluid intake and outcomes in persons with CKD is unclear. We evaluated whether urine volume, as a marker of fluid intake, is associated with death or dialysis in the African American Study of Kidney Disease and Hypertension.

Methods: We performed Cox regressions in 1093 AASK participants who submitted 24-h urine samples at baseline to determine the association between urine volume and the composite outcome of death or dialysis. Participants were categorized into <1.5 L, 1.5 to <2.5 L, and ≥2.5 L urine volume per day groups. Models were adjusted for age, gender, randomized group, BMI, SBP, measured GFR, proteinuria, diuretic and/or ACE-i use, heart disease, and urine osmolality. Those with the lowest urine volume served as the reference. We also evaluated the association between every 500 mL higher urine volume with the composite outcome and performed cubic spline regression models using similar adjustment.

Results: The mean age was 54 yrs, 61% male, mean GFR 46 mL/min/1.73m², mean proteinuria 326 mg/g, and 64% used diuretics. Mean urine volume was 2.2 L (SD 0.9), and 232, 500, and 361 had urine volume <1.5 L, 1.5 to <2.5 L, and ≥2.5 L, respectively. The hazard ratios of death or dialysis were 0.68 (95% CI, 0.51-0.91) and 0.88 (95% CI, 0.68-1.13) for those with urine volume ≥2.5 L and 1.5 to <2.5 L, respectively. Each 500 mL higher urine volume was associated with 9% lower risk of death or dialysis (95% CI, 0.85-0.96). Urine volume was linearly and inversely associated with these outcomes (Figure).

Conclusions: Higher 24-hour urine volume was associated with lower risk of mortality or dialysis among African Americans with hypertensive kidney disease. An interventional study to determine whether increasing fluid intake improves outcomes in hypertensive CKD should be considered.

Funding: Private Foundation Support

PUB21

Stable Isotopic Surrogates with Urinary Proteomics for Assessing Renal Tissue Damage in CKD Andrew Z. Wei, Pan Liu, Tomokazu Souma, Ellen Brooks, Craig B. Langman, Jing Jin. Feinberg School of Medicine, Northwestern University, Chicago, IL.

Background: Pathologic proteinuria is the hallmark of most chronic kidney diseases (CKD), including congenital anomalies of the kidney and urinary tract (CAKUT) and focal segmental glomerulosclerosis (FSGS). Often, functional kidney loss is evaluated in part by albuminuria. However, lab tests that can identify kidney-specific markers of ongoing tissue damage for the prediction of CKD progression remain unavailable. We report a novel urinary proteomic approach aimed at detecting urine proteins reflective of renal tissue damage by employing stable isotope labeling with amino acids in cell culture (SILAC, or SILAM when whole mouse serum is radiologically labelled) followed by qMS for substantiating and quantifying urine proteins.

Methods: Two CKD stage-match ed urines from children with either CAKUT or FSGS were obtained with IRB approval. One patient had nephrotic syndrome secondary to biopsy proven FSGS, while the other had CAKUT associated with a neurogenic bladder. Both had significant proteinuria. To evaluate the differences in cell-derived vs. plasma-derived protein contents in CAKUT and FSGS urine, each was mixed with either 6/1 SILAC-labeled HEK293 lysate or 0.6 SILAM-labeled mouse serum. Following digestions with either trypsin or lys-C respectively, the resulting peptide fragments were analyzed by LC-MS/MS and mapped to the known human proteome.

Results: FSGS vs. CAKUT urines differed in the number overlapping proteins with the SILAC cell extract: 16 vs. 52 of cell-derived proteins, respectively, whereas serum-derived urinary proteins were more balanced (28 vs. 29 between FSGS and CAKUT). Cellular proteins that were detected in both FSGS and CAKUT urines were also markedly different in their concentrations even after being normalized against the SILAC standards. For instance, Actin that was identified in both had an abundance that was 40 times higher in CAKUT, consistent with the gross anatomical damage typically being worse in CAKUT at the late stages of CKD.

Conclusions: Our pilot using the SILAC methodology demonstrated important differences in tissue derived proteins in the urine of two subjects with CKD (FSGS vs. CAKUT). We hope that this pilot will eventually enhance the future detection of ongoing kidney tissue damage so to direct clinicians toward targeted therapeutics to treat category and tissue-specific mechanisms of CKD progression.

Funding: Private Foundation Support
The Prediction of Systolic Blood Pressure at Representative Time-Points for 24 Hour Mean Systolic Blood Pressure on 1-Year Renal outcomes in Diabetic CKD Patients

Jiwoon Ryu, Sejoong Kim, Ran-hui Cha, Haejong Lee, Jung Pyo Lee, Myung Jin Cho, Yong Rim Song, Su Kim, Cheju Halla Hospital, Seoul, Republic of Korea; Chunccheon Sacred Heart Hospital, Chunccheon, Republic of Korea; Anyang Severance Heart Institute, Seoul, Republic of Korea; National Medical Center, Seoul, Republic of Korea; Seoul National University Boramae Medical Center, Seoul, Republic of Korea; Seoul National University Bundang Hospital, Seongnam, Gyeonggi-Do, Republic of Korea; Seoul National University College of Medicine, Seoul, Republic of Korea.

Background: Control of blood pressure (BP) in diabetic chronic kidney disease (CKD) patients is important in preventing target organ damage. 24-hour ambulatory BP measurement (ABPM) is the best known in BP monitoring, but it is not easy to use. APoDiTe study suggested systolic blood pressure (SBP) of specific time-points that can represent the 24-hour mean SBP (mSBP) were 7:00 AM and 9:30 PM in chronic kidney disease (CKD) patients. We followed the study 1 year later and evaluated whether SBPs at these time-points can predict renal outcomes after 1 year such as 24-hour mSBP in diabetic CKD patients.

Methods: We recruited 125 diabetic CKD patients with from 4 centers in Korea 1 year later. Baseline SBPs at 7:00 AM and 9:30 PM were evaluated whether they have predictive correlation for the change of renal function, proteinuria after 1 year compared with 24-hour mSBP. The renal outcomes were an increase in random urine protein/creatinine ratio than baseline value or estimated glomerular filtration rate (eGFR) deterioration which means a decrease in eGFR ≥ 5 mL/min/1.73m².

Results: The followed mSBPs at 7:00AM, 9:30PM and 24-hour mSBP were 135.4 ± 26.0 mmHg, 147.7 ± 131.8 mmHg and 139.2 ± 26.0 mmHg, they did not change significantly from baseline SBPs (paired t-test, p = 0.861; p = 0.537; p = 0.294). The SBP at 7:00AM correlated with eGFR deterioration in univariate analysis, after multivariate analysis, SBP at 7:00AM has significant association with eGFR deterioration (odds ratio: 1.026; 95% confidence interval (CI): 1.111-1.052; P = 0.046). In an association with proteinuria progression, SBP at 7:00AM has a correlation in univariate analysis, but in multivariate analysis, SBPs at any time-points has no association with proteinuria progression. In subgroup analysis, the association between SBP at 7:00 AM and eGFR deterioration persisted in CKD stage 3-5 patients (odds ratio: 1.037; 95% CI: 1.005-1.070; P = 0.024).

Conclusions: These data suggested that the SBP at 7:00 AM may have better prediction on 1-year eGFR deterioration in diabetic CKD patients, especially in subgroup of CKD stage 3-5 patients. Whereas SBPs at any time-points may not be correlated to 1-year proteinuria progression in diabetic CKD patients.

The Prediction of Systolic Blood Pressure at Representative Time-Points for 24 Hour Mean Systolic Blood Pressure on 1-Year Renal outcomes in Diabetic CKD Patients

Jiwoon Ryu, Sejoong Kim, Ran-hui Cha, Haejong Lee, Jung Pyo Lee, Myung Jin Cho, Yong Rim Song, Su Kim, Cheju Halla Hospital, Seoul, Republic of Korea; Chunccheon Sacred Heart Hospital, Chunccheon, Republic of Korea; Anyang Severance Heart Institute, Seoul, Republic of Korea; National Medical Center, Seoul, Republic of Korea; Seoul National University Boramae Medical Center, Seoul, Republic of Korea; Seoul National University Bundang Hospital, Seongnam, Gyeonggi-Do, Republic of Korea; Seoul National University College of Medicine, Seoul, Republic of Korea.

Background: Control of blood pressure (BP) in diabetic chronic kidney disease (CKD) patients is important in preventing target organ damage. 24-hour ambulatory BP measurement (ABPM) is the best known in BP monitoring, but it is not easy to use. APoDiTe study suggested systolic blood pressure (SBP) of specific time-points that can represent the 24-hour mean SBP (mSBP) were 7:00 AM and 9:30 PM in chronic kidney disease (CKD) patients. We followed the study 1 year later and evaluated whether SBPs at these time-points can predict renal outcomes after 1 year such as 24-hour mSBP in diabetic CKD patients.

Methods: We recruited 125 diabetic CKD patients with from 4 centers in Korea 1 year later. Baseline SBPs at 7:00 AM and 9:30 PM were evaluated whether they have predictive correlation for the change of renal function, proteinuria after 1 year compared with 24-hour mSBP. The renal outcomes were an increase in random urine protein/creatinine ratio than baseline value or estimated glomerular filtration rate (eGFR) deterioration which means a decrease in eGFR ≥ 5 mL/min/1.73m².

Results: The followed mSBPs at 7:00AM, 9:30PM and 24-hour mSBP were 135.4 ± 26.0 mmHg, 147.7 ± 131.8 mmHg and 139.2 ± 26.0 mmHg, they did not change significantly from baseline SBPs (paired t-test, p = 0.861; p = 0.537; p = 0.294). The SBP at 7:00AM correlated with eGFR deterioration in univariate analysis, after multivariate analysis, SBP at 7:00AM has significant association with eGFR deterioration (odds ratio: 1.026; 95% confidence interval (CI): 1.111-1.052; P = 0.046). In an association with proteinuria progression, SBP at 7:00AM has a correlation in univariate analysis, but in multivariate analysis, SBPs at any time-points has no association with proteinuria progression. In subgroup analysis, the association between SBP at 7:00 AM and eGFR deterioration persisted in CKD stage 3-5 patients (odds ratio: 1.037; 95% CI: 1.005-1.070; P = 0.024).

Conclusions: These data suggested that the SBP at 7:00 AM may have better prediction on 1-year eGFR deterioration in diabetic CKD patients, especially in subgroup of CKD stage 3-5 patients. Whereas SBPs at any time-points may not be correlated to 1-year proteinuria progression in diabetic CKD patients.

The Prediction of Systolic Blood Pressure at Representative Time-Points for 24 Hour Mean Systolic Blood Pressure on 1-Year Renal outcomes in Diabetic CKD Patients

Jiwoon Ryu, Sejoong Kim, Ran-hui Cha, Haejong Lee, Jung Pyo Lee, Myung Jin Cho, Yong Rim Song, Su Kim, Cheju Halla Hospital, Seoul, Republic of Korea; Chunccheon Sacred Heart Hospital, Chunccheon, Republic of Korea; Anyang Severance Heart Institute, Seoul, Republic of Korea; National Medical Center, Seoul, Republic of Korea; Seoul National University Boramae Medical Center, Seoul, Republic of Korea; Seoul National University Bundang Hospital, Seongnam, Gyeonggi-Do, Republic of Korea; Seoul National University College of Medicine, Seoul, Republic of Korea.

Background: Control of blood pressure (BP) in diabetic chronic kidney disease (CKD) patients is important in preventing target organ damage. 24-hour ambulatory BP measurement (ABPM) is the best known in BP monitoring, but it is not easy to use. APoDiTe study suggested systolic blood pressure (SBP) of specific time-points that can represent the 24-hour mean SBP (mSBP) were 7:00 AM and 9:30 PM in chronic kidney disease (CKD) patients. We followed the study 1 year later and evaluated whether SBPs at these time-points can predict renal outcomes after 1 year such as 24-hour mSBP in diabetic CKD patients.

Methods: We recruited 125 diabetic CKD patients with from 4 centers in Korea 1 year later. Baseline SBPs at 7:00 AM and 9:30 PM were evaluated whether they have predictive correlation for the change of renal function, proteinuria after 1 year compared with 24-hour mSBP. The renal outcomes were an increase in random urine protein/creatinine ratio than baseline value or estimated glomerular filtration rate (eGFR) deterioration which means a decrease in eGFR ≥ 5 mL/min/1.73m².

Results: The followed mSBPs at 7:00AM, 9:30PM and 24-hour mSBP were 135.4 ± 26.0 mmHg, 147.7 ± 131.8 mmHg and 139.2 ± 26.0 mmHg, they did not change significantly from baseline SBPs (paired t-test, p = 0.861; p = 0.537; p = 0.294). The SBP at 7:00AM correlated with eGFR deterioration in univariate analysis, after multivariate analysis, SBP at 7:00AM has significant association with eGFR deterioration (odds ratio: 1.026; 95% confidence interval (CI): 1.111-1.052; P = 0.046). In an association with proteinuria progression, SBP at 7:00AM has a correlation in univariate analysis, but in multivariate analysis, SBPs at any time-points has no association with proteinuria progression. In subgroup analysis, the association between SBP at 7:00 AM and eGFR deterioration persisted in CKD stage 3-5 patients (odds ratio: 1.037; 95% CI: 1.005-1.070; P = 0.024).

Conclusions: These data suggested that the SBP at 7:00 AM may have better prediction on 1-year eGFR deterioration in diabetic CKD patients, especially in subgroup of CKD stage 3-5 patients. Whereas SBPs at any time-points may not be correlated to 1-year proteinuria progression in diabetic CKD patients.

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

996
PUB126
The Efficacy of Hemodialysis in Preventing Contrast-Induced Nephropathy in Patients with Pre-Existing Renal Insufficiency: A Single Center Experience of the Institute of Nephrology, Uppsala, Sweden; 3Mosaiques Diagnostics GmbH, Hannover, Germany; 4University of Glasgow, Glasgow, United Kingdom; 5Royal Hospital of Sun Yat-sen University, Guangzhou, China; 6The Royal Veterinary College, Hatfield, United Kingdom

**Background:** Contrast-induced nephropathy (CIN) is defined as the impairment of renal function—measured as either a 25% increase in serum creatinine (sCr) from baseline or a 0.5 mg/dL (44 μmol/L) increase in absolute sCr value—within 48-72 hours of intravenous contrast administration. The reported incidence of CIN varies widely, largely depending upon the presence or absence of risk factors, primarily including underlying chronic kidney disease (CKD). The risk is also higher among patients with heart failure or hemodynamic instability. There are increasing number of reports that CIN is associated with significant in-hospital and long-term mortality. The aim of the current study was to assess whether prophyactic immediate hemodialysis (HD), after intravascular contrast media administration in patients with pre existing renal insufficiency, could be used in order to preserve residual renal function.

**Methods:** 39 patients (30 men, 9 women) who underwent procedures with administration of intravascular contrast media, were studied. Subjects had a mean value of eGFR 22.5 mL/min/1.73m², mean age 75.7 years and mean value daily diuresis 1.2 L. In all patients a central venous catheter was placed and a 3hr Hemodialysis (HD) session was performed, 2 hours after contrast media administration. SerumCr levels were measured at the day of contrast media administration and 3 days after HD.

**Results:** None of the patients had any deterioration of their sCr value or of their daily diuresis, while no other complications were noticed during HD session.

**Conclusions:** Daily HD following contrast exposure, so more multicenter, randomized studies on the subject are needed to explore the potential role of exosomes in the progression of IgAN.

PUB127
Urinary Peptide Biomarkers of CKD in Dogs Valerie Brunchuch,1 Lena Pelander,1 Benedicte Buffin-Meyer,2 Julie Klein,3 Benjamin Breuil,4 Petra Zürib,5 Pedro Magalhães,6 William Mullen,7 Joost Schanstra,8 Jonathan Elliott,9 Harriet M. Syme,10 Jens Häggström,10 Ingrid Ljungvall,11 INSEMR U1048, Toulouse, France; 2Swedish University of Agricultural Sciences, Uppsala, Sweden; 3Mosaiques Diagnostics GmbH, Hannover, Germany; 4University of Glasgow, Glasgow, United Kingdom; 5Royal Veterinary College, Hatfield, United Kingdom; 6The Royal Veterinary College University of London, London, United Kingdom

**Background:** Chronic kidney disease (CKD) is a clinically important cause of morbidity and mortality in dogs. This heterogeneous disease is insidious in onset and often not recognized until late in the course of disease. Currently available tools lack sensitivity to identify CKD in dogs.

**Methods:** We have analyzed the urinary peptide profile of dogs with CKD with the aim to evaluate if capillary electrophoresis coupled to mass spectrometry (CE-MS)-based urinary peptide analysis can discriminate healthy dogs from dogs with CKD with high sensitivity and specificity.

**Results:** Analysis of the urinary peptide profile with CE-MS demonstrated the presence of ~5400 peptides in dog urine. Comparison of 15 healthy and 15 dogs with CKD identified 133 differentially excreted peptides after correction for multiple testing. Sequence information was obtained for 35 peptides out of the 133, and included 33 collagen (I and IV) and 2 uromodulin fragments, urinary peptides that were also found to be differentially excreted in humans with CKD. The 133 and 35 sequenced peptides were combined in two support vector machine classifiers called 133P and 35P, respectively. These models were validated in an independent, cohort of 20 dogs where the analyst was removed from the classifier training. The 133P classifier predicted CKD with a sensitivity of 80% [95% confidence interval (CI), 44 to 97%], a specificity of 80% (95% CI, 44 to 97%) and an area under the curve (AUC) of 0.88 (95% CI, 0.72 to 1.04). The 35P classifier predicted CKD with a sensitivity of 80% [95% confidence interval (CI), 44 to 97%], a specificity of 98% (95% CI, 55 to 100%) and an area under the curve (AUC) of 0.89 (95% CI, 0.73 to 1.05).

**Conclusions:** In conclusion, this first study of the urinary peptide profile of dogs with CKD identified peptides that predicted presence of CKD in dogs with high accuracy. Future studies should validate its usefulness for early CKD diagnosis and prediction of progression in a clinical setting. [equal contribution VB and LF]

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

PUB128
Urinary Exosomes and the Loading of CCL2 mRNA as Biomarkers of IgA Nephropathy Patients Ye Feng, Linli Li. Institute of Nephrology, Zhong Da Hospital, Southeast University, Nanjing, China.

**Background:** Proteinuria is the major clinical risk factor for progressive loss of renal function in immunoglobulin A nephropathy (IgAN) patients. Excessive amount of proteins enter the urinary tract which might be toxic to cells facing the urinary space and increases the exosome excretion in urine. Here we aimed to explore the role of urinary exosomes and the loading chemokine; CCL2 mRNA serves as biomarkers of IgAN.

**Methods:** We isolated exosomes from urine samples of IgAN patients(N=55) at the time of renal biopsy and healthy controls(N=24). Samples from 14 patients with average 15.9-month follow-up after treatment were also collected. Kidney histological damage of IgAN patient was scored according to the Oxford classification. The protein and urinary exosomes were quantified by Bradford Protein Assays and Western blotting (using Alix, CD63 as exosome markers). Exosomal RNA was extracted by mirNeasy micro kit (Qiagen) and CCL2 mRNA was quantified through RT-PCR.

**Results:** Interestingly, rarely exosome was detected in healthy controls through western blotting with exosomal markers including CD63 and Alix. Exosome excretion in urine was increased with increasing severity of proteinuria in IgAN patients. The level of urinary exosomal protein closely correlated with levels of proteinuria and tubular injury marker, NGAL. Follow-up studies showed significantly less exosome excretion with decreased levels of proteinuria. It indicated that overloaded protein could increased exosome excretion from tubular epithelial cells. Moreover, according to the Oxford classification of IgAN, patients with higher endocapillary hypercellularity showed remarkably larger amount of urinary exosomes. Besides, exosomal CCL2 mRNA was significantly upregulated in IgAN compared with controls, and correlated with the deterioration of renal function as determined by eGFR. Exosomal CCL2 mRNA also increased in patients with high scores of tubular atrophy and interstitial fibrosis.

**Conclusions:** Proteinuria is toxic to tubular epithelial cells and endocapillary damage may increase exosome excretion in urine in IgAN. Urinary exosomes production and the CCL2 mRNA might be the promising biomarkers of IgAN reflecting the deterioration of renal function and pathologic damage. Further studies are needed to explore the potential role of exosomes in the progression of IgAN.

PUB129
Fibrinogen: A Possible Predictor of Microalbuminuria Stage in Type 1 Diabetic Nephropathy Wenbo Zhao,1 Hui-qun Li.2 1The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; 2the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.

**Background:** Analysis of the correlation of fibrinogen and albuminuria stage in type 1 diabetic.

**Methods:** nephropathyAs a Cross-sectional study, we collected hospital clinical data of 394 cases for type 1 diabetes, without albuminuria group (299 cases), microalbuminuria group (73 cases) and macroalbuminuria group (22 cases), analyzing albuminuria progress related influence factors for multiple factors regression.

**Results:** The levels of fibrinogen was in the three groups respectively for(3.06 ± 1.79)g/L, (4.46 ± 1.15)g/L(P=0.000). In the without albuminuria group and microalbuminuria group, the multi-factor Logistic regression analysis showed fibrinogen (Fib) = 0.408, P = 0.005, OR = 1.504), and retinopathy, UA, RDW into the model. In microalbuminuria group and macroalbuminuria group, the multi-factor Logistic regression analysis showed fibrinogen (Fib) was not into the model. But retinopathy, HDL, Waist-to-hip ratio into the model.

**Conclusions:** Fibrinogen associated with microalbuminuria stage in type 1 diabetic nephropathy, that could be independent predictors of early renal damage in type 1 diabetic nephropathy.

PUB130
Prevalence of Co-Morbidities by Ethnicity in a UK Primary Care CKD Cohort Rupert Major,1,2 Gang Xu,3,4 Laura Gray,1 Nigel J. Brunskill,2,3 1Department of Health Sciences, University of Leicester, Leicester, United Kingdom; 2University Hospitals of Leicester, Leicester, United Kingdom; 3Department of Infection, Immunity and Inflammation, University of Leicester, Leicester, United Kingdom; Group Team: PSP-CKD Study

**Background:** Cardiovascular (CV) and endstage renal disease events in CKD are more common in non-white ethnicities compared to white ethnicities. The prevalence of
co-morbidities in CKD in Black and South Asian ethnicities outside of North America is possible; however, this may account for these higher renal and CV event rates.

Methods: We analysed cross-sectional data from the PSp-CKD study (ClinicalTrials.gov NCT01688141). Individuals were analysed if they had a baseline eGFR <60 ml/min/1.73m² and an ethnicity code. The groups’ baseline characteristics between ethnicities were compared using t-tests and Chi².

Results: 18,058 (78.1%) individuals out of 23,129 had ethnicity recorded. Of these, 17,264 (95.6%) were White, 263 (1.5%) Black and 243 (1.4%) were South Asian. Individuals of Black and South Asian ethnicities were more likely to be male and younger. Mean eGFRs were similar across ethnicities but South Asians had higher mean ACR in both those with and without diabetes mellitus (DM). In Black individuals a diagnosis of hypertension (HTN) was less common but both systolic and diastolic blood pressures had higher mean values. DM was more prevalent in South Asians and HbA1c was higher too. Both Black and South Asian groups had lower rates of CV disease.

Conclusions: In South Asians with CKD, DM was present in more than 40% and glycaemic control was worse. A HTN diagnosis was less common in Black individuals but both systolic and diastolic blood pressures had higher mean values. DM was more prevalent in South Asians and HbA1c was higher too. Both Black and South Asian groups had lower rates of CV disease. Targeted management of these co-morbidities in South Asian and Black populations with CKD may be warranted.

Cohort Characteristics by Ethnicity

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>n= White</th>
<th>n= South Asian</th>
<th>p-value</th>
<th>n= Black</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>17,264</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Asian</td>
<td>263</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>243</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p-values refer to comparison to White ethnicity. For continuous variables values refer to means and figures in parentheses refer to standard deviations.

### PUB131

A Retrospective Analysis of Positive Predictors for the Utility of Ultrasound in the Diagnosis and Management of CKD in an Outpatient Population

**Background:** Given the economic constraints of today’s health care system, there is an increasing emphasis on cost-effectiveness and judicious use of resources. Choosing Wisely is a campaign that encourages health care providers in all aspects of medicine to look for ways to reduce the use of unnecessary tests while maintaining quality care for patients. The aim of this study is to add to the existing body of “diagnostic research” by assessing the diagnostic yield and clinical utility of ultrasound in the setting of chronic kidney disease.

**Methods:** A retrospective multi-variant analysis was performed using data collected from 2 hospitals in New Brunswick, Canada, involving patients presenting for initial outpatient nephrology consultations before January 2015. Data on patient presenting history and symptoms at the time of initial nephrology consult were collected via chart review. Demographic, laboratory, imaging and procedural data ranging from one year prior up to and including one year following the initial nephrology consult date was collected via electronic data extraction. A focus group attended by nephrology and radiology staff was used to determine what ultrasound findings would represent a “positive” result that would effectively change diagnosis and management. Multivariate regression analysis is being used to analyze the relationship between patient characteristics and ultrasound results.

**Results:** At the time of submission, of the 357 patients collected in the initial chart review, 304 (85%) were captured within our data extraction and matched to patient database demographic information with an initial nephrology consult ID and date. 221 of 304 (73%) had matches to the laboratory dataset (1 lab result). A total of 26,602 labs records were extracted for those 221 patients. 48 of 221 patients (22%) had ultrasounds performed. 53 ultrasounds were performed on 48 patients with 5 patients having had 2 ultrasounds. 7 of 221 (3%) had matches to pathology reports, indicating that biopsy was performed. Ultrasound findings were as follows: normal study (43%), increased echogenicity and cortical thinning (17%), re-checks with abnormalities (15%), non-obstructing calculi (8%) simple renal cysts (7%), renal atrophy (6%) and de novo lesions (4%).

**Conclusions:**

Funding: Private Foundation Support

### PUB132

Greater Acid Retention in Patients with More Advanced CKD Is Associated With Faster eGFR Decline

**Background:** Acid (H⁺) retention measured by microdialysis causes progressive GFR decline in animal models of chronic kidney disease (CKD), even in the absence of metabolic acidosis by plasma acid-base parameters, it worsens with declining GFR, and greater H⁺ retention causes faster GFR decline in these CKD models. Patients with reduced eGFR but no metabolic acidosis also have H⁺ retention (Wesson, et al. JIP 500:FS30) and eGFR decline rate was faster in the absence of dietary H⁺ reduction in CKD patients with stage 3 (Goraya et al. KI 86:1031, 2014) compared to stage 2 (Mahajan, et al. KI 78:303, 2010) eGFR (4.3 vs. 2.4 ml/min/1.73m²/year). We tested the hypothesis that faster eGFR decline in more advanced CKD stages is associated with greater H⁺ retention.

**Methods:** Twenty-six CKD 1, 2, and 36 CKD 3, macroalbuminuric, non-diabetic CKD subjects underwent measurement of H⁺ retention by comparing the observed to the expected increase in plasma [H⁺] in response to retained HCO₃⁻ (dose-unracted excretion) two hours after an oral NaHCO₃ bolus (0.5 meq/kg bw), assuming 50% body weight HCO₃⁻ space of distribution. Specifically, H⁺ retention = [retained HCO₃⁻/0.5 x body weight] – observed increase in plasma [H⁺/HCO₃⁻] x (0.5 x body weight). Cystatin C-based eGFR was measured at baseline and then yearly for five years.

**Results:** Baseline eGFR in ml/min/1.73m² was as follows: CKD 1=101±8, CKD 2=76±9, and CKD 3=40±7. The yearly rate of eGFR decline, expressed as ml/min/1.73m²/year, was faster in CKD 2 than CKD 1 (2.3±2.1 vs. 1.7±3.0, p<0.0001) and was faster in CKD 3 (3.7±7.1 vs. CKD 2 (p=0.0001). The Bonferroni correction required a p-value of <0.003 for significance among group comparisons for H⁺ retention. Accordingly, H⁺ retention was greater in CKD 2 vs. CKD 1. Patients with more advanced CKD and lower eGFR require more aggressive dietary H⁺ reduction to better resolve underlying H⁺ retention and thereby possibly optimize the kidney protective benefits of this therapy.

**Conclusions:** These data show that the faster rate of eGFR decline in CKD patients with lower initial eGFR was associated with greater H⁺ retention which might mediate their more rapid progression. The data suggest that CKD patients with more advanced CKD and lower eGFR require more aggressive dietary H⁺ reduction to better resolve underlying H⁺ retention and thereby possibly optimize the kidney protective benefits of this therapy.

### PUB133

Time-Average Proteinuria during Follow-Up and Renal Prognosis in Patients with Benign Nephrosclerosis

**Background:** Heavy proteinuria at the time of diagnostic renal biopsy has been reported as an independent risk factor for deteriorating renal function in benign nephrosclerosis (BNS). However, few studies have investigated the relationship between the amount of proteinuria during follow-up and long-term renal prognosis in BNS. The purpose of this study was to assess the relationship between time-average proteinuria (TAP) and renal prognosis in BNS.

**Methods:** Patients with biopsy-proven BNS from the Jikei University Hospital participating in this study. Multivariate regression analysis using a 30% decline in eGFR as a cut-off was used to evaluate the effects of TAP and other clinicopathological findings on the risk for renal events (a 30% decline in eGFR from baseline or ESRD). Proteinuria was measured every 6 months, and the mean value was used as an indicator of TAP.

**Results:** This study included a total of 67 BNS patients [mean age 51±12 years old, eGFR: 51±24 ml/min, urine protein excretion at baseline: 0.78 g/g Cr (0.51 - 1.79)]. The rate of renal events in patients with higher TAP was significantly elevated as compared to those in patients with lower TAP (Figure; Log-rank trend test, P<0.001). The adjusted model indicated a significant association between TAP and renal events (HR: 3.84, CI: 2.00-7.51), which was independent of higher baseline proteinuria, glomerulosclerosis and other clinicopathological findings on the risk for renal events (a 30% decline in eGFR from baseline or ESRD). Proteinuria was measured every 6 months, and the mean value was used as an indicator of TAP.
Angiotensin 2 and Innate and Adaptive Immunity in a Model of CKD Caused by Brief Treatment with L-NAME and Salt Overload


**Background:** We showed previously (AJPRenal 2006) that short-term NO inhibition by L-NAME (N) and salt overload (HS) promotes severe hypertension and renal injury that regresses after treatment is ceased, but progresses slowly to chronic kidney disease (CKD) thereafter. Here we investigated whether Ang2, innate and adaptive immunity are involved in the pathogenesis of CKD in this late phase.

**Methods:** Male Munich-Wistar rats received HS (2% Na) and N (32 mg/kg/d) for 1 mo. Control rats (C) received HS only. Four wks after all treatments had been ceased, tail-cuff pressure (TCP, mmHg), albuminuria (ALB, mg/d), glomerulosclerosis (GS, %), ischimic glomerulitis (IG, %), interstitial collagen 1 (COLL, %), renal content of IL1β (pg/mg), as well as interstitial infiltration (cells/mm²) by macrophages (MΦ), lymphocytes (Ly), angiotensin 2+ (Ang2+) and NLRP3+ cells were assessed in 14 rats (Post-HS+N 4, Post-HS 4, Post-N 4, C 4). All measurements were repeated in additional rats, followed for 24 wks while receiving either no treatment (Post-HS+N, n=15) or Losartan, 50 mg/kg/d (Post-HS+N+L, n=11).

**Results:** Mild hypertension and renal injury/inflammation, along with increased infiltration by Ang2+ cells and activation of the NLRP3 pathway, were observed in Post-HS+N 4. After 24 wks, ALB, GS and COLL were aggravated in association with persistently high levels of MΦ, Ly, Ang2+ cells and NLRP3/IL1β. In addition, the IL1β levels correlated positively with GS, MΦ and Ang2+ cells. Losartan prevented the increase in TCP, ALB, COLL and GS, but aggravated IG. Likewise, MΦ, Ly, Ang2+ and IL1β were attenuated, and IL1β correlated positively with ALB.

**Conclusions:** Activation of innate and adaptive immunity, even after the initial insult is ceased, may interact with Ang2 to mediate the development of CKD in this model. FASPS/ECP/NPq

<table>
<thead>
<tr>
<th></th>
<th>TCP</th>
<th>ALB</th>
<th>GS</th>
<th>IG</th>
<th>COLL</th>
<th>MΦ</th>
<th>Ly</th>
<th>Ang2</th>
<th>NLRP3</th>
<th>IL1β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-HS+N 4</td>
<td>164±3</td>
<td>51</td>
<td>302</td>
<td>1.7</td>
<td>34±2</td>
<td>151</td>
<td>71</td>
<td>11±1</td>
<td>5±1</td>
<td>51±1</td>
</tr>
<tr>
<td>Post-HS 4</td>
<td>164±3</td>
<td>240</td>
<td>13±1</td>
<td>11±1</td>
<td>40±3</td>
<td>25±4</td>
<td>171</td>
<td>11±1</td>
<td>32±2</td>
<td>33±2</td>
</tr>
<tr>
<td>Post-N 4</td>
<td>164±3</td>
<td>240</td>
<td>13±1</td>
<td>11±1</td>
<td>40±3</td>
<td>25±4</td>
<td>171</td>
<td>11±1</td>
<td>32±2</td>
<td>33±2</td>
</tr>
<tr>
<td>Post-HS+N+L 4</td>
<td>164±3</td>
<td>240</td>
<td>13±1</td>
<td>11±1</td>
<td>40±3</td>
<td>25±4</td>
<td>171</td>
<td>11±1</td>
<td>32±2</td>
<td>33±2</td>
</tr>
</tbody>
</table>

**PUB135**

Factors Related to Proteinuria Relapse in Childhood IgA Nephropathy

Yuko Shimah,1 Koichi Nakanishi,1 Taketsugu Hama,1 Masashi Sato,1 Yu Tanaka,1 Hironobu Mukaiyama,1 Hiroko Togawa,2 Hiroshi Kaito,2 Kandai Nozu,2 Ryojiro Tanaka,2 Kazumoto Iijima,2 Hiroyuki Suzuki,1 Norishige Yoshikawa,1,2 Pediatrics, Wakayama Medical University, Wakayama City, Japan; 2Dept. of Pediatrics, Kobe Univ. Graduate School of Medicine, Kobe, Japan; 3Graduate School of Medicine, University of the Ryukus, Nishihara-cho, Japan; 4Pediatric nephrology, Hyogo prefectural Kobe children's hospital, Kobe, Japan; 5Clinical Research Center, Wawakayama Medical University, Wakayama, Japan.

**Background:** Proteinuria remission is the most significant predictive factor for renal outcome in childhood IgA nephropathy (IgAN). Even if the proteinuria remission could be once obtained, some of the patients show proteinuria relapse during the long-time disease course. The purpose of this study is to clarify the incidence and factors related to proteinuria relapse in childhood IgAN.

**Methods:** Retrospective analysis of 309 cases with proteinuria remission among 538 consecutive biopsy-proven IgAN children from July 1976 to June 2013 to compare clinical and pathological findings between patients with proteinuria relapse and others.

**Results:** Ninety patients (29.1%) showed proteinuria relapse during the observation period (median 7.0 [25%–75%: 4.0–11.0] years). Clinical findings showed significant differences (relapse vs non-relapse) in onset age (11.3±3.3 vs 9.9±2.8 years, p<0.005) and the duration from onset to proteinuria remission (3.0±1.9 vs 2.7±2.6 years, p=0.02). According to the pathological findings, there were significant differences in the ratio of tubular atrophy/interstitial fibrosis present (65.4% vs 47.4%, p<0.005). The Kaplan-Meier analysis suggested that the patients with proteinuria relapse had significantly lower renal survival rates than the others at 16 years (91.9% [95% CI: 78.5–96.3%] vs 99.5% [95% CI: 75.9–99.9%], p<0.01). Proteinuria relapse is the only significant factor for renal survival in the 309 cases that remission of proteinuria was once obtained (hazard risk 3.15e [95%CI (2.8–3.5)]).

**Conclusions:** About one third of the proteinuria remission patients showed proteinuria relapse again regardless of treatments. Tubular atrophy such as a chronic lesion was significantly related to the proteinuria relapse.

**PUB136**

Impact of Oral Sucrosomial Iron in Anemia of CKD Patients and Its Relation with Mineral Bone Disease Parameters

Joanir Grives,1,2 401 General Military Hospital of Athens, Athens, Greece; 1RENAL CLINIC “ATHENS-NEPHROLOGY”, ATHENS, Greece.

**Background:** Iron deficiency is one of the main causes of anemia in patients with chronic kidney disease (CKD), and iron supplements constitute the basis of their therapy. Oral sucrosional iron, a preparation of ferric diphosphate carried inside a phospholipidic membrane, is characterized by higher gastrointestinal absorption and bioavailability than other iron formulations, as well as lower incidence of side effects. Different biochemical abnormalities of metabolic bone disease have been associated with anemia of CKD. However, all of these abnormalities are closely inter-related and their individual effect on the development of anemia is uncertain. The study purpose was to assess the efficacy and tolerability of the treatment with sucrosional iron in anemic patients with CKD and also to investigate the relationship between anemia, renal function and a set of metabolic bone disease biomarkers.

**Methods:** 30 patients (mean age 74.2±1years, range: 39-86 years) with CKD stage 3-5 (eGFR: 18–59 mL/min, range: 12-81) and anemia along with iron depletion. All the patients received oral sucrosional iron once daily. Hematological profile, renal function and bone-mineral data were recorded at the beginning of the study and every 2 months until the end of the study protocol.

**Results:** We noticed that Hct levels increased from 33.3±1.8% at the beginning of the protocol to 36.6±2.7% in the end (p<0.05). Hemoglobin levels were 10.9±0.7 g/dl at the beginning of the study and ended to be 11.8±0.7 g/dl (p<NS). Ferritin levels also increased from 42.7±24.47 to 98.89±12.69 g/dl (p<NS). The above improvement of renal anemia profile drove the renal function (eGFR) of our patients to remain stable, during the 18th month of the period of the study. Correction of anemia helped PTH levels to decline over the study period from 359.0±447.24 pg/ml to 163.72±89.12 pg/ml (p<NS). Ca, K, Na levels remained stable without also significant changes. Oral iron was well tolerated and no significant adverse effects were recorded.

**Conclusions:** Oral sucrrosional iron seems to be a safe and efficacious alternative in managing CKD patients with anemia. Whether an association between PTH and hemoglobin also exists in patients with CKD is still unclear, yet in this study we noticed an association between PTH, eGFR and correction of anemia in CKD-patients.

**PUB137**

Clinical and Histopathological Characteristics in “Smoldering” ANCA Positive Vasculitis and Nephritis Over One Year before Burst of RPGN

Eri Muto,1,2 Youngma Kang,3 Shunichiro Endo,3 Yawo Oikawa,3 Hiroko Kakin,1 Tomomi Endo,1 Hiroyu Suzuki,1 Motoko Yanagita,2 Tatsuo Tsukamoto,1 1Kitano Hospital, The Tazuke Kofukai Medical Research Institute, Osaka, Japan; 2Kyoto University Graduate School of Medicine, Kyoto, Japan; 3Hokkaido Renal Pathology Center, Sapporo, Japan.

**Background:** RPGN is most frequent phenotype of renal involvement of AAV with typical pathology of crescentic GN accompanying necrotizing vasculitis. As in most cases RPGN is the start to investigate ANCA positivity and AAV, the clinical and especially pathological information in “smoldering” phase before the burst of RPGN is limited. Some ANCA positive patients, however, could be under histological analysis due to mild but apparent urinary abnormality. Previously, the comparing those who did not develop RPGN, those developed RPGN showed positive PCTitis and arteriolar wall thickening (Kang, Muto et al, 17th ANCA Workshop 2015). The clinic- pathological features of further accumulated cases were analyzed.

**Methods:** Cases received renal biopsy due to positive nephritic urine and serum ANCA were surveyed in three different hospitals in Japan. They did not complain any systemic symptoms of vasculitis. As rapidly progressive renal dysfunction. They were evaluated among them, the clinical and histological features of those developed burst of rapidly progressive glomerulonephritis(RPGN) due to ANCA associated vasculitis later were analyzed.

**Results:** 6 cases (female: male=2:4 age 17-82, average 56.1 years) showed active hematuria and proteinuria. ANCA titers were 18-8800 EU, Crea = 0.8-1.45mg/dl. Histologically no necrotizing lesion nor vasculitis, however, wall thickening of arteriolar
were noted. At that occasion, 2 cases were diagnosed as IgA nephropathy. After average of 1.7 years during when all cases did not receive steroid therapy except one, developed RPGN. All second biopsy of 5 of them showed crescentic GN with active and necrotizing vasculitis. Before burst of RPGN, ANCA were stably high or gradually elevated.

**Conclusions:** At least 10 months before the burst of RPGN, inflammatory swelling of arteriole might have started in ANCA positive patients showing nephritic hematuria and proteinuria even without systemic symptom of vasculitis. The accumulation of these “smoldering” AAN which later developed RPGN should be performed to propose predictive clinical or histological parameters and appropriate therapeutic approach.

**Funding:** Private Foundation Support

**PUB138**

**Urinary Angiotensinogen (uAOG) Levels Are Associated with Development of CKD in Type 1 Diabetes**

Daniel Batlle,1 Alejandro Sanchez,2 Sheeba H. Ba aqel,3 Jan Wysocki,1 Minghao Ye,2 Ahmed M. Khattab,1 Alfredo Onteddu,2 Xiaoyao Gao,1 Ionut Bebu,1 Mark E. Molitch,2 George Washington University, Rockville, MD; 3Northwestern University Feinberg School of Medicine, Chicago, IL Group/Team: For CKD Biomarkers Consortium and DCCT/EDIC Research Group.

**Background:** uAOG has been reported to be increased in diabetic kidney disease (D KD) but its predictive value for D KD has not been demonstrated. Although AOG, like albumin, is filtered by a disrupted glomerular barrier, it is also produced intrarenally and thus any excess of AOG can activate the Renin Angiotensin System within the kidney and trigger CKD progression. We examined if AOG was associated with the development of DKD using biosamples from participants in the Epidemiology of Diabetes Intervention and Complications (EDIC).

**Methods:** In a nested case-control design we performed a preliminary analysis of 34 cases from EDIC participants in whom GFR eventually fell to <60ml/min/1.73m² (Stage 3 CKD) as the study outcome. Controls were 51 EDIC subjects in whom eGFR remained >60ml/min/1.73m², followed over the same period and matched for age, gender, DM duration. Matching was done during the earliest EDIC visit where urine samples for AOG evaluation were available prior to development of CKD3 (average of ~2 yrs before CKD3, range 1-7). Analysis was by conditional logistic regression. Prevalence Risk Decline (PRD, eGFR loss >3.5 ml/min/1.73m²/yr) was an index used to predict ESRD. In a separate post-hoc exploratory analysis, uAOG levels were compared in a subset of the primary renal case/control group of 20 cases with PRD versus 53 without PRD, of whom 20 and 13 respectively were CKD3 cases. Analysis was by logistic regression with nominal p-values and AUC.

**Results:** The median uAOG in cases was higher than that of controls (13.9 vs 3.8µg/mg, p = 0.027). uAOG was associated with the development of CKD3 after adjustment for eGFR (p=0.019) and HbA1c (p=0.043) but not for eAER (p=0.638). The median uAOG in PRD decliners was higher than in non-decliners (29.8 vs 4.2µg/mg, norninal p =0.063). AOG was associated with eGFR decline after adjustment for HbA1c (p = 0.045) but not for eGFR (p=0.067) nor AER (p=0.13). The AUC for OOG was 0.77, a value not significantly better than that for AER 0.759.

**Conclusions:** Urinary AOG is associated with the development of Stage 3 CKD. In addition, increased uAOG independently of eGFR or HbA1c is also associated with progressive renal decline, a strong index of progression to ESRD. uAOG is not significantly better than eAER predicting CKD or PRD.

**Funding:** NIDDK Support

**PUB139**

**Idiopathic Nodular Glomerulosclerosis (ING) in an African American (AA) Male with Hepatitis C**

Nirmal K. Kondeti,1 Anand C. Reddy,2 Jayasri Duggirala.3 1Texas Tech University of Health Sciences, Odessa, TX; 2Perrinian Research, Tampa, FL.

**Background:** ING in non-diabetic patients are rare. We report this case to suggest the existence of yet unknown etiologies of ING other than previously known.

**Methods:** A 68-year-old AA male with BMI(22.5), hypertension and smoking presented with anasarca. His physical examination and laboratory workup showed SBP -156/96, 4+ pedal edema, hemogram was normal except for platelet(117), creatinine 2.4, Urea 25, albumin 2.5, HbA1c of 5, 24hr urine protein 7.7gm, Hepatitis C antibody reactive, vasculitis workup was negative. On immunoelcrophoresis no free kappa light chains seen. Non specific increase in Alpha 2 globulins, monoclonal protein seen in gamma fraction of protein electrophoresis. Renal biopsy demonstrated nodular glomerulosclerosis. Congo red staining was negative. Immunofluorescence microscopy with human IgG, IgA, IgM, C3, lambda, fibrinogen, kappa and lambda immunoglobulin light chains was negative. No electron dense deposits.

**Results:**

**Conclusions:** Kimmelstiel and wilson described findings of nodular glomerulosis as a pathognomonic of diabetic nephropathy. Other causes of ING are diabetic nephropathy, amyloidosis, light chain disease, fibrillary and immunocytomatous glomerulopathy, Collagen type 3 disease, nodular membranoproliferative glomerulonephritis and takayasu’s arteritis. However our patient had a long history of smoking and hypertension, normal A1c and renal biopsy findings we diagnosed ING by exclusion. One cannot conclude that those risk factors alone caused his ING and ignore Hepatitis C antibody, MGUS as possible risk factors which have currently treated with angiotensin converting enzyme inhibitors along with other anti hypertensive medications, smoking cessation. Long term follow up is needed to see if his renal function improve after treatment of hepatitis c and also with regular follow up on A1c as he may develop DM later.

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

**PUB140**

**The Factors Influenced on Change in Systolic Blood Pressure Variability in CKD Patients: The APoDiTe2 1-Year Follow-Up Study**

Jiwon Ryu,1 Sejoong Kim,2 Ran-hui Cha,3 Hajeeong Lee,2 Jung Pyo Lee,2 Myung jin Choi,2 Young rim Song,2 Yun So Kim.1 1Cheju Halla Hospital, Seoul, Republic of Korea; 2Chuncheon Sacred Heart Hospital, Chuncheon, Republic of Korea; 3Hallym Univ. Sacred Heart Hospital, Anyang, Republic of Korea; 4National population health Research Center, Republic of Korea; 5Seoul National University Boramae Medical Center, Seoul, Republic of Korea; 6Seoul National University Bundang Hospital, Seongnam, GyegongDo, Republic of Korea; 7Seoul National University College of Medicine, Seoul, Republic of Korea.

**Background:** The blood pressure variability (BPV) may be affected by several factors such as medication, underlying disease and others. We evaluated what factors may influence the change in BPV in the APoDiTe study in chronic kidney disease (CKD) patients.

**Methods:** We recruited 378 hypertensive CKD patients with 1-year follow-up from 4 centers in Korea. The Systolic BP (SBPV) was the mean value of the differences between systolic BP at every 30 minutes for 24 hours. The factors affecting BPV were considered such as anti-hypertensive drugs, diabetes mellitus (DM), smoking, alcohol, exercise, and CKD stages.

**Results:** After 1-year observation period, SBPV were increased by 2.9 mmHg (Initial SBPV, 20.8 ± 11.9 mmHg; final SBPV, 23.7 ± 10.7 mmHg; P < 0.001 by paired t-test). SBPV in patients treated with 2 different anti-hypertensive drugs (renin-angiotensin esterase inhibitor or angiotensin receptor blockers (RAAS blocker) and beta blockers (BB), BB + calcium channel blockers (CCB)) and 3 drugs (RAAS blocker, BB and CCB) did not influence on changes in SBPV. In diabetic patients, non-smokers and patients on early-stage CKD (stage 1-2), SBPV was not changed during the observation (P = 0.072, P = 0.079 and P = 0.281 by paired t-test, respectively).

**Conclusions:** We found that SBPV in CKD patients may be increased over times, and that multiple anti-hypertensive drug users may prevent the increase in SBPV, rather than the type of anti-hypertensive drugs.

**PUB141**

**CKD in an Underserved Population with Cardiovascular Disease**

Hector Alvarado verduzco,1 Carola A. Marabotto gonzalez,2 Avantee V. Gokhale,1 Tarek Rashid,3 Anjali Acharya.2 1JACOBI MEDICAL CENTER, BRONX, NY; 2Jacobi Medical Center, Albert Einstein College of Medicine, Bronx, NY; 3Jacobi Medical Center, BRONX, NY; 4None, Fort Lee, NY.

**Background:** Chronic kidney disease (CKD) is a growing major health problem worldwide carrying a high morbidity and mortality as well as increased costs. Patients with underlying cardiovascular disease have a higher risk of CKD than the general population; however its prevalence in our diverse community hasn’t been reported.

**Methods:** We conducted a retrospective review of our medical records to evaluate the prevalence of CKD in the Cardiology clinic during 6 months. Patients of age 18 years or older were included. Descriptive statistics were used and analysis was done using SPSS.

**Results:** A total of 498 patients were included, 192 (38.6%) Hispanic, 149 (29.9%) African-American, 14 (2.8%) Caucasians, 38 (7.6%) others, and 105 (21.1%) unclassified. Of this sample, 32% had CKD, which was defined according to an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m² calculated from the MDRD equation.

**Conclusions:** CKD is highly prevalent in the Cardiology clinic in our unique population with high ethnic diversity, >75% of patients belonging to US minorities. These
results should help increase the awareness of this problem in the outpatient setting to promote early diagnosis and treatment of this condition, as well as prompt referral for specialized evaluation in Nephrology.

### PUB142

**Serum Myeloid-Related Protein 8 and 14 (MRP8/14) Are Increased in CKD Patients, Making It a Probable Novel Biomarker for Prognosis**

Tatsuki Matsumoto,1 Yoshinori Taniguchi,1 Daisuke Hashimoto,1 Masami Ogasawara,2 Tomohiro Eguchi,1 Hirofumi Nishikawa,2 Kazu H. Ode,2 Yoshiko Shimamura,2 Taro Horino,1 Yoshio Terada,2 Kochi University, Nankoku, Japan; 1Kochi university, Nankokushi, Japan

**Background:** Myeloid-Related Protein 8/14 complex (MRP8/14) is an endogenic ligand of toll-like receptor (TLR)-4, and is considered to be an inflammatory marker. Although it has been reported that MRP8/14 related to arteriosclerosis and coronary lesion in type 2 diabetes, there are no reports about the relationship between MRP8/14 and chronic kidney disease (CKD). We studied the association between MRP8/14 levels and renal function or the other parameter and renal prognosis in CKD.

**Methods:** A total of 432 patients (mean age 60±17) with CKD were enrolled. Serum samples were collected, and MRP8/14 levels were measured by using ELISA kit. Serum creatinine (Cr), blood urea nitrogen (BUN), uric acid (UA), urine proteins/Cr ratio, and the other parameter of renal function or the other parameter and renal prognosis in CKD.

**Results:** Serine MRP8/14 levels were positively associated with serum Cr (p<0.007, r=0.135), BUN (p<0.001, r=0.175), UA (p=0.011, r=0.127) levels, and urinary protein/Cr ratio (p<0.001, r=0.221), and Body Mass Index (BMI) (p<0.001, r=0.189). MRP8/14 levels were inversely associated with eGFR (p=0.006, r=0.137). MRP8/14 levels significantly increased in CKD stage 5 (p<0.05; vs stage 4). Moreover, MRP8/14 levels in CKD patients with diabetes and hypertension were significantly increased (p<0.05), compared to patients without diabetes and hypertension. Stepwise multiple regression analysis showed that MRP8/14 levels correlated well with BMI, Hb and urinary protein levels. The higher levels of MRP8/14 patients have a tendency of poor prognosis in 3 years.

**Conclusions:** Serum MRP8/14 significantly correlated with renal function and BMI in CKD patients, and might show the prognosis of CKD.

### PUB143

**A Parent-Child Case of Hyperlipoproteinemia and Early-Onset Obesity Complicating Obesity-Related Glomerulopathy**

Masanori Takaiwa,1 Takayuki Miyaya,1 Matsuyama Red Cross Hospital, Matsuyama, Japan; 1Okayama university, Okayama, Japan.

**Background:** The relationship between the obesity-related glomerulopathy (ORG), typically characterized by proteinuria, glomerulomegaly and FSGS, and the high heritability of severe obesity is unknown. Hence, the accumulation of family cases of ORG is useful for searching the genetic factors of ORG. We report a parent-child cases of hyperlipoproteinemia with ORG combined.

**Methods:** Case 1: A 11-year-old Japanese boy was found to have obesity, progressive proteinuria and hematuria at the age of 3. At the time of the biopsy, he exhibited significant proteinuria (UP/CR ranging from 1.44 to 4.04). Serum albumin and eGFR were normal. CAKUT and congenital malformation syndromes were not found. He presented with obesity (BMI 33.2), hyperlipoproteinemia (triglyceride 234 mg/dl; total cholesterol 296 mg/dl). The biopsy detected glomerulomegaly and FSGS (perihilar variant). After the hospitalization receiving 2000 kcal diet, he lost weight and showed amelioration of UP/CR (from 0.61 to 1.28). He is diagnosed ORG and receiving valsartan. 5 years later, he maintained improved BMI (23.0), blood pressure, triglyceride (300 mg/dl), total cholesterol (138 mg/dl), and HbA1c (6.6%). In parallel, the urine dipstick analysis was normalized.

**Conclusions:** Although further investigation is required, this parent-child case may suggest the benefit to clarify the relationship between ORG and the genetic causes of hyperlipoproteinemia. A family history of hyperlipoproteinemia could be a potent indicator for diagnosing ORG and might avoid unnecessary use of steroids and immunosuppressants. Vice versa, early diagnosis of ORG might lead to a sufficiently early detection of hyperlipoproteinemia to prevent the cardiovascular complications.

### PUB144

**The Diagnostic Significance of Urine PR/CR Ratio and Its Replacement Capability of 24 Hours Urine Protein in Indian Non Diabetic Nephropathy Patients**

Harisharan R. Manganda,1 Jitendra Kumar,1 Punit Pruthi,1 Asian institute of medical sciences, Faridabad, Haryana, India; 1internal medicine, Asian Institute of Medical Sciences, FARIDABAD, India

**Background:** The measurement of urinary protein excretion provides a sensitive marker of kidney disease from early to advanced stages. U Pr/CR ratio as a screening tool helps in categorisation of diseases and helps in early intervention and treatment strategy but 24 hrs urine protein still remains as a gold standard. It may be scientifically incorrect to use these tests interchangeably across all patient population.

**Methods:** Correlations between quantitative variables of 300 patients were evaluated using Pearson’s Correlation coefficient (SPSS) software version 15.0 was used for the statistical analysis. Diagnostic nephropathy, ESRD patients on dialysis, Multiple myeloma patients were excluded

**Results:** Correlation between 24 hrs UP and U Pr/CR is poor in patients with proteinuria range < 150 mg/hr (r=0.193) and 150-300mg/hr (r=0.173). This may be because the validation in international literature is mainly for albumin but in our study it was protein that was focussed, as it has varied sources. Moderate in >300 mg/24 hour (r=0.48). Best in 24 hrs UP range of 900-3000 mgs and U Pr/CR ratio of 0.9-3.

**Conclusions:** U Pr/CR ratio even in random fresh urine samples taken at any time of the day shows good correlation and seems to be an reliable alternative for 24 hrs UP. Advised 24 hours urine creatinine should be checked along with 24 hrs urine protein to know the adequacy of urination.
In Search of Mesoamerican Nephropathy: Albuminuria as a Marker for Renal Damage in an Agricultural Community on Guatemala’s Southern Coast

**Ever O. Cipriano,**1 **Marcos Rothstein,**1 **Vicente J. Sanchez polo.**2

1Barnes-Jewish Dialysis Center, St. Louis, MO; 2Guatemalan Social Security Institute, Guatemala City, Guatemala; 3Nephrology, Instituto Guatemalteco de Seguridad Social, Guatemala, Guatemala.

**Background:** In 2002, in El Salvador, a non traditional Nephropathy was described among young male adults, sugar cane workers, in the geographical region that includes Southeast Mexico, Guatemala, Belize, El Salvador, Honduras, Costa Rica and Panama. This Chronic Renal Disease of Non-Traditional Causes has claimed many lives at the Central American level and in Guatemala this entity has also been observed particularly in habitants of the coast of Pacific region of Guatemala.

**Methods:** OBJECTIVES Identify kidney damage using albuminuria as a marker of renal damage in high risk population of southern coast in Guatemala. METHODS Cross-sectional, population-based prevalence study Conducted in the agricultural communities of El Terrero and La Gomera in Escuintla, Guatemala. All individuals ages 10 and older were included. Labs – All patients had a urinalysis. Serum glucose and creatinine was randomly checked in patients with + albuminuria on urinalysis.

**Results:** See the Pictures.

**Conclusions:** A high prevalence of albuminuria (as a marker of renal disease) was noted in the studied rural community along the Guatemalan coast. There was no observed relationship between sugar cane workers and prevalence albuminuria or hematuria. Majority of identified patients with CKD did not have diabetes.

---

Performance of 8 Equations to Evaluate Baseline and Postoperative eGFR Changes in Patients with Morbid Obesity Undergoing Bariatric Surgery


**Background:** Many current equations employed to estimate GFR do not take account anthropometric variables. Gold standard measured GFR techniques show reduction in glomerular hyperfiltration in obese individuals after significant weight loss. The aim of this study was to evaluate the performance of 8 equations to detect eGFR changes after bariatric surgery.

**Methods:** We retrospectively analyzed a cohort of morbidly obese patients subjected to bariatric surgery between 2000-2014. We compared 8 eGFR equations before and 12 months after surgery. T test or Wilcoxon test were used for comparison of repeated measures.

**Results:** 168 patients were analyzed, mean age of 38.3 ± 9 years. All equations that included anthropometric measures showed a decrease in eGFR at 12 mo, in accordance to what has been shown with measured GFR, while all formulas that do not include anthropometric measures displayed an increase in eGFR (Table).

**Conclusions:** In this study, equations that included anthropometric variables demonstrated reduction in glomerular hyperfiltration, similarly to what has been reported in studies with gold-standard measured GFR. Other currently used equations standardized to a body surface of 1.73m² should not be employed in patients with morbid obesity. The only equation developed for obese individuals is the Salazar Corcoran, yet there is a need of eGFR concordance studies in obese individuals between measured GFR and estimation equations.

---

### Table: Performance of 8 Equations to Evaluate Baseline and Postoperative eGFR Changes

<table>
<thead>
<tr>
<th>Equation</th>
<th>Baseline eGFR Mean ± SD</th>
<th>12 mo eGFR Mean ± SD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD-GFA (m=0.73m²)</td>
<td>100.3 ± 11.8</td>
<td>100.4 ± 14.3</td>
<td>0.93</td>
</tr>
<tr>
<td>CKD-GFA adjusted to BSA (m=0.73m²)</td>
<td>145.2 ± 23.6</td>
<td>127.5 ± 26.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MDRD (m=1.73m²)</td>
<td>110 ± 23.1</td>
<td>110 ± 25.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MDRD adjusted to BSA (m=1.73m²)</td>
<td>127.5 ± 24.2</td>
<td>127.5 ± 24.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CKD-GFA adjusted to 40% total body weight</td>
<td>101.6 ± 6.5</td>
<td>141.5 ± 6.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CKD-GFA adjusted to lean body weight</td>
<td>110 ± 26.5</td>
<td>110 ± 26.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CKD-GFA adjusted to total body weight</td>
<td>127.5 ± 36.9</td>
<td>127.5 ± 36.9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Cockcroft-Gault adjusted to total body weight, ** Cockcroft-Gault adjusted to lean body weight, *** Cockcroft-Gault adjusted to 40% of total body weight. BSA: body surface area.

---

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Accurate eGFR Reporting in Children Independent of Height

Emil Den Bakker,1 Isabelle Hubbeck,2 Joanne Van Wijk,3 Reinoud R. Gemke,4 Arend Bokkenkamp,1 4VU Medical Center, Amsterdam, Netherlands; 4VU University Medical Center, Amsterdam, Netherlands; 5VUMC, Duiven, Netherlands; 6Umc, Amsterdam, Netherlands; 7Vrije Universiteit University Hospital Amsterdam, Amsterdam, Netherlands.

Background: Reporting estimated GFR (eGFR) instead of serum creatinine (crea) leads to earlier recognition and more timely referral of patients with suspected kidney failure and has been implemented in current guidelines both for adults and children. Due to varying muscle mass, which is related to height, most creatinine-based equations for children require height, a patient characteristic not standard available in many settings. An approach using age-related creatinine reference data has been developed by Pottel et al (2008). Cystatin C (CysC), an alternative marker for GFR, is independent of muscle mass and CysC-based eGFR does not require anthropometric data. Combining crea and CysC-based eGFR has been shown to significantly increase the accuracy of GFR estimation in children.

Methods: Methods Single injection inulin clearance tests were done in a convenience sample of children on clinical grounds with a simultaneous serum crea and CysC measurement. GFR was estimated from crea using the CKid1 -1[-endfil]->-1[-endfil] equation (Schwartze et al, 2012) (height-dependent) and Pottel (height-independent) equations and by the cysC-based CKid2 equation (Schwartze et al, 2012). The mean of the pairs of the crea and CysC based equations was calculated and the bias and p30 accuracy analyzed. 1-459 measurements (9-545 bloodsamples) and adolescents aged 1 month to 19.5 years. Of the creatinine-based equations CKid1 (bias 4.7 ml/min/1.73m2, p30 accuracy 82.1%) outperformed Pottel (bias -15.6, p30 accuracy 76.3%). CKid2 (bias 14.3, p30 accuracy 80.8) performed similarly to CysC. The combination of a crea and a CysC based equations markedly increased accuracy and decreased bias. The mean of Pottel and CKid2 (bias -0.6, p30 accuracy 88.5%) was calculated as the mean of crea and CysC (bias 2.5, p30 accuracy 75%).

Conclusions: Combining the Pottel creatinine and the CKid2 Cystatin C-based eGFR equations enables accurate allows for GFR estimation in children independent of height with good accuracy and which allows for direct can eGFR be reported directly by the laboratory.

Kidney Function in HIV-Infected Patients Seen in a Community Clinic: Characteristics and Natural History of the Disease

Roosel M. Brito,1 Justine Johnson,2 Eric J. Lai,3 Rochelle E. Castro,2 Edward A. Graviss,2 Duc T. Nguyen,3 Angelina Albert,4 Ann S. Barnes,5 Wadi N. Suki,2 Houston Methodist, Houston, TX; 2Houston Methodist Research Institute, Houston, TX; 3Legacy Community Health, Pearland, TX; 4Legacy Community Health, Pearland, TX; 5None, Houston, TX.

Background: The kidney plays a role in the metabolism and excretion of some antiretroviral drugs (ARV), and this makes it more vulnerable to various types of injury that can lead to blood and urinalysis abnormalities. Our aims were to identify patients with reduced renal function according to the KDIGO stages of kidney disease; characterize the nature of the kidney disease encountered and to determine the rate of loss of renal function.

Methods: Methods Retrospective cohort study (2012-2016) in 3,719 HIV-infected patients seen in a Federally-Qualified community clinic. Blood and urine laboratory results were extracted from medical records. Changes in eGFR were derived from multiple serum creatinine values collected over time.

Results: Data measured for each patient and staged patient’s kidney function based on the KDIGO Clinical Practice Guideline Figure 1.153 patients (4.1%) had CKD. As compared to patients with better preserved kidney function patients with CKD were likely to have a lower level of HGB than non-CKD patients median 13.5 vs 14.4 g/dl and lower level of albumin median 4.3 vs 4.4 g/dl p<0.001 and higher levels of K+ median 4.0 vs 4.3 mol/L in the non-CKD group p=0.01. Na+ and CL were not significantly different between the two groups. C0 was 22mol/L in the CKD patients vs 23mol/L in the non-CKD group p<0.001. The CKD patients also had a significantly greater decline in their eGFR, from first to the last follow-up reflecting a median percentage change of -26.5% versus 0 ml/min/1.73m2 (IQR 9.2, 8.5) in non-CKD patient p<0.001. The median rate in eGFR changes per year was -4.0 vs -0.2 ml/min/1.73m2/year in the non-CKD counterpart p<0.001. Data from urinalysis were insufficient for significant statistical analysis.

Conclusions: CKD was present in 4.1% of a population of HIV-patients. The disease did not appear to have any distinctive characteristics. However, in the affected patients the rate of loss of renal function appeared to be fairly rapid.

Utility of Reticulocyte Haemoglobin Content as a Marker of Iron Deficiency Anaemia in Black CKD Patients in South Africa

Aishatu M. Nalado,1 Suratadevi Naicker,2 Aminu Kano Teaching Hospital, Kano, Nigeria; 2University of the Witwatersrand, Johannesburg, South Africa; 3MEDICINE, Charlotte Maxeke Academic hospital, Johannesburg, South Africa.

Background: Anaemia is a common cause of morbidity and mortality among CKD patients. Early diagnosis of iron deficiency anaemia (IDA) is essential to initiate prompt treatment and improve prognosis. Various biochemical parameters are used to diagnose IDA with varying validity. We evaluated the ability of CHr to predict IDA in black prevalent CKD patients.

Methods: Methods This was a cross- sectional study of 258 pre-dialysis CKD patients and 141 age- and sex-matched healthy controls at the renal outpatient clinic of Charlotte Maxeke Johannesburg Academic Hospital between 1 June 2016- 30 December 2016. Haematological and biochemical parameters were analysed, using standard laboratory methods. Univariate and multivariate logistic regression was conducted to determine the predictors of IDA. Receiver operator characteristic (ROC) curves were conducted on CHr, TSAT and Ferritin. Parametric ROC analysis was used to determine the validity of CHr in the diagnosis of IDA. The validity of CHr was compared with TSAT and Ferritin using the ROC curves.

Results: Table 1 shows characteristics of the study population. The prevalence of IDA was 26% and the prevalence of functional IDA was 13-fold higher in CKD patients as compared to non-CKD patients (18.6% vs 1.4%, P<0.001). The discriminating value of iron deficiency by CHr is fairly good (AUC=73%; sensitivity=71.2%; specificity=71.2%), but lower than that of the conventional parameter (TSAT and Ferritin) (0.88 vs 0.73; P=0.02).

Conclusions: Although the predictive value of CHr in diagnosing IDA among prevalent CKD patients was lower than the conventional methods, CHr can still be proposed in our environment, when considering the trade off in terms of cost, accessibility and ease of performance.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Sacubitril/Valsalta in CKD: A Nephrologist Point of View

Borja Quiroga, Antonio De santos wilhelm, David S. Sapiencia Sanjines, Yamila Saharaui, Antonio manuel R. Gonzalez, Vicente Alvarez,Hospital Universitario de La Princesa, Madrid, Spain; Nephrology, Hospital Universitario de La Princesa, Madrid, Spain; Hospital de La Princesa, Madrid, Spain; Nephrology, Hospital Universitario de La Princesa, Madrid, Spain; Spanish National Health Service, Madrid, Spain.

**Background:** The angiotensin receptor neprilysin sacubitril/valsalta reduces cardiovascular morbidity and mortality in patients with systolic dysfunction (SD) as shown in the PARADIGM-HF study. Renal function in patients with chronic kidney disease (CKD) has not been evaluated as a hard endpoint in clinical trials. In this study, we include patients with CKD and SD in order to assess their renal function after initiating SAC.

**Methods:** In this prospective study, we included 41 consecutive patients with CKD and SD. We included patients with NYHA class II to IV being receiving maximal tolerated doses of optimal medical therapy including angiotensin converting enzyme inhibitors (ACEI), beta-blockers and mineralocorticoid receptor antagonist if appropriate. At baseline, comorbidities and epidemiological data was collected and low doses of SV were initiated. At month 1 and 3, doses of sacubitril/valsalta were rise up to maximal doses. At each visit (baseline, 1 month and 3 month), we evaluated renal function, estimated glomerular filtration rate (GFR) with CKD-EPI, pro-brain natriuretic peptide and changes in body composition using bioimpedance spectroscopy (BIS).

**Results:** Of the 41, 30 patients (73.2%) were men, with a mean age of 76.1±13 years. Regarding comorbidities, 39 patients (95.1%) had hypertension, 20 (48.8%) were diabetic, 30 (73.2%) had dyslipidemia and 5 (12.2%) had history of cerebrovascular disease. Thirty six patients (87.8%) had history of ischemic heart disease, with a mean left ventricular ejection fraction of 33.5±8. Creatinine at baseline was 1.55±0.52 mg/dL (GFR estimated by CKD-EPI 46.2±20 ml/min/1.73m²). After one month of treatment GFR improved a mean of 2.6 (0.5-1) ml/min/1.73m² (p=0.03). At fourth month, renal function was stable and no differences in GFR were observed respecting baseline (p=0.47). Diuretics were diminished or eliminated in 30 patients (73.1%). However, no differences in overhydration (measured using BIS) during the study were observed.

**Conclusions:** SV is safe in CKD and offers a transient improvement in renal function. Long-term clinical trials are required to confirm this results.

**PUB152**

Length of Stay Implications of Anemia in Patients with Heart Failure Exacerbation in an Inner-City Hospital

Avantyee V. Gokhale, Samuel Mon-Wei Yu, Poonam Mahato, Pitchaphon Nissasiorakarn, Anjali Acharya, Jacobi Medical Center, Bronx, NY; Jacobi Medical Center, Albert Einstein College of Medicine, Bronx, NY.

**Background:** Anemia is a known risk factor for poor survival, frequent hospitalization, and impaired life quality in patients with heart failure. Severe anemia (hemoglobin (Hb) < 9 g/dL) is associated with poor hospital and patient outcomes in heart failure patients with chronic kidney disease. However, this relationship in patients with mild-to-moderate anemia is unclear. Hence, we assessed the relationship of admission Hb to the length of stay (LOS) during a hospitalization in patients admitted with acute decompensated heart failure (ADHF) in an inner-city hospital catering mainly to a minority patient population.

**Methods:** 118 consecutive patients admitted between 01/01/15 to 06/30/16 with a diagnosis of ADHF were included. Retrospective chart review was performed to gather demographics, lab data on admission and LOS. The cohort was stratified based on the presence of mild-to-moderate anemia defined by Hb levels, <12 for women and <13 for men and a lower Hb cut-off level of 9. Statistical analyses included descriptive statistics and multivariable regression analyses.

**Results:** Of 118 patients (mean age=69), 69 (59%) had mild-to-moderate anemia. They were older (71±13 vs. 66±14, p=0.01), but had similar gender distribution (males: 54% vs. 59%) compared to those without anemia (p=0.49). More aggressive anemic patients were on beta-blockers (83% vs. 63%, p=0.02). Despite similar pro-BNP levels, anemic patients had a longer LOS [median (IQR): 8 (5-14) vs. 6 (5-8), p<0.03] and a higher fraction with LOS > 7 days (54% vs. 29%; p=0.001). LOS was inversely associated with Hb levels on admission (beta=-0.16, p=0.01) and the association persisted beyond demographics, history of chronic kidney disease, beta blocker use, ACEI/ARB use, diuretics and BUN/creatinine on admission (beta=-0.18, p=0.03). Finally, compared to anemic patients, patients with normal Hb levels had lower odds of prolonged LOS (>7 days) [OR (95% CI): 0.32 (0.16-0.64), p<0.001 after adjustment.

**Conclusions:** In conclusion, LOS is inversely associated with admission hemoglobin in ADHF patients. Even among patients with mild-to-moderate anemia, these findings confirm results of STAMINA-HF. Hence, Hb could be a modifiable risk factor for decreasing LOS, however, larger prospective studies are needed to confirm our findings.

**PUB153**

Global Longitudinal Strain (GLS) as Cardiac Imaging in Mid-Range Heart Failure (HF) (LVEF 40-49%) and CKD Stages 1-5ND

Secundino Cipriano, Jose Lomban, Jesus Calvino, Nicolle Menendez, Ana maria Sanjuanro amado, Juan Latorre, Nuria C. Lopez, Lourdes Gonzalez tabares, Belen Rodriguez delgado.

Nephrology, Eaxi Cervo-Lugo-Monforte, Balea, Spain; Cardiology, Eoxi Cervo-Lugo-Monforte, Balea, Spain; Nephrology, Eoxi Cervo-Lugo-Monforte, Lugo, Spain.

**Background:** CKD carry a high CV risk and imaging plays a key role in assessing the severity and providing risk stratification. HF mid range LVEF 40–49% is considered that represent a grey area, most probably have primarily mild systolic dysfunction and features of diastolic dysfunction. A novel method is GLS tissue doppler imaging, which evaluate the deformation of deformation in space and time of myocardial fibers during systole and diastole. The aim of this study is to assess GLS in CKD stages 1-5ND with mid range HF.

**Methods:** 105 pts (22.9% W, 50.5% DM2), median age 73 years. 21% CKD I&2; 53.1%, CKD 3A&3B; 25.7% CKD 4&5. All evaluated anthropometrically, and body composition was by BIVA (EFK, Agern, Fl, Ita). Anemia markers, bone metabolic disease, renal function (GFR CKD-EPI & ACR) were assessed. Peripheral arterial disease by ankle-arm-index (AAI) and carotid US and AGEs by skin autofluorescence and vascular age as well. Echocardiography tissue doppler was performed by the same author (JAL) and derived measures were GLS, E/A, E/Val LA (LV1-Voll.A/ae (m²)).

**Results:** Mean LVEF 45.15±2.6. Mean GLS -12.6±3.8% (Normal: -20%). GLS was significantly higher with Charlson Index (r:.297; p=0.05), vitamin D (r:.347; P=0.023), E/A (r:.337; p=0.039); Vol LA index (r:.268; p=0.040). DM vs noDM (-11.80±3.5% vs -13.4±4.6; p=0.007); PAD vs NPAD (-10.2±4.0% vs -13.4±3.5%; p=0.024); atherosclerosis vs no atherosclerosis (NS).[Image1] shows GLS through CKD stages.

**Conclusions:** CKD from early stages, left ventricular becomes stiff and less compliant. HF mid range LVEF 40–49% constitute a grey area poorly studied. In CKD may be an early mortality marker. The evolution of left ventricular functionality with GLS assess CV risk. Further prospective studies are need to confirm these findings.

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

Underline represents presenting author.
PUB155

CKD and Carotid Atherosclerosis Are Associated with Symptomatic Stroke
Keiko Tanaka,1 Haruhito U. Uchida,2 Nobuo Kajitani,2 Yuki Kakio,3 Masashi Kitagawa,4 Hitoshi Sugiyama,4 Jun Wada.1 1Okayama, Japan; 2Okayama University, Okayama, Japan; 3Okayama University Graduate School, Okayama, Japan; 4Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.

Background: Symptomatic stroke is the most prevalent cardiovascular and neurological diseases in Asia. However, the relationship between stroke, atherosclerosis and chronic kidney disease (CKD) has not been fully investigated. We aimed to investigate the relationship between CKD, symptomatic stroke, and carotid atherosclerosis.

Methods: We enrolled 455 subjects who underwent carotid ultrasonography in our hospital. Three hundred eleven patients were examined with carotid ultrasonography at the onset of symptomatic brain infarction, and 144 patients without any symptoms were examined. Carotid intima-media thickness (IMT), rate of internal carotid artery vasoconstriction, and maximal plaque size were measured using high-resolution B-mode ultrasonography.

Results: The mean age was 68.5 ± 11.0 years, and the mean estimated glomerular filtration rate (eGFR) was 68.8 ± 18.2 ml/min/1.73m². After adjustment for cardiovascular risk factors, the mean IMT in patients with CKD showed significant progression in comparison to those without CKD. Moreover, the IMT and eGFR were negatively correlated in patients with stroke (r = -0.169, p = 0.003). The mean IMT, plaque size, and vasoconstriction area were found to be significant determinants of symptomatic stroke after the adjustment of multivariate risk factors. The eGFR was found to be a negative determinant of stroke after adjusting for risk factors (OR (95%CI) = 0.877 (0.777-0.990), p = 0.034).

Conclusions: This study demonstrated that CKD could be associated with the progression of carotid atherosclerosis in patients with symptomatic stroke.

PUB156

The Role of Peritoneal Dialysis in Congestive Heart Failure: One Center Experience
Panagiotis E. Giannou,2 Panagiota E. Giannou,2 Sciennes, Okayama, Japan. 2Masashi Stroke doctors are not familiar with the process and not advice it to patients as an alternative nephrologists could identify patients with CHF who would benefit from PD, as the whether PUF could extend patient’s lifespan. The close cooperation of cardiologists and seems that the benefits of the therapy far outweigh its risks. The possible mechanisms of safety. Given that the complications such as peritonitis or leaks are relatively rare, it that hemodynamic stability, improved lower limps edema and ascites.

symptoms, improved quality of life, maintained satisfactory diuresis (>1000ml/day) thus vasoconstriction, and maximal plaque size were measured using high-resolution B-mode ultrasound.

Background: Peritoneal ultrafiltration (PUF) could be an effective strategy for the treatment of wastewater without compromising cardiac output and thus the renal function in patients with advanced congestive heart failure (CHF). The objective of this study is to determine the therapeutic role of PD in the management of patients with advanced CHF and renal dysfunction.

Methods: We studied retrospectively 15 patients who met the following inclusion criteria: (i) at least two nonscheduled hospitalizations for acute heart failure (AHF), the last episode of the last six months (ii) functional class NYHA III / IV (iii) presence of renal dysfunction [estimated glomerular filtration rate (eGFR) <60 ml / min/1.73 m²].

Results: After the first 6 months patients improved the stage of heart failure (from stage NYHA III / IV in II / III), dramatically reduced hospitalizations due to cardiac symptoms, improved quality of life, maintained satisfactory diuresis (>1000ml/day) thus maintained residual renal function (mean eGFR: 35 ml/min/1.73 m²), preserved hemodynamic stability, improved lower limps edema and ascites.

Conclusions: All the data gathered to date from observational studies on the role of PUF as treatment adjuvant to standard pharmacotherapy, in patients with severe CHF refractory to optimal treatment, are encouraging and indicate their efficacy as well as safety. Given that the complications such as peritonitis or leaks are relatively rare, it seems that the benefits of the therapy far outweigh its risks. The possible mechanisms of clinical improvement in patients with CHF by PUF appear to be multifactorial. The reduction of preload and clearance of vasoactive-inflammatory agents seem to be the main factors. Only the results of multicenter, randomized trials may answer the question whether PUF could extend patient’s lifespan. The close cooperation of cardiologists and nephrologists could identify patients with CHF who would benefit from PD, as the method is not widely used because it does not apply to all centers, but mainly because doctors are not familiar with the process and not advice it to patients as an alternative therapy.

PUB157

Resistin as a Predictor of Hospital Admission Due to Cardiovascular Events
Filipa B. Mendes,1 Luisa H. Pereira,1 Ana P. Silva,2 Pedro L. Neves.3 1Centro Hospitalar do Algarve, Faro, Portugal; 2Hospital de Faro E.P.E., Faro, Portugal; 3Centro Hospitalar Algarve, Faro, Portugal.

Background: The hormone resistin appear to have a relevant role on several pathological pathways in complex illness such as diabetes, cardiovascular disease, liver disease, chronic kidney disease, auto-immune disease and several inflammatory conditions. More than that, high serum resistin levels have been associated with increased risk of cardiovascular disease in the general population. Diabetic and renal impaired patients seems to present with the biggest risk. The aim of this study is to determine the role of serum resistin levels as a predictor of hospital admissions triggered by cardiovascular episodes in type 2 diabetic patients with mild to moderate CKD.

Methods: An observational study enrolled 78 diabetic patients with mild to moderate CKD which were screened and selected in an outpatient diabetic nephropythology clinic and were followed from January 2008 to December 2016.

Results: Out of the total 78 patients included, 13 were admitted at the hospital and newly diagnosed with cardiovascular pathology. There was a statistically significant result for resistin as a predictor of cardiovascular related hospital admissions (p <0.05). Laboratory parameters such as creatinine clearance, albumin, HbAlc, phosphorous, PTH, insulin resistance, CRP, resistin and active vitamin D, were positively related to cardiovascular hospital admissions.

Conclusions: Serum resistin levels demonstrated to be a valuable instrument to predict cardiovascular hospital admissions in type 2 diabetic patients with mild to moderate CKD. Also, other factors often altered in type 2 diabetes and patients with renal impairment were associated with hospital admissions but didn’t prove to have any potential in predicting hospital admissions in this group.

PUB158

The Role of Proteinuria on Vascular Function in Hypertensive Patients with CKD
Vagner S. Meira, Claudio P. Loivos, Mario F. Neves, Carla C. Lemos, Márcia R. Klein, Maria Ines Barreto-Silva, Rachel Bregman. State University of Rio de Janeiro, Rio de Janeiro, Brazil.

Background: CKD is associated with cardiovascular disease (CVD), however the best marker for this alteration is not established. Proteinuria is a marker of progression of CKD and endothelial damage. Left ventricular mass index (LVMI) and arterial stiffness (AS) are related to target organ damage. Endothelial dysfunction (ED) is associated with CVD. We evaluated the association of proteinuria with CVD markers in CKD patients.

Methods: We evaluated 97 patients, eGFR: CKD-EPI (categories 3-4). Proteinuria evaluated in urine sample (mg/g). LVMI evaluated by echocardiography and LVMI obtained by dividing it by the body surface area. AS evaluated by carotid-femoral (CF) pulse wave velocity (PWV). ED evaluated through the technique of flow-mediated dilation (FMD) of the brachial artery. We analyzed 4 subgroups regarding to age and proteinuria: Group1: age <65 years, proteinuria<300mg/g; Group2: age≥65 years, proteinuria<300mg/g; Group3: age <65 years, proteinuria³300mg/g; Group4: age≥65 years, proteinuria³300mg/g. All patients followed during 18 months. Statistical analysis: SPSS-20.

Results: Data for all patients: mean ± SD. Age 64 ± 10 years; 57% of males; eGFR: 30.6 ± 9.8ml/min/1.73 m²; systolic blood pressure (SBP): 151 ± 22mmHg; pulse pressure (PP): 70 ± 19mmHg; DMF: 10.3 ± 6.8%; CFPWV: 10.8 ± 3.4m/s; LVMI: 106.8 ± 43.5g/m²; Median proteinuria: 320mg/g (43-4992). Proteinuria did not show a significant correlation with LVMI nor FMD, and was associated with SBP after adjustment for age (p=0.0001), PP (p=0.0001) and CFPWV (p=0.001). CFPWV(m/s) values: Group1: 9.3 ± 1.6, Group2: 10.3 ± 2.6, Group3: 9.1 ± 1.9, Group4: 13.4 ± 3.6. Group 2 vs 4 p=0.03. eGFR showed a decrease ≥5ml/min/1.73m²/year in 14% of the patients. Cardiovascular events: 6.2% (acute myocardial infarction or stroke), end-stage renal disease:5.2% and death:1%. All outcomes were observed in patients with higher proteinuria and CFPWV.

Conclusions: DMF was not different among the groups. AS was higher in those with higher proteinuria and independent of the eGFR. Therefore, proteinuria but not eGFR, neither age, may be associated with the AS and consequently with CVD in this population. We suggest that the simple evaluation of proteinuria, can be used as an early marker of cardiovascular disease in CKD, instead of more complex techniques.
Secondary Hyperparathyroidism Is Independently Associated with Left Ventricular Diastolic Dysfunction in Patients with CKD

Methods: This study included 332 pre-dialysis CKD patients (estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m²). Two-dimensional echocardiography was performed to assess the left ventricular ejection fraction (LVEF), Tissue Doppler imaging was used to measure the early mitral inflow velocity (E) and the peak early mitral annular velocity (E′). Diastolic function was estimated by the E′ and the ratio of E to E′ (E/E′). The associations of echocardiographic index with clinical and laboratory variables (age, sex, diabetes, hypertension, eGFR, albumin, uric acid, calcium, phosphate, total cholesterol, hemoglobin, C-reactive protein, and intact parathyroid hormone (iPTH)) were investigated by univariate (Pearson’s correlation, r) and multivariate analysis (multiple linear regression analysis, β).

Results: Of the 332 patients, 198 were in CKD stage 3, 84 in CKD stage 4, and 50 in CKD stage 5. The degree of diastolic dysfunction was more severe (lower E′ and higher E/E′) with increasing CKD stage. There were no significant differences between these CKD groups in LVEF. In univariate analysis, the intact PTH levels correlated with E′ (r = -0.321, P < 0.001) and E/E′ (r = -0.297, P < 0.001). However, they did not correlate with index of systolic dysfunction (LVEF). In multivariate analysis, the intact PTH levels were significantly associated with E′ (β = -0.349, P < 0.001) and E/E′ (β = -0.322, P < 0.001) following adjustment for other confounding factors.

Conclusions: Increased intact PTH levels were independently associated with decreased E′ and increased E/E′ in patients with CKD, suggesting that SHPT are associated with left ventricular diastolic dysfunction in patients with CKD.

Diagnosis of CKD, Thrombotic Cardiovascular Events, and Prescription Trends for Aspirin and Oral P2Y12 Inhibitors among Veterans with CKD

Methods: We conducted a prospective observational study in patients with chronic kidney disease (CKD) who visited a hospital due to dyspnea and generalized edema. During hospitalization, volume status was evaluated using body composition monitor (BCM-Medical Care) and 2D-echography. After 1 week and 1 month later, we assessed the difference in the prescription counts between consecutive fiscal years.

Results: The point prevalence of CKD among Veterans increased by 49% from 2.30% to 3.42%. Of 226,982 total thrombotic CV events, 56.7% occurred in Veterans with CKD. Of the 378,233 Veterans with CKD, 66.7% were on aspirin and 25% received oral aspirin. Half of all prescriptions for aspirin and P2Y12 were associated with increased odds of nephrotic proteinuria. A significant difference in the prescription counts between consecutive fiscal years.

Conclusions: A rapid growing chronic disease among Veterans. Thrombotic CV events are common in Veterans with CKD. There is a dramatic rise in prescriptions for P2Y12 among Veterans with CKD. Optimal use of P2Y12 needs to be defined in Veterans with CKD in order to maximize benefits, minimize risks and justify healthcare-associated costs.

Funding: Private Foundation Support

Association of Blood Pressure (BP) with Proteinuria among Children with CKD

Methods: Cross-sectional analysis of the baseline visit in the CKD: Hypertension Adherence in Teens (CHAT) study. Children were 11-19 yrs, had CKD, and were prescribed a1 BP medication. Children had a clinic BP, 3 consecutive standardized home oscillometric BPs, and 24-hr ambulatory BP (ABPM). BP index (BPi; measured BP/95th percentile of BP; BPi = indicates hypertension) was calculated to standardize comparisons between BP measurements. Multiple logistic regression adjusted for age, sex, race, body mass index z-score, and estimated glomerular filtration rate was used to determine how each BP measurement associated with significant [urine protein:creatinine (Upcr):>0.2 but <2.0] and nephrotic (Upcr:2.0) proteinuria.

Results: 116 children with baseline first am Upcr available were included. Mean age 15.6 ±2.6 yrs, 53% African American, 55% male, 32% hypertensive, 39% with significant proteinuria, 10% with nephrotic proteinuria. CKD Stage: I 23%; II 38%; III 26%; IV 6.3%; V 7.3%. No BP measurements were associated with Upcr >0.2 but <2.0 in adjusted models. SBPi by every measurement method was associated with an increased odds of nephrotic proteinuria. Clinic DBPs was the only method of DBP measurement not associated with nephrotic proteinuria.[Table].

Conclusions: SBP by every measurement method was associated with nephrotic proteinuria. Overall, BP by ABPM was most closely associated with nephrotic proteinuria, providing additional support for its value in monitoring hypertension in progressive, heavily proteinuric CKD.

Funding: NIDDK Support

Assessment of Volume Status in Edematous CKD Patients: What to Choose

Methods: We conducted a prospective observational study in patients with chronic kidney disease who visited hospital due to dyspnea and generalized edema. During hospitalization, volume status was evaluated using body composition monitor (BCM-Fresnius Medical Care) and 2D-echography. After 1 week and 1 month later, we reevaluated their volume status by BCM and 2D-echography.

Results: Of total 28 patients, mean age of the patients was 58.85±14.47. 14(50%) visited hospital due to dyspnea and 23(82.1%) due to pitting edema. Patients’ edema was treated with diuretics (60.7%) and low salt diet or low salt diet only. Pitting edema, CKD stage, creatinine, NT-proBNP and UPCR (urine protein creatinine ratio) were significantly increased in relative overhydration (ROH=7%) group compared with non-relatives overhydration group. 10(35.7%) patients had left ventricular hypertrophy, and 10(35.7%) patients had abnormally increased left atrial volume. At baseline and 1 week later, there were little correlations with overhydration volume (OH, ECW, ECV/ICW) with ejection fraction, left atrial volume and end-diastolic left ventricle diameter. BCM volume and 2D Echography were followed up after 1 month. Patients’ symptoms were relieved during the treatment period with a significant weight difference (p value < 0.001). However, there were no significant differences in 2-D echo findings during 1 week nor 1 month. There were significant difference between the baseline and 1 month in overhydration value as well as body weight.

Conclusions: Current findings suggest that volume status may be more accurately assessed with bed side body composition monitor than echographic measurement.
Overhydration parameters on day 1 and imonth

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Month 1</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>85.5</td>
<td>72.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body weight (%)</td>
<td>9.0</td>
<td>8.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Extracellular water (%)</td>
<td>11.8</td>
<td>10.5</td>
<td>0.02</td>
</tr>
</tbody>
</table>

PUB163
Pathological Cardiac Remodeling Is Induced by Unilateral Urinary Obstruction (UUO) and Is Attenuated by Renin and Angiotensin Inhibition

**Background:** Cardiac hypertrophy and fibrosis are frequently observed in patients with chronic kidney failure. The mortality of cardiac disease is nearly doubled in chronic kidney disease (CKD) patients. Reno-cardio syndrome, or cardiorenal syndrome (CRS) type 4, is used to define cardiac dysfunction associated with chronic kidney injury. Despite close interactions between kidney dysfunction and cardiovascular disease, as evidenced by large amounts of clinical data, the underlying cellular and molecular mechanisms of cardiorenal syndrome remain poorly understood. Here, we report a study of cardiac remodeling in the context of chronic kidney failure, induced by unilateral urinary obstruction (UUO) in mice. CKD is induced after ligation of the left urethra for 21 days, as evidenced by the doubling of serum creatinine in treated mice. Despite no significant changes in cardiac function, we observed significantly increased cardiac mass, and enlarged cardiac myocytes, in UUO-induced CKD mice. Further examination, by trichrome and immunofluorescence staining of collagen type 1 and fibronectin, revealed the presence of significant extracellular matrix deposition in the cardiac interstitium. Significantly increased expression of ECM genes was detected by quantitative real time PCR, immunostaining, and immunoblotting. Further analysis indicated increased expression of TGF-β and TGF-β receptor 2, and increased phosphorylation of Smad 2 and 3; these suggest activation of the canonical TGF-

**Methods:**

**Results:**

**Conclusions:**

PUB164
Iron Therapy Is Associated with a Higher Incidence of CKD in Type 2 Diabetes Mellitus (DM2): A Retrospective Analysis of Veteran Patients in the VINCI Database

**Background:** Anemia is common with DM2 and iron therapy may exacerbate DM2. Iron is a key participant in both energy metabolism and oxidative stress with cellular damage. It is not clear if standard iron therapy in DM2 produces a corresponding deleterious effect in the clinic. We undertook a retrospective study on the effect on iron therapy on CKD progression veterans with DM2.

**Methods:** Data from a large cohort of veterans diagnosed with DM2 and Anemia by ICD (N=349,713) followed between 2002-2017 were used to determine the effect of iron therapy. Data from the Veterans Administration Informatics and Computing Infrastructure (VINCI) were analyzed using SQL and SAS. Patients were divided into those who did not receive iron therapy (No-Iron, N=185,272) and those who received iron therapy (Iron-Rx, N=164,441). Progression to ESRD was determined by an increase in creatinine values to above 1.5, 3.0 or 6.0 mg/dL. Groups were also compared for all-cause mortality, new onset CVA, MI and retinopathy. Significance was determined by Chi-square test.

**Results:** Results are outlined in the Table. Less than half of patients (47%) with anemia received iron therapy. The number of subject with creatinine values 3.0 and 6.0 were significantly higher in the Iron-Rx group (P<0.001). Incidence of stroke (CVA), myocardial infarction (MI) and retinopathy was higher (P<0.001) in the Iron-Rx group. As all-cause mortality (P<0.001).

**Conclusions:** Incidental or intentional iron therapy associates with significantly higher advance to ESRD and higher incidence of MI, CVA, and mortality, all consistent with advancing macro-vascular disease. Significant increased retinopathy signals concurrent micro-vascular disease.
Prevalence of Reduced Bone Density in Systemic Lupus Erythematosus Patients: A Single-Center Study and a Meta-Analysis

Yi Yang,1 Gang Xu,2 Shuwang Ge,3 Tongji Hospital, Huazhong University of Science and Technology, WUHAN, China; Tongji Hospital, Tongji Medical College, Huazhong Univ of Science and Technology, WUHAN, China; Tongji hospital affiliated to Tongji medical college, Huazhong University of Science and Technology, Wuhans, Hubei, China, Wuhans, China.

Background: The reported frequency of reduced bone mineral density (BMD) in systemic lupus erythematosus (SLE) patients vary widely. The data in Chinese SLE patients undergo minimal study. Risk factors associated are still under debate from different countries. We aimed to (1) detect the frequency and possible risk factors of reduced BMD in patients with SLE in our single center, and (2) conduct a meta-analysis concerning the frequency of reduced BMD in SLE with evidence from published studies.

Methods: We aimed to (1) detect the frequency and possible risk factors of reduced BMD in patients with SLE in our single center, and (2) conduct a meta-analysis concerning the frequency of reduced BMD in SLE with evidence from published studies.

Results: In our single-center study, 91 female SLE patients were assessed. 52.7% of the patients had low BMD, 56.0% had osteopenia and 19.8% had osteoporosis. Prevalence of osteoporosis was higher in post-menopausal patients compared with pre-menopausal patients at total hip and femoral neck. Body weight was positively associated with BMD in all measured sites and menopause duration was negatively associated with lumbar spine and total hip BMD. In the meta-analysis, 71 reports with 33527 SLE patients were included. Low BMD, osteopenia and osteoporosis at any site were present, respectively in 45%, 38% and 13% of the SLE patients. The prevalence of osteoporosis increased with the advancing of age, while U-shaped associations between age and the prevalence of low BMD and osteoporosis were found. Lumbar spine was indicated to have severer bone loss compared to total hip and femoral neck in both our cross-sectional study and meta-analysis.

Conclusions: SLE Patients showed a high prevalence of reduced BMD. Low body weight, menopause duration, old age and disease-related factors might be the possible associated risk factors of bone loss.

Funding: Government Support - Non-U.S.

Effect of Intravenous Sodium Ferric Gluconate on Serial Platelet Counts in CKD Patients with Iron Deficiency Anemia

Neville R. Dossabhoy,1,2 Pallavi D. Shirsat,1,2 Sangeeta Pal,1,2 Medicine/Nephrology, VA Medical Center, Shreveport, LA; 1LSU Health Shreveport School of Medicine, Shreveport, LA.

Background: Iron deficiency often leads to reactive thrombocytosis; theoretically, its correction should lead to a lowering of the platelet count (PLT). Only a few studies have investigated this aspect, with some showing a reduction in PLT, whereas others did not.

We investigated the effect of iron repletion with intravenous (IV) sodium ferric gluconate (SFG) on serial PLT counts in CKD patients with iron deficiency anemia (IDA).

Methods: We conducted a retrospective chart review, including patients with CKD and IDA who were treated with IV SFG. Patient demographics were recorded, as were baseline laboratory values for creatinine, eGFR, Hgb, iron stores and PLT. Serial, post-dose PLT values were recorded weekly for 4 weeks.

Results: A total of 118 doses of IV SFG (mean ± SD = 191±63 mg) were studied in patients with age 53±15 years, Creatinine 4.3±4.1 mg/dL, Hgb 8.7±1.8 g/dL and T-sat 12±7%. All CKD stages were represented in the study sample. Hgb and Fe stores improved post-dose. The variation in post-dose PLT over time is depicted below. All the values up to 4 weeks were elevated compared to the baseline, with the 2-week mark reaching significance (P = 0.007).

Conclusions: Correction of iron deficiency did not lower PLT in CKD patients with IDA who received IV SFG. In fact, PLT were elevated compared to baseline throughout the 4-week period of follow-up, reaching statistical significance at the 2-week mark. This finding stands in contrast to some previous evidence and current popular theories. It confirms the previous report that PLT counts were not significantly reduced with IV dextran used as total dose infusion. Our finding may raise the possibility that increased PLT in the short-term post-dose, may contribute to the thrombotic events noted in clinical trials of erythropoiesis stimulating agents in CKD patients.

<table>
<thead>
<tr>
<th>Week</th>
<th>Mean PLT Count</th>
<th>Median PLT Count</th>
<th>Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>226</td>
<td>176</td>
<td>307</td>
</tr>
<tr>
<td>1</td>
<td>239</td>
<td>197</td>
<td>350</td>
</tr>
<tr>
<td>2</td>
<td>259</td>
<td>215</td>
<td>392</td>
</tr>
<tr>
<td>3</td>
<td>276</td>
<td>229</td>
<td>436</td>
</tr>
<tr>
<td>4</td>
<td>307</td>
<td>248</td>
<td>522</td>
</tr>
</tbody>
</table>

P-values vs Baseline 0.054 0.007 0.012 0.018

Loop Diuretics Associate with Greater Risk of Sarcopenia in Non-Dialysis-Dependent CKD Patients

Seiko Ishikawa,1 Shotaro Naito,1 Shintaro MANDAI,1 Soichiro IIMORI,1 Naohiro NOMURA,1 Eisei SOHARA,1 Eiichiro KANDA,2 Tomokazu OKADO,1 Tatemitsu RAIZU,1 Shinichi UCHIDA,1 Tokyo Medical and Dental University, Tokyo, Japan; 2Tokyo Kyosai Hospital, Meguro, Japan.

Background: Sarcopenia is defined as progressive decline of skeletal muscle mass and function with age. Few studies have investigated the actual situation of sarcopenia in non-dialysis-dependent chronic kidney disease (NDD-CKD) patients.

Methods: We conducted a cross-sectional study comprised of 217 NDD-CKD patients over 65 years of age. Total body skeletal muscle mass was measured by dual-energy X-ray absorptiometry. Sarcopenia was diagnosed using the criteria of Asian Working Group for Sarcopenia. Adjusted odds ratios (aOR) for sarcopenia were estimated by using multivariate logistic models after stratifying the patients into 3 groups according to CKD stages.

Results: Mean age was 75.6±6.6 years, mean body mass index was 22.8±3.6 kg/m², and mean eGFR was 30.6±13.3 ml/min/1.73 m². 30.4% of the patients had diabetes mellitus (DM), 18.4% were treated with loop diuretics, and 25.3% were diagnosed as sarcopenia. Adjusted by age and gender (Model 1), the aOR in CKD5 group was 2.60 [95% confidence interval (CI) 1.04-6.50] compared to CKD 3 group. Adjusted by age, gender, and either DM (Model 2) or loop diuretics (Model 3), the aORs for CKD groups were statistically insignificant. On the other hand, each of DM and loop diuretics were associated with risk of sarcopenia [DM: aOR 2.02 (95%CI 1.01-4.07); Model 2; loop diuretics: aOR 3.07(95%CI 1.32-7.12); Model 3]. Furthermore, adjusted by age, gender, CKD groups, DM and loop diuretics (Model 4), the aOR for DM was statistically insignificant whereas the aOR for loop diuretics remained significant [loop diuretics: aOR 2.64(95%CI 1.10-6.33)]. In all models, age was an independent risk factor for sarcopenia.

Conclusions: Age and loop diuretics were independently associated with sarcopenia. In particular, loop diuretics were associated with increased risk of sarcopenia more than renal function and DM. Previous studies have shown that loop diuretics suppress skeletal muscle differentiation. This is the first study to show the risks of sarcopenia associated with usage of loop diuretics in a cohort of NDD-CKD patients. Since loop diuretics are commonly used in patients with advanced CKD treatment of volume overload, consideration for risk of sarcopenia may be necessary in such patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
The Endoscopic Findings of Double Balloon Enteroscopy in Patients with CKD and Obscure Gastrointestinal Bleeding

Mohamad A. Hanouneh,2 Steven Menez,2 Diana S. Najjar,2 Qiuyu Jin,3 Ahmed El-Telbany.1
1Department of Medicine, Cleveland Clinic, Cleveland, OH; 2Department of Nephrology, Johns Hopkins University, Baltimore, MD.

Background: Obscure gastrointestinal bleeding is a common problem and associated with increased morbidity and mortality. Scarce data exist describing the small bowel characteristics of patients with chronic kidney disease (CKD) who present with obscure gastrointestinal (GI) bleeding. The aim of the study is to investigate the endoscopic findings of double balloon enteroscopy in patients with CKD who present with obscure GI bleeding.

Methods: We recruited 66 adult patients with CKD stages III-V who had obscure GI bleeding and underwent double balloon enteroscopy between 2002 and 2013. Stages of CKD were defined based on the glomerular filtration rate. Glomerular Filtration Rate (GFR) Estimation by Modification of Diet in Renal Disease (MDRD) Equation. Stage III for GFR 30-59, stage IV for GFR 15-29 and stage V for GFR <15. Obscure GI bleeding was defined as persistent or recurrent gastrointestinal bleeding (hematochezia, melena, hematochezia or positive fecal occult blood test) with negative upper and lower endoscopies.

Results: A total of 66 patients were included in the study, of whom 37 patients had CKD stage III, 11 patients had CKD stage IV and 18 patients had CKD stage V. The median serum creatinine in the entire study population was 1.89 mg/dL [1.39, 3.28]. The source of bleeding was identified on 45 patients (68.2%). The most common findings of double balloon enteroscopy were arteriovenous malformation (AVM) in 30 (45.5%) of whom 18 patients had CKD stage III, 4 patients had CKD stage IV and 8 patients had CKD stage V. Overall, the most common locations of the AVM were the jejunal (73.3%). Other causes of obscure GI bleed include erosions (n=7, 10.6%) and ulcers (n=7, 10.6%).

Conclusions: Arteriovenous malformation (AVM) is the most common finding of double balloon enteroscopy in patients with chronic kidney disease who have obscure GI bleeding.

Correlation and Agreement between BIS-1 and CKD-EPI Equations to Estimate GFR in a Wide Cohort of Older Patients

Chronic kidney disease (CKD) is highly prevalent among older adults in Latin America. KDIGO proposes the use of Chronic kidney disease Epidemiology collaboration (KDPI-EPI) equation however this equation is not specific for patients aged over 70 years. Its application results on the inclusion of these patients on advanced stages of CKD increasing the burden on CKD programs. The Berlin Initiative Study (BIS-1) equation, compared to CKD-EPI equation, would improve the precision and accuracy of glomerular filtration rate estimation (GFRs) in patients aged over 70 years. There are limited reports of its use in Latin America and there is no data available for Argentina. Therefore, the aim of this study is to assess correlation and concordance between BIS-1 equation and CKD-EPI equations in a wide cohort of patients.

Methods: Plasma creatinine was measured on a cohort of 28,411 patients aged over 70 years from Hospital Italiano de Buenos Aires, CABA, Argentina. Other causes of obscure GI bleed include erosions (n=7, 10.6%) and ulcers (n=7, 10.6%).

Results: The mean age was 75±7 years. 65.7% (n= 18,678) female and 34.4% (n= 9763) male. Mean GFR estimated by CKD-EPI was 68±17 mL/min/1.73m² and for BIS-1 was 60±15 mL/min/1.73m² (p<0.01) There was a significant correlation between both equations (p<0.01). BIS-1 included significant more patients on GFR from 15 to 60 mL/min than CKD decreasing the number of patients on the rest of the stages (see Table 1). On graph 1 Bland-Altman graph showed that below 30 and above 60 mL/min the difference of the obtained results for both equations were outside the limits of concordance.

Conclusions: BIS-1 decreases the number of patients included in advanced stages of CKD (4 and 5) but, nevertheless, increases the number for stage 3B; without reducing the burden of patients on CKD programs.

Assessment of CKD Stage 3/4 Using Multiparametric Magnetic Resonance Imaging

Huda Mahmoud,1 Charlotte E. Buchanan,2 Eleanor Cox,2 Benjamin L. Prestwich,2 Nicholas M. Selby,2 Susan Francis,1 Maarten W. Taal1,3 Sir Peter Mansfield Imaging Centre, Nottingham, United Kingdom; 1University of Nottingham, Nottingham, United Kingdom, 2Centre for Kidney Research and Innovation, Derby, United Kingdom.

Background: Progression of Chronic Kidney Disease(CKD) occurs secondary to inflammation and fibrosis independent of the underlying etiology. Recent advances in Magnetic Resonance Imaging(MR) allow assessment of renal structure and function. We performed a multiparametric MR study to assess its utility and reproducibility in CKD patients.

Methods: 26 CKD Stage 3-4 patients with kidney biopsies and 13 healthy volunteers(HV) had 2 multiparametric renal MR scans performed 7-14d apart on a 3T Philips Ingenia scanner. Structural assessments included renal volume, longitudinal-relaxation time(T₂) and Diffusion-Weighted Imaging(DWI) as markers of fibrosis and/or inflammation. Functional assessments included Arterial Spin Labelling(ASL) to measure renal perfusion and Blood Oxygenation Level Dependant Imaging(BOLD) as an indicator of renal oxygenation. The Coefficient of Variance(CoV) was calculated for each measure between the scans.

Results: CKD patients: mean 57±15yrs, eGFR 39±13mL/min/1.73m², uPCR 120±18mg/mmol. HVs were age-matched, had normal eGFR and no proteinuria. CKD cortical and medullary T₂ values were higher than HVs, 1580±29ms & 1739±78ms compared to 1396±64ms(p<0.0001) & 1700±107(p<0.0001) respectively, indicating more fibrosis/inflammation. CKD had lower renal perfusion values(p=0.003) and a trend for lower DWI values than HVs, no difference in volume and T₂*(BOLD) were found. Correlations were found between T₂ values and the extent of interstitial fibrosis observed on histology(p<0.02). Reproducibility was excellent for cortical and medullary T₂ (CoV 2.6% & 2.0% respectively), T₂*(CoV 2.6%), ADC(CoV 8.2%) and volumes(CV 3.0%)

Conclusions: This study demonstrates that multiparametric MR differentiates between HVs and CKD patients and is reproducible. The MR results reflect the known pathological changes expected in CKD: increased fibrosis and/or inflammation, and the presence of fibrosis and/or inflammation, but interestingly did not demonstrate a difference in T₂* a potential marker of renal hypoxia. Further studies are required to build on this initial work to determine how best multiparametric MR can be used to assess whole kidney pathology and prognosis.

Funding: Private Foundation Support
**PUB175**

The Risk of Hip Fracture in Patients Suffering from Different Stages of CKD

**Ammar Qureshi,1 Fernando R. Aguilar,1 Nesreen Benhamed.2**

1Georgetown University Hospital, Washington, DC; 2Internal Medicine, Marshall University, Huntington, WV; 3Internal Medicine, MUSOM, Barboursville, WV.

**Background:** Patients with CKD are at an increased risk of hip fracture than the normal population, which is attributed to the resulting vitamin D deficiency caused by the failure of the kidney to activate vitamin D. Failure in the calcium-phosphorus homeostasis also adds to the poor bone condition. The aim of our study is to analyze the correlation between the stage of CKD (determined by GFR) and incidence of hip fracture.

**Methods:** Data was extracted from the 2005’12 nationwide sample (NIS) registry. We stratified these patients based on the stages of CKD (Stage 1 GFR > 90 mL/min; Stage 2 GFR 60-89 mL/min; stage 3 GFR 30-59 mL/min; stage 4 GFR 15-29 mL/min; stage 5 < 15 mL/min). The incidence of hip fracture was calculated in each stage of CKD. Patients with CKD were matched with those without CKD using propensity score matching to determine the all-cause mortality in patients with hip fracture and those without hip fracture in patients with CKD.

**Results:** A total of 2.85 million patients were diagnosed with chronic kidney disease including ESRD in the year between 2005 and 2012. When stratifying according to the stages of CKD, stages 3 (0.54 % p=0.007 OR 0.70) and ESRD (0.76% p=0.007 OR 1.15) had the highest rates of sustaining a hip fracture when compared to the other stages of CKD. 1.35 % of these patients suffering from chronic kidney disease and hip fractures died during their hospital stay. The odds of sustaining a hip fracture with a patient suffering from chronic renal disease were 1.3 times. The difference in rates of sustaining a hip fracture between those patients diagnosed with renal osteodystrophy and those who were not was not found to be significant (p= 0.93).

**Conclusions:** Our data showed that patients end stage renal stage disease had a significantly higher chance of sustaining a hip fracture than patients in other stages of the CKD. Hence a worsening GFR could be correlated with the odds of sustaining a hip fracture, which means that as the stage of CKD progressed, patients were more prone to hip fractures. These patients also had a higher mortality risk, however this could be a confounding factor since patients who are inflicted with both CKD and hip fracture could be sicker patients. There was no difference in the incidence of hip fractures if the patient was diagnosed with renal osteodystrophy.

**PUB176**

Cyclosporine as Rescue Therapy for Focal Segmental Glomerulosclerosis Patients Who Were Refractory to Steroid Combination with Tacrolimus

**Xiyu Li, Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China.**

**Background:** A proportion of adults with focal segmental glomerulosclerosis (FSGS) are refractory to treatment of steroid combination with tacrolimus due to persistent severe hypoalbuminemia and proteinuria. It is a challenge to find rescue therapies that are effective and safe in treating such difficult patient. Cyclosporine may be a promising alternative to tacrolimus for such patients.

**Methods:** In this prospective observational study, nineteen patients with adult-onset FSGS who did not respond to treatment with steroid (daily prednisone 0.5 mg/kg per day) and calcineurin inhibitors (target level of 4-10 ng/ml) for 12 weeks were studied from January 2013 to September 2016. Oral cyclosporine was administered (target trough level of 200-250 ng/ml) for 24 weeks, and then with tapering cyclosporine was given (target trough level of 50-100 ng/ml) for another 24 weeks. Oral prednisone was started at 0.5 mg/kg per day. Primary outcome variables were remission. Secondary outcome variables were time to remission, relapse rate, changes in serum creatinine and estimated glomerular filtration rate.

**Results:** One patient discontinued cyclosporine because of reversible acute nephrotoxicity, and 18 patients completed at least 12 weeks of cyclosporine therapy. Five patients (27.8%) experienced complete remission and 7 patients (38.8%) experienced partial remission. Primary resistance to cyclosporine was seen in 6 patients (33.3%). The mean time to partial remission and complete remission was 6.2 ± 3.4 weeks and 12.6 ± 4.5 weeks, respectively. After a mean follow up of 28.3 months, 33.3% (4/12) of patients who had remission experienced relapses. Two patients who were resistant to cyclosporine therapy had a doubling of serum creatinine concentration during follow-up.

**Conclusions:** Cyclosporine may be a suitable therapeutic option for treatment of adult-onset refractory FSGS. However, controlled studies with more patients are needed to compare the efficacy and safety of cyclosporine with tacrolimus in treating FSGS.

**PUB177**

Relationship between Renalase and Kidney Disease in 72 Patients with Renal Biopsy

**Nan Hu;1 Sha Y. Huang;2 Chuang-Ming Hsu;1 Xin-Zhong Qin;1 Feng Chen;1 Ning-Wei Qiu;1 Qureshi,2 Fernando,1 Huang,2,3 Sha,2,3 Nan,2,3 Xu,2,3 Zhang.1 Huashan Hosp., Shanghai, China; 2Department of Nephrology, Shenzhen People's Hospital, Shenzhen, China; 3Key Renal Laboratory of Shenzhen, Shenzhen, China.**

**Background:** Renalase is the only one amine oxidase that can be synthesized by renal tubular epithelial cells and renal cell apoptosis was assessed with TUNEL stain.

**Methods:** Twenty patients with CKD were measured by the IHC method. The tubular injury was detected and calculated by PAS and renal tubular epithelial cell apoptosis was assessed with TUNEL stain.

**Results:** The expression of renalase in renal biopsy with significantly lower levels than in patients with renal cell carcinoma of normal kidney tissue (Fig 1). In patients undergoing renal puncture biopsy, renal tubule injury index, as well as tubular epithelial cell apoptosis index showed a negative linear correlation with renalase (Fig 2). The results showed that renalase probably increase the expression of bcl-2 protein.

**Conclusions:** The research proved that it may reduce the renal tubular injury and apoptosis of renal tubular epithelial cells through the mitochondrial apoptosis pathway, finally achieve the purpose of delaying the progress of renal failure.

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

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

Underline represents presenting author.
PUB178

Urine Liquid Biopsy of the Kidney  Tadashi Yamamoto,1,4 Keiko Yamamoto,1 Yoshishito Hirao,1 Bo Xu,2 Shigeru Miyazaki,2 Hitosato Miyazaki,1 Shinya Hirao,1 Shinya Karube,1 Shintaro Kukimoto,1 Shinya Shimizu,1 Kyoji Ichimura,1 Shigeru Miyazaki,1 Yoshitoshi Yamamoto,1 Shinrakuen Hospital, Niigata, Japan; 2Shinrakuen Hospital, Niigata, Japan; 3Shinrakuen Hospital, Niigata, Japan; 4Shinrakuen Hospital, Niigata, Japan.

Background: Many studies have been done to identify kidney disease biomarkers by proteomics of urine. However, urine biomarkers sufficient enough from scientific and practical views have not been identified yet. One of the reasons may come from the study design. For example, to identify biomarkers for chronic kidney disease (CKD), urine samples collected from CKD patients with proteinuria was analyzed by proteomics, resulting that plasma proteins have mostly been identified. To overcome the problem and to identify biomarkers informing the sites of injury, we aimed to identify urine biomarkers for injury at each different tissue compartment in the kidney and to make a panel test (urine kidney biopsy), which may inform pathological changes as kidney biopsy.

Methods: Several kidney compartments (glomerulus, proximal tubule, distal tubule, collecting duct, kidney cortex and medulla) are laser-microdissected from formalin-fixed paraffin-embedded human kidney specimens and peptides digested with trypsin were collected by the on-site direct digestion (OSDD) method for mass spectrometry. These proteomes were compared each other and also with those of plasma and urine to select proteins, which were uniquely identified in each compartment and not found in the plasma but found in the urine. In particular, small-sized T lymphocytes and granulomatous changes. No plasma cells or eosinophils were observed. The T cell clonality test for TCRG using the renal tissues revealed T-cell lymphoma. A year and a half later, renal dysfunction was recognized by increased creatinine. Further kidney biopsies showed global glomerulosclerosis in 5 out of 21 glomeruli and advanced fibrosis. Immunohistochemistry for injury at each different tissue compartment in the kidney and to make a panel test (urine kidney biopsy), which may inform pathological changes as kidney biopsy.

Conclusions: By the urine liquid biopsy of a biomarker panel for kidney compartment events, injuries at different compartments in the kidney were individually and quantitatively evaluated by a non-invasive manner.

Funding: Private Foundation Support

PUB179

A Rare Case of Granulomatous Interstitial Nephritis Associated T Cell Lymphoma Miho Karube,1 Shintaro Masuko,1 Hideki Shimizu,2 Hikaru Kukimoto,1 Shinya Kaname,1 Kyorin University School of Medicine, Tokyo, Japan; 2Kyorin university, Tokyo, Japan.

Background: Introduction: Although granulomatous interstitial nephritis is known to be associated with sarcoidosis and tuberculosis, it has been rarely reported in T cell lymphoma.

Methods: Results: A 50-year-old woman was referred to our hospital because of abdominal lymphadenopathy two years ago. Open lymph node biopsy revealed granulomatous lymph nodes. A year and a half later, renal dysfunction was recognized by increased levels of serum Cr 1.95 mg/dl and urine j2 microglobulin 17.62 mg/l, and renal biopsy was performed, showing global glomerulosclerosis in 5 out of 21 glomeruli and advanced tubulointerstitial nephritis with a marked infiltration of CD3+T cells, CD4+ and CD8+ T lymphocytes and granulomatous changes. No plasma cells or eosinophils were observed. The T cell clonality test for TCRG using the renal tissues revealed T cell monoclonal proliferation, thus together with a serum increase in soluble IL-2 receptor levels (2,880 U/ml), she was diagnosed with T cell lymphoma. After glucocorticoid and standard chemotherapy, renal function slightly improved and re-biopsy of the kidney showed improved T cell infiltrations, associated with advanced tubulointerstitial changes with fibrosis.

Conclusions: Discussion: We reported a rare case of granulomatous tubulointerstitial nephritis in a patient with T cell lymphoma. T cell lymphoma should be considered in tubulointerstitial nephritis of unknown origin.

PUB180

Efficacy of AST-120 in Patients with CKD: A Systematic Review and Meta-Analysis Mei-Yi Wu,1 Ying-Chun Chen,2 Department of Nephrology, Taipei Medical University- Shaung Ho Hospital, Taipei, Taiwan; 2Taipei Medical University, Shuang Ho Hospital, Taipei, Taiwan.

Background: AST-120 (Kremezin), which is an oral spherical carbonaceous adsorbent of the precursor of indoxyl sulfate (IS), has been reported to be potential for retarding disease progression in patients with chronic kidney disease (CKD). In the present study, we aimed to evaluate its efficacy in slowing disease progression in CKD patients.

Methods: We systematically searched for clinical trials published in PubMed, Medline, and Cochrane databases. Randomized controlled trials of AST-120 in CKD patients were selected. The primary outcomes were the composite of renal outcome and all-cause mortality. The secondary outcome was the changes in serum IS level.

Results: Eight studies providing data for 3320 patients were included in the meta-analysis. Among patients treated with AST-120, the summary RR of composite of renal outcome was 0.97 (95% CI 0.88-1.07) using a random effects model (heterogeneity I²=0%). The summary RR of all-cause mortality was 0.94 (95% CI 0.73-1.2) using a random effects model (heterogeneity I²=0%). Change of IS level from baseline to the end of the study was higher in patients treated with AST-120 (mean difference: -0.34 mg/dl; 95% CI, -0.48 to -0.2, 4 trials) compared with placebo.

Conclusions: This review provides evidence that AST-120 can effectively lower IS level but still controversy in slowing disease progression and all-cause mortality. Further studies are needed to assess which is the optimal CKD population to be treated by AST-120.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PUB182

Renadyl™, Improving GFR and Quality of Life: Results of 3rd Biannual Survey 2017

Natarajan Ranganathan, Kevin M. Hanlon, KIBOW BIOTECH INC, Newtown Square, PA; Kibow Biotech, Newtown Square, PA.

**Background:** Kibow Biotech’s “Enteric Dialysis™” concept based off of the modulation of the gut microbiome to maintain healthy kidney function has proved to be helpful in many of those suffering from CKD. Kibow’s product “Renadyl™” has been available since 2010 and is continually being studied to assess just how effective it is. A short survey given to 600 Renadyl customers was distributed to ascertain how their GFR changed, and the impact on their quality of life after adding the dietary supplement Renadyl™ into their standard care of therapy.

**Methods:** “Renadyl™,” a symbiotic dietary supplement was assessed in its ability to maintain healthy kidney function (stabilize GFR), and ability to improve quality of life. A survey was distributed to 600 customers asking for GFR when they began taking Renadyl; and at their most recent doctors visit, as well as Age, Race, ethnicity, and if Renadyl™ had improved their overall quality of life or not. Statistical analyses were performed on the GFR data to estimate Renadyl™’s impact on GFR, and quality of life. Of the 600 surveys sent, 210 (35%) responses were received (116 male, 94 female).

**Results:** The average age of a Renadyl user was 69 years old. The average survey participant had been using Renadyl for 2.05 years. Of the surveys received, 140 contained complete information, including GFR. The lowest baseline GFR recorded was 4, the highest was 100 (ESRD to Healthy). The average baseline GFR of a survey participant was 29 (Stage IV). The most recent GFR reported varied from 5 to 102. The highest GFR impact was an increase of 65, and the largest decrease in GFR was -43. The average change in GFR for a survey participant was an increase of 2.39. Among the survey respondents, 88% reported that Renadyl™ improved their quality of life.

**Conclusions:** Chronic kidney disease is generally recognized as a degenerative process. However, with over 4,000 customers we sought feedback from 15% of them to assess the impact of Renadyl™ usage over an average of 2.05 years. The longest using participant used the product for 7 years, the shortest for 6 months. With the ability to stabilize and improve GFR, it may be possible to delay the progression of kidney failure at all stages. Improving quality of life in 88% of participants certainly signifies the advantages of using Renadyl™ in patients with compromised renal function worldwide.

**Funding:** Private Foundation Support

---

PUB183

Chemotherapy Induced Neuropathy in CKD Patients

Biruh Workneh,1 Louie H. Morsey,1 He Zhou,2 Bijan Najah,1 ’Baylor College of Medicine, Houston, TX; ’MD Anderson Cancer Center, Houston, TX.

**Background:** Chemotherapy induced neuropathy (CIPN) is a prominent feature of traditional and targeted therapy for cancer, and contributes significantly to the frailty of cancer patients. Frailty and peripheral neuropathy are also features of chronic kidney disease (CKD), and we sought to determine the influence of CKD on the severity of CIPN. We studied patients with cancer who had clinically established CIPN and screened them for an objective measure of abnormal nerve conduction with vibration perception threshold (VPT) analysis, which has been shown to predict outcomes such as falls, foot ulceration and quality of life.

**Methods:** We recruited 17 subjects >50 years of age with cancer who had clinically established CIPN. VPT analysis was performed on each subject and recorded at plantar foot sites: bilaterally: heel, 5th metatarsal and big toe. We defined the CKD group by an eGFR <60ml/min at the time of testing, and recorded demographics and comorbidities.

**Results:** A description of both CKD and non-CKD groups are listed in Table 1. VPT scores were recorded at the following plantar foot sites and results are shown in Figure 1. The CKD consistently had lower scores across VPT testing sites, and reached significance in the right big to region. Multivariate analysis suggested that diabetes diagnosis prior to chemotherapy may be independently associated with the development of neuropathy, but did not reach significance.

**Conclusions:** Although preliminary, our results show that the presence of CKD is associated with a decreased severity of neuropathy and that diabetes may be independently associated with more severe neuropathy related to cancer treatment.

**Funding:** Other NIH Support - NIH-R21

---

PUB184

Immunization: An Important Addition to Standard Care in Glomerulonephritis Patients

Melissa Lan, Coleman Rotstein, RORY F. McQuillan, Daniel C. Catrnan. University Health Network, TORONTO, ON, Canada.

**Background:** Glomerulonephritis (GN) is a group of rare kidney diseases that can progress to end stage renal failure. GN patients are at increased risk for infection given nephrotic remission/relapse patterns, exposure to immunosuppressant therapy, and/or possible progression to chronic kidney disease. Thus our focus on guidelines indicating that hepatitis B, pneumococcus, influenza, and varicella are vaccine preventable infections.

**Methods:** Using the model for Quality Improvement (QI), a multifaceted GN immunization protocol (GNIP) was adopted after a needs assessment found that the first 20 patient charts had no documented immunization history. Patient (N=64) preference assessment for receipt of immunizations was by family physician (FP) 65.6%, primary nephrologist 10.9%, hospital clinic 6.3%, and walk-in clinic 4.7%. Investigation of options for vaccine administration helped construct a fish bone diagram and process map that further focused the GNIP. Physician and patient communication and documentation tools were created and the protocol initiated. The GNIP assessed/recommended hepatitis B, pneumococcus, tetanus-diphtheria-acellular pertussis, varicella, and herpes zoster immunizations plus annual administration of the inactivated influenza vaccine.

**Results:** Outcome measures at 4-months post-GNIP implementation: 1. 73% (92/126) of patients assessed for GNIP now have documented immunization history. 2. 63.5% (80/126) of patients assessed for GNIP have now received immunization recommendations. 3. 19.4% (90/465) of the recommended immunizations have now been administered. Additional findings: 3.1% (4/130) of patients refused to participate in the GNIP; major FP issue is the high-dose hepatitis B immunization requirement; most critical is the communication links between patient, FP, and GN clinic.

**Conclusions:** The GNIP fulfills an unmet medical need in GN care. This QI project highlights that need and indicates a developmental process for implementation of a solution. Early results indicate improved immunization documentation, an increase in immunization administration, and the potential for increased patient infection protection.

**Funding:** Private Foundation Support

---

PUB185

Depression and CKD – A Deadly Combination with Insufficient Screening

Haldane Porteous,1 Stefan C. Hemnings,1 Daphne H. Knucly,1 John Hopkins Medicine, Baltimore, MD; 2Johns Hopkins University, Baltimore, MD; 3Johns Hopkins University School of Medicine, Baltimore, MD.

**Background:** The prevalence of depression in the general population is approximately 7 percent but in patients with chronic kidney disease (CKD) depression rates are significantly higher, approximately 22 percent. There is a 30 percent increased risk of death in CKD patients with depression compared to CKD patients without depression. Additionally, the former are subjected to increased hospitalization rates, poorer treatment compliance, and decreased quality of life. Unfortunately, despite these known adverse associations, depression in CKD remains underdiagnosed and undertreated. Screening for depression via validated tools which are widely available could identify at risk patients and early intervention with pharmacological or non-pharmacological treatment could possibly improve patient outcomes.

**Methods:** A pre/post intervention quality improvement project involving CKD stage 3-5 patients using the validated Patient Health Questionnaire-2 (PHQ-2) depression screening tool was conducted within the Nephrology Fellows’ Continuity Clinic. From September 2016 to November 2016, 202 charts were audited to determine the depression screening rate of patients. The intervention phase consisted of clinician education on the importance of screening for depression as well as a built-in electronic smart phrase based on the PHQ2 tool. Between December 2016 and February 2017, 202 charts were audited

**Conclusions:** Although preliminary, our results show that the presence of CKD is associated with a decreased severity of neuropathy and that diabetes may be independently associated with more severe neuropathy related to cancer treatment.

**Funding:** Other NIH Support - NIH-R21

---

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

Underline represents presenting author.

1012
to determine the post intervention screening rate. From March 2017 and April 2017, 50 charts were reviewed to determine if the post-study result was sustained.

**Results:**
Pre-intervention screening rate was 1.48 percent. Post-intervention screening rate increased to 10.45 percent. Post-study screening rate was 12.01 percent.

**Conclusions:**
Depression is prevalent in CKD patients and is associated with increased mortality. This quality improvement project demonstrated that clinic education and an electronic smart phrase based on a validated screening tool are two metrics associated with a sustained improvement in depression screening. Research studies are needed to identify other metrics which can be used to improve depression screening so that CKD patients can receive early treatment which may reduce the risk of hospitalization and/or death.

**PUB186**

**Advance Care Planning in the CKD Stages 3-5 Non-Dialysis Population 65 Years and Older**

**Background:** In the chronic kidney disease (CKD) academic outpatient predialysis clinic, there were no identified protocols or procedures for advance care planning (ACP) for this chronic CKD stages 3-5 population 65 years and older. Research has indicated the value of ACP and the collection of advance directives in patients with chronic disease states. This quality improvement project addressed the identified gap of lack of evidence-based ACP interventions specific to this population.

**Methods:**
The purpose of this quality improvement project was to (a) assess the effectiveness of an evidence-based educational intervention versus usual care in increasing completion of medical durable powers of attorney (MDPOAs) and advance directives (A) by these selected high risk (HR) CKD patients (b) determine the effect of independent variables on this CKD population education in completion of ACP for the purpose of tailoring an evidence-based ACP program. Pre-dialysis CKD stage 3-5 patients’ (N = 60) response to an advance care planning intervention and the completion of advance directives and medical durable power of attorney (DPOA) was audited to determine descriptive and inferential statistics (frequency distribution, Pearson’s chi square planning test for independence and McNemar’s test).

**Results:**
Results indicated statistical significance (p < .05) in the increase in collection of advance directives in the educational versus the control group. The results also demonstrate statistical significance (p < .05) in the collection of MDPOAs in an outpatient CKD clinic in patients 65 years and older.

**Conclusions:**
This quality improvement project has shown with the right resources, effective communication with staff and providers, an open clinical population, a cost effective and sustainable delivery system for ACP in an outpatient clinic in line with the organizational mission can be a reality. Ultimately, improving the process of educating patients about end-of-life care and collection of advance directives and MDPOAs will improve end-of-life care and decrease hospital costs related to end-of-life care as well as bring revenue to the practice.

**PUB187**

**Provider Experience with Implementation of a Pragmatic Randomized Trial of CKD Screening in Primary Care: A Qualitative Report**

**Martin J. Frigaard,1 Leticia Rolon,2 Howell J. Lo,3 Anna Rubinsky,4 Delphine S. Tuot,5 Neil R. Powe,6 Michael Shlipak,7 Carmen A. Peralta,8 1Kidney Health Research Collaborative, Oakland, CA; 2None, San Francisco, CA; 3University of California San Francisco/SFVAMC, San Francisco, CA; 4Priscilla Chan and Mark Zuckerberg San Francisco General Hospital & University of California SF, San Francisco, CA; 5San Francisco VA Medical Center, San Francisco, CA; 6UCSF Medical Center, San Francisco, CA; 7University of California, San Francisco, San Francisco, CA.

**Background:**
Provider burden from participation in pragmatic randomized clinical trials (RCT) is not well documented. To inform future research, we surveyed providers who had recently completed a pragmatic RCT of CKD screening in primary care. We characterized their insights and thoughts regarding perceived burden of the intervention and self-reported CKD knowledge at the end of the trial.

**Methods:**
The protocol required participation in the RCT between February 2016 to March 2017. All primary care providers (PCPs) received education about the study and reviewed a list of eligible patients for exclusion. Additionally, PCPs randomized to intervention reviewed CKD results, co-signed notes with CKD-related recommendations, and followed up on patients. Clinical pharmacists provided hypertension medication management and CKD education. We sent a 5-question (three yes/no, two open-ended), anonymous web-based survey to all participating providers.

**Results:**
Of 33 providers, 20 (61%) completed the questionnaire. Among respondents, 12 (60%) providers agreed to “I learned how to improve care for patients with CKD” and 12 (60%) answer yes to “I changed the plan of care of one or more patients” from participation in the program. The most frequently reported changes included better understanding of CKD testing strategies, more confidence to educate patients on CKD and safe NSAID use, and addition of ACE/ARB or diuretic for hypertension treatment. The majority 16 (80%) replied “no” to whether the program increased burden. The most frequent reason for increased burden was more time spent on patient counseling about study correspondence and CKD results.

**Conclusions:**
Pragmatic RCTs of a CKD screening trial in primary care didn’t report substantial increases in burden. Providers also reported perceived improvements in CKD knowledge and applying practice improvements.

**Funding:** NIDDK Support
Methods: A cross sectional chart review was performed in May 2017 in outpatient renal clinics. A total of 127 (31%) patients had current active documentation of PPI use. Examination of the duration of PPI use, 124 patients (97.6%) had documentation of PPI use for more than 8 weeks. Seventy four (59%) patients were deemed to be using them for an inappropriate (e.g. asymptomatic GERD) or unknown indication. Cost estimates using the price per pill accounted for a total 30-day cost of $25,652.78 with the cost of inappropriate use. This results in a yearly cost of $18,789.37 and an average cost per patient of $147.95.

Conclusions: Inappropriate PPI use in advanced CKD not only has clinical implications but also an economic impact with respect to pill burden and associated costs incurred. PPI de-prescribing protocols should be implemented to address inappropriate use and alleviate these unnecessary drug costs.

PUB193

Proteomic Analysis of the Epithelial Secretome Implicates Jagged-1 in Tubule Dysfunction and Paracrine Communication

Results:

Methods: To confirm EGFR activation and TGF-β signaling in the nephron, we performed Western blot analysis and immunohistochemistry to examine the phosphorylation of ERK1/2 and β-catenin, respectively. We also examined the effects of ecdysone on aldosterone levels in vivo and in vitro.

Conclusions: These results support the hypothesis that activation of EGRF or TGF-β signaling in the proximal tubule promotes the secretion of paracrine factors driving epithelial dysfunction and fibrosis.

Funding: NIDDK Support - NIAID, Veterans Affairs Support

PUB194

Ecdysone Elicits Chronic Renal Impairment via Mineralocorticoid-Like Pathogenic Activities

Methods: Virtual screening tools were employed to identify compounds homologous to ecdysone and putative ecdysone-interacting proteins. The kidney effect of ecdysone was compared with that of aldosterone.

Conclusions: Computer-assisted molecular structure matching revealed that ecdysone is highly homologous to aldosterone. Moreover, virtual screening based on compound-protein interaction profiles identified mineralocorticoid receptor, the cognate receptor for aldosterone, as one of the top ranking proteins with strong interaction with ecdysone. To validate the biological functionality, ecdysone was applied to isolated renal cell cultures. Furthermore, ecdysone disrupted cellular tight junction and retarded cell motility, akin to the effect of aldosterone.

Funding: NIDDK Support, Veterans Affairs Support

PUB191

The Expectation, Concern, and Experience of Patients towards Integrative Chinese-Western Medicine and Acupuncture in a Chinese University Hospital in 2014: A Qualitative Study

Results: The interview covered the scopes regarding 1) barrier towards integrative service, 2) motivation to seek alternative and complementary treatment, 3) experience in the use of Chinese medicine and 4) preferred mode of integrative service. Data saturation was observed at the third round of interview. Twenty-one patients with a wide spectrum of demographics were interviewed. Two to six key themes were identified under each scope with specific examples from DKD patients. Overall, patients with severe DKD tended to seek alternative options for disease management. However, the efficacy, safety, finance, convenience of access and lack of referral channels were key barriers in consulting integrative service. Organisational support from the government plays a critical role in enabling patients to utilise integrative services.

Conclusions: Our findings document specific expectation and concerns from DKD patients over the access of integrative medicine for the future consideration of health service provision and research design. Funding support: The University of Hong Kong and Hong Kong Society of Nephrology Research Grant.

Funding: Government Support - Non-U.S.
Conclusions: Our findings suggest that edoxymore possesses minocloroticoid-like activities that impair renal function and elicit renal injury.

PUB195
Tamoxifen Attenuates Fibrosis by Suppressing PI3K/Akt and mTOR/ p70S6K Pathways through Src Kinase in Obstructive Nephropathy in Rats
Chang Seong Kim, Hong Sang Choi, Ha yeon Kim, Eun Hui Rhee, Seong Kwon Ma, Soo Wan Kim. Chonnam National University Medical School, Gwangju, Republic of Korea.

Background: Tubulointerstitial fibrosis is the final pathway of chronic progressive kidney diseases. The kinase and mammalian target of rapamycin (mTOR) pathway play a critical role in the pathogenesis of renal fibrosis. Here we investigated the effects of tamoxifen on renal fibrosis and its underlying molecular mechanisms in the obstructive nephropathy rat model.

Methods: Renal fibrosis was induced by unilateral ureteral obstruction (UUO) in male Sprague-Dawley rats for 14 days. Tamoxifen (10mg/kg) was given by oral gavage after UUO operation. We also treated human proximal tubular epithelial (HK-2) cells with tamoxifen (5 μM) in the presence or absence of tumor growth factor (TGF-β1 (2 ng/mL), estrogen receptor (ER)-α antagonist ICI (5 μM), and ER-α receptor siRNA to examine the effects of tamoxifen treatment on TGF-β1-stimulated renal fibrosis via ER-α.

Results: Tamoxifen treatment ameliorated the UUO-induced renal fibrosis with decreased expression of α-smooth muscle actin (SMA), fibronectin and connective tissue growth factor (CTGF). Phosphorylation of Src (Thr 416), PI3K/Akt and mTOR/p70S6K protein was also significantly decreased after tamoxifen-treated compared to vehicle-treated UUO kidneys. These renoprotective effects were not associated with inhibition of TGF-β1. In HK-2 cells, tamoxifen suppressed TGF-β1-induced protein expression of αSMA and CTGF, and phosphorylation of Src, PI3K/Akt and mTOR/p70S6K, which was counteracted by the treatment with ICI and silencing ER-α with siRNA.

Conclusions: Tamoxifen treatment attenuates renal fibrosis in the obstructed kidneys of rats with UUO. Tamoxifen-induced anti-fibrotic effect is associated with the suppression of Src kinase activity followed by inhibition of phosphorylation of PI3K/Akt and mTOR/p70S6K signaling pathways in HK-2 cells.

PUB198
Interleukin (IL)-17 Production by Tubulointerstitial Human γδ T Cells in Renal Fibrosis and CKD
Helen G. Healthy,1,2 Becker Meng-Po Law,1,2 Xiangu Wang,1,2 Katrina Kilday,1,2 Melissa Rit,1,2 Ray Wilkinson,1,2 Andrew J. Kassianos.1,2 Conjoint Kidney Laboratory, Pathology Queensland, Brisbane, QLD, Australia; 1Kidney Health Service, Royal Brisbane and Women’s Hospital, Brisbane, QLD, Australia.

Background: γδ T cells are effector lymphocytes recognised as having important functional roles during chronic inflammatory processes. Mouse studies suggest a pathological role for γδ T cells in immune-mediated models of kidney disease. This study evaluates γδ T cells present in human fibrotic chronic kidney disease (CKD).

Methods: We extracted γδ T cells from healthy kidney tissue and diseased biopsies with and without fibrosis. γδ T cells were identified, enumerated and phenotyped by twelve-colour flow cytometry. Localisation and production of the pro-inflammatory cytokine IL-17 by γδ T cells was examined by multi-colour immunofluorescence microscopy.

Results: We detected significantly elevated numbers of γδ T cells (CD45+CD3-δ/γ) in diseased biopsies with interstitial fibrosis compared with diseased biopsies without fibrosis and healthy tissue kidney. The increased numbers of γδ T cells correlated significantly with loss of kidney function (eGFR). Furthermore, expression levels of CD161, a marker of human IL-17-producing T cells, were increased on γδ T cells from fibrotic biopsies compared with non-fibrotic kidney tissue. Immunofluorescent analysis of fibrotic kidney tissue localised the accumulation of γδ T cells within the tubulointerstitial compartment, adjacent to proximal tubular epithelial cells (PTEC), defined as tubular cells expressing aquaporin-1. Notably, we identified these tubulointerstitial γδ T cells as a key source of pro-inflammatory cytokine IL-17.

Conclusions: The correlation of IL-17-producing γδ T cells with histologically and functionally more severe CKD suggests a pathological role. Further functional dissection of renal γδ T cells is now required for the development of therapeutics capable of blocking this previously untapped immune cell population.

Funding: Government Support - Non-U.S.

PUB199
Histone Deacetylase 6 Inhibition Counteracts Epithelial–Mesenchymal Transition of Peritomal Peritoneal Cells and Prevents Peritoneal Fibrosis
Lizhong Xu,1 Na Liu,1 Yingfeng Shi,1 Shougang Zeng.1,2 Rhode Island Hospital, Albert Merck School of Medicine, Providence, RI; 2Department of Nephrology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China.

Background: Peritoneal fibrosis is an important pathological remodeling feature in peritoneal dialysis patients. Little is known about epigenetic regulation of its development and progression.

Methods: We examined effects of HDAC6 inhibition on epithelial–mesenchymal transition (EMT) of cultured human peritoneal mesothelial cells (HPMCs) and development of peritoneal fibrosis in a rat model induced by high glucose dialysate.

Results: In cultured HPMCs, treatment with highly selective HDAC6 inhibitor tabalustatin A, or HDAC6 silencing with siRNA inhibited transforming growth factor β1 (TGF-β1)-induced EMT, manifesting as increased α-SMA, fibronectin, and collagen I expression and increased E-cadherin expression. In a rat model of peritoneal fibrosis induced by high glucose dialysate, HDAC6 prevented submesothelial thickening and decreased collagen I and α-SMA expression. Tabalustatin A treatment inhibited TGF-β1 expression and Smad-3, epithelial–mesenchymal transition STAT3, and NF-κβ phosphorylation. HDAC6 inhibition suppressed production of inflammatory cytokine/chemokines and reduced macrophage infiltration in injured peritoneum. Moreover, tabalustatin A effectively inhibited peritoneal increase of CD31(+) blood vessels and expression of vascular endothelial growth factor after high glucose dialysate injection.

Conclusions: HDAC6 inhibition may attenuate peritoneal fibrosis by inhibiting multiple pro-fibrotic signaling pathways, EMT, inflammation and angiogenesis.

Funding: Government Support - Non-U.S.

PUB200
Meprin Metalloproteases and Meprin Targets Secreted in the Urine of African American Men with Diabetic Kidney Injury: Insights on Underlying Mechanisms
Elinemda M. Ongeri, Lei Cao, Lisa M. Felton, Ava Boston. Biology, North Carolina A&T State University, Greensboro, NC.

Background: Minority ethnic groups are disproportionately affected by diabetic kidney disease (DKD). Susceptibility genes identified include meprins, zinc metalloproteases of the astacin family, which are abundantly expressed in kidney epithelial cells. Meprins are also differentially expressed in podocytes and leukocytes (monocytes and macrophages). Meprins have been implicated in the pathology of DKD in humans and rodent models. Single nucleotide polymorphisms in the meprin β gene were associated with DKD in the Pima Indians, a US ethnic group with extremely high incidence of DKD. Decreased expression of meprin A and B in podocytes and leukocytes in DKD suggests a role for meprins in rodent DKD. Recently we showed that meprin deficiency enhances kidney injury in mice with STZ-induced type 1 diabetes. However, the cellular and molecular mechanisms by which meprins modulate DKD are not understood. We have gained insights from identified meprin targets in the kidney, which include modulators of inflammation (e.g IL-1β), IL-6, pro-IL18, MCP-1) and extracellular matrix (ECM) proteins (e.g collagen IV, laminin, fibronectin, and nidogen-1).

Methods: Fasting urine samples were collected from three groups of African American males aged 18-65 years with nondiabetic controls, 2) diabetes, and 3) diabetes with diagnosed kidney disease. ELISA assays were used to determine the levels of albumin, creatinine, and MCP-1. Western blot analysis was used to determine the levels of meprin A, meprin B, nidogen-1, fibronectin, and laminin.

Results: Meprins and meprin targets were not detectable in the urine of non-diabetic controls or diabetes with albumin to creatinine ratios (ACR)<10. Diabetic patients with ACR≥30 had high levels of urinary meprins, fibronectin, laminin, and nidogen-1, with a ~3-fold increase in levels for patients with ACR>200. For nidogen-1, we detected both full-length (~136 kDa) and a 55 kDa fragment.
Conclusions: The data suggest proteolytic processing of nidogen-1 by meprins in DKD to allow the trigger release of other ECM proteins from the basement membrane. More importantly, this could serve to reduce ECM buildup and thus reverse the fibrosis associated with DKD. The correlation between diabetic kidney injury and the levels of meprins and meprin targets in urine suggests that they could serve as diagnostic tools for DKD.

Funding: Other NIH Support - NIMHD, NIGMS

PUB200

Fibroblast Growth Factor 23 (FGF-23) Regulates HK-2 Cell Proliferation, Migration, and Response to TGF-β1


Background: Plasma FGF-23 concentration increases early in the course of chronic kidney disease (CKD), and rises progressively with deteriorating renal function. Elevated FGF-23 is associated with progression of CKD, and may play a direct role in the development of renal injury and tubulointerstitial fibrosis. The aims of this study were to investigate the effects of FGF-23 on proliferation, migration, viability and pro-fibrotic gene expression in a human tubular epithelial cell line (HK-2), and to determine whether FGF-23 modulates the transcriptional and functional effects of TGF-β1.

Methods: HK-2 cells were incubated with FGF-23 (0.1-100 ng/ml) and TGF-β1 for 72 h. ERK1/2 phosphorylation was measured by immunoblotting. Expression of E-cadherin, N-cadherin, connective tissue growth factor (CTGF), collagen type 1α (coll1α1) and TGF-β1 was assessed by RT-qPCR (normalised to GAPDH/RPS7). Cell migration was measured using a scratch wound healing assay, and proliferation and viability monitored by crystal violet staining and measurement of caspase 3/7 activity. The MEK inhibitor PD184352 (1 µM) and the TGF-β1 receptor 1 (FGFR1) antagonist SU5402 (10 µM) were used to investigate involvement of MEK-ERK signalling and FGFR activation, respectively.

Results: FGF-23 increased ERK phosphorylation and stimulated cell proliferation, which was completely attenuated by PD184352. Scratch wound closure was stimulated by FGF-23 in a concentration dependent manner, and this was blocked by SU5402. TGF-β1 decreased wound closure, and this was partially ameliorated by FGF-23. FGF-23 suppressed coll1α1 expression, and at 100 ng/ml partially inhibited TGF-β1-driven increases in coll1α1, N-cadherin, and CTGF expression. FGF-23 and TGF-β1 each inhibited E-cadherin expression, but there was no additive inhibitory effect. FGF-23 did not modify TGF-β1 mRNA expression or TGF-β1-mediated caspase 3/7 activation.

Conclusions: FGF-23 stimulates migration and proliferation of HK-2 cells most likely through engagement of FGFR1 and MEK-ERK pathway activation, and partially reverses pro-fibrotic and anti-repair responses to TGF-β1. These results suggest FGF-23 facilitates tubular repair and regeneration processes. The relevance of these findings to progressive neuron loss in the CKD patient warrants further study to establish their translational potential.

Funding: Commercial Support - Elanco Animal Health

PUB202

Effects of the Combination of Losartan, Mycophenolate Mofetil, and Tamoxifen on the Development of Albuminuria and Glomerulosclerosis in an Experimental Model of Hypertensive Nephroclerosis

Camilla Fanelli, Humberto Delle, Rita de Cossia Cavagli, Wagner Dominguez, Irene L. Noronha. University of Sao Paulo, Sao Paulo - SP, Brazil.

Background: The renoprotective effects of tamoxifen (TAM) in CKD induced by chronic inhibition of nitric oxide (L-NAME experimental model) have previously been demonstrated. TAM has been shown to prevent albuminuria, glomerular damage and interstitial fibrosis, despite having no effect on the sustained hypertension. In the present study, we sought to determine whether the addition of an ARB (losartan; LOS) and an immunosuppressor (mycophenolate mofetil; MMF) to TAM treatment could promote further renoprotection in L-NAME-treated animals.

Methods: In 25 male Wistar rats, CKD was induced by oral administration of 70 mg/kg/d of L-NAME, accompanied by a 3.2% high-salt diet. The rats were divided into 5 groups: L-NAME (untreated); LOS (treated with LOS, 50 mg/kg/d); MMF (treated with MMF, 10 mg/kg/d); TAM (treated with TAM, 10 mg/kg/d); and LOS+MMF+TAM (treated with all 3). Five additional animals only received the high-salt diet (Control). Blood pressure (BP), albuminuria (uALB), glomerular sclerosis (GS), interstitial fibrosis (INT) and αSMA accumulation, as well as renal cortical macrophage (ED1) and T-cell (CD3) infiltration, were evaluated after 30 days of treatment.

Results: Data are presented as Mean ± SE. For One-way ANOVA: p<0.05: vs. Control, *vs. NAME, †vs. LOS, ‡vs. MMF, ††vs. TAM. For Student’s t-test: p<0.05: *vs. TAM.

Conclusions: The LOS+MMF+TAM combination completely normalized the urinary albumin excretion rate and glomerulosclerosis in L-NAME-treated rats. That combination was also more effective than was TAM monotherapy in reducing hypertension and glomerular ischemia in L-NAME-treated rats. Although the LOS+MMF+TAM combination did not improve interstitial fibrosis or myofibroblast (αSMA) infiltration, it was more efficient than was TAM alone in preventing T-cell infiltration.

Table of Results

<table>
<thead>
<tr>
<th>BP (mmHg)</th>
<th>uALB (mg/24h)</th>
<th>GS (%)</th>
<th>INT (%)</th>
<th>αSMA (%)</th>
<th>ED1 (%/cortex)</th>
<th>CD3 (%/cortex)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>127±3</td>
<td>151±3</td>
<td>13±3</td>
<td>5±7</td>
<td>48±6</td>
<td>51±6</td>
</tr>
<tr>
<td>LOS</td>
<td>183±5(4)</td>
<td>149±5</td>
<td>16±5</td>
<td>8±7</td>
<td>64±4</td>
<td>51±6</td>
</tr>
<tr>
<td>MMF</td>
<td>172±3(6)</td>
<td>119±5</td>
<td>13±3</td>
<td>7±5</td>
<td>61±4</td>
<td>57±3</td>
</tr>
<tr>
<td>TAM</td>
<td>258±3(4)</td>
<td>158±5</td>
<td>12±3</td>
<td>6±4</td>
<td>67±4</td>
<td>71±4</td>
</tr>
<tr>
<td>LOS+MMF+TAM</td>
<td>164±3(4)</td>
<td>141±4</td>
<td>12±3</td>
<td>5±4</td>
<td>51±4</td>
<td>57±3</td>
</tr>
</tbody>
</table>

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

Underline represents presenting author.
Unilateral Ureteral Obstruction Induces an Inflammatory Renal Phenotype Along with Sequential Induction of NGAL in Plasma and Peripheral Blood Mononuclear Cells

Cristian A. Amador, Carolina A. Lobos, Mauricio A. Lozano, Stefanny M. Figueroa, Alexis A. Gonzalez, Pontificia Universidad Católica de Valparaíso, Valparaíso, Chile; Universidad Autónoma de Chile, Santiago, Chile. Group/Team: Laboratory of Renal Physiopathology.

Background: Chronic Kidney Disease (CKD) is a worldwide health problem with poor accurate diagnostic tools, and closely linked to other major diseases. Renal inflammation has been proposed as a relevant mechanism for the CKD development, occurring at early stages of injured kidneys. Studies in patients and experimental animals have shown that the Neutrophil Gelatinase Lipoecalin-Associated (NGAL) is increased in the kidney, plasma or urine during CKD progression. Whether NGAL is increased in immune cells during early stages of CKD remains unknown. We performed the unilateral ureteral obstruction (UUO), as a high throughput model of CKD, in order to analyze the NGAL abundance in Peripheral Blood Mononuclear Cells (PBMC) during early inflammatory stage.

Methods: Male C57BL/6 were subjected to a complete UUO (in left kidney) or Sham surgery, and sacrificed after 3 and 7 days (n=8 per group).

Results: We observed tubular dilation in obstructed kidneys sections at day 3 and 7 (p<0.05), without changes in plasma creatinine or plasma urea. The left kidney of UUO mice showed augmented mRNA levels of IL-1β, TGF-β1, MCP-1 and CCL5, an inflammatory chemokine, at day 3 and 7. Additionally, we observed an increase in CD68 and IL-12 mRNA levels, as markers of activated macrophages in the left kidney of UUO mice. All these changes were accompanied by the increase of NGAL mRNA abundance in left kidney from 3 to 4-fold, at 3 and 7-days respectively (vs. Sham group), which correlated with protein expression of plasma NGAL in an increase 24.1 µg/L in Sham vs. 103.8 µg/L and 134.5 µg/L in UUO, at 3 and 7 days respectively. Finally, we observed an induction of NGAL in PBMC after 7-days of UUO, without changes in other pro-inflammatory cytokines/chemokines.

Conclusions: The inflammatory renal phenotype caused by UUO implicate the sequential up-regulation of NGAL; first in kidney and plasma, and later in PBMC. This sequential induction of NGAL suggests a role in inflammatory cells during the early stages of CKD (Supported by FONDECYT 1115054 and Research Project PUCV 039:407:2017).

Funding: Government Support - Non-U.S.
gas chromatography. Various OCPs included: α-HCH, β-HCH, γ-HCH, aldrin, dieldrin, p,p′-endosulfan, p,p′-DDE, p,p′-DDD and p,p′-DDT was calculated using MDRE method. Effect of OCPs on renal cells was assessed by in-vitro studies using human renal proximal tubular epithelial cells (HK-2). The cultured cell line was treated with α-HCH, β-endosulfan and p,p′-DDE. HK-2 cells were tested for ROS generation and mRNA expression of NAPDH oxirase, TGF-β1, α-SMA and E-cadherin gene.

Results: All 9 pesticides were detected in the blood samples of all study subjects; however, α-HCH, aldrin, β-endosulfan, p,p′-DDE were found to be significantly higher in CKDu group as compared to healthy controls. β-endosulfan and p,p′-DDE were found to have significantly higher levels in CKD patients as compared to CKDk patients. Increased levels of these pesticides showed significant positive correlation with urinary albumin excretion and inverse correlation with eGFR. Further, significant increase in ROS generation and increased expression of NADPH, NF-κB and TGF-β1 was observed in HK2 cell lines on exposure to OCPs. In addition to that, decreased expression of E-cadherin and increased expression of α-SMA genes were observed in HK-2 cell lines indicating significant EMT changes on exposure to the OCPs suggestive of fibrotic changes.

Conclusions: Levels of certain organochlorine pesticides, such as α-HCH, aldrin, β-endosulfan, p,p′-DDE were elevated in CKDu. These agents may result in nephrotoxicity through various mechanisms, such as activation of oxidant stress, RAAS, inflammatory and pro-fibrotic pathway.

PUB207
Repeated Dosing of Cisplatin in Mice Leads to Long-Term Loss of Kidney Function and Fibrosis Indicative of CKD. Ciraia Sharp, Mark A. Droll, Tess Dupre, Levi J. Beverly, Leah J. Siskind. University Of Louisville, Louisville, KY; University of Louisville, Louisville, KY; James Graham Brown Cancer Center, Louisville, KY.

Background: Cisplatin (CDDP) is a potent therapy used for many solid cancers. Its dose-limiting toxicity is nephrotoxicity, leading to acute kidney injury (AKI) in 30% of patients. AKI results in rapid loss of kidney function and an increased mortality rate. Longitudinal studies have indicated that AKI patients are more likely to develop chronic kidney disease (CKD), and other studies have indicated that AKI can progress to CKD. CKD is defined by development of renal fibrosis, renal function loss, and an increased mortality rate. There are no current therapies for CDDP AKI/CKD. This is due to the fact that the mouse model used to study CDDP AKI may not recapitulate the dosing regimen humans receive. Mice are administered one high dose of CDDP that leads to death 3-4 days after treatment. In contrast, patients receive low doses of CDDP over an extended period of time to curtail nephrotoxicity.

Methods: To address the limitation of this mouse model, we developed a repeated dosing regimen of CDDP (mice treated with 7 mg/kg CDDP 1x/wk for 4 wks and sacrificed at Day 24), which induces fibrosis indicative of CKD. However, CKD is a progressive disease that develops over many years in humans. Thus, we wanted to determine long-term renal outcomes of mice treated with our repeated dosing regimen of CDDP. Briefly, 8 wk old FVB mice were treated with our CDDP repeated dosing regimen. Results: We found that mice were able to survive at least 6 months post-treatment, allowing this model to be used to look at long-term kidney outcomes. Kidney injury NGAL levels returned to baseline 6 months post-treatment in CDDP treated mice, but these mice still had elevated BUN levels compared to vehicle treated mice (1.8-fold). Mcp-1, Pai-1, and Cbn2a mRNA levels remained elevated indicative of chronic inflammation and cell cycle arrest (6.7, 2.4, and 6.6-fold, respectively). Furthermore, fibrosis was still present as indicated by Sirius red (SR) stain and α-SMA IHC (35% SR+ vs. 0.5% α-SMA+).

Conclusions: These data suggest that while initial injury is resolved 6 months post CDDP treatment, there are long-term effects on renal function and inflammation marked by a trend towards worsened fibrosis, suggesting this model can be used as a bona fide model of CKD.

Funding: NIDDK Support

PUB208

Background: Aberrant receptor tyrosine kinase signaling has been implicated in development and progression of Chronic Kidney Disease (CKD). We investigated the effects of a novel small molecule receptor tyrosine kinase inhibitor, ANG3070, in vivo and in vitro models of CKD.

Methods: We tested the effect of ANG3070 in vitro in TGFb-stimulated collagen production in renal fibroblasts (NRK-49F cells) and on multiple endpoints in a co-culture system of human renal epithelial cells and fibroblasts. For in vivo studies, male Sprague-Dawley rats were uninephrectomised and received weekly subcutaneous injections of deoxy-corticosterone acetate (DOCA) while drinking water with 1% NaCl. After two weeks, animals were randomized to receive ANG3070 (50 mg/kg, po, bid) or vehicle. At week 6, a comprehensive panel of renal functional and histological endpoints was evaluated to assess the effect of compound treatment.

Results: ANG3070 inhibits TGFbeta-stimulated collagen production in renal fibroblasts and in a co-culture system mimicking the renal milieu, ANG3070 reduced markers of fibroblast activation (e.g. α-SMA and N-cadherin) and of fibrosis (e.g. Collagen III). Uni-nephrectomized rats treated with DOCA and salt after two weeks showed marked kidney histological damage and renal dysfunction, as shown by overt proteinuria and elevated urine levels of kidney injury marker 1 (KIM1). Compared to vehicle treated animals, treatment with ANG3070 for four weeks mitigated kidney damage and reduced renal collagen deposition as judged by picrosirius red staining. ANG3070 treatment was associated with reduced urinary proteinuria and improved renal function.

Conclusions: In preclinical experiments, the novel receptor tyrosine kinase inhibitor ANG3070 shows promise as a possible treatment for CKD.

Funding: NIDDK Support, Other U.S. Government Support

PUB209
Podocytes and Proximal Tubular Epithelial Cells Participate in ST2 Related Renal Fibrosis. Yong Chul Kim, Seung Hee Yang, Ran-hui Cha, Mi-yeon Yu, Haejung Lee, Jung Pyo Lee, Dong Ki Kim, Sunggwon Kim, Yoon Su Kim. Kidney Research Institute, Seoul National University, Seoul, Republic of Korea; National Medical Center, Seoul, Republic of Korea; Seoul National University Boramae Medical Center, Seoul, Republic of Korea; Seoul National University College of Medicine, Seoul, Republic of Korea; Seoul National University Hospital, Seoul, Republic of Korea.

Background: Suppression of tumorigenicity 2 (ST2) which is involved in renal inflammation and it is also correlated with disease severity in chronic kidney disease (CKD). Here, we report the ameliorating effect of the ST2 blockade as well as the role of ST2 in the progression renal fibrosis.

Methods: Serum and urine levels of ST2 were measured in 296 CKD patients. And ST2 mRNA levels were quantified in blood and urine cells. Immunohistochemistry (IHC) stain of ST2 was performed in kidney biopsy samples of CKD patients. Further, urine cells were co-stained with podoclyxin/aquaporin-1 and ST2 to characterize the cell type. And fibrosis induced by TGF-β in primary cultured podocytes and proximal tubular epithelial cells (PTECs) were evaluated with fibronectin and ST2 mRNA expressions. Anti-ST2 monoclonal antibody (mAb) was treated to evaluate the neutralizing effect of ST2 on renal fibrosis. Finally, ST2 and fibronectin mRNA expression was measured in CKD mouse model (UUO; Unilateral Ureteral Obstruction).

Results: Serum (P = 0.002) and urine (P < 0.001) ST2 levels increased as renal function deteriorated. Urine ST2 levels adjusted by urine creatinine showed the same pattern (P < 0.001). Serum (P = 0.023) and urine (P = 0.03) ST2 expressions were elevated in CKD stage 5 patients compared with other stages. ST2 HIC stain in CKD stage 5 showed 3-fold increase than CKD stage 1. A large portion of urine cells were ST2-rich podocytes/PTECs and we observed the proportion of these cells increased as renal function decreased in flow-cytometry. When the patients were subdivided by 0.5 g/kg proteinuria, patients with more proteinuria had a higher concentration of urine ST2 (P = 0.02). After fibrosis induction in primary cultured podocytes/PTECs, mRNA and protein expressions of fibronectin, ST2 showed positive correlation with the fibrosis severity: Anti-ST2 neutralized the fibrosis. In UUO mouse model ST2 and fibronectin expression was increased over time (P < 0.01).

Conclusions: Elevated serum and urine ST2 levels are associated with the progression of CKD and podocytes/PTECs involved in this process. ST2-mediated signaling may have a considerable role in the progression renal dysfunction. And ST2 blockade is a potential therapeutic target for renal preservation.

Funding: Government Support - Non-U.S.

PUB210
Abstract Withdrawn
High Intensity Interval Training (HIIT) Attenuates Proteinuria in Nephrectomy 5/6 Rats (N5x5/6) Samuel T. Filho,1 Luciana Jorge,1 Natalia Reinecke,2 Alexandre Saud,2 Rafael Luiz,2 Wesley Silva,2 Rodrigo R. Rampaso,1 Nestor Schor,1 None, São Paulo, Brazil; UNIFESP, São Paulo, Brazil; 1Universidade Federal de São Paulo/Escola Paulista de Medicina, São Paulo, Brazil; 2Universidade Federal de São Paulo, São Paulo, Brazil.

Background: HIIT is characterized by intense and intermittent exercises, interspersed with periods of low intensity and/or rest. Recent studies suggest that HIIT stimulates physiological adaptations equal or better comparable to continuous training of moderate intensity. However, the effect of HIIT on renal function and in CKD is not well known. The aim of this study was to evaluate the effects of HIIT on renal function and physical capacity in Nx 5/6 rats.

Methods: Adult Wistar rats, divided into two groups (n=6/group): Nx 5/6 + exercise (NE) and Nx 5/6 sedentary (NS). Physical training protocol started after 7 days of surgical procedures, 3 days/week, 10 sprints at 90% of maximum capacity, 8 weeks total. To evaluate physical capacity, all animals underwent a maximal physical capacity test before and after training. The mean arterial pressure (MAP), proteinuria (uProt) as urea nitrogen in the blood (BUN) was evaluated.

Results: HIIT was not able to modify the MAP, but attenuated the increase in the proteinuria rate (38.2±4.4 vs.63.5± 1.9mg/24h, p<0.001). Mean BUN was higher in NS in comparison to NE group. (101.2±10.4 vs 83.1± 2.0mg/dl, p<0.001). HIIT also improved physical capacity as seen in maximal physical capacity test (27.2±2 vs 38.1±2 min).

Conclusions: These results suggests that 8 weeks of HIIT can minimize the impact of CKD, with lower increase of BUN and proteinuria. Thus, HIIT could have a protective effect and may be a time-efficient strategy for non-pharmacological treatment to minimize the complications of CKD.

Funding: Government Support - Non-U.S.

---

PUB212

Immunoglobulin G4 Related Disease with Polycythemia Vinaya R. Soundararajan,1 Yameen Rashid,1 Ramesh Soundararajan.1

1Medicine, Midwestern University College of Medicine, Downers Grove, IL; 2St James Hospital, Chicago Heights, IL; 3University of Illinois College of Medicine, Willowbrook, IL.

Background: (Ig)G4-related disease is a systemic fibro-inflammatory condition characterized by a lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells with elevated IgG4 Levels. The disease presents as involving one organ or may present as a systemic disease affecting multiple organs. We report a case of IgG4-related disease presenting with associated polycythemia. This combination has not been reported in the literature to the best of our knowledge.

Methods: A 41-year-old African-American male construction worker presented with a creatinine of 4.0 mg/dl and was found to have mild microscopic hematuria. His urine analysis showed 5-8 RBCs/HPF and proteinuria. His creatinine was normal 4 years ago. He had a history of hypertension and NSAID usage. Patient also recently was diagnosed with polycythemia, and his hemoglobin was 20 g/dl. Ultrasonof his kidneys suggested bilateral large lobular kidneys. He was otherwise asymptomatic. Workup showed a negative JAK 2 mutation and a urine protein of 600 mg per gram of creatinine. His vasculitis and hepatitis workups were negative, except for a low C3 and C4. The patient also had some enlarged inguinal nodes, which were biopsied but not diagnostic.

Results: Patient had phlebotomy initially to decrease his hemoglobin. He underwent a kidney biopsy which showed lymphoplasmacytic infiltration of the renal interstitium, with an increased number of IgG4-positive plasma cells. Patient’s creatinine decreased to 3.4 mg/dl after stopping his NSAIDs and phlebotomy. After the biopsy, patient was started on 40 mg prednisone a day. The patient’s original IgG4 level was 1140 mg/dl. After 4 weeks of prednisone, the level decreased to 260 mg/dl (normal is less than 120 mg/dl). His creatinine also came down to 2.7 and his proteinuria and hematuria resolved. Prednisone is currently being tapered. His Hb decreased to 13 g/dl. He developed a systemic disease cellular infiltrative disease which can involve multiple organs, including pancreas, lymph nodes and kidneys. It predominantly causes tubular interstitial infiltration in the kidney. Patient is responding well to prednisone. Other treatments including rituximab have been used to treat this disease.
Meanwhile, the proportion of infiltrated eSMa+CD206+ double positive cells in sulfatide treated UIR kidney and CKD 3 and 5 patients were investigated.

**Results:** Severity of renal fibrosis and the proportion of eSMa+CD206+ double positive cells was attenuated after sulfatide injection. At the same time, sulfatide reduced senescence, shown by decreased levels of SA-β-Gal. Sulfatide stimulated polarization from M1 to M2 by increasing INOS, STAT1, SOCS3 and decreased arginase, STAT3. Pro-fibrotic transcripts, fibronectin and TGFβ1, was decreased by adding sulfatide-selective NKT. The expression level of NGAL and IL-1β, a marker of kidney damage and inflammation, was attenuated. Similarly, adoptive transfer of sulfatide-selective type II NKT cells attenuated expression of SMA and fibronectin. In stage 5 CKD patients, the density of eSMa+CD206+ double positive cells were 3.3 times higher than stage 3.

**Conclusions:** Sulfatide-selective NKT cell mediates macrophage polarization skewed from M2 to M1 macroage via switching on STAT1 resulting in ameliorating renal fibrosis. Infiltration of myofibroblasts co-expressing M2 marker are also decreased by sulfatide accompanying by reduced fibrosis. Inducing the polarization of macrophages by modulation of NKT cells can be suggested as therapeutic target for curbing fibrosis.

**PUB215**

**A Case of Immunoglobulin G4-Related Disease in Association with Polymyalgia Rheumatica**

**Misaki Yoshida,** Kiyoshi Ito, Kazunori Yamada, Eiko Shimizu, Nobuhiro Suzuki, Takahiro Matsunaga, Takeshi Zoshima, Satoshi Hara, Ichiro Mizushima, Hiroshi Fujii, Mitsuhito Kawano. Kanazawa University Hospital, Ishikawa, Japan

**Background:** Immunoglobulin G4-related disease (IgG4-RD) presents with atypical features in 10% of patients. Several case reports have described IgG4-RD in association with rheumatoid arthritis, but there has been no report of IgG4-RD in association with polymyalgia rheumatica (PMR). We report a case of IgG4-RD in a patient with PMR.

**Methods:** A 68-year-old man with a history of lung cancer was admitted with bilateral submandibular swelling, left lower back and pelvic girdle pain for two months. He was found to have elevated C-reactive protein (CRP), hypergammaglobulinemia, hypocholesterolemia, and a positive antinuclear antibody (ANA) test during a clinic visit one month prior to admission. The CRP level on admission was 3.7 mg/dl. He not only met the 2012 ACR/EULAR Provisional Classification Criteria for Polymyalgia Rheumatica, but also had unexplained hypocomplementemia (C3, 64 mg/dl; C4, 4 mg/dl; CH50, 11 U/ml), hypergammaglobulinemia, and a high ANA titer (x20480). Additional blood tests showed an elevated serum IgG level (543.0 mg/dl) and IgG4/IgG ratio (23.4%). Computed tomography (CT) revealed swelling of the bilateral submandibular glands and enhanced CT showed multiple low-density lesions in the kidneys. Renal biopsy showed tubulointerstitial nephritis with marked infiltration of IgG4-positive plasma cells (72/high-power field). There was a clear border between affected and unaffected areas in the kidney interstitial lesions. IgG4-RD was diagnosed using comprehensive diagnostic criteria. Prednisolone 30 mg/day was initiated and the PMR symptoms rapidly disappeared.

**Results:**

**Conclusions:** This is the first reported case of IgG4-RD in association with PMR. The immunological features of PMR and IgG4-RD are different, but the reason for concurrent presentation in this patient remains unclear. One possibility is that these two diseases are related to malignancy in some cases. Further studies are needed to clarify the pathogenesis of this condition.

**PUB216**

**Difference of Two AKI to CKD Transition Models in Mice**

**Kenzo Yamami,1 Daisuke Nakano,1 Tetsushi Yamashita,1 Yoshifumi Hamasaki,1 Eisei Noiri,1 Akira Nishiyama,2 Masami Nangaku,2 Kent Doi.3 1 Kagawa University, Kagawa, Japan; 2 Kagawa University Medical School, Kitas-Gun, Japan; 3 The University of Tokyo, Tokyo, Japan; 4 University of Tokyo, Tokyo, Japan; 5 the University of Tokyo School of Medicine, Tokyo, Japan.

**Background:** Recent clinical studies have demonstrated AKI is a major risk factor for CKD. Experimental studies using animal models have been conducted so far to clarify the mechanisms underlying progression from AKI to CKD, but effects of differences between animal models on experimental results has not been sufficiently examined.

**Methods:** We developed two mouse AKI-to-CKD models by combining renal ischemia-reperfusion injury and nephrectomy; unilateral ischemia-reperfusion injury with contralateral nephrectomy (UIR+UNx) and without nephrectomy (UIR), and evaluated their differences of post-ischemia injury and erythropoietin producing ability. We developed two mouse AKI-to-CKD models by combining renal ischemia-reperfusion injury and nephrectomy; unilateral ischemia-reperfusion injury with contralateral nephrectomy (UIR+UNx) and without nephrectomy (UIR), and evaluated their differences of post-ischemia injury and erythropoietin producing ability.

**Results:** Renal interstitial fibrosis and erythropoietin producing dysfunction in the UIR+UNx group was significantly milder than that of the UIR group. Intravital microscopy showed contralateral nephrectomy significantly increased blood flow of peritubular capillary (PTC) in post-ischemic kidney. Intravital microscopy showed contralateral nephrectomy significantly increased blood flow of peritubular capillary (PTC) in post-ischemic kidney. Intravital microscopy showed contralateral nephrectomy significantly increased blood flow of peritubular capillary (PTC) in post-ischemic kidney. Intravital microscopy showed contralateral nephrectomy significantly increased blood flow of peritubular capillary (PTC) in post-ischemic kidney. Intravital microscopy showed contralateral nephrectomy significantly increased blood flow of peritubular capillary (PTC) in post-ischemic kidney. Intravital microscopy showed contralateral nephrectomy significantly increased blood flow of peritubular capillary (PTC) in post-ischemic kidney.

**Conclusions:** Improvement of blood flow in PTCs in UIR+UNx group might have a significant impact on renal interstitial fibrosis and erythropoietin production. These differences suggest that careful interpretation is necessary for animal experiments that evaluate AKI to CKD progression.

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

**Underline represents presenting author.**

**PUB217**

**Abstract Withdrawn**

**PUB218**

**Investigating a Ciliopathy – CEP164 Expression throughout Human Embryonic Development**

**Laurie A. Devlin,1 Lynne M. Overman,1 Susan Lindsay,2 John Sayer.1 1 Institute of Genetic Medicine, Newcastle University, Newcastle upon tyne, United Kingdom; 2 HDBR, Newcastle University, Newcastle Upon Tyne, United Kingdom.

**Background:** Nephropathies-related ciliopathies (NPHP-RC) are a collection of disorders that share a common NPHP1 phenotype, caused by defects in the biogenesis or functioning of primary cilium. NPHP-RC are major contributors to juvenile renal failure and are often associated with neurological, retinal and hepatic abnormalities. Recessive mutations in CEP164 (NPHP15), a distal appendage centrosomal protein, have been identified in some families with NPHP-RC. These patients have a heterogeneous, multi-system phenotype, presenting with features such as retinal degeneration, Leber congenital amaurosis, developmental delay and intellectual disability.

**Methods:** We utilised the MRC Wellcome Trust Human Development Biology Resource (HDBR) to obtain human embryonic and fetal tissues. Immunohistochemical staining of CEP164 was completed on paraffin embedded tissue sections, from Carnegie stage (CS) 23 (approximately 8 post conception weeks (pcw)) to 19 pcw. Specifically, CEP164 expression in the kidney, eye and brain (hindbrain) were examined.

**Results:** In human embryonic and fetal tissues, CEP164 had a widespread expression pattern throughout development, with expression in many organs including the kidney, liver, lung and stomach. In all kidney sections analysed, CEP164 was expressed in developing renal tubules; this was maintained throughout development. CEP164 expression was also seen in retinal tissue, during all developmental stages, in defined cell layers. There was strong CEP164 expression in ependymal cells of the choroid plexus as well as cells lining the brain ventricles.

**Conclusions:** CEP164 has widespread, but defined expression throughout human embryonic development. There is strong expression in the kidney, retina and defined regions of the brain. This supports the multi-system pathology present in patients with CEP164 NPHP-RC.
Three-Dimensional Reconstruction of AQP-1 and UT-A2 Expression in a 7-Day-Old Mouse Kidney

Ning-Yu Liu,1 Ling Gu,2 Shi-Jie Chang,2 Jie Zhang,3 Jesper S. Thomsen,4 Arne A. Andreasen,1 Erik I. Christensen,3 Xiao-Yue Zhai.1 1Department of Histology and Embryology, China Medical University, Shenyang, China; 2Department of Biomedical Engineering, China Medical University, Shen Yang, China; 3Department of Biomedicine – Anatomy, Aarhus University, Aarhus C, Denmark.

Background: Mouse kidneys undergo a couple of weeks of maturation of morphology and transportation mechanisms related to the urine concentration after nephrogenesis ceases at postnatal (P) day 3. The present study investigated the location of AQP-1 and UT-A2 based on three-dimensional reconstruction of nephrons. The aim was to analyze the formation of water and urea transport in Henle’s loop in developing kidneys. The morphological basis for mechanism of medullary osmotic gradient formation is discussed.

Methods: Serial 2.5-µm-thick epoxy sections from a 7-day-old mouse kidney were prepared and stained with toluidine blue. Selected sections representing different levels of the kidney were re-embedded, and cut into consecutive 0.5-µm-thick epoxy sections, using custom-made computer software.

Results: Firstly, AQP-1 was, like in the adult kidney, expressed densely along proximal tubules (PT), except the initial part several hundred micrometers in length. Secondly, AQP-1 were expressed in the entire length of DVR running in vascular bundles (VB) and descending thin limbs (DTL) of LLN running in the interbundle region. Thirdly, the majority of DTL of SLN did not express AQP-1. These SLN DTLs were localized in close proximity to AQP-1 positive DVR in the VB. UT-A2 was expressed alone in the last third of DTL of SLN running also in VB.

Conclusions: The distribution of AQP-1 and UT-A2 in the 7-day-old kidney is mainly consistent with that in adult kidneys. This indicates that the urine concentrating function of the kidney is at least partly established at this time point. This is especially evident in the medulla, suggesting that the morphologic and molecular basis for the intrarenal countercurrent exchange has been set up in the medulla at P7.

Funding: Government Support - Non-U.S.

Prediction of Ambulatory Hypertension Based on Clinical Blood Pressure Percentile: The SHIP AHOY Study

Gilad Hamdan,1 Elaine M. Urbina,2 Marc Lande,3 Kevin E. Meyers,2 Joshua A. Samuelu,2 Mark Mitsnefes,2 Joseph T. Flynn,4 Cincinnati Children’s Hospital, Cincinnati, OH; 5Cincinnati Children’s Hospital, Cincinnati, OH; 6Rochester, NY; 7Seattle Children’s Hospital, Seattle, WA; 8The Children Hospital of Philadelphia and University of Pennsylvania, Philadelphia, PA; 9University of Texas, Houston, TX. Group/Team: SHIP AHOY Study.

Background: Ambulatory blood pressure (ABP) provides a more precise measure of BP status than clinic BP but ABP adds additional cost to evaluation for HTN. Therefore, our objective was to determine the clinic BP percentile at which the likelihood of ambulatory HTN increases to optimize application of ABP in adolescents.

Methods: We evaluated clinic BP (mean of 6 measures with auscultatory technique) and ABP (SpaceLabs OnTrak), anthropometrics, and labs in 132 adolescents (mean 15.8 ± 1.4 years, 66% white, 57% male). Clinic BP percentile and ABP status (normal vs HTN) were determined by age, sex and height-specific pediatric cut-points, and patients were divided into five SBP %ile groups: <50, 50-80, 80-90, 90-95, and ≥95. Association between clinic BP percentile group and ABP status was compared using ROC analysis. Patterns of RAAS Blockade Use in Children with CKD

Jason T. Lee,2 Mark Mitsnefes,1 Charles E. McCulloch,1 Elaine Ku.1 1Cincinnati Children’s Hospital, Cincinnati, OH; 2University of California San Francisco, San Francisco, CA.

Background: There is limited data on patterns of anti-hypertensive use in children with CKD. RAAS (renin-angiotensin-aldosterone-system) blockade is known to retard progression to ESRD. Our objective was to understand patterns of RAAS blockade use during different stages of CKD.

Methods: We analyzed data from the Chronic Kidney Disease in Children (CKiD) Study, a national observational study of children with CKD. We used mixed models to determine person-specific trajectories of renal function decline using all available eGFR measurements as means of partitioning follow-up time into distinct CKD stages (3-5). We then determined the prevalence of ACE inhibitor (ACEi)/ARB continuation, discontinuation, or initiation for each CKD stage separately in cross-sectional analysis. We also stratified our analysis by proteinuria level (urine protein creatinine (UPC) ratio) of <2.5, 2.5-5, >5, using the first available measurement at entry into each CKD stage.

Results: We included 572 CKiD participants, of whom 105 had available data in stage 3a, 175 in stage 3b, 208 in stage 4, and 84 in stage 5. Across CKD stages 3a-5, 52.4%, 65.1%, 59.1% and 54.8% of children were treated with ACEi/ARBs. There was significant therapeutic inertia in CKD stage 3 (Figure), whereas in CKD stage 4, 10.5% of children started ACEi/ARBs and 5.7% stopped therapy. In CKD stage 5, 6.0% started ACEi/ARB and 21.4% of children stopped therapy. No differences in potassium level were noted in ACEi/ARB users versus non-users except in CKD stage 5 where hyperkalemia was more prevalent in users of ACEi/ARB (18 vs. 3.9%). Patterns of ACEi/ARB use did not differ in stratified analysis by proteinuria (Figure).

Conclusions: ACEi/ARBs appear underused in the pediatric population during early stages of CKD, especially in those with significant proteinuria. Nearly half of children not on ACEi/ARB therapy were proteinuric, and therapy was not initiated until later stages of CKD which may be suboptimal for delaying progression to ESRD.

Funding: Other NIH Support - NHLBI
Impact Cases of Renin–Angiotensin Systems Gene Polymorphisms on Physiological and Pathophysiological Processes in Two Japanese Patients

**Patients**

1. Keiichiro Miyazaki, 1 Keisuke Sugimoto, 2 Tomoki Miyazawa, 4 Takui Enya, 1 Hidemiho Yamagita, 3 Mitsuru Okada, 4 Tsukasa Takemura.

1 Pediatrics, Kindai University Faculty of Medicine, Osaka, Japan; 2 Kindai University Faculty of Medicine, Osaka, Japan; 3 Tondabayashi Hospital, Tondabayashi, Japan; 4 Pediatrics, Kindai University School of Medicine, Sakai, Japan; 5 Kindai University school of medicine, Osakaokayama, Japan.

**Background:** Renin-angiotensin systems (RAS) play an important role in organ development and physiological function. Defects in genes encoding RAS genes proteins may exhibit CASKUT including renal tubule dysplasia (RDT). The majority of children with RDT at birth may present with significantly low blood pressure leading to perinatal death. In contrast, mutations and polymorphism spectrum of the RAS-related genes to clinical outcomes exist. We present two case of AGT gene related abnormality. 

**Methods:** Case 1: a 4-year-old boy. He was born at 37 weeks, with a birth weight of 2374 g. After birth, he was treated for hyperventilation and cyanosis without low blood pressure. Renal dysfunction, bilateral kidney atrophy and expansion of the left renal pelvis were observed. He also had delayed mental development, low stature, and low body weight. CT showed a thin skin and partial defects of the occipital region. Blood test showed evidence of increased active renin concentration (72 pg/ml [normal: 2.5–21.4 pg/ml]), although the plasma renin activity was normal. Renal biopsy showed immature glomeruli, cystic enlargement of the renal tubules. Gene analysis revealed a heterozygous mutation (C→T substitution) in the AGT gene in exon 5. This was caused by a deletion with RSD from AGTR1 gene abnormality. 

**Results:** In the patient described above, the diagnosis of RAS was confirmed by the detection of a deletion in the AGTR1 gene. The patient was treated with telmisartan (TLM; 10 mg/kg/day) and showed improvements in renal function and growth. 

**Conclusion:** The findings in this case suggest the importance of genetic testing in patients with RAS-related disorders. Further studies are needed to confirm the role of TLM in the management of these patients.

**PUB223**

Nephropathy in STZ-Induced Diabetic Mice: Characterization of Renal Injury and Effects of Standard of Care on Renal Dysfunction

1. Judi A. Muncy,2 Michael P. Quaire,3 Kathleen O. Morasco,4 Erding Hu,5 Denise I. Eganifer.2 Glaxo SmithKline, King of Prussia, PA; 2 GlaxoSmithKline Pharmaceuticals, king of Prussia, PA.

**Background:** Human diabetic nephropathy (DN) manifests as a complication of chronic diabetes and is characterized by a progressive decline in glomerular filtration rate, histopathologic changes, persistent albuminuria and elevated arterial blood pressure. While many promising murine models of diabetes mellitus exist, no current model of diabetes reliably recapitulates the full spectrum of human DN phenotype. The aim of the present study was to longitudinally characterize renal dysfunction and injury in a model combining diabetes and hyperlipidemia.

**Methods:** Diabetes was induced in ApoE-deficient mice by injection of streptozotocin (STZ) at 55 mg/kg for 5 days. Mice were monitored for 8 weeks. 

**Results:** ApoE+STZ mice weighed less than ApoE controls, but there was no difference in body weight gain over 20 weeks between groups. ApoE−STZ mice exhibited stable hyperglycemia and polyuria over 20 weeks compared to controls with no quinapril treatment. There were no significant differences in renal morphology among groups. 

**Conclusion:** Based on the discordance between the phenotype exhibited in this study and the human disease, it appears that this model is not an adequate model for the study of human DN. Further studies are needed to determine the mechanism of renal injury in this model.
Results: BG levels were higher in STZ rats than in Sham rats (P<0.05) and were unaffected by TLM. Compared with Sham, STZ rats displayed significant increases in GFR, as well as renal cortical 3-NT production, LC3-II and PINK1 levels, with these effects prevented by TLM. BNP3 (dimer) and p62 levels did not differ among groups, nor did BP. LCM/MS/Ms spectral count analysis of urine from STZ rats identified four mitochondrial proteins that were not detected in urine from Sham or STZ/TLM groups: ATP synthase subunit S (ATP5S), adenylate kinase 2 (AK2), O2-dependent coproporphyrinogen-III oxidase (gene: Cpox) and elongation factor Tu (TuFm).

Conclusions: During the normoalbuminuric stage of DM, targeted degradation of oxidative stress-induced mitochondria is evidenced by a TLM-sensitive elevation in renal cortical levels of the mitophagy-related proteins, LC3-II and PINK1. This results in urinary excretion of four mitochondrial proteins that may represent early diagnostic markers for diabetic nephropathy.

Funding: Government Support - Non-U.S.

PUB228
Huangkai Capsule Attenuates Podocyte Damage in Diabetic Kidney Disease by Regulating NALP3 Inflammasome and Insulin Resistance-Related Signaling
Yinglu Liu, Yigang Wan. Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, China.

Background: In China, Huangkai capsule (HKC) has been applied extensively for treatment of albuminuria in patients with early diabetic kidney disease (DKD). However, the therapeutic mechanisms still need to be elucidated. In the process of DKD, the activation of NALP3 inflammasome and the inhibition of insulin resistance (IR)-related signalings play important roles in the development of podocyte damage, insulin resistance and proteinuria.

Methods: Rats were randomly divided into 4 groups, the Sham-operated group, the Vehicle-given group, the HKC-treated group and the ROS-treated group. HKC, ROS and saline were daily administrated for 8 weeks after the induction of DKD by high-fat diet, unilateral nephrectomy and streptozotocin injection. Albuminuria, biochemical indicators, NALP3 inflammasome-related factors, IR-related markers (HOMA-IR), glomerular pathological changes, as well as the key signaling molecules in MAPK and PI3K/Akt pathways and podocyte structural molecules in kidneys were examined, respectively.

Results: Results showed that, urinary albumin, HOMA-IR, foot process effacement, glomerular pathological changes of MC, active caspase-1 and PINK1 were increased in the HKC and decreased the decreased expression of p-MAPK/AK2, p-PI3K, p-Akt2, neprin and nephrin in the kidneys of the DN model rats were ameliorated in different extent after treatment of HKC or ROS. More notably, HKC synchronously inhibited NALP3 inflammasome activation, promoted MAPK and PI3K/Akt signalings and up-regulated nephrin and neprin protein expressions, which is different from ROS.

Conclusions: In summary, by means of the DN model rats, we demonstrated that NALP3 inflammasome activation and IR-related signalings inhibition contribute to podocyte damage. HKC, as a natural regulator in vivo, can improve podocyte injury by inhibiting NALP3 inflammasome activation and promoting IR-related signalings.

Funding: Government Support - Non-U.S.

PUB229
High Glucose Induction of the GLUT1 Glucose Transporter and Mechano-Growth Factor (MGF) in Human Mesangial Cells (HMC) Portends Their Roles in Human Diabetic Nephropathy
Yongxin Gao,1 Leighton R. James,1 Abdulagani A. Bakar Baher,1 Nanjo Shih,2 Emma P. Bueno,3 Charles W. Heilig,1,3 UF COM- Jacksonville, Jacksonville, FL;4University of Florida, Jacksonville, FL.

Background: We previously reported increased mesangial cell (MC) GLUT1 and MGF expression in mouse MC in response to 20 mM high glucose (HG) exposure. This contributed to excess MC extracellular matrix (ECM) production. We also previously reported glomerular GLUT1, NFkB and ECM are increased and/or activated in mouse models of diabetic and nondiabetic glomerulosclerosis (GS). Here, we tested HMC for potential GLUT1 and MGF responses to 20 mM high glucose which might contribute to excessive ECM production in vitro, and by implication human diabetic GS in vivo.

Methods: METHODS: 1. HMC were grown to 80 - 100% confluence at 37°C, 5% CO2 in 5 mM glucose medium, then changed to 5 or 20mM glucose medium for 4 days, prior to harvest of total cell proteins or immunofluorescent (IF) staining. 2. Western blotting of HMC proteins and semiquantitation by optical densitometry with normalization of selected proteins to the housekeeping protein beta-Tubulin. 3. Immunofluorescent staining and semiquantitation of selected proteins in cultured HMC, using Alexa-Red and DAPI nuclear stain. 4. Specific antibodies were obtained against: GLUT1, MGF, IκBα, IκBε, pIKK β, pIKK α, all purchased from Cell Signaling Technology. 5. Results: GLUT1 protein increased 4-fold in HMC in response to 20 mM glucose, vs control 5 mM glucose, P < .05. 2. MGF protein increased 3.9-fold in 20 mM glucose, P < .05, while 3.Nuclear NFkB p50 increased 3.3-fold in 20 mM glucose, and nuclear NFkB p65 increased 2.8-fold, P < .0005 for both. 4.CTGF increased 3.9-fold in 20 mM glucose, P < .005. 5. Resulting FN protein expression increased 6.8-fold in 20 mM glucose, P < .05.

Conclusions: CONCLUSIONS: 1.We found that HMC express both GLUT1 and MGF, which increased in 20 mM glucose, with NFkB activation, increased CTGF and ECM. 2. These mimic the responses we previously observed in mouse MC. 3. Increased GLUT1 and MGF portend important roles in HMC ECM production.

Funding: Commercial Support - Dialysis Clinics Inc., Private Foundation Support

PUB230
Extraacellular Vesicles (EV) and Aerobic Exercise Improve Proteinuria in Rats with Diabetic Nephropathy
Rodolfo R. Rampaso,2 Rafael Luiz,2 Natalia Reinecke,1 Kleinon A. Silva,1 Luciana Jorge,1 Edson A. Pessoa,1 Nestor Schor,1 Universidade Federal de São Paulo, São Paulo, Brazil;2Universidade Federal de Sao Paulo/Escola Paulista de Medicina, Sao Paulo, Brazil;3University of Missouri, Columbia, AL.

Background: The aim of this study was to evaluate the effects of application of extracellular vesicles with aerobic exercise training in controlling the progression of diabetic nephropathy, and its possible renoprotective effects.

Methods: Adult male Wistar rats divided into 4 groups: Sedentary controls, (SED, n=8), Diabetes/Sedentary (DM-SED, n=8), Diabetes/Aerobic Exercise (DM-EXE, n=8), Exercise/Controls (EXE,n=8), Extracellular Vesicles/Diabetes-Sedentary (EVD/SED,n=8) and Vesicles/Diabetes-Exercise (EVD/EXE,n=8). DM was induced with streptozotocin (STZ), 50mg/kg i.v. EV (5 application 80ug every 12 days/60 days) was injected into the tail vein. The physical training was done on treadmill 60 min/day, 5 days a week for 8 weeks. Weekly it was determined the Maximal Exercise Test (set at 65-70% of MTe). Glycemia 24h post training (glycemia), MTe, creatinine clearance/BW (Cr/CBW), mean arterial pressure (MAP), proteinuria (uProt)

Results: Results of this study show that EV application attenuates proteinuria in Diabetic rats. When physical exercise was added to the treatment, this improvement was potentized. Both, exercise and EV reduced weight loss in Diabetic groups, but only exercised groups prevented increases in glycemia and MAP. Therefore, preliminary data suggest that aerobic exercise and application EV can minimize effects in diabetic renal injury, and could reduce the progression to renal failure.

Funding: Government Support - Non-U.S.
Astragaloside IV Synergizes with Captopril in Ameliorating Renal Fibrosis in Uninephrectomized db/db Mice

Jing Kiu, Dickson W. Wong, Bin Li, Ye Li, Loretta Y.Y. Chan, Joseph C K Leung, Kar Neng Lai, Sydney C. Tang. The University of Hong Kong, Hong Kong, China.

Background: Astragaloside IV (AS-IV) is an active ingredient of Astragalus membranesuce, the most frequently prescribed Chinese herbal medicine for diabetic kidney disease (DKD). AS-IV monotherapy has been demonstrated to ameliorate podocyte apoptosis, foot process effacement, mesangial expansion, glomerulosclerosis and interstitial fibrosis. Dual renin-angiotensin system (RAS) blockade has not been recommended for DKD due to a lack of efficacy. Since AS-IV is reported to regulate TGF-beta to ameliorate fibrosis, the prospect of combining AS-IV with renin angiotensin blockade warrants investigation.

Methods: Spontaneously diabetic db/db mice and their corresponding non-diabetic db/m littermates were uninephrectomized or sham-operated and received 8 weeks of captopril, AS-IV, combined captopril/AS-IV or vehicle control orally before sacrifice. Urine albumin-to-creatinine ratio (UACR), plasma cystatin C, blood glucose, blood pressure and expression of oxidative stress and fibrosis markers at mRNA and protein levels were determined. Histopathological changes were also examined.

Results: Uninephrectomized db/db mice developed progressive albuminuria, glomerulosclerosis, tubulointerstitial fibrosis and tubular atrophy with dilatation with upregulated cortical expression of TGF-beta, alpha-smooth muscle actin, collagen and fibronectin and NOX4. Mice that received either captopril or AS-IV treatment had ameliorated albuminuria versus control. Mice that received combined treatment displayed the lowest glomerular index injury, tubular injury index, UACR and plasma cystatin C. Blood pressure and glucose were comparable between groups.

Conclusions: Captopril and AS-IV confer synergistic renal anti-fibrotic and anti-oxidative effects in uninephrectomized db/db mice. These findings could potentially be translated into clinical practice. Funding support: Hong Kong Society of Nephrology Research Grant

Funding: Government Support - Non-U.S.

Mitochondrial DNA in the Urine: A Potential Biomarker Reflecting Systemic Mitochondrial Stress in Type 2 Diabetes Mellitus

Fang Liu,2 Yu Qing,2 Ting Cai,1 Junwei Yang.1 Second Affiliated Hospital, Nanjing Medical University, Nanjing, China; 2Nanjing Medical University, Nanjing, China.

Background: Both mitochondrial dysfunction and chronic sterile inflammation were the most common features in type 2 diabetes. Since extracellular mitochondrial DNA (mtDNA) could also be released as both a biomarker of mitochondrial dysfunction and a damage-associated molecular pattern factor, our objective was to investigate the clinical significance of mtDNA in type 2 diabetes mellitus.

Methods: In vivo, mtDNA contents extracted from the samples of both diabetic patients and diabetic mice were measured by RT-qPCR. In vitro, endothelial cell lines were used to investigate the effect of mitochondrial stress triggered by high glucose on the changes of mtDNA content both inside and outside cells.

Results: As compared to the control group, we found that the plasma mtDNA contents were increased in diabetic patients while the proximal, distal and medullary urinary mtDNA contents were significantly higher in the diabetic patients. However, in STZ-induced diabetic mice, although mtDNA contents in the plasma did not change significantly, mtDNA contents extracted from the muscle, heart, liver and kidney were significantly decreased in a time-dependent manner while the creatinine-adjusted urinary mtDNA contents were increased. On this basis, we found that mtDNA might be filtered through the dialysis membrane further suggested that the mtDNA might be released from the diabetic tissues and subsequently filtered into the urine. For exploration of the role of mitochondrial stress, in vivo, we first confirmed that high glucose could induce the increase of extracellular mtDNA contents, meanwhile, the decrease of intracellular mtDNA contents in both dose-dependent and time-dependent manners. Next, by using resveratrol to attenuate the mitochondrial oxidative stress, we found resveratrol could increase the intracellular mitochondrial content and decrease the extracellular mtDNA content.

Conclusions: Our results indicated that mtDNA might be released from the cell as a response of mitochondrial stress under diabetic conditions. Thus, mtDNA which was subsequently filtered into the urine might be a biomarker reflecting systemic mitochondrial stress in type 2 diabetes mellitus.

Funding: Government Support - Non-U.S.

Diabetic Myonecrosis: A Rare and Less Known Complication of Diabetes

Sherin A. Ahmed1,2, Zeshan sharif Choudhry1, Smita Gunda1,3
1Cambridge University Hospitals, Cambridge, UK; 2Kings Lynn, United Kingdom; 3Renal, Queen Elizabeth hospital, Kings Lynn, United Kingdom.

Background: We report a case of spontaneous myonecrosis and compartment syndrome involving the upper limb in a poorly controlled type 1 diabetic with microvascular complications. Patient had recurrence in left thigh within a month, which was managed conservatively. To our knowledge this is the first report of Diabetic Myonecrosis(DMN) with upper limb as the index site of presentation.

Methods: 39 yr old female type1 diabetic with poor compliance, retinopathy, neuropathy and nephropathy, presented with acute onset pain and swelling of left arm. Clinically had swelling with severe tenderness, skin was intact with no redness. Limb movements were full and pulses intact. Initial bloods showed no evidence of infection Blood Glucose-50.9 mmol/L US Doppler-negative She was treated with antibiotics, anticoagulation and regular opioids for pain. CT showed a compartment syndrome with increased suspicion of compartment syndrome. Pain was rapidly worsening with decrease in range of movement and loss of pulse. Hence she was taken up for theatre and intraoperatively deltoid and triceps were found to be necrotic. Histology confirmed necrosis of individual fibers consistent with DMN. Patient recovered well after surgery and is now presenting with pain in thigh muscles within a month, when MRI showed high signal changes and intramuscular fluid consistent with DMN, needing conservative management. At a later date patient presented with fulminant hepatic failure and subsequently died.

Results: DMN was first described in 1965. It is a rare and under diagnosed complication of long standing and poorly controlled diabetes. DMN is common in females and type 1 diabetics, with a predilection for thigh muscles.70% cases have nephropathy. Clinically presents with acute onset pain, swelling and tenderness. Commonly misdiagnosed as cellulitis, thrombosis or fascitis. MRI is the most useful evaluation tool. Responds well to conservative management and can be self limiting but with high recurrence rate. Pathogenesis may involve atheroclerosus, hypoxia-reperfusion injury or necrotising. Although short term prognosis is good, long term survival is <5yrs. DMN poses a burden to health service mainly due to lack of early recognition leading to otherwise avoidable investigations and treatment. Hence a high index of suspicion is needed in long standing diabetics with acute muscle pain. Management aiming at strict blood sugar control, rest and analgesics.

The Disassociation of Glycated Albumin (GA) and Hemoglobin A1c (HbA1c) Is Associated with Decline of Glomerular Filtration Rate (GFR) Evaluated by Inulin Clearance (Cin) in Type 2 Diabetes Akihiro Tsuda,1 Hideki Tominaga,2 Shinshi Hatori,1 Nobuo Ishimura,1 Masaaki Nakatani,1 Katsuhito Mori,1 1Department of Nephrology, Endocrinology, Metabolism, and Molecular Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan; 2Meijiashi Hospital, Osaka, Japan; 3Osaka City University Graduate School of Medicine, Osaka, Japan.

Background: It is well known that GA provides a better measure to estimate glycemic control in hemodialysis patients with diabetes mellitus (DM), and that the assessment of glycemic control by HbA1c in those patients might lead to underestimation (Inahata M, et al. J Am Soc Nephrol, 2007). However, to date, no data exist regarding to the question whether and how GA and HbA1c are dissociated in those with non-dialysis chronic kidney disease (CKD) patients with DM and nonDM.

Methods: One hundred forty nine non-dialysis CKD patients (75 DM and 74 nonDM; age, 59.3 ± 13.0 years (diabetics) and 55.4 ± 13.9 years (non-diabetics); 71 males (47.7%) were enrolled. GFR was evaluated by C_in. The factors related to the dissocation between GA and HbA1c in DM patients and nonDM patients were examined.

Results: There was a significant and positive correlation between GA and HbA1c in each stage of CKD (both DM and nonDM; age, 59.3 ± 13.0 years (diabetics) and 55.4 ± 13.9 years (non-diabetics); 71 males (47.7%) were enrolled). The factors related to the disassociation of GA and HbA1c in diabetes mellitus patients were examined.

Conclusions: GA and HbA1c is dissociated in diabetes, but not in non-diabetes. The dissociation of GA and HbA1c in diabetes is significantly associated with decreased GFR. HbA1c values in diabetic patients underestimate glycemic control index, particularly in those with lower GFR. Thus, evaluation of glycemic control by HbA1c in diabetic CKD patients should be carefully appreciated.

The Renal Effect of the SGLT2 Inhibitors on the Japanese Type 2 Diabetes Mellitus Patients With Diabetic Nephropathy Kazuo Kobayashi,1 Nobuo Hatori,1 Hiroyuki Sakai,1 Takayuki Furuki,1 Masaki Miyakawa,2 Masanao Toyoda,2 1Committee of Hypertension and Kidney disease, Kanagawa Physicians Association, Yokohama, Japan; 2Tokai University School of Medicine, Isehara, Japan.

Background: Some large-scale clinical trials with SGLT2 inhibitors(SGLT2i) have revealed significant improvements in cardiovascular events and diabetic nephropathy(DMN) in patients with type 2 diabetes mellitus (T2DM). However, it is not clear whether similar results are observed in Japanese patients with T2DM.

Methods: To clarify the effects of SGLT2i in Japanese patients, data from T2DM patients with DM who are visiting members of the Kanagawa Physicians Association, and who were taking SGLT2i were extracted.
logarithmic value of ACR were -0.43 was divided into four groups (“very good”, “good”, “usual”, and “bad”) and the change of decreased from 96.8 to 73.9 (p<0.05). The degree of adherence with dietary treatment has also been partially accepted, and further discussion on the relationship between the change of systolic BP at office were independently correlated with the change of ACR.

blocker agent, “very good” adherence with dietary treatment, the usage of empagliflozin, respectively. By multiple linear regression analysis, the age, the usage of aldosterone BMI, blood pressures, GFR and UACR, intervention contributes to 3.8 mL/min/1.73m². Body weight (kg), 76.5 ± 23.4 to 74.9±23.7 mL/min/1.73m² (p<0.01), and the mean value of ACR significantly decreased from 96.8 to 73.9 (p<0.05). The degree of adherence with dietary treatment was divided into four groups (“very good”, “good”, “usual”, and “bad”) and the change of.

Conclusions: This retrospective study confirmed that the results of large-scale clinical practice in patients with type 2 diabetes and eGFR (HR 0.92, 95%CI 0.89-0.95) (fig2) contributed to risk of requiring RRT (both with glucosuria (N=470), it was 2.511 (1.539-3.833, P<0.001) when compared to those without glucosuria (N=20,245). In Non-DM subjects ≥126mg/dl, or on medication (N=288,528) performed in 6 district in Japan, and identified those who died by 2012. We followed the screened participants at the 2008 specific health check and eGFR decreased from 78.2 ± 10.2 to 71.7 (p<0.05). eGFR decreased from 78.2 ± 11.7 to 76.3 (p<0.05). At censor date, 41 patients had commenced RRT (all dialysis). 29 died without prior RRT were determined. Censor date was 1/03/2017. Competing risk analysis were included. Baseline characteristics, incidence of RRT or death were determined. Censor date was 1/03/2017. Competing risk analysis demonstrated that the severity of glomerular lesions (class IIb + III) and DM history ≥10 years were significantly associated with the odds of DR (OR, 95%CI: 3.588 (1.598-7.964); p=0.002 and 2.511(1.217-5.182); p=0.013, respectively) when adjusting for baseline proteinuria, hematuria, e-GFR, interstitial inflammation. In the cohort study, a multivariate COX analysis demonstrated that the DR remained an independent risk factor for progression to ESRD when adjusting for important clinical variables and pathological findings (p < 0.05).

Conclusions: These findings indicated that the severity of glomerular was significantly associated with DR and DR was an independent risk factor for the renal outcomes in patients with DM, which suggested that DR can predict the prognosis of patients with type 2 diabetes and DN.

### PUB236

#### Semi-Individualised Chinese Medicine Treatment as an Adjuvant Management for Diabetic Nephropathy – Preliminary Results of an Add-On, Randomised, Controlled, Multi-Centre, Open-Label Pragmatic Trial

**Background:** We followed the screened participants at the 2008 specific health check and 189 patients had previous renal biopsy (58% had diabetic kidney disease ≥126 mg/dl, or on medication). Of the above 250 patients, 141 were recruited in the cohort study who received follow-up for at least 1 year and the influence of DR on renal outcome was assessed using Cox regression. Renal outcome was defined as the progression to end-stage renal disease (ESRD) or the initiation of renal replacement therapy.

**Methods:** In the cross-section study, 250 patients with T2DM and biopsy-proven DN were divided into two groups: 130 in the DN without DR group (DN group), and 120 in the DN+DR group. Logistic regression analysis was performed to identify risk factors for DR. Of the above 250 patients, 141 were recruited in the cohort study who received follow-up for at least 1 year and the influence of DR on renal outcome was assessed using Cox regression. Renal outcome was defined as the progression to end-stage renal disease (ESRD) or the initiation of renal replacement therapy.

**Results:** In the cross-section study, compared with the DN group, patients in the DN+DR group had longer duration of T2DM, poorer renal function, more serious glomerular lesions and interstitial inflammation (p<0.05). The logistic regression analysis demonstrated that the severity of glomerular lesions (class IIb + III) and DM history ≥10 years were significantly associated with the odds of DR (OR, 95%CI: 3.588 (1.598-7.964); p=0.002 and 2.511(1.217-5.182); p=0.013, respectively) when adjusting for baseline proteinuria, hematuria, e-GFR, interstitial inflammation. In the cohort study, a multivariate COX analysis demonstrated that the DR remained an independent risk factor for progression to ESRD when adjusting for important clinical variables and pathological findings (p < 0.05).

**Conclusions:** These findings indicated that the severity of glomerular was significantly associated with DR and DR was an independent risk factor for the renal outcomes in patients with DM, which suggested that DR can predict the prognosis of patients with type 2 diabetes and DN.

### PUB239

#### Competing Risk of RRT and Death in Patients with Diabetes and CKD

**Background:** Diabetic nephropathy (DN) commonly causes chronic kidney disease (CKD). The CKD-QLD registry is an Australian state-wide registry of patients with CKD followed up in public hospital renal units who have provided informed consent. Enrolment commenced in 2011. We determined competing risk of survival to renal replacement therapy (RRT) and death without RRT in registry patients with DM and CKD who had undergone renal biopsy.

**Methods:** Patients with DM enrolled from 22/01/2011 - 15/11/2016 inclusive with previous renal biopsy were included. Baseline characteristics, incidence of RRT or death without prior RRT were determined. Censor date was 1/03/2017. Competing risk analysis was performed with RRT as the event of interest and death as the competing event. Age, eGFR and macroalbuminuria status (y/n) at enrolment were covariates.

**Results:** 189 patients had previous renal biopsy (58% had diabetic kidney disease ≥126 mg/dl, or on medication). Mean follow up at censor date was 3.1 years (586 patient-years). Mean age was 60.6 years. Mean enrollment eGFR was 36ml/min (SD 17.1), 77% had macroalbuminuria. At censor date, 41 patients had commenced RRT (all dialysis). 29 died without prior RRT. Competing risk analysis revealed that only age (HR 0.94, 95%CI 0.93-0.96) (fig1) and eGFR (HR 0.92, 95%CI 0.89-0.95) (fig2) contributed to risk of requiring RRT (both p<0.001).

**Conclusions:** In this high-risk group of patients receiving specialist nephrology care, younger age and lower baseline eGFR were associated with higher risk of requiring RRT.

**Funding:** Veterans Affairs Support, Government Support - Non-U.S.
Changes of Parathyroid Hormone and 25 Hydroxy Vitamin D3 in Diabetic Patients with Maintenance Dialysis (MD) and Their Related Factors

Background: The differences and influences of intact parathyroid hormone (iPTH) and 25 hydroxy vitamin D3 in diabetic patients with MD are not clear.

Methods: There were 180 patients underwent maintenance hemodialysis (MHD) and 99 patients underwent peritoneal dialysis (PD). MHD patients were divided into two groups: those with DM as a diabetic hemodialysis group (DH), those without DM as a non-diabetic hemodialysis group (NDH). PD patients with DM as a diabetic peritoneal dialysis group (DP), those without DM as a non-diabetic peritoneal dialysis group (NDP). The clinical data between DH and NDH, DP and NDP were compared respectively, and analysis of possible influencing factors of iPTH and 25(OH) D3 levels were carried out.

Results: The iPTH in DH was lower than that in NDH (P<0.001). 25(OH) D3 in DH was also significantly lower than that in NDH. The level of iPTH was negatively correlated with history of diabetes, and positively correlated with dialysis years, phosphates, alkaline phosphatase (P<0.001) and 25(OH) D3 (P=0.016). The multiple linear regression (MLR) analysis showed the history of diabetes (P=0.012) and years of dialysis (P=0.028) were independent factors of iPTH. The concentration of 25(OH) D3 was negatively correlated with history of diabetes (P<0.001), and positively correlated with dialysis years, phosphates, magnesium, albumin and iPTH (P<0.05). The MLR analysis showed the history of diabetes (P<0.004) was independent factor of 25(OH)D3. The iPTH in DP group was also lower than that in NDP group ([25.7±211.1]pg/ml VS [39.7±338.9]pg/ml). In patients with PD, iPTH was negatively correlated with glycosylated hemoglobin (P<0.003), hemoglobin (P=0.045) and correction of calcium, positively correlated with serum phosphatase (P=0.009), alkaline phosphatase (P=0.013). The MLR analysis showed in patients with PD glycosylated hemoglobin (P<0.040) and serum phosphatase (P=0.024) were independent factors of iPTH. 25(OH)D3 in MPD was negatively correlated with age (P<0.044), and positively correlated with hemoglobin (P=0.037), albumin (P=0.002) and urea nitrogen (P<0.024). The MLR analysis showed in MPD glycosylated hemoglobin (P=0.009) was independent factor of 25(OH)D3.

Conclusions: Diabetic patients with dialysis have lower iPTH and 25(OH)D3. Diabetic history, Hb, albumin maybe have some effects on them, should be pay more attention on them.

Figure 1. Association between fasting plasma glucose and HbA1c (n, measurements=371,149). The original ADAG study equation for the glucose/HbA1c association shown as dashed line. (A) Overall population; and according to strata of (B) eGFR and (C) haemoglobin.

Can HbA1c Be Trusted in Anaemia or CKD? Analyses from the Copenhagen Primary Care Laboratory (CopLab) Database

Background: Glycated hemoglobin (HbA1c) is used to diagnose and evaluate glycemic control in diabetes. Several clinical conditions may alter the blood glucose/HbA1c relationship by affecting erythropoiesis or erythrocyte lifespan. In a large population in primary care, we investigated (1) whether we could confirm the relationship between fasting plasma glucose (FPG) and HbA1c measurements, and (2) the clinical implications of anemia or CKD for the interpretation of HbA1c.

Methods: From a primary care laboratory, we examined valid measurements of both HbA1c and FPG, as well as measurements of hemoglobin (Hb) and eGFR. We stratified our observations according to CKD stage and according to anemia level. The prediction of the mean FPG from HbA1c alone, and jointly from HbA1c and Hb and eGFR respectively was estimated by thin plate regression splines.

Results: In 155,565 individuals (48% men), the FPG/HbA1c relationship imitated the ADAG linear regression equation. The glucose/HbA1c relationship was unaffected in most patients with mild to moderate CKD and in cases of mild to moderate anemia. Only in severe hyperglycemia (HbA1c >100 mmol/mol) and concurrent anemia or eGFR<45 ml/min the correlation changed, so that glucose concentration was overestimated by HbA1c in anemia and underestimated in CKD (Figure 1). Very few patients in our population had eGFR<30 ml/min (0.82%) or severe anemia (0.11%), demonstrating that HbA1c can be used without adjustment in primary care to estimate glycemic control.

Conclusions: Funding: Government Support - Non-U.S.
albuninuria needs to be evaluated. We hypothesize that lower sodium intake improves the beneficial effect of silybin and NAC on albuminuria.

Methods: We conducted a sub-analysis of the randomized-controlled trial where 75 subjects with diabetic nephropathy with albumin-creatinine ratio (ACR) of >750 mg/g and eGFR 15-60 ml/min on the background of angiotensin inhibition received either placebo or NAC or silybin or combination for 3 months to test their anti-proteinuria effect. Daily sodium intake was estimated by measuring 12-hour urinary Sodium excretion. Urinary ACR and other independent variables were measured at baseline and end of 3-month intervention.

Results: The study population was 62.97±4.8 years old, 89% male, 65% Hispanic, 27% non-Hispanic white and 7% non-Hispanic blacks, had BMI of 35.0±8.54 kg/m², eGFR of 36±4±13.3 ml/min, and ACR of 565 [216,1018] mg/g at baseline. None of the interventions reduced the urinary excretion of albumin (post ACR: 638 [224, 1161] mg/g). Mean sodium intake was 4064±2642 mg/d at baseline and 3816±1664 mg/d at 3-month. There was no difference in any of the demographic, clinical and laboratory parameters between the groups categorized by sodium intake. On univariate analysis, ACR correlated positively with systolic BP (r=0.3, p=0.088), and negatively with age (r=-0.2, p=0.03) and eGFR (r=-0.27, p=0.02, only at the end of intervention) but there was no correlation between ACR and sodium intake on both occasions. In multivariable regression model including age, eGFR, sodium intake, use of diuretic and ACEI, different treatment arms, application of interaction term between treatment arms and sodium intake did not predict albuminuria at the end of intervention (interaction NS).

Conclusions: There was no modification by the sodium daily intake on the effect of silybin or NAC on albuminuria in patients with diabetic nephropathy.

Funding: Other NIH Support - NIH-NCCAM AT04490 and VA Merit Review

I101CX000624

PUB243

GLP1RA Facilitate Improved Glycemia, Reduction in Insulin Requirements, and Weight Loss in Renal Transplant Recipients Kanuya Kameshwar,1 Jamie X. Cheong,2 Shilomo J. Cohen,3 1Royal Melbourne Hospital, Victoria, Australia; 2Western Health, Melbourne, NSW, Australia; 3Western Health, Victoria, Australia, Melbourne, NSW, Australia.

Background: While treatment options for diabetes have increased, there is little experience with these agents in renal transplant recipients. This study examined 13 renal transplant recipients with pre-existing diabetes mellitus (PDM) or post-transplant diabetes mellitus (PTDM) treated with GLP1 receptor agonists (GLP1RA).

Methods: 7 PDM & 6 PTDM patients, a mean of 60 months post-transplant were given either a B.D. pump (Byetta) or weekly preparation (Bydureon) of exenatide.

Results: At baseline, 10 were on insulin (6 PDM, 4 PTDM) with a mean total daily insulin (TDI) requirement of 100 IU/day, 1.6 other glucose lowering agents in 9 patients. Mean weight 88.8 kg, Hba1c 8.4% and creatinine 120 µmol/L. 3 patients were intolerant of Byetta, while all 8 patients on Bydureon tolerated treatment. After a median follow-up of 11 months, 4/10 patients ceased insulin (2/6 PDM, 2/4 PTDM) with a mean reduction in TDI of 71 IU/day. Weight decreased by a mean of 5kg and was greater for those who reduced TDI. Mean Hba1c at follow-up was 7.8%, with a mean reduction of 0.28%. Patients were on an average of 2.2 other agents at follow-up. Of 6 patients with documented NAFLD initially, all had improved liver function on treatment. Patient satisfaction was high, evidenced by continuation of the extra injections even when on insulin.

Conclusions: GLP1RA usage in renal transplant recipients with diabetes significantly reduced TIDI, weight; improved glycemic control, and achieved greater freedom from hypoglycemia with few adverse effects. These agents prove invaluable in managing abnormal glucose metabolism amongst transplant recipients and warrant further clinical evaluation.

Funding: Clinical Research Support

PUB245

Levels of Soluble RAGE but Not Endogenous Secretory (ES) RAGE Differ between Type 2 Diabetic versus Control Subjects in the United Arab Emirates Abdilsalam Alabode, Claire K. Inman,2 Anisur Rahman,3 J. Deyo,4 Hyo Sook Fangfei NewYork-Presbyterian/Weill Cornell Medicine, New York, NY; 2Moody Healthcare, Atlanta, GA; 3Diabetes Endocrinology Research, Advanced Medical Care, Abu Dhabi, United Arab Emirates; 4New York University Abu Dhabi, Abu Dhabi, United Arab Emirates; 5NYU Abu Dhabi, United Arab Emirates; 6NY Medical Center, New York, NY; 7NY medical center, New York, NY; 8New York University Abu Dhabi, Abu Dhabi, United Arab Emirates; 9Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates; 5SMC, Abu Dhabi, United Arab Emirates; 6New York University Langone Medical Center, New York, NY.

Background: The United Arab Emirates (UAE) is experiencing increasing rates of obesity, type 2 diabetes (T2D) and its complications. We tested if soluble levels of cell surface-cleaved RAGE (sRAGE) or endogenous secretory RAGE (esRAGE), the product of alternative mRNA splicing of AGER, are associated with T2D and obesity in the UAE. AGER expression is upregulated in case-control models performed in the UAE DM population. AGER is associated with cardiovascular disease, as well as with total and cardiovascular mortality in the Malmö Diet and Cancer Study and the Framingham Heart Study. In the present study, we sought to determine if AGER, its soluble variants, and AGER-related molecules are differentially expressed in T2D and control UAE subjects.

Methods: We measured plasma hsC-reactive protein (hsCRP), high-sensitivity C-reactive protein; Vit D; HbA1c; and TNF-α in a combined UAE population. Genetic and unique obesity-dependent factors may underlie lack of association between esRAGE in cases vs. controls, which may affect vulnerability to T2D and its complications in the UAE population.

Results: Univariate comparisons of T2D case and control subjects revealed differences in sRAGE (1,033±453 vs. 1,169±664 ng/ml, respectively; p=0.02) but not in esRAGE. Moreover, adjustment revealed that differences in sRAGE were significant after correction for age and sex and additionally for waist-to-hip ratio (WHR); total cholesterol (TC); HDL; hsCRP; Vit D; or triglyceride (TG) levels separately. In cases or controls, we tested associations of body mass index (BMI) with WHR or WSR and sRAGE and esRAGE. In controls but not T2D cases, sRAGE and esRAGE were significantly associated with BMI after correction for age and sex and additionally for fGFR; blood pressure; TC; HDL; hsCRP; Vit D; creatinine; and TG and Hba1c in a combined model. In the case of WHR, in controls and T2D cases, there were no associations with sRAGE, but only in T2D cases, WHR was associated with esRAGE after correction for age and sex and blood pressure; TC; HDL; hsCRP; Hba1c; creatinine; TG; esRAGE, Vit D and TG in a combined model.

Conclusions: Levels of sRAGE but not esRAGE distinguish T2D case vs. controls in the UAE population. Genetic and unique obesity-dependent factors may underlie lack of association between esRAGE in cases vs. controls, which may affect vulnerability to T2D and its complications in the UAE.

Funding: Government Support - Non-U.S.

PUB246

The Cardiometabolic Risk Factor Proneurotensin Is Increased In Renal Dysfunction Thomas Efekt,2 Ming-Zhi Zhang,1 Raymond C. Harris,1 Dorit Schleinitz,3 Peter Kovacs,2 Anke Tönjes,1 1Yanderbilt University Medical Center, Nashville, TN; 2IFB AdiposityDiseases, Leipzig University Medical Center, Leipzig, Germany; 3Department of Endocrinology and Nephrology, University of Leipzig, Leipzig, Germany.

Background: Proneurotensin, the stable N-terminal fragment of the neurotensin precursor hormone, is significantly associated with the development of obesity, diabetes, cardiometabolic disease, as well as with total and cardiovascular mortality in the Malmö Diet and Cancer Study and the Framingham Heart Study. In the present study, we investigate the regulation of the cardiometabolic risk factor proneurotensin in human and murine renal dysfunction.

Methods: Circulating proneurotensin levels were quantified by ELISA in 581 patients with chronic kidney disease (CKD cohort) covering the whole spectrum of estimated
glomerular filtration rate (eGFR) categories from G1 to G5. Furthermore, proneurotensin was measured in the German Sorbs population (N = 1041) to validate the associations with renal function in a general cohort. Moreover, mNts mRNA expression was investigated in an animal CKD model, i.e. eNOS⁻/⁻ C57BLKS db/db mice, and compared to littermate controls without CKD.

Results: Median circulating proneurotensin levels significantly and continuously increased with deteriorating renal function (eGFR category G1: 129.0; G2: 143.8; G3: 178.3; G4: 224.9; G5: 283.6 pmol/l; p < 0.001) in the CKD cohort. Furthermore, proneurotensin was independently associated with eGFR and albumin/creatinine ratio in patients with CKD. In the general cohort of the Sorbs from Germany, impaired renal function remained an independent and positive predictor of proneurotensin levels. In CKD mice, mNts mRNA expression in subcutaneous and visceral adipose tissue, as well as in the liver and kidney, was unchanged as compared to controls.

Conclusions: The cardiometabolic risk factor proneurotensin is significantly and independently associated with renal function in both a CKD and a general cohort comprising of >1600 patients. Altered mNts mRNA expression might not be the cause for increased proneurotensin levels in CKD. Our results further support proneurotensin as a strong and relevant cardiometabolic risk factor in patients with renal dysfunction.

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

**PUB247**

**Development of a New Mouse Model of Diabetic Kidney Disease**

Xiaolin Hu,1 Tiantzhou Zhang,1,2 Donna W. Yuen,2 St. Michael’s Hospital, Toronto, ON, Canada; 2St. Michael’s Hospital Keenan Research Centre for Biomedical Science, Toronto, ON, Canada.

**Background:** Despite advances in our understanding of its pathogenesis, diabetic nephropathy (DN) remains a common and serious complication of diabetes that can progress to kidney failure, and for which few effective therapies exist. A major barrier to the development of new treatments is the lack of a mouse model that replicates key features of late stage human DN, such as interstitial fibrosis, in part because diabetic mice do not typically develop significant renal angiotensin system (RAS) activation.

**Objectives:** To develop and validate a new mouse model of diabetic nephropathy.

**Methods:** Mice transgenic for human renin cDNA under the control of the transthyretin promoter (TTRRen) were employed as a model of RAS hyperactivation. Diabetic disease was induced in TTRRen mice by intercrossing with diabetic Akita mice (Akita⁻/⁻ TTRRen⁻/⁻ mice).

**Results:** Both Akita⁻/⁻ TTRRen⁻/⁻ and their non-hypertensive Akita⁻/⁻ TTRRen⁺/⁺ controls developed hyperglycemia beginning at 6 wks of age, although Akita⁻/⁻ TTRRen⁺/⁺ mice also developed increased blood pressure (151±4 vs. 91±1 mmHg), marked albuminuria (urine albumin excretion: 411±1669 vs. 1197±246 ug/day), and an increase in serum creatinine (69±6 vs. 57±6 umol/L). Structurally, Akita⁻/⁻ TTRRen⁻/⁻ mice displayed markedly increased glomerulosclerosis (glomerular picrosirius red (PSR) score: 0.56±0.11 vs. 0.37±0.06) and interstitial fibrosis (PSR intensity: 0.12±0.03 vs. 0.04±0.01) compared to their Akita⁻/⁻ TTRRen⁺/⁺ controls. Fibrotic gene transcripts (COL1A1 and COL3A1) were also increased in Akita⁻/⁻ TTRRen⁺/⁺ mice.

**Conclusions:** Taken together our results suggest that Akita⁻/⁻ TTRRen⁺/⁺ mice recapitulate key features of human DN, including glomerular and interstitial fibrosis.

**PUB248**

**Uric Acid and Hemodynamic Responses to Angiotensin II Infusion in Adolescents with TID Compared to Adults with TID for ≥ 50 Years of Disease Duration**

Julie A. Lovblom,1 Leif E. Lovblom,2 Hillary A. Keenan,1 Michael Brent,2 Narinder Paul,2 Vera Bril,1 Bruce A. Perkins,1 David Cherney.1 Joslin Diabetes Center, Boston, MA; 1Dept. of Medical Imaging, Div. of Cardiothoracic Radiology, University Health Network, Toronto, ON, Canada; 2Dept. of Medicine, Div. of Neurology, University of Toronto, ON, Canada; 3Dept. of Medicine, Div. of Endocrinology and Metabolism, Mount Sinai-University Health Network, University of Toronto, Toronto, ON, Canada; 4Dept. of Medicine, Div. of Ophthalmology and Vision Sciences, University of Toronto, ON, Canada.

**Background:** Plasma uric acid (PUA) is associated with activation of the renin-angiotensin-aldosterone system (RAAS), promoting hypertension and kidney disease in patients with type 1 diabetes (TID). Our aims were to (1) compare blood pressure and renal hemodynamic responses to RAAS activation by angiotensin II (ANGII) infusion in patients with type 1 diabetes (T1D) ≥ 50 years of T1D, (2) determine if PUA levels modified these responses in such T1D cohorts and (3) study the effect of exogenous ANGII on PUA levels.

**Methods:** PUA levels and changes in biomarkers of bone and mineral metabolism (BMM) were measured during clamped euglycemia in 28 T1D adolescent participants (17-18 years), 54 young adults (20-45 years) and 50 adults (≥ 50 years) with T1D ≥ 50 years of T1D, (2) determine if PUA levels modified these responses in such T1D cohorts and (3) study the effect of exogenous ANGII on PUA levels.

**Results:** Mean ± SEM PUA levels were 0.04 ± 0.03 vs. 0.04 ± 0.03 mmol/L in adolescents and young adults with T1D compared to adults with T1D ≥ 50 years. Changes in BMM (Tab. 1).

**Conclusions:** PUA is a safe,“green”and cost-effective solution to simplify the preparation of the acid HD concentrate and can reduce costs, storage and transport of the bags and dialysis staff workload.

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

**PUB249**

**Safety and Cost-Effectiveness of In-House Preparation and Centralized Distribution of Acid Dialysis Concentrate**

Paolo Lentini,1 Luca Zanoli,2 Antonio Granata,1 Carlo Boccatto,3 Roberto Dell’Aquila,3 1St. Joseph General Hospital ULSS 7 Pedemontana, Bassano del Grappa, Italy; 2University of Catania, Catania, Italy; 3None, Catania, Italy; 4Consultants, Milano, Italy.

**Background:** It is important to focus the effort of the caregivers on the activities able to generate the most favourable ratio of cost/benefit: during hemodialysis(HD), basic and acid concentrate are used. Making them available at the HD machines requires a considerable efforts in terms of workload and logistic. While basic concentrate is usually provided from a cartridge of dry bicarbonate, acid concentrate is supplied to the machine in a 5-litr bag(Single-PatientDialysisDeliverySystem-SPDDS). However, the acid concentrate can be supplied to the HD machine via a CentralConcentrateDeliverySystem(CDDS).

**Methods:** We adopted, 1st Center in Italy, an automated CDDS(GranomixisPlus®, Fresenius Med. Care-DE) based on a fully mixing unit that performs the dilution of a highly concentrated ingredient in HD water, and a storage and distribution unit that stores the concentrate and distributes it to the HD machines via a dedicated tubing that runs in parallel to the HD water distribution line. Here we evaluated the 1st-year safety, environmental impact and cost-efficiency ratio ofCDDS.[Fig.1]

**Results:** CDDS was used in 75%±(8%), whereas SPDD was used in10pts that require peculiar treatments with personalized HD fluid composition.11000 treatments/year were performed with CDDS in our center. CDDS was associated with a reduction of staff workload (avoided movement/manangement of 59180 kg of material), more space in our storehouse (avoided disposal of 11470 kg of plastic material and 7150 kg of concentrate residuals) and a big money saved ($27544), in absence of any clinical bath-related adverse events[Tab.1].

**Conclusions:** CDDS is a safe,“green”and cost-effective solution to simplify the preparation of the acid HD concentrate and can reduce costs, storage and transport of the bags and dialysis staff workload.

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

**PUB250**

**Changes in Biomarkers of Bone and Mineral Metabolism (BMM) Associated with Cross-Over Use of Citrate (CD) and Acetate (AD) Acidified Bicarbonate-Based Dialysates**

Ludmila Anderson,1 Linda H. Ficociello,1 Paul Balter,2 Alice Topping,3 Claude Mulfon,2 Robert J. Kossmann.1 Fresenius Medical Care North America, Waltham, MA; 1Renal Research Institute, New York, NY.

**Background:** Dialysates commonly contain acetate or citrate as the acidifying agent. This retrospective analysis of chronic hemodialysis (HD) patients who switched dialysate from AD to CD and back to AD, assessed changes in corrected serum calcium (SCc) and iPTH during these time periods.

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

**Conclusions:** Longstanding diabetes modifies the relationship between the RAAS and PUA, resulting in systemic and central RAAS activation.
Methods: Patients with AD treatment data for 3 months (baseline, [BL]), followed by CD for 9 months (Q1-Q3), and back to AD for 3 months (Q4) were analyzed. Mean pre-HD laboratory values were compared by quarters. Subanalyses were conducted by BL iPTH (<130, 130-600, >600 pg/ml). Changes in medications (Ca-based phosphate binders [CaPB], cinacalcet, in-center vitamin D [iVitD]) were explored. Paired t-test, chi², p<0.05 were used.

Results: Switching dialysate from AD to CD among patients with BL iPTH ≤ 600 pg/ml was associated with increase in pre-HD iPTH at Q1 that leveled off at Q2-Q3. Among patients with BL iPTH > 600 pg/ml, iPTH decreased (BL: 1.044.1 vs. Q3: 835.3 pg/ml). Switching dialysate from AD to CD was not associated with changes in iPTH. Minor changes in CSC followed AD to CD, and CD to AD, switched (Table). From BL to Q4, % of patients treated with CaPB (32% vs. 34%, p=1.0) and cinacalcet (46% vs. 51%, p=0.7) remained similar, and in-center iVitD use increased from 71% to 78% (p<0.001).

Conclusions: Clinically modest changes in iPTH and CSC followed AD to CD, and CD to AD, conversion. Patients with BL iPTH ≤ 600 pg/ml had mean iPTH increase in Q1 and level off at Q2-Q3, and patients with BL iPTH > 600 pg/ml had mean iPTH decrease.

Funding: Commercial Support - Fresenius Medical Care North America

PA <5 patients had a higher risk for all-cause death.

PUB252
ESRD and the Risk of Admissions for Recurrent Gastrointestinal Bleeding (GIB): Quality Improvement (QI)
Ahmad Anjik, 1 Nicole Piero, 1 Chalarus V Thakar, 2 Cincinnati V.A., Cincinnati, AL; 1University of Cincinnati, Cincinnati, OH; 2University of Florida Hospital, Cincinnati, OH.

Background: ESRD patients face a high risk of readmissions. GI bleed is life-threatening complication in ESRD patients; with the risk of bleeding up to 3-5 folds as compared to non-chronic kidney disease (CKD) patients. Our study aim was to evaluate the characteristics of ESRD patients experiencing GI bleed, including recurrence.

Methods: As a part of QI project, we assessed admissions under renal consult services in ESRD patients admitted to our VA facility from July–December 2016. Clinical operational data included: patients age, cause of ESRD, type of dialysis access, the source of GI bleed, the cause of GI bleed, endoscopy results and intervention, blood products requirement, anticoagulation use with hemodialysis, the use of antiplatelet and proton pump inhibitors (PPI), recurrence of GI bleed, and length of time till recurrence.

Results: During 6 months, there were 50 ESRD patients experiencing 64 admissions. Six patients with ESRD had 10 encounters with GI bleed in the 6 months period, 4 of the 6 patients had recurrent GI bleed. Three patients were diagnosed with arteriovenous malformation (AVM) as the cause of GI bleed, one with polyps and one with gastritis and one the cause of GI bleed was unknown. All patients with AVM had severe acute blood loss that needed blood transfusions, and all of them needed one or more interventions with endoscopy, all patients with AVM had recurrence of GI bleeding. The time for recurrence ranged from 1 to 3 months, recurrence occurred despite PPI use. 2 of the AVM patients also had arterio venous graft as their access, and one with tunneled catheter.

Conclusions: ESRD patients with GI bleed experience frequent recurrence. AVM as the cause of GI bleed had 100% recurrence within 30-90 days. These patients also experienced severe bleeds requiring treatment, and PPI did not reduce the risk of recurrence. Cause of AVM related bleeds in ESRD and prevention of recurrent bleeding need larger studies.

PUB253
Is the Association between Vascular Access by Catheter and Mortality in Incident Hemodialysis Patients Confounded by Sociodemographics and Comorbidities? Marcia T. Martins, 1 Marcelo B. Lopes, 2 Gildete B. Lopes, 2 Antonio A. Lopes. 1 CLINIRIM, Salvador, Brazil; 2 Federal University of Bahia, Salvador, Brazil.

Background: Compared to access with arteriovenous fistula (AVF), access of hemodialysis (HD) by catheter for end-stage kidney disease patients has been associated with older age, greater prevalence of comorbidities and higher mortality. The present study investigated if the reported higher mortality in patients receiving HD by venous catheter than AVF could be explained by age, other sociodemographic factors and comorbidities.

Methods: The data are from a prospective cohort (PROHEMO) of 421 incident HD patients treated in 4 units of Salvador, BA, Brazil. All patients were on HD for >6 months (72%) < 3 mo). To estimate hazard ratio (HR), Cox’s proportional hazard models with cumulative covariate adjustments were used.

Results: Mean age was 51.0±14.9 yr. HD was performed by fistula for 119 and catheter for 302 patients. During a mean follow-up of 2.5 years, 51 deaths occurred in patients with HD by fistula (death rate=8.37/100 person-years) and 99 in patients with HD by catheter (death rate=14.73/100 person-years). The etiologic fraction of death attributed to catheter was 43.2% [(14.73-8.37)/14.73] 95% confidence interval – 14.1%, 63.3%. The adjusted HRs of death associated with HD by catheter are shown in the Table.

Conclusions: The results of this cohort of incident HD patients add strong support against the use of catheter for vascular access. As shown the association of catheter with higher mortality was only slightly reduced after adjustments for numerous risk factors of death, including age and comorbidities.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
CI = confidence interval; Model 1: Adjusted for age (continuous), sex, race (non-white vs white), economic class (poor/very poor vs higher), education, marital status, living with family, private health insurance and months on dialysis; Model 2: Adjusted for heart disease, ischemic heart disease, cerebrovascular disease, hypertension, diabetes, peripheral vascular disease, cancer, plus variables and model 1; Model 3: Adjusted for hemoglobin, leucocyte count, ferritin, albumin plus variables in model 2.

PUB254

Subclinical Hypothyroidism and Its Associations Observed in ESRD Patients in a Tertiary Care Hospital

**Background:** Chronic kidney disease (CKD) has been known to affect thyroid hormone metabolism. End stage renal disease (ESRD) and Subclinical Hypothyroidism (SCH) are independent risk factors for cardiovascular disease (CVD) mortality. There is paucity of data regarding SCH prevalence in patients with ESRD in developing countries. We aimed to study the prevalence of SCH in our ESRD population and its correlation with patient demographics.

**Methods:** We enrolled all 112 ESRD patients on maintenance hemodialysis at the dialysis center of Jinnah Hospital Lahore. Thyroid function tests were performed on early morning venous samples (fasting) of all patients. Subclinical hypothyroidism (SCH) was labeled when the serum thyroid-stimulating hormone (TSH) level was high (range: 4.2-10 mIU/mI) but the corresponding serum-free thyroxine (FT4) level was within normal limits (range: 0.93-1.7 ng/dl).

**Results:** The mean age of the patients was 42 ± 10.86 years (range 24-60 years) and 74 (66.1%) were males. The mean duration of ESRD was 4.46 ± 10.86 years (range: 0.93-1.7 ng/dl).

**Conclusion:** The prevalence of SCH in this ESRD population was 0.246 ± 0.072 ng/dl (range 0.04-0.49 ng/dl) and 1.05 ± 0.25 ng/dl. The mean TSH was 2.60±0.81 mIU/mL (range 0.10-4.0 ng/dl). Of these 12 patients with SCH, significant association was found between gender of these patients and presence of SCH with p-value 0.011. Eight (67%) patients were females. No significant association of SCH was found between age group and duration of ESRD.

**Key Points:**
- SCH is a common condition in CKD patients.
- SCH is associated with higher CVD risk.
- Gender is a significant determinant of SCH in CKD patients.

**Disclosure:** The study was supported by the LRH research fund.

PUB255

Teaching Thinking of Continuing Education in the Implementation of the Integrated Management of Medicine, Nurse, and Technology for Hemodialysis Specialized Nurses

**Background:** In order to provide good quality service and achieve continuous improvement of medical quality, we carry out the integrated management of medicine, nurse and technology in the department of blood purification of the first affiliated hospital of Xi'an Jiaotong University. In 2016, this paper we discuss the influence factors and methods of the continuing education in integrated management of medicine, nurse and technology for hemodialysis specialist nurses.

**Methods:** The influencing factors and improvement methods of the continuing education of dialysis specialist nurses include two aspects. The first is nurses’ subjective influencing factors which focus on improving the nursing staff's own value awareness level and professional thought training, the function of nursing staff in the quality control system of staff participation, constantly playing subjective initiative, self-learning, improving professional ability knowledge, and their own value and improve the comprehensive quality. The second is continuing education development connotation which focus on the standardized training of basic nursing, professional skills, patients health education and scientific research consciousness, and the improvement of teaching methods for active acquisition of knowledge, the ability to analyze problems, solve problems, team collaboration, logical reasoning, literature retrieval, comprehensive evaluation, and communication and expression skills.

**Conclusion:** In the implementation of the integrated management of blood purification, nurses play an important role, involving all aspects of clinical quality management, we should give improve their quality, and finally implement the continuous improvement of clinical medical quality.

PUB256

The Use of Indices of Volume Status to Predict the Incidence and Severity of Sleep Disordered Breathing in Hemodialysis Patients

**Background:** Sleep disordered breathing (SDB) is a prevalent condition resulting in a considerable increase in cardiovascular related death (Moe et al., 2001). Patients with chronic kidney disease (CKD) are known to be at an increased risk for the development of SDB, including obstructive sleep apnea (OSA), for reasons that are not entirely clear (Kimmel et al., 1989). Given the already elevated cardiovascular related morbidity that patients with CKD face, it is especially important to diagnose and treat SDB in this patient population. Defining the predictors of high risk for OSA in patients with CKD would facilitate diagnosis and treatment of OSA. The purpose of this study is to evaluate a variety of physiological factors accessible during hemodialysis to determine which of these factors is most closely associated with incidence and severity of OSA.

**Methods:** Participants were provided with the Watch-PAT200® Device (Itamar Medical) to assess the occurrence of apneic and hypopneic events. This device can be used to measure the respiratory disturbance index (RDI) during sleep at home. A SFB7 multi-frequency bioelectrical impedance analyzer/monitor from ImpediMed was used to measure changes in tissue water content before, during, and after hemodialysis. This allowed for objective measures of volume status in each patient in order to make indirect assessments of intravascular volume based on changes in the hematocrit during hemodialysis.

**Results:** All of the patients (n=5) studied have demonstrated evidence of SDB by calculating AH1 and AH2: 78.99 and 73.51 respectively. The average AH1 was higher when assessing data from Sunday nights alone (39.75). There were similar findings with oxygen desaturation indices (19.37 vs. 26.95, respectively). Weights above estimated dry weight were slightly higher on Mondays prior to hemodialysis when compared with weekly averages (2.30 vs. 2.15 kg).

**Conclusion:** This data supports prior findings that CKD patients are at an increased risk for SDB. Initial data from this study demonstrates that apneic and oxygen desaturation events are higher on Sunday nights, supporting the hypothesis that volume overload and potential soft tissue edema of the upper airways may be at play. Further data collection of volume status for correlation with SDB using bioelectrical impedance is underway.

**Funding:** Private Foundation Support

PUB257

Effect of Anti-HCV Positivity on Nutritional Status and Albumin of Hemodialysis Patients

**Background:** Anti-HCV positivity is associated with low serum albumin and is assumed to result from malnutrition. The effect of anti-HCV positivity on nutritional status and hence albumin of end stage renal disease (ESRD) patients on hemodialysis is unknown. The aim of this study was to assess the effect of anti-HCV positivity on nutritional status and albumin of ESRD patients.

**Methods:** All stable HD patients in our dialysis center were included. Thirty five (35) out of 128 total patients were positive for anti-HCV antibody. This included the patients with untreated active disease (positive HCV RNA) and early cirrhosis as well. Patients with decompensated liver disease were excluded. The following lab data was collected for these patients:

- Mean albumin in anti-HCV positive patients was 3.55 grams /dl and in control group was 3.62 grams /dl (p-value 0.043).
- Similarly the duration on maintenance hemodialysis was 35.6 months and 29.3 months in anti-HCV positive and control group respectively. These differences were not significant We noted that the duration of HD between these two groups was not significant.
- Mean albumin in anti-HCV positive patients was 3.55 grams /dl and in control group was 3.62 grams /dl (p-value 0.043).
- The average AHI was higher in the anti-HCV positive group (19.37 vs. 26.95).

**Conclusion:** The effect of anti-HCV positivity on nutritional status and albumin of hemodialysis patients is unknown. This study is the first to investigate the effect of anti-HCV positivity on nutritional status and albumin of hemodialysis patients. The results of this study suggest that anti-HCV positivity is associated with lower serum albumin levels in hemodialysis patients.
The Aggressiveness in Patients with Chronic Renal Failure Tomasz J. Izryniec,1,2 Dept. of Health Promotion and Community Medicine, Medical University of Silesia, Faculty of Health Sciences, Katowice, Poland; 1Dept. Nephrology/ENDO, MSW i A Hospital, Katowice, Poland. Group/Team: Warchulska-Giergielewicz Team.

Background: The aggressiveness is perceived as the feature of functioning a clearly evident predisposition to aggression. Its diversity depends on personal and situational factors. The aim was to assess the level of aggressiveness in uremic patients (CRF) and determine risk factors of aggressive behaviors.

Methods: The acceptance of illness, life satisfaction, control of emotions, depression and pain as well as total aggressiveness were examined using psychological tests and scales in 50 non-dialyzed-ND (59±16y) and 100 hemodialyzed-HD (62±14y) patients. The study attempted to select personal, clinical and biochemical features, which apply to patients with aggressiveness higher than the average (AHA) for the general population.

Results: CRF-patients characterized the mean acceptance of the disease and life satisfaction, higher than the average control of emotions, occurrence of depression and chronic pain. The aggressiveness was similar to observed in general population. HD differed from ND in less percentage of people with depression (41% vs 64% p=0.004), occurrence of pain (38% vs 60% p=0.05) and physical aggression (16x± 20x7pt p=0.007). Women differed from men in an occurrence of pain (ND-79% vs 42% p=0.004), lower suppression of anxiety (HD-20.6± vs 23x3pt p=0.002), greater acceptance of illness (17±9 vs 21x1pt p=0.008). ND with AHA differed from others: in age (45±13 vs 63±15y p=0.001), higher percentages of university educated (46% vs 13.5% p=0.007) and married (38% vs 16% p=0.049), absence of apathy and incidence of nausea, vomiting. A lower concentration of sodium (137±4 vs 141±4 mM/L, p=0.001) was observed. HD with AHA differed from others: in percentages of men (75% vs 52%, p=0.035), married (50% vs 30% p=0.046) and time of dialysis (4±4 vs 6±7y p=0.007). They more frequently suffered from a headache (45% vs 20% p=0.02). A lower acceptance of illness (17±9 vs 25±10pt p=0.003) was also a differentiating parameter.

Conclusions: 1. The aggressiveness of uremic patients is not higher than observed among general population 2. The progression of renal insufficiency and implementation of hemodialysis lead to the reduction of aggressive behavior 3. The lower acceptance of the illness differs dialedyzed patients with aggressiveness higher than the average from the others.

Cardiovascular Autonomic Control during Early Hemodialysis Predicts Hospitalized Cardiovascular Events in Renal Failure Patients Chih-chin Kao,1,2 1Taipei Medical University Hospital, Taipei, Taiwan; 2Taipei Medical University, Taipei, Taiwan.

Background: Labile blood pressure (BP) was associated with increased risk of cardiovascular (CV) mortality. However, the relationship of continuous dynamics of cardiac function during hemodialysis and hospitalized CV events is not known well. Autonomic Control during Early Hemodialysis Lead to the Reduction of Aggressive Behavior 3. The Lower Acceptance of the Illness Differed Dialedyzed Patients with Aggressiveness Higher than the Average from the Others.

Methods: We enrolled renal failure patients who received chronic hemodialysis in Taipei Medical University Hospital. Each participant received continuous hemodynamic variability exam using ICON® (Osypka Medical. Inc, USA) during hemodialysis. The “beat-to-beat” hemodynamic parameters [heart rate (HR), stroke volume (SV), cardiac output (CO), and systemic vascular resistance index (SVRI)] were recorded. We prospectively followed these patients until the occurrence of hospitalized CV events or the end of study in May, 2017. Analysis was done by hourly basis and several approaches were carried out to explore the dynamical changes of these parameters.

Results: A total of 35 patients were included and the mean age was 57±14 years and 24 (68.6%) were male. 15 patients developed hospitalized CV events (study group), including congestive heart failure (n=5), coronary artery disease (n=8), stroke (n=1), and peripheral arterial occlusive disease (n=1). Patients with hospitalized CV events were compared to those without CV events (control group). There was a significant difference in the 2nd, 3rd and 4th hourly averaged coefficient variance (standard deviation/mean) of HR between groups. No significant differences were found in hourly averaged SV, CO, and SVRI. The differences between 2nd and 1st hour coefficient variance of SV and CO between groups (control: 0, study: 1, Figure 1).

Conclusions: The higher averaged coefficient variance of HR in the 2nd, 3rd, and 4th hour; and the increase of coefficient variance of SV and CO in the early hours of hemodialysis have predictive value for lower hospitalized CV events, which implies that chronic dialysis patients who have better autonomic control system may have better CV outcome.

Figure 1. The differences of average [2nd-1st hour (1)], [3rd-2nd hour (2)], and [4th-3rd hour (3)] coefficient variance of SV and CO between groups (control: 0, study: 1).
The Prevalence of Intradialytic Hypotension under Different Diagnostic Criteria and the Association with Mortality

Zhiyu Wang,1 Zijin 1. Chen,1 Zuanhong Jiang,2 Xiaonong Chen.2
1Department of Nephrology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; 2Division of Nephrology, Division of Nephrology, Ruijin Hospital, Shanghai Jiao Tong University, Shanghai, China, Shanghai, China.

Background: Intradialytic hypotension (IDH) is one of the common complications during hemodialysis, however its diagnostic criteria are highly controversial. To fully understand the prevalence of IDH in our center and figure out which diagnostic criteria is better for Chinese maintenance hemodialysis (MHD) patients, we choose several IDH definitions and analyze their association with mortality.

Methods: The patients were recruited from Blood Purification Center of Ruijin Hospital undergoing hemodialysis during July 2012. Pre-, in- and post-dialysis blood pressure were recorded. Patients’ clinical characteristics, laboratory results and cardiac ultrasound results were collected. SPSS 23.0 was used to analyze data and conduct survival analysis.

Results: Totally 219 MHD patients underwent 16844 hemodialysis in 6 months. The prevalence rate, overall and individual frequency of IDH fluctuates greatly. For every IDH criteria, the patients were divided into the group IDH(+) and the group IDH(-). Survival analysis found that IDH (an absolute systolic blood pressure (SBP) < 90 mmHg or with a decrease of SBP 20 mmHg) can decrease the risk of patients’ cardiovascular mortality but wasn’t relevant to all-cause mortality. Further analysis showed these patients had better cardiac functions mainly reflecting in lower Pro-BNP, lower prevalence rate of left ventricular hypertrophy and higher left ventricular ejection fraction than IDH(-) patients. Noted that the better outcome was found between other IDH criteria and mortality.

Conclusions: The prevalence rate, overall and individual IDH frequency of IDH are of high variability when diagnosed by different IDH criteria. All IDH episodes defined by our selected definitions are of no association with all-cause mortality. An absolute SBP<90 mmHg or with a decrease of SBP>20 mmHg can decrease the risk of cardiovascular mortality due to their better cardiac function. Large scale researches should be conducted to find optimal IDH definition and explore the association of IDH and mortality.

Evaluation of Three Hemodialysis Filters and Their Impact on Kt/V and Anti-Xa Activity in Chronic Hemodialysis Patients Hemodialyzed with Tinzaparin, a Low Molecular Weight Heparin and Anti-Xa Activity in Chronic Hemodialysis Patients Hemodialyzed

PUB263

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

Correlation of Pulmonary Hypertension with Vitamin D Deficiency in ESRD Patients

Firoozeh Farahmand, Richmond Heights, MO.

Background: Data regarding incidence of pulmonary hypertension (PH) and its mechanisms in ESRD are scarce. PH is a devastating disease without a cure. Studies suggest oxidative stress as a mediator of PH. Vitamin D is a membrane antioxidant. Low serum vitamin D also stimulates the renin-angiotensin–aldosterone system (RAAS) resulting in vasoconstriction. The aims of this study were to evaluate the incidence of PH among patients with ESRD and to study its correlation with vitamin D levels.

Methods: A retrospective cohort of PH in ESRD patients treated with HD for at least 3 months followed in a dialysis unit. Patients without vitamin D assessment were excluded. Subject characteristics were recorded, including age, gender and race. PH was defined as an estimated systolic pulmonary artery pressure (PAP) higher than 25 mm Hg using echocardiograms performed by cardiologist.

Results: A total of 100 HD patients were included in the study. The mean age of our patients was 59±11.4 years. The mean duration of HD was 28±14 months. The mean ejection fraction was 54±7%. The prevalence of PFH was 51%. 9% of patients with PH were female that was statistically (p<0.05). 70% of patients with PH had a 25(OH)D level ≤30ng/ml (p=0.05).

Conclusions: Our findings demonstrate high incidence of PH among ESRD patients under maintenance HD and it is strong association with Suboptimal vitamin D. Further investigations are required to evaluate the beneficial effects of cholecalciferol in PH in ESRD patients.

The Clinical Significance of Hyperparathyroidism Detected by Ultrasonography in Hemodialysis Patients and Analysis of Related Factors

Zijin Chen,2 Zuanhong Jiang,2 Zhiyu Wang,1 Xiaonong Chen.1
1Nephrology Department, Ruijin Hospital affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China; 2Ruijin Hospital affiliated to Shanghai Jiaotong University, Shanghai, China; Department of Nephrology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China.

Background: Analysis the prevalence of hyperparathyroidism detected by ultrasonography in hemodialysis patients. Combined with clinical characteristics, analysis of related factors of hyperparathyroidism, and invest the value of intact parathyroid hormone (iPTH) as a predictor of parathyroid hyperplasia.

Methods: Maintenance hemodialysis (MHD) patients were treated in Ruijin hospital affiliated to Shanghai Jiaotong University School of Medicine in July 1st, 2015 to Dec 31th, 2015. All clinical data, sex, primary disease, dialysis vintage, biochemical data and medication were collected at baseline. Parathyroid hyperplasia was detected by Philips iE33 color Doppler sonography system (transducer with frequency 11 MHz). Results: Totally 96 MHD patients were enrolled in this study from July 2015 to Dec 2015. Among 96 MHD patients, 54 (57.3%) patients had parathyroid hyperplasia detected by ultrasonography, including 41 (42.7%) patients with left parathyroid hyperplasia and 44(45.8%) patients with right parathyroid hyperplasia. 29 (30.2%) patients had both hyperplasia. The prevalence of parathyroid hyperplasia in patients with dialysis vintage <36 months, 36–72 months and >72 months was 34.6%, 54.5% and 68.8%, respectively. Significant difference was between three groups (p=0.018). Compare parathyroid hyperplasia group (n=54) and no parathyroid hyperplasia group (n=42), there was significant difference in dialysis vintage (p=0.001), serum phosphorus (p=0.011), intact parathyroid hormone (iPTH) (p=0.001) and active Vitamin D treatment(p=0.001). Receiver operating characteristic (ROC) curve showed that iPTH level could predict parathyroid hyperplasia (AUC=0.75, p=0.001, 95%CI 0.66-0.85). When iPTH level was over 456.9 pg/ml, the sensitivity and specificity of ultrasonography were 57.4% and 88.1%, respectively.<p>

Conclusions: Parathyroid hyperplasia is one of the common complications in uremic patients. Ultrasonography is one of the effective methods to evaluate the parathyroid gland status. Long parathyroid vintage, higher iPTH level and active Vitamin D treatment are associated with parathyroid hyperplasia. When iPTH > 400pg/ml, it is recommended to evaluate parathyroid hyperplasia by routine parathyroid ultrasonography.
A Case of Chronic Cerebral Edema with Recurrent Dialysis Disequilibrium

Ugochi A. Osborn, Chinonye C. Ogbonnaya-Odor. University of Texas Houston, Pearland, TX.

**Background:** Dialysis disequilibrium syndrome can be defined as symptoms occurring during or after intermittent hemodialysis as a result of cerebral edema and increased intracranial pressure. The exact mechanism is unknown. However patients at risk for acute cerebral edema include patients with hepatic encephalopathy, strokes, patients with elevated BUN, hyponatremia, malignant hypertension. We present a patient with chronic cerebral edema which was unmasked by hemodialysis.

**Methods:** Case 40 y/o female with history of Lupus nephritis leading to End Stage Kidney Disease on hemodialysis three times a week for five years, previous ruptured anterior communicating aneurysm rupture which was surgically treated by clipping 19 years prior and hypertension. She presented after recurrent episodes of severe headaches with nausea and vomiting which was occurring 1hr into dialysis. One month prior she presented with similar intensity headaches. CT imaging revealed cystic mass with vasogenic edema and midline shift. She was initially treated with dexamethasone with mild improvements in headaches but returned after her symptoms initially resolved. Repeat CT head demonstrated radiation necrosis and hydrocephalus without obstruction. Ventriculoperitoneal shunt was placed and symptoms resolved.

**Results:**

**Conclusions:** Discussion/Conclusion This case serves as a reminder of the importance of close monitoring of patients on chronic dialysis with history of intracranial instrumentation, as cerebral edema can occur as a consequence leading to dialysis disequilibrium syndrome.

**Funding:** Private Foundation Support

---

**Practices and Patterns of Hemodialysis in South Asia**

Sonika Puri, Gaurav.

**Background:** South Asian (SA) region faces a high burden of end stage renal disease (ESRD) and has a large gap between demand and supply for renal replacement therapy (RRT). We present the assimilated findings of a survey of nephrologists of the SA region on prevalent hemodialysis (HD) and vascular access (VA) practices in their respective units.

**Methods:** Nephrologists or Internal Medicine specialists running HD centers in the SA region were sent an online questionnaire. Literature was reviewed to fill gaps for missing data. Responses obtained were then converted into graphs using google survey automated software.

**Results:** 1700 physicians were contacted. Overall response rate was 10%. Maximum responses were from India and Pakistan (0% from Afghanistan, Bhutan and Maldives).

Average cost per HD sessions varies from $10 to $100. Prevalent AV access trend: AV fistula use: 80% (India) to 40% (Myanmar) Temporary catheter use: 30% (Pakistan) to 10% (Sri Lanka). Tunneled catheter use: 30% (Sri Lanka) to 1% (Myanmar) Incident AV fistula use: 80% (India) to 40% (Myanmar) Temporary catheter use: 30% (Pakistan) to 10% (Sri Lanka). Tunneled catheter use: 30% (Sri Lanka) to 1% (Myanmar) Incident AV fistula use: 30% (Sri Lanka) to 1% (Myanmar) Temporary catheter use: 30% (Pakistan) to 10% (Sri Lanka).

**Discussion/Conclusion** There is evident regional disparity between availability of nephrologists and HD units within this region. Few patients utilize AVF for incident HD or undergo HD three times a week. There is greater need for public-private funding to provide quality ESRD care in this region.

**Funding:** Clinical Revenue Support

---

**Economic and ESRD indicators in SA Countries**

<table>
<thead>
<tr>
<th>Country</th>
<th>Total Health Expenditure (% of Gross Domestic Product)</th>
<th>ESRD Prevalence (per 1000)</th>
<th>HD Centers (per 10,000)</th>
<th>Estimated no. of HD sessions (per 10,000)</th>
<th>Estimated no. of HD patients</th>
<th>Estimated no. of nephrologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>4.7</td>
<td>39</td>
<td>112</td>
<td>2,700</td>
<td>21,000</td>
<td>1,800</td>
</tr>
<tr>
<td>Pakistan</td>
<td>5.6</td>
<td>100</td>
<td>20</td>
<td>285</td>
<td>2,750</td>
<td>140</td>
</tr>
<tr>
<td>Nepal</td>
<td>3.8</td>
<td>35</td>
<td>1</td>
<td>51</td>
<td>219</td>
<td>40</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>3.8</td>
<td>45</td>
<td>6</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>2.5</td>
<td>NA</td>
<td>20</td>
<td>200</td>
<td>20</td>
<td>NA</td>
</tr>
</tbody>
</table>

* Source: WHO and World Bank 2014

NA- Not Available

---

**All That Is Red Is Not Blood**

Fahad Alobaidi, Bijin Thajudeen. University of Arizona, Tucson, AZ.

**Background:** The usual color of effluent fluid is either clear or straw colored. Occasionally there can be reddish discoloration. Common causes of reddish discoloration include hemolysis, blood leak, hyperbilirubinemia and hydroxocobalamin administration. Here we report two scenarios where effluent fluid was colored.

**Methods:** 33-year-old male with history of advanced heart disease, left ventricular assist device admitted with fluid overload and acute renal failure. His hemoglobin was 6.5 g/dl at admission and cause of anemia was thought to be due to chronic hemolysis form use of LVAD. He was started on continuous renal replacement therapy for management of volume overload. The effluent was clear for first two days. On day three he received vitamin B12 injection as part of management of anemia. Few hours following the injection there was reddish discoloration of the effluent fluid [figure 1]. A urine dipstick analysis of the fluid was negative for blood and absence of any blood leak alarm make hemoglobin less likely as the cause of discoloration. The color intensity gradually decreased and was clear by day 7. Case 2 is a 45-year male with history of end stage liver disease admitted with sepsis. He was started on CRRT for AKI, volume overload and anuria. The effluent fluid showed discoloration form the start of CRRT and persisted until CRRT was discontinued [figure 2]. There was also a yellowish discoloration of the CRRT filter. Laboratory tests showed total bilirubin of 45 mg/dl.

**Results:** These two cases highlight the importance of checking effluent fluid color and identify the causes of discoloration.
Clinical Features of Cardiac Surgery Associated AKI Dependent on Dialysis – A Single Center Retrospective Analysis Hongwei Cao,1 Hong Ye,1 Junwei Yang.2 Center for kidney disease, Second Affiliated Hospital, Nanjing Medical University, Nanjing, China; 2Second Affiliated Hospital, Nanjing Medical University, Nanjing, China.

Background: Cardiac surgery associated acute kidney injury (CSA-AKI) is one of the most common postoperative complications. CSA-AKI dependent on dialysis is closely related to the mortality. Previous CSA-AKI, particularly the incidence of dialysis dependence, has been reported differently. This retrospective analysis of the clinical characteristics of CSA-AKI dependent on dialysis is to provide a clinical reference for reducing the incidence of CSA-AKI and improving the prognosis of this population.

Methods: The clinical features of patients with CSA-AKI dependent on dialysis from January 1, 2016 to December 31, 2016 in our hospital were collected and analyzed. The basic characteristics, surgical protocols, dialysis protocols and the follow-up were recorded. Patients with chronic kidney disease were excluded. Dialysis indications were as follows: fluid overload, hyperkalemia, severe metabolic acidosis, diuretic resistance and failure of other organs.

Results: Of the 250 patients who underwent cardiac surgery, 14 with CSA-AKI (5.6%) required continuous renal replacement therapy (CRRT). In addition to a case of child with congenital heart disease, mean age of the other 13 patients was 56±17 years old, and 10 were male (76.9%). 8 patients underwent the combined heart surgery (57.1%), and 3 underwent the most complicated surgery, Bentall, aortic arch replacement, stent atrial trunk and coronary artery bypass grafting (21.4%). 2 of 14 patients were placed with intra-aortic balloon pump and 3 needed extracorporeal membrane oxygenation after operation. 6 patients received CRRT (42.8%) immediately after operation and 8 received CRRT 8-60 hours after operation. 11 patients (78.6%) underwent CRRT for at least 72 hours. 8 patients survived and the rest died in the hospital including the 3 patients who needed ECMO. The survived 8 patients were followed at least three months. 3 of them had complete recovery of renal function, the rest had persistent renal insufficiency, 1 undergoes routine dialysis.

Conclusions: CSA-AKI dependent on dialysis is a common complication after cardiac surgery, especially those undergoing combined cardiac surgery. It is one of the main factors related to the mortality after cardiac surgery.

Funding: Government Support - Non-U.S.

Use of CRRT for Myoglobin Clearance in a Patient with Rhabdomyolysis Khaled Bodehes, Rebecca Frazier.1 Northwestern, Chicago, IL; 2Nephrology, Northwestern University, Chicago, IL.

Background: Myoglobin pigment released from muscle tissue in rhabdomyolysis is a known cause of acute kidney injury (AKI) in a variety of clinical presentations. Clearance of myoglobin via dialysis has been debatable. We present a case of anuric AKI secondary to rhabdomyolysis in which we used CRRT to assist with myoglobin clearance.

Methods: A 29-year-old male with a history of opioid use for back pain presented with lower extremity pain which was then attributed to a compartment syndrome of unknown etiology. He underwent fasciotomy resulting in a severe rise in his serum creatinine phosphokinase (up to 220000 units/L), with subsequent anuric AKI and hyperkalemia despite aggressive generous hydration with intravenous fluids. We proceeded with continuous renal replacement therapy (CRRT) and elected to do continuous veno-venous hemodiafiltration (CVVHDF) with a high-flux filter for highest possible clearance. We then measured myoglobin in the effluent dialysate fluid as well as in the blood on different time intervals. Myoglobin was indeed filtered into the dialysate fluid. We calculated a clearance of up to 18000 mcg/hour. Serum CKP level came down to 167,580 units/L within 24 hours, indicating a 25% decrease. Our patient continued to require RRT for 17 days, afterward his renal function started to recover and his urine output increased to the point that he was taken off of RRT.

Results: Conclusions: In some patients with CRBSI, bacteremia leads to metastatic complications, such as endocarditis, osteomyelitis, endocardial abscess, septic arthritis or other soft tissue abscesses. As metastatic complications confer high morbidity and mortality, clinicians should pay close attention to patients’ symptoms and physical examination findings. In addition, early use of investigations such as trans-esophageal echocardiography whenever applicable may help in early identification of unusual complications and prompt timely interventions.

Determinants of Successful Outcomes after Percutaneous Angioplasty of Arteriovenous Fistulas and Grafts Used for Hemodialysis Vijay Shah,1 Malgorzata A. Kochanek,1 Christopher Johnson,2 Mohammed Khadir,2 Rakesh Navuluri,3 Rita L. McGill,2 Mary S. Hammes.1 University of Chicago Medicine, Chicago, IL; 2Interventional Radiology, The University of Chicago, Chicago, IL.

Background: Arteriovenous fistulas (AVF) and grafts (AVG) may develop venous stenoses caused by neointimal hyperplasia, commonly treated with percutaneous transluminal angioplasty (PTA). We prospectively evaluated the associations of clinical characteristics with one month outcomes of PTA.

Methods: ESA patients referred for PTA of a patent AVF or AVG from 10/2016 - 4/2017 who consented were included. Demographic, clinical data, indication for PTA and the type and location of each lesion were collected. Each stenosis was evaluated in two orthogonal planes so percentage of stenosis could be calculated as compared to a reference vessel, before and after PTA. Clinical outcomes were ascertained from dialysis unit nurse practitioners one month after PTA. Success was defined as dialyzer blood flows of 450 mL/min during dialysis, without: prolonged bleeding, cannulation pain, high venous pressure, low arterial pressure, pulling clots, infiltrations, poor clearance, infections, or swelling of the arm, neck or head.

Results: We observed 63 stenoses in 46 participants. Success at one month after intervention was seen in 33 patients who had 45 stenoses. Clinical characteristics are presented by outcome in Table.

Conclusions: Success after PTA of a hemodialysis AVF or AVG malfunction was positively associated with use of aspirin, Renin-angiotensin aldosterone inhibitors (RAAS), and referral for high venous pressures. We did not demonstrate any significant associations between procedural success and anatomic features or measurements. Future work is needed to examine longer term outcomes and clarify the role of aspirin in dialysis vascular access.
Resection of Arterial Pseudoaneurysm Followed by a Prosthetic (PTFE) Loop Graft Brachial-Basilic AV Fistula Juan Carlos Garcia Yanez, Jesus A. Nava martinez, Monica L. Mendoza. Clinica de Accesos Vasculares, Servicios Medicos y de Equipoamiento SERME, Tlalnepantla, Mexico.

Background: This is the first case described in which the presence of a pseudoaneurysm at the site of anastomosis by Doppler ultrasound, is surgically resected and the same humeral vessel is used for the placement of a brachio basilic loop graft.

Methods: A 32-year-old male patient with chronic renal disease of undetermined etiology who required renal replacement therapy. Initiates conventional hemodialysis with temporary vascular access. History of vascular access: 1. Right Internal jugular venous catheter with duration of 4 months, withdrawn by change to fistula. 2. Left radial-cephalic arteriovenous fistula, which lasted 5 months, currently thrombosed. 3. Right Internal jugular venous temporal catheter placed 8 months ago, current access. 4. Left brachial-cephalic arteriovenous fistula 4 months ago, develops pulse, but does not form a thrill. The presence of a pseudoaneurysm in the anastomosis site with the presence of a Ying Yang sign is evidenced by Doppler ultrasonography, and the possibility of rupture is decided to be admitted to the operating room for resection.

Results: We present the case of a 32-year-old man, who came to the Vascular Access Clinic with suspicion of aneurysm. Doppler ultrasonography was performed, the presence of an arterial pseudoaneurysm was detected at the anastomosis site with a Ying Yang sign, and immediate surgical repair was considered in view of the possibility of rupture. During surgery of resection of the pseudoaneurysm, showed suitable diameters in the basilic vein and in the brachial vascular were evidenced, so that the placement of a synthetic graft 6 mm (Advanta™ VXT PTFE Vascular Graft). The most appropriate treatment should be selected according to the cause, location, size and accessibility of the pseudoaneurysm, as well as the sequential plan of vascular access for each individual patient. In view of the growing number of patients with chronic renal disease on hemodialysis with multiple comorbidities, in which the sites for the creation of an arteriovenous fistula are limited, it is of vital importance to choose the optimal treatment of pseudoaneurysm by helping with the technologies available to us. Preserving permeability, decreasing recurrence and prolonging the useful life of vascular access and consequently the quality of life of patients.

PUB273

Outcome and Mechanisms of Central Vein Thrombosis Due to Catheter in Hemodialysis Patients Kazunori Oshima,1 Naoki Ikegaya,2 Fumiaiki Nagaki,3 Tatsuo Yamamoto,4 Hiromichi Kume,5 Takuya Yoshida,6 George Seki,7 Akira Hishida,7 1Dept. of Medicine, Yaizu City Hospital, Yaizu, Japan; 2Dept. of Nephrology, Izai City Hospital, Izai, Japan; 3Dept. of Nephrology, Shimada Municipal Hospital, Shimada, Shizuoka, Japan; 4Dept. of Nephrology, Fujieda City Hospital, Fujieda, Japan; 5Dept. of clinical nutrition, Univ. of Shizuoka, Shizuoka, Japan.

Background: Though frequent occurrences of central vein thrombosis (VT) due to hemodialysis (HD) catheters have been reported, there are little data about the anticoagulation treatment and outcome of VT. Moreover, patients with uremia exhibit altered coagulation with both increased thrombotic and bleeding risks. We evaluated the outcomes of treatment and mechanisms of VT to catheters in HD patients.

Methods: Patients who had one temporary HD access were prospectively assessed with ultrasonography prior to catheter insertion and at the time of removal. Patients with VT were treated with warfarin unless otherwise contraindicated, and evaluated with ultrasonography every two weeks after removal. Next, to analyze mechanisms of VT, we retrospectively compared immature platelet counts (IPC) in between patients starting HD with arteriovenous fistulas and those with central venous catheters, since immature platelets are activated platelets with an increased prothrombotic potential.

Results: Fifteen jugular and 5 femoral catheters were placed in twenty patients at the induction of HD. Thirteen patients with jugular and 1 patient with femoral catheters presented VT at the time of removal. Nine patients were treated with warfarin, and VT disappeared within 1 month in seven patients and the size of VT decreased in 2 patients. In therapy, 31 patients starting HD with the catheters showed significantly increased IPC compared to 17 patients with fistulas (6920 vs. 3840 µL, p < 0.05).

Conclusions: We confirmed the high frequency of VT with HD catheters and observed the possible benefits of warfarin treatment in VT due to HD catheters. Additionally, starting HD with catheters may increase thrombotic events by activating platelets.

PUB274

Patency of Arteriovenous Grafts in Hemodialysis Patients: A Single Center Retrospective Study Xiaojin Bian, Hong Ye. 2nd Affiliated Hospital, Nanjing Medical University, Nanjing, China.

Background: It is difficult to maintain a working access for patients on hemodialysis. Despite current Dialysis Outcome Quality Initiatives recommendations of “Fistula First”, not everyone qualifies for fistula, and those patients undergoing the treatment, a graft can experience graft failure. The patency of arteriovenous grafts (AVG) and complication of AVG in hemodialysis patients was analyzed. This study also examines factors associated with AVG patency.

Methods: From January 2014 to December 2016, maintenance hemodialysis patients undergoing an arteriovenous graft in our hospital were followed. The AVG was examined three times at 3.6 and 12 month after fistulation. Complications, including bleeding, infection, steal syndrome, aneurysm, thrombosis and central venous stenosis were evaluated at 12 month after fistulation. Data were collected from electronic medical records, including date of first and subsequent interventions, salvage technique, medical comorbidities, and use of antiplatelet medications. Logistic regression was used to determine the odds ratio for risk factors associated with patency. Cox proportional hazard models were used statistic analysis.

Results: A total of 155 unique patients had an AVG. Of the 155 patients 68% were female, 70% were hypertensive, and 64% were diabetic. The locations of the grafts were 31% arm and 69% forearm. Configurations, including loop and straight, were 63% and 37%, respectively. The primary patencies were approximately 90%, 69% and 59% at 3, 6 and 12 months, respectively. The cumulative patencies were 92%, 80% and 69% at 3, 6 and 12 months, respectively. The incidence of all complications is 41.9% (65 of 155) at 12 month Primary patency was not found to be different with respect to location and type and configuration of graft and type of intervention. Primary patency for patients with diabetes and complicated vascular access history were significantly different from other patients, with a P<0.039 and P=0.0431 respectively.

Conclusions: Arteriovenous grafts in hemodialysis patients had excellent patency and some complications. Neither location nor configuration affects the primary patency of A V Gs. Diabetes and fistulation history were detrimental factors for patency of AVGs.

Funding: Government Support - Non-U.S.
Conclusions: Patient preference for TDC and satisfaction is important and can result in a successful outcome in pregnant patients. Nonetheless, in keeping with the National Kidney Foundation guidelines as well as the Fistula First, an arteriovenous fistula should be offered to hemodialysis patients.

PUB278

The Use of the Early Cannulation Prosthetic Graft (Gore Acuseal) for 15 Patients as a Lower Extremity Prosthetic Hemodialysis Access

Bing Tang,1 Yong Xu,2 Yuanning Li,1 Xinxin Liu,1 Bei Hou,1 Kun Wu,2 Renal Division, Carnation Hospital, ChangSha, China; Hemodialysis center, the Third affiliated Hospital of Xiang Ya School of Medicine, Central Sooht University, ChangSha, China.

Background: With the life expectancy of end-stage renal disease increasing, the quality and availability of the native arteriovenous access can be limited and reduced with time, the option of using prosthetic AV will become necessary. The purpose of this study is to report the safety and effectiveness of the Gore Acuseal Graft using as a lower extremity prosthetic vascular access for chronic hemodialysis patients who have exhausted upper extremity vascular access or have central venous stenosis.

Methods: Between December 2016 and May 2017, 15 patients who underwent implantation of the Gore Acuseal prosthetic AV access were included in the study. The graft configuration all were superficial femor-a-saphenous. follow-up of time to first cannulation, patency rate, rates of seroma, access thrombosis, steal syndrome, pseudo-aneurysm and infection were performed and recorded.

Results: Graft implantation was technically successful in all 15 patients. No patient was lost during a mean follow-up time of 3.6±1.6 months (range, 1.7-6 months). Mean time to first cannulation was 136.8±97.2 hrs (range, 24-364hrs). Primary functional patency rate was 93.3%. Primary blood flow was 200-230ml/min. First puncture time was 136.8±97.2 hrs (24-384hrs), an average follow-up of 3.6±1.6 months (1.7-6.0 months). Seroma, thrombosis, pseudo-aneurysm, or graft infection was never observed. Steal syndrome occurred in one patient. Cannulation is easier than other types of regular prosthetic access reported by nurses. Cannulation sites usually stop bleeding in 15 minutes with pressure after treatment, no hematoma was observed .12 patients were removed central venous catheter or ligated dysfunctional fistula at early stage of postoperatively 6 days. Central venous stenosis complications were not observed. Follow-up of blood flow rate all were greater than 250ml/min.

Conclusions: Lower extremity Gore Acuseal graft implantation was safe and effective, with less complications. It can be widely applied for chronic hemodialysis patients who have exhausted upper extremity vascular access or have central venous stenosis.

PUB297

Comparison of the Early Cannulation Graft (Gore Acuseal) and Standard Graft (Gore Interering) for Prosthetic Vascular Access for Haemodialysis

Kun Wu,1 Yuanning Li,1 Yong Xu,2 Xinxin Liu,1 Bei Hou,1 Bing Tang,2 Hemodialysis Center, The Third Affiliated Hospital of Xiang Ya School of Medicine, Changsha, China; 2Renal Division, Carnation Hospital, ChangSha, China.

Background: Gore Acuseal is a new early cannulation prosthetic access, it can be cannulated for dialysis within 3 days. The characteristic of this prosthetic access is an attractive alternative to CVC in those requiring urgent dialysis patients. The purpose is to compare the safety and efficacy of early cannulation graft(Gore Acuseal) to standard graft (Gore Interering) for prosthetic vascular access for Haemodialysis.

Methods: This is a prospective observational study of all AVGs placed since December 2016 in our hospital. Outcomes including time to first cannulation, patency rate, rates of seroma, access thrombosis, steal syndrome, pseudo-aneurysm and infection in early cannulation graft (Gore Acuseal) comparison to standard grafts(Gore Interering).

Results: Sixteen Gore Acuseal grafts and nineteen Gore Interering grafts were implanted in the study period. The Gore Acuseal graft configuration was superficial femora-saphenous(n=15), upper arm axillo-axillary (n= 1); The Gore Interering graft configuration was superficial femora-saphenous(n=15), upper arm brachial-axillary (n=1), brachial-cephalic or basilic (n=3). No patient was lost during a mean follow-up time of 3.6±1.6 months(range,1.7-6 months). Primary functional patency rate was 93.8% vs Gore Interering 73%, Secondary patency rate (93.8% vs 89.5%). Mean time to first cannulation was 5.6±4 days(range, 1-16 days) vs 11 ± 8 days (range 10-35 days), the differences were statistical significance(p<0.05). Seroma (0 vs 64.2%, p<0.05), AV access infection (0 vs 21%). Steal syndrome occurred in one patient with Gore Acuseal graft. Primary blood flow rate has no difference in both grafts.

Conclusions: Comparing with Gore Interining, Gore Acuseal Graft implantation was safe and effective, easier access with higher patency rate, less seroma, thrombosis, and infection. It is a viable option for patients who require urgent hemodialysis instead of temporary or tunneled catheters.

PUB280

Changes in Blood Pressures, Adequacy, and Access Flow Rates before and after Arteriovenous Access Thrombectomy

Sheetal Chaudhuri,1 Hao Han,2 Tommy C. Blanchard,7 Yue Jiao,2 Marta Reviriego-Mendoza,2 Hanjie Zhang,1 Murat Sor,1 Elsa Koh,7 John W. Larkin,1 Len A. Usyvat,7 Peter Kotanko,2,4 Franklin W. Maddux,2 Renal Research Institute, New York, NY; 1Fresenius Medical Care North America, Waltham, MA; 2Fresenius Vascular Care, Malvern, PA; 3Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Thrombotic events are a common complication in hemodialysis (HD) patients with arteriovenous fistula and grafts (AVF/AVGs), and are a major cause of dialysis access failure and many negative outcomes. To date, there are no established predictors associated to thrombotic events in AVFs/AVGs. We investigated the trends in levels of pre-dialysis systolic and diastolic blood pressure (preSBP/preDBP), dialysis adequacy, and access flow rates before and after an AVF/AVG thrombectomy in attempt to identify potential predictors of thrombotic events in HD patients.

Methods: We analyzed data from 1,847 Fresenius Medical Care North America HD patients before and after an AVF/AVG thrombectomy between 2015-2016. The preSBP, preDBP, Ki/V, and access flow rate was tracked in HD patients for 90 days before and after the thrombectomy, and plotted using a penalized B-spline to fit the mean with 95% confidence limits.

Conclusions: Comparing with Gore Interning, Gore Accuseal Graft implantation was effective, with less complications. It can be widely applied for chronic hemodialysis patients who have exhausted upper extremity vascular access or have central venous stenosis.

PUB281

Associations between Arteriovenous Fistula/Graft Failure Rates and Catheter Rates

Sheetal Chaudhuri,1 Hao Han,1 Tommy C. Blanchard,7 Marta Reviriego-Mendoza,2 John W. Larkin,1 Elsa Koh,7 Murat Sor,1 Len A. Usyvat,7 Peter Kotanko,2,4 Franklin W. Maddux,2 Fresenius Medical Care North America, Waltham, MA; Fresenius Vascular Care, Malvern, PA; Renal Research Institute, New York, NY; Icahn School of Medicine, New York, NY.

Background: The rates of central venous catheter (CVC) use in hemodialysis (HD) patients have been relatively unaltered over the last decade. In 2016, the United States Renal Data System estimated that about 68% of incident HD patients utilize a CVC at 90 days after starting HD, and approximately 20% of patients never transition to a permanent vascular access (VA). We aimed to study the correlation between vascular access surgeons who have high arteriovenous fistula/graft (AVF/AVG) failure rates and the catheter rates and the catheter rates in patients within the clinics associated with the vascular access surgeons.

Methods: We obtained AVF/AVG creation and failure rates by vascular access tracking system. We calculated the failure rate for each surgeon by identifying catheter creation after successful AVF/AVG use. We identified the clinics where surgeons had highest number of patients and computed the correlations between the percentage of patients without catheters per clinic and the percentage of patients with a failed AVF/AVG.

Results: We found a negative correlation between the percentage of HD patients without catheters and the percentage of patients with failed AVF/AVG.

Conclusions: Out findings suggest that the quality of AVF/AVG creation is associated with catheter rates and outcomes in HD patients. Additional studies are necessary to confirm this observation.

Funding: Commercial Support - Fresenius Medical Care North America
Marta Longitudinal Patterns of Quality of Life and Dialysis Modality Use: Publication-Only

PUB283

Background: Previous studies postulate that maintenance hemodialysis (MHD) patients dialyzed with tunneled cuffed catheter (TCC) have poorer outcomes compared to patients using arteriovenous fistula (AVF). This study aimed to compare the effects of two kinds of vascular accesses on anaemia in MHD patients.

Methods: Thirty-five MHD patients were recruited from the dialysis center of Tongji Hospital of Tongji University. Patients were classified into two groups according to their different vascular accesses: TCC group (n=15) and AVF group (n=20). Two groups were matched for age, gender, primary disease, duration of dialysis and usage time of access. We compared hemoglobin (HB), CRP, IL-6, TNF-α and Kt/v between the two groups.

Results: There were no significant differences in the age, gender, blood pressure, BNP, creatinine, blood lipids, albumin, PTH, calcium, phosphorus, ferritin transferrin, TSAT, SF, folic acid, VitB12 and EPO dose between the two groups. Compared to the TCC group, the blood flow and Kt/v in AVF group were significantly increased and the Hb levels, blood flow and Kt/v in AVF group were significantly increased. There was a negative correlation between the Kt/v and Hb levels (r=0.36, P<0.05), while the CRP, IL-6 and TNF-α levels were significantly decreased. There was a significant decrease in CRP, IL-6 and TNF-α levels and Kt/v between the two groups.

Conclusions: Compared to the AVF, the TCC is not good for the improvement of anaemia in MHD patients. That may result from increasing microinflammation state and inadequate dialysis.

Funding: Government Support - Non-U.S.

PUB284

Patients Favor Solo Home Hemodialysis to In-Center Hemodialysis – Results of a Patient Preference Survey

PUB285

A New Material for Dialysis Fluid Regeneration

PUB286

The Making of Successful In-Centre Nocturnal Haemodialysis: Well-Being, Sleep, and Free Time

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

Underline represents presenting author.
of Anemia in Dialysis Patients
Evaluation of the Quality of eHR Data to Assess the Clinical Features
Brigitte Optimal Transitions: A New Approach to Improve Home Dialysis
PUB287
Optimal Transitions: A New Approach to Improve Home Dialysis
Methods: An anonymous survey was distributed to current and previous INHD patients. The survey consisted of questions regarding demographics, length of dialysis, quality of sleep during dialysis, and free text areas for comments regarding facilities, reasons for starting and continuing INHD, and the impact of INHD. Thematic analysis was conducted on the free text sections.
Results: 58 patients were identified as current INHD (n=24) and previous INHD (n=34) patients. From these 34 patients, 21 discontinued due to: renal transplantation (n=11), transfer to a different unit (n=5), conversion to HHD (n=1) or PD (n=1) and death (n=5). These 21 patients were not included in the survey. From those surveyed (n=36), 27 (75%) were male, the average time on HD was 52 months and the average time on INHD was 9 months. Compared to usual HD, 26 (72.2%) rated INHD as causing less disruption, 25 (69.4%) stated they preferred INHD, and 24 (66.7%) felt better on INHD. The most common reasons to start and continue INHD were to have more time during the day and for the perceived health benefits (changes to medications, better blood results, improved breathlessness and generally feeling better). The main reasons for stopping were the side effects of longer dialysis or daytime tiredness.
Conclusions: Overall patient satisfaction with INHD was high due to the positive impact on lifestyle and perceived health benefits. Those that left the programme did so due to a change in clinical care, side effects of longer dialysis or daytime tiredness. These findings have identified the benefits of INHD from the patient perspective and the modifiable factors to enhance patient experience.

PUB288
Evaluation of the Quality of eHR Data to Assess the Clinical Features of Anemia in Dialysis Patients
Samantha St. Laurent,1 Rafael Alfonso-Cristancho,1 Tony Okoro,1 J. Morel Symons,1 Kirsten L. Johansen,2 Laura M. Dember,2 Vanja Sikirica,1 Alistair C. Lindsay,1 GlaxoSmithKline,1 Collegeville, PA; 2University of California, San Francisco, San Francisco, CA; 3University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.

Background: Electronic health records (eHR) have great clinical research potential if the information is sufficiently accurate. Here, we assess the quality and completeness of data in eHR from a large dialysis organization (LDO) in the US, focusing on demographic and clinical variables.

Methods: We used Kahn’s framework (Analytic Methods, 2012) to assess data quality from ~229,000 de-identified patients across 2,900 US centers in 2015. We focused on the following quality domains: 1) missing values and anomalies in data, 2) accurate relationships between data tables, 3) temporal relationships, and 4) logical events.

Results: Low missingness was seen for age (0.08%), sex (0.04%), and analysis treatment (0%) data. Hemoglobin (Hb) values were assessed via quality domains 1-4. Hb labs were recorded for 96% of the LDO cohort (range 0.46-8.9 g/dL; mean 10.9 g/dL, same result obtained with or without zero values). Anemia (defined by Hb <13.0 g/dL for males and <12.0 g/dL for females) was observed in 99% of patients with Hb labs. Extreme Hb values (<5.0 g/dL or >20.0 g/dL) were reported for ~0.17% of patients with Hb labs. Among patients with Hb labs, 78% had non-zero Hb values (<10.0 g/dL the KDIGO threshold for anemia of CKD treatment). Of these patients, 11% were below this threshold for a span of at least 90 days based on subsequent lab draw dates, and 3% were below it for 180 days. Of patients with Hb <10 g/dL, 98% were receiving an erythropoiesis stimulating agent.

Conclusions: Using Kahn’s framework, an objective analysis of eHR from an LDO found that certain demographic features, treatment, and Hb levels were consistently recorded. 99% of all patients were anemic; 78% of patients with Hb labs had a Hb level requiring treatment (<10 g/dL, the KDIGO hemoglobin criteria). Although 90% of these patients were given an erythropoiesis stimulating agent, 11% remained anemic for at least 90 days. Future work will assess mortality data linkages, and temporal data relationships between clinical variables, lab tests, and subsequent clinical treatments.

Funding: Commercial Support - GlaxoSmithKline

PUB289
Automation Anemia Management Algorithm System for Hemodialysis Patients Reduces the Staff Resources
Yukito Yoshidoka,1 Tadashi Otsukab,1 Ryuji Aoyagi,1 Takashi Yokoc,1 The Jikei University School of Medicine, Tokyo, Japan; 2Tachikawa general hospital, Nagauka, Japan; 3Niigata University, Niigata, Japan.

Background: Anemia treatment in hemodialysis(HD) patient involves adequate supply of iron and an erythropoiesis stimulating agent (ESA). We have used Darbepoetin Alfa as ESA from 2007 and managing anemia using an algorithm from 2010. Then facility-level hemoglobin(Hgb) was improved(11.2±0.9g/dL, mean±SD). Our anemia management algorithm requires the following variables: Hgb, ferritin, Hgb Trend (HgT), ESA dose. HgT is calculated automatically. The doctor verifies the results of AMAS and gives orders via AMAS. The nurse confirms the order on the tablet device.

Results: Before starting AMAS, the nurse evaluated the algorithm of all patients (n=188) using a total average of 168 minutes. The doctor issued dose prescriptions to an average of 98 patients over an average of 83 minutes. The nurse confirmed orders over the total average of 143 minutes(total 394 minutes). There were an average of 0.8 errors per evaluation. After starting AMAS, the doctor verified AMAS results for all patients over an average of 32 minutes. The nurse confirmed orders over the total average of 128 minutes(total 160 minutes). There was no error after the introduction.

Conclusions: Staff resources devoted to anemia management decreased significantly as a result of utilizing AMAS.

Funding: Private Foundation Support

Sample Screen from Automation Anemia Management Algorithm System.

PUB290
Application of Continuous Quality Improvement in Anemia Management of Maintenance Hemodialysis Patients
Hua Liu,1 Hongli Jiang,1 Dialysis Center of First Affiliated Hospital of Medicine School, Xi’an Jiaotong University, Xi’an, Shaanxi, China; 2First Affiliated Hospital of Medical College of Xi’an Jiaotong University, Xi’an, China.

Background: In recent years, with the continuous improvement of dialysis technology, the focus of dialysis management is gradually changing over to improve the treatment quality of hemodialysis patients. Plan-do-check-act (PDCA) is the scientific cycle which should be followed by the comprehensive quality management. We used PDCA cycle to explore the clinical effect of the continuous quality improvement on anemia management of the MHD patients.
**Methods:** After we found the general standard rate of anemia in outpatients in 2014 (37.8%) was lower than that in 2013 (39%), we choose overall analysis (Hgb≤10g/dl) from 2014 to 2016 for MHD patients in the First Affiliated Hospital of Xi’an Jiaotong University, based on application of PDCA cycle management model, used the fishbone diagram as a management tool to analyze the reasons. Then, we analyzed clinical stage indexes comparatively.

**Results:** Based on PDCA medical quality improvement for the doctor factors, health care policy, patient factors, dialysis and so on, we adopt the following methods, including strengthening the monitoring efforts, standardizing application of iron; strengthening the follow-up and treat of new patients, paying attention to prevention and treatment of hyperparathyroidism and other complications, strengthening the patient’s propaganda, improving the drug compliance and disease attention, improving malnutrition and the dialysis adequacy, providing different patients with individual dialysis choice, improving the dialysis adequacy and other measures to improve the microinflammatory state in patients. After these methods, the overall standard ratio increased 10.7% in 2015 (48.5%) and 14% in 2016 (51.8%) compared with 2014 (37.8%).

**Conclusions:** Continuous quality improvement management can promote the improvement of chronic complications in MHD patients such as anemia. We need to continue to make efforts to train staff, technical standards, and quality management in the treatment of MHD patients.

**Results:** We included 91 patients (age: 58.89, SBP: 143.89 mmHg, DBP: 80.83 mmHg, women 53.8%, LVMi: 149.63, EPR 0.525%, FEY 63.15, Feremia 66.44, Feritin 368.8, TSAT 26.59), 43.96% had anemia, corresponding to group 1. In group 2, 52 patients, the multiple regressions were significant: Hb (p = 0.099), TSAT (p =0.039). In the specific analysis of group 1: Hb (p = 0.011), serum iron (p = 0.05), TSAT (p = 0.03). For group 2, Ferritin (p = 0.026), serum iron (p = 0.01) and TSAT (p=0.018) were significant as independent variables for contractility.

**Conclusions:** In this study, we demonstrated the association of iron on contractility regardless of the presence or not of anemia in dialysis patients. These findings correlate with those studies performed in patients with heart failure, except that our population has a conservative ejection fraction, with the majority of studies with patients with decreased ejection fraction.

**Results:** Patients who had Hb levels ≤ 10 g/dl had lower mean serum ferritin levels compared with patients with Hb levels > 13 g/dl (p=0.01). There were no significant differences in inflammatory markers, lipid levels or ESA use.

**Conclusions:** Based on PDCA quality improvement management model, we used the fishbone diagram as a management tool to analyze reasons, apply improvement measures and quality management, in order to reduce the prevalence of anemia. We found that increasing Hb levels are statistically significant correlation with improvement of kidney disease, improving the self-report of cardiovascular disease and increasing quality of life scores. These findings are important and should be further confirmed in larger trials.

**Funding:** This study was a multi-center, cross-sectional and observational study. The patients were divided into two groups according to the presence (Group 1) or not (Group 2) of anemia, (hemoglobin (hb) < 13 g / l men and < 12 g /l women, in chronic HD patients). In the multiple regressions were significant: Hb (p = 0.009), TSAT (p = 0.039). In the specific analysis of group 1: Hb (p = 0.011), serum iron (p = 0.05), TSAT (p = 0.03). For group 2, Ferritin (p = 0.026), serum iron (p = 0.01) and TSAT (p=0.018) were significant as independent variables for contractility.

**Conclusions:** Our findings are important and should be further confirmed in larger trials.
significantly stronger in the non-PAD group compared to PAD group (23.6 kg vs 17.0 kg, P = 0.005). Thigh circumferences (the mean of both sides) were also significantly larger in the non-PAD group compared to PAD group (41.7 cm vs 39.7 cm, P = 0.005).

Univariate regression analyses showed that frailty, age, number of oral medicine, and history of myocardial infarction (MI) had significant correlations with PAD. Multivariate logistic regression analysis demonstrated that the factors independently associated with PAD were as follows: frailty (OR = 2.061, 95% CI: 1.091-3.894, P = 0.030) and MI (OR = 3.742, 95% CI: 2.051-6.831, P < 0.001).

Conclusions: PAD is associated with frailty in HD patients.

**PUB295**

Assessment of Fluid Shifts of Dialysis Patients Using Plasma Water Index to Predict Intradialytic Hypotension Tadashi Otsuka, Ryohei Kaseda, Tadashi Otsuka, Ryohei Kaseda, to Predict Intradialytic Hypotension

**Background:** Intradialytic hypotension (IDH) is the major risk factor for mortality in hemodialysis (HD), which often occurs when plasma fluid removal outpaces the rate of refilling in the patient whose dry weight (DW) is underestimated. IDH is characterized by congestive heart failure (CHF). There is no standard measure of ultrafiltration on fluid shifts in the extra- and intracellular fluid spaces. We aimed to put plasma weight index (PWI) into practical use for probing relevant DW, as a marker of plasma refilling rate, and categorized patient’s fluid shifts in combination with hANP, an intravascular volume marker. In addition, relationships between those markers and pretilial edema (PTE) just before HD, as an interstitial fluid marker, were examined.

**Methods:** This study retrospectively examined records of 156 dialysis patients from December 30, 2015, to January 5, 2016 in Tachikawa medical hospital. IDH was defined by current KDOQI guidelines [a decrease in euvolemic BP (SBP) to a 20 mmHg or mean arterial pressure[10 mmHg as well as associated symptoms]. CHF group was defined as patients with dyspnea and lower SpO2 level (<96%).

**Results:** IDH and CHF occurred in 28.2% and 7.7% of all patients respectively. Patients with IDH had higher PWI levels than those without IDH (1.71±2.40 vs. 2.65±1.70, P = 0.007). PWI > 2.0 was predictive of high incidence of IDH (OR = 2.40, 95% CI: 1.12-5.12, P = 0.020), but not associated with incidence of CHF (OR 1.00, 95% CI: 0.30-3.30, P = 1.000). On the other hand, hANP > 100 pg/ml was predictive of high incidence of CHF (OR 3.52, 95% CI: 1.06-11.71, P = 0.004), but not associated with incidence of IDH (OR 0.79, 95% CI: 0.37-1.71, P = 0.550). We subdivided the patients into 4 groups by the two cut-off points of PWI and hANP. In the PWI < 2.0 and hANP < 100 pg/ml group, there was no CHF occurrence and incidence of IDH was relatively low (23.7%). PWI of patients with PTE was 1.71 ± 2.40, those without PTE (1.68 ± 3.4 vs. 3.07 ± 1.51, P = 0.001), and PWI had no significant difference between those with or without PTE (62 pg/ml; IQR 39-128 vs. 52 pg/ml; IQR 27-93, P = 0.060).

**Conclusions:** Assessment of fluid shifts by PWI and hANP would be useful for detection of DW status. PWI keeps fluid in interstitium and become a reservoir to intravascular volume during HD. Thus, PTE is possible to keep blood pressure during HD.

**PUB298**

Clinical Profile and Survival of Children and Adolescents under Renal Replacement Therapy in a Single Center in Brazil Maria Goretti M. Penido, Célina F. Rezende, Andre S. Alvaranga, Mariangela L. Cherchiglia, Viviane L. Nery, Federal University of Minas Gerais, Belo Horizonte, Brazil; Pediatric Nephrology Unit, Santa Casa de Belo Horizonte Hospital, Belo Horizonte, Brazil; Nephrology Center, Santa Casa de Belo Horizonte Hospital, Belo Horizonte, Brazil; Pediatric Nephrology Unit, Federal University of Minas Gerais, Belo Horizonte, Brazil.

**Background:** There are few available data that estimate the clinical profile and survival of pediatric renal replacement therapy (RRT). The aim of this study was to outline the clinical profile and survival of 82 children and adolescents under RRT followed at the Nephrology Center of Santa Casa Hospital in Belo Horizonte, from 2008 to 2016.

**Methods:** Cohort study of children and adolescents <18 years old with at least 3 months of registration to cohort admission. Patients excluded were those who died in the first 3 months under RRT, acute patients and those ≥18yrs. The databases of the Center as well as patient records were consulted. The following statistic tests were used: Student t, Mann Whitney, Wilcoxon, Fisher exact test and Kaplan-Meyer curves.

**Results:** We evaluated 82 pediatric patients (52M) with the median age of 9.5 years. 57% showed low height-for-age and-gender and the BMI was normal in 88%. The primary diagnosis was glomerulonephritis (36.6%), 82% were followed by nephrologists before beginning RRT, and 64.5% presented residual diuresis. Comparison between the admission exams vs 6 and 12 month exams after the beginning of the RRT, showed significant statistical growth of hemoglobin, albumin, alkaline phosphatase, parathyroid hormone and calcium levels. Hemodialysis was the main treatment modality (71%). The long-term double-lumen catheter was the most used vascular access (49%). During the study, 34 patients (41.5%) were transplanted and 94% received the graft from deceased donors. The median waiting time in RRT until the transplant was 20 months, and the median age of transplantation was 12 years of age. The survival rate in 8 years was 80.6%, with sepsis being the main cause of death (56%).

**Conclusions:** The majority of our patients were male, with glomerulonephritis, followed by nephrologists before starting RRT, on hemodialysis, with the long-term double-lumen catheter for vascular access. 34 patients were transplanted and received the graft from deceased donors. The median time on a waiting list and the age of transplantation was 20 months and 12 years, respectively. The survival in 8 years was 80.6%, with sepsis as the main cause of death. More studies are needed to improve the quality of care provided to pediatric RRT patients.
Epidemiological, Social, and Economic Profile of Children and Adolescents under Renal Replacement Therapy in a Single Center in Brazil

Maria Goretta M. Penido,1,2 Celina F. Rezende,4 Andre S. Alvarenga,4 Maringela L. Cherchiglia,1 Viviane L. Nery,2 Federal University of Minas Gerais, Belo Horizonte, Brazil; Pediatric Nephrology Unit, Santa Casa de Belo Horizonte, Belo Horizonte, Brazil; Pediatric Nephrology Unit, Federal University of Minas Gerais, Belo Horizonte, Brazil; Nephrology Center, Santa Casa de Belo Horizonte, Belo Horizonte, Brazil.

Background: Pediatric chronic kidney disease is a long-term disease and is associated with morbitiy, premature death and low quality of life. The progressive decline of renal function compromises all organs of the organism as well as psyche, behavior, family dynamics and income. The aim of this study was to outline the epidemiological, social and economic profile of 82 pediatric patients under renal replacement therapy (RRT) followed at the Nephrology Center of Santa Casa Hospital in the city of Belo Horizonte from 2008 to 2016.

Methods: Cohort study with children and adolescents <18 years old with at least 3 months of registration to cohort admission. Patients exluded were those who died in the first 3 months under RRT, acute patients, and those >18 years of age. The databases of the Center as well as patient records were consulted. The following statistic tests were used: Student t, Mann Whitney, Wilcoxon and Fisher exact test.

Results: We evaluated 82 pediatric patients (52M) with the median age of 9.5 years and the following age ranges: infants (16%), preschoolers (22%), school-aged (28%), adolescents (34%). Fifty-seven patients did not live in Belo Horizonte and the mother was the caretaker in 80.5%. The per capita income was ≤1 minimum wage in 89%, 95% of the patients received RRT from the government, 60% use government transportation for their treatment, and the majority (94%) are enrolled at the primary care unit and received the majority of their medicines from those units. Among those at scholastic age (54%), 85% attended school regularly. Fifty-seven percent showed low height-for-age-and-gender and the body mass index was normal in 88%. Hemodialysis was the main treatment modality (71%).

Conclusions: The profile of our pediatric patient was: a boy with low height, on hemodialysis, older than 7 years of age, not living in the city, per capita income was ≤1 minimum wage, enrolled at primary care unit, received RRT and transportation from the government, attending school regularly, cared for by their mothers. More studies are needed to improve the understanding of the epidemiological, economic and social characteristic of pediatric RRT.

Agreeability between Dialysis Unit Blood Pressure and Ambulatory Blood Pressure Monitoring in Dialysis Patients


Background: Hypertension in dialysis population is associated with increased cardiovascular mortality and morbidity. Majority of therapeutic decisions are taken based upon dialysis unit blood pressure (BP) readings.

Methods: Ambulatory BP monitoring (ABPM) was performed for 44 hours in between 2 dialysis sessions beginning immediately post-dialysis. ABPM was recorded every 20 min during the day (7 am to 11 pm) and every 30 min during night (11 pm to 7 am) on non-fistula arm. A total of 70% readings were excluded from the study. Hourly means were averaged to obtain interdialytic systolic and diastolic blood pressure readings over 44 hours. Pre and post dialysis blood pressure were recorded by dialysis personnel using oscillometric device attached to dialysis machine. These pre and post dialysis BP measurements were averaged over one week. Agreement between dialysis unit blood pressure and interdialytic ABPM were assessed by Bland-Altman plot and Lin’s concordance correlation coefficient (CCC).

Results: Of 40 patients, 68% were males. Average age was 54.7± 12.3 years. Mean dialysis vintage was 2.85± 2.9 years. About 49% were diabetic, 97% were hypertensive and 23% had IHD. Mean 44 hour ABPM reading was 142.9 ± 18.6 / 82.6±13.8 mm Hg. Limits of agreement between dialysis unit blood pressures and ABPM were wide across all BP parameters by bland-altman plot. Lin’s CCC (see table) also showed poor agreement between two readings (ABPM and dialysis unit readings).

Conclusions: There is a disagreement between dialysis unit blood pressure and ABPM. Irrespective of BP parameter, agreement remains poor between 2 measurements. We suggest assessing out of dialysis unit BP readings to make therapeutic decisions in dialysis patients.

Agreement between dialysis unit BP and ABPM

Bland-Altman parameters: Limits of agreement Lin’s CCC

Pre-dialysis SBP -10.7 ± 5.0 0.01
Pre-dialysis DBP 0.0 ± 2.7 0.75
Post-dialysis SBP -26.4 ± 12.3 0.64
Post-dialysis DBP -30.4 ± 2.3 0.75
1 week before pre and pre HD SBP -28.3 ± 21.8 0.74
1 week before pre and pre HD DBP -1.8 ± 17.1 0.81

Intradiastolic Bioimpedance Cardiography Measurement to Assess Cardiovascular Responses during Hemodialysis

Jining Wu, Hong Ye, Junwei Yang. Second Affiliated Hospital, Nanjing Medical University, Nanjing, China.

Background: In hemodialysis, extracorporeal circulation is applied to remove accumulated uremic toxins, electrolyte and fluid in plasma into the dialysate through a membrane during a 4h HD session 3 times a week. The rate of exclusion in 4h is approximately 10 times faster than that of previous accumulation for 2 or 3 days. Hemodynamic stress during HD results in recurrent segmental ischemic injury that drives cumulative cardiac damage. We performed an observational study of the cardiovascular effect of dialysis sessions using intradiastolic thoracic bioimpedance cardiography to examine the acute effects of dialysis on the cardiac function in stable patients.

Methods: In this observational study, we enrolled 114 patients from a single hemodialysis unit. Bioimpedance cardiography measurements included cardiac index, stroke volume index, systemic vascular resistance index, acceleration index and thoracic fluid content.

Results: Patients had mean±SEM ultrafiltration rates of 3.8±2.9 ml/kg per hour during HD. All measures of systolic contractile function fell during HD, with partial recovery after dialysis. Interestingly, during the first 5 mins of hemodialysis, cardiac index and stroke volume index reduced obviously compared to the base level before dialysis. All patients experienced some degree of segmental left ventricular dysfunction, with severity proportional to ultrafiltration rate and BP reduction.

Conclusions: It suggested that bioimpedance cardiography could assess the acute cardiac effects of dialysis during hemodialysis treatment. And fluid overload could in part explain the fall of cardiac index during dialysis.

Funding: Government Support - Non-U.S.
PUB304

Stakeholder Priorities for Cardiovascular Outcomes for Trials in Hemodialysis

Emma O’Long,1 Andrea K. Viecelli,1 Martin Howell,2 Allison Tong,3 Jonathan C. Craig,1 David C. Wheeler,3 Sir Charles Gairdner Hospital, Perth, NSW, Australia; 2The University of Sydney, Sydney, NSW, Australia; 3University College London, London, United Kingdom; 4University of Sydney, Sydney, NSW, Australia; 5University of Sydney/Children’s Hospital, Sydney, NSW, Australia; 6University of Sydney, Sydney, NSW, Australia; 7Renal Department, Royal North Shore Hospital, Sydney, NSW, Australia.


Background: Cardiovascular disease (CVD) is life-threatening and critically important for patients on hemodialysis, their caregivers and health professionals but has been measured inconsistently and variably across trials in hemodialysis.

Methods: In an international online survey (available in English, Hindi), participants rated the importance of 10 cardiovascular outcomes (derived from a systematic review) on a 9-point Likert Scale, with a score of 7+ suggesting critical importance. To determine relative importance participants also completed a best-worst scale. Means, medians and proportions were analyzed for each outcome.

Results: In total, 395 participants (including 105 [27%] patients/caregivers) from 51 countries participated. The mean rating and mean preferences scores (both with 95% confidence intervals) are shown in Figure 1 and 2. In absolute terms, all outcomes were rated as critically important (mean score >7); by both patients and healthcare professionals. On relative preference, myocardial infarction was found to be the most important outcome by all stakeholders.

Conclusions: Patients and health professionals identify all cardiovascular outcomes as important but myocardial infarction as the most important outcome to be measured in hemodialysis trials.

Funding: Private Foundation Support

PUB305

Aldosterone and Insulin Resistance: A Vicious Combination in Patients on Maintenance Hemodialysis

Hitoshi Minakuchi,1 Shu Wakim,1 Hiroshi Itoh.2

1Keio University, Tokyo, Japan; 2Keio University School of Medicine, Tokyo, Japan.

Background: We recently showed that in patients with chronic kidney disease, insulin resistance (IR) is associated with an increase in plasma aldosterone levels (Kidney Int., 2013). However, the role of this association in patients on maintenance hemodialysis has not been determined.

Methods: A total of 128 patients on hemodialysis were enrolled. The associations of plasma aldosterone or insulin resistance with various parameters were examined. Blood specimens were collected after overnight fasting and IR was evaluated by the homeostasis model of insulin resistance (HOMA-IR). We defined the patients both of whose aldosterone and HOMA-IR were above the tertile of each parameter in this cohort as HH group. Various clinical parameters in HH group were compared to those in other groups. Group of both of whose aldosterone and HOMA-IR were below the median of each parameter.

Results: Aldosterone levels were associated with age, HbA1c levels, HOMA-IR, and plasma levels of albumin, creatinine, potassium, uric acid, and insulin. Multiple regression analysis showed that the HOMA-IR was independently associated with aldosterone levels. Aldosterone levels were also associated with cardiac hypertrophy and with carotid artery stenosis. The HOMA-IR was associated with age, sex, past history of diabetes or dyslipidemia, body mass index, HbA1c, platelet count, hemoglobin, white blood cell count, and LDL plasma levels of total protein, creatinine, uric acid, phosphorus, high-density lipoprotein, triglycerides, and aldosterone. Multiple regression analysis showed that age, sex, uric acid, body mass index, and aldosterone were independent risk factors. The HOMA-IR was associated with cardiac hypertrophy. HH group exhibited more severe cardiac hypertrophy, contractile dysfunction and carotid artery stenosis compared with control group.

Conclusions: In patients on maintenance hemodialysis, plasma aldosterone levels and insulin resistance are closely interrelated, each of which is associated with cardiovascular tissue damages. The constellation of increased aldosterone levels and insulin resistance is related to severe cardiovascular damages.

Funding: Government Support - Non-U.S.

PUB306

Geographical Variations of Comorbidities in ESRD Patients

Yu Jiao,1 Virginia Carvajal-Mendoza, John W. Larkin, Len A. Lysaught, Jeffrey L. Hynes, Franklin W. Maddux.1 Fresenius Medical Care North America, Waltham, MA.

Background: Patients with end stage renal disease (ESRD) are known to commonly suffer from several comorbidities including anemia, vascular diseases, and diabetes. National benchmarks exist for many comorbidities in ESRD patients, yet geographical profiles have not been defined. We characterized the prevalence of common comorbidities in dialysis patients by geography in the United States and investigated whether geographical variations exist.

Methods: Data from patients treated at Fresenius Kidney Care clinics in 2016 was analyzed. We characterized the 17 common comorbidities in patients: anemia, cardiovascular disease, diabetes, dysrhythmias, hypertension, infection, peripheral or arterial vascular disease, congestive heart failure, hyperparathyroidism, chronic obstructive pulmonary disease, pneumonia, ischemic heart disease, myocardial infarction (including cardiac arrest), cerebrovascular disease, cancer (except skin neoplasm), drug or alcohol dependence, HIV/AIDS and gastrointestinal bleed. Patients were stratified according to the number of comorbidities: 1, 2, 3, 4, 5, 6, or >6. We calculated the mean, maximum, and minimum percentages of patients with the selected comorbidities within each of the 50 states in the United States.

Results: Data from 246,903 patients was analyzed. Of the 17 comorbidities investigated, we observed nationally that a mean of 91.2% of patients had ≥1 comorbidity (range: 68.2% to 96.4%), 20.9% had ≥4 comorbidities (range: 4.5% to 35.5%) and 0.81% had ≥8 comorbidities (range: 0% to 2.8%). We identified considerable variations in the number of comorbidities affecting patients in differing states. For instance, in West Virginia 35.52% of patients suffered from ≥4 of the comorbidities, while in North Dakota only 4.55% had ≥4 of the comorbidities. For cardiovascular dysrhythmias, we found that in patients residing in New Hampshire exhibited the highest prevalence (17.9%) and those in New Mexico (4.3%) had the lowest prevalence. Similar disparities were identified among the 17 comorbidities investigated.

Conclusions: Our analysis indicates that profiles of comorbidities affecting ESRD patients vary by geography. These findings may be useful for the development of improved management strategies that account for regional health disparities.

Funding: Commercial Support - Fresenius Medical Care North America

PUB307

Effect of Albumin on the Efficacy of Fluid Removal in Hypoalbuminemic Patients

Dona Ahadian,1 Etienne Macked,1 Bethany E. Karl,1 Ravindra L. Mehta.1,2

1University of California San Diego, San Diego, CA; 2University of California San Diego Medical Center; San Diego, CA.

Background: Intradialytic hypotension limits adequate fluid removal in hypoalbuminemic patients with acute kidney injury (AKI) or end stage renal disease (ESRD). Intravenous albumin has been used in such patients with varying results.

Methods: We are conducting a prospective cohort interventional study that included 31 patients with albumin levels less than 3 g/dl with AKI or ESRD who required fluid removal with hemodialysis. In this cross-over design patients were randomized to receive 100 mL of either 9% sodium chloride solution or 25% albumin intravenously prior to their first dialysis session and alternated between the two solutions until up to 6 sessions. Patients’ vital signs and ultrafiltration removal rate were recorded every 30 minutes during dialysis. 116 dialysis sessions were completed in total, 60 received normal saline and 56 received albumin.

Results: Intradialytic hypotension was defined as a decrease in systolic blood pressure by ≥20 mm Hg or a decrease in mean arterial pressure by ≥10 mm Hg. In total, 77 hypotension episodes (48 in saline and 29 in albumin groups) occurred in 39 dialysis sessions (21 total number of hypotension episodes for saline and 2 for albumin group (p value=0.68). Hypotension occurred 30 minutes after the start of dialysis in saline versus 37 minutes in the albumin groups (p value=0.045).

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

Underline represents presenting author.
value = 0.81). The median hypotension duration was 45 minutes for saline and 30 minutes for albumin groups (p value = 0.32). In the 48 saline hypotension episodes, 24 (50%) were accompanied by hypotensive symptoms, 11 (22.9%) required saline administration, and 16 (36.9%) was required to decrease or stop as therapeutic interventions. In the 29 albumin hypotension episodes these numbers were 12 (41.4%), 3 (10.3%), and 8 (27.6%), respectively. In albumin sessions more ultrafiltration fluid was removed compared to saline sessions (-2000 mL in albumin versus -1700 mL in saline).

Conclusions: In hypoalbuminemic patients who need hemodialysis, addition of albumin prior to dialysis results in later onset of hypotension, less incident of hypotensive episodes, fewer hypotensive therapeutic interventions such as saline administration or ultrafiltration rate decrease, shorter duration of intradialytic hypotension, and larger volume of fluid removed. However, these results were not statistically significant.

Funding: Commercial Support - Grifols

PUB308

Associations of Endothelial Function, Arterial Stiffness, and Heart Rate Variability with Physical Activity

Anoop Sheshadri,1 Piyawan Kittikulnam,1 Kirsten L. Johansen,1 2 Chulalongkorn university, Bangkok, Thailand; 3 University of California, San Francisco, San Francisco, CA; 4 University of California, San Francisco, San Francisco, CA.

Background: In the general population, higher levels of PA are associated with lower cardiovascular risk and better endothelial function, but it is not clear whether the association holds at the lower end of the PA spectrum. We sought to determine whether PA is associated with endothelial function and heart rate variability.

Methods: We recruited 55 dialysis patients ≥18 years of age receiving in-center hemodialysis (HD, n=47) or peritoneal dialysis (PD, n=8), on dialysis for ≥3 months and able to walk. We measured PA by pedometer. We tested endothelial function (reactive hyperemia index or RHI), using the EndoPAT-2000, which measures flow-mediated dilatation after a 5-minute arterial occlusion, and also measures arterial stiffness (augmentation index adjusted to heart rate of 75 or AI75), and heart rate variability (standard deviation of NN intervals or SDNN). All measurements were taken before HD sessions for those patients on HD.

Results: Participants’ median age was 58 years and 80% were male. Overall, PA was low at 2631, IQR 1361-5768 steps per day. RHI was impaired for the group as a whole (median RHI and IQR 1.47 – 1.87), as was SDNN at 20.55, IQR 12.55 – 31.92, AI75 was not substantially impaired at 11, IQR – 2 – 22%. After adjusting for age and sex, PA was not statistically significantly associated with endothelial function, augmentation index, or heart rate variability, despite positive associations in the general population and other populations with chronic disease. Adding vintage, diabetic status, and coronary artery disease status to the model did not affect this association.

Conclusions: It is likely that other factors beyond PA dominate in contributing to less traditional cardiac risk factors such as endothelial dysfunction and heart rate variability in patients treated with dialysis, although it is also possible that the majority of patients occupied too low a stratum of PA to generate a meaningful association.

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

PUB309

The Relation between Fibroblast Growth Factor 23, Cardiovascular Risk, and Body Composition in Patients Undergoing Hemodialysis

Maria Oleszewska, Krzysztof Hoppe, Krzysztof Schwerner, Malgorzata Kudziu, Ewa Baum, Krzysztof Pawlaczyc, Andrzezej Oko. Poznan University of Medical Sciences, Poznan, Poland.

Background: Fibroblast growth factor 23 (FGF23) is a key player in the regulation of bone-mineral homeostasis. Bone mineral disease is associated with negative cardiovascular outcomes in patients with chronic kidney disease. The aim of the study was to assess the relation between FGF23, cardiovascular risk and body composition in patients undergoing hemodialysis (HD).

Methods: This was a study involving a group of 74 HD patients (mean age 62.9±11.8 years, male n=40), divided into 2 subgroups (gr1=1109.88; gr2=1109.88 [mmol/L] depending on the median FGF23 value. Serum FGF23 was measured with ELISA. Markers of bone turnover, markers of inflammation, and one of the main cause is cardiac arrhythmias.

Results: It is likely that other factors beyond PA dominate in contributing to less traditional cardiac risk factors such as endothelial dysfunction and heart rate variability in patients treated with dialysis, although it is also possible that the majority of patients occupied too low a stratum of PA to generate a meaningful association.

Funding: NIDDK Support

PUB310

Association between Pre-Dialysis Electrolytes and Incidence of Arrhythmia in Long Interdialytic Interval among Chronic Hemodialysis Patients

Kampangtop Tangweproang, Renal Division, Bhumibol Adulyadej Hospital, Saimai, Thailand.

Background: End stage renal disease patients have high risk of cardiovascular death.

Methods: A retrospective, single-center study was performed among a thrice a week-hemodialysis patients without documented arrhythmias to compare the incidence of arrhythmias between long and short interdialytic intervals and determine the associated factors which relate to the events. 24-hour Holter monitoring was done twice in long and short interdialytic intervals within one week. Holter diagnoses were defined by the ACC/AHA clinical recommendations. Patients’ baseline data and pre-dialysis serum were collected.

Results: The data analysis of 28 patients who were studied, showed that there were 18 (64.3%) males and 10 (35.7%) females with mean age of 63 years. Non-sustained ventricular tachycardia (VT) was detected in 3 of 28 patients (10.7%) and only occurred in long interdialytic interval. In 8 of 28 patients (28.6%) had higher incidence of overall arrhythmias in long interdialytic interval while the left patients had no significant arrhythmias or no difference of arrhythmias in both intervals. Only male patients had higher incidence of both non-sustained VT and supraventricular arrhythmias in long interdialytic interval. Lower predialysis serum potassium (4.64 ± 0.40 compared to 5.45 ± 1.49, p-value 0.035), lower predialysis calcium (8.26 ± 1.05 compared to 8.95 ± 0.51, p-value 0.027) and lower predialysis serum magnesium (1.91 ± 0.32 compared to 2.34 ± 0.33, p-value 0.004) were found as independent factors for patients who had higher incidence of arrhythmias in long interdialytic interval.

Conclusions: Higher incidences of arrhythmias during long interdialytic interval occasionally occurred in chronic hemodialysis patient. Low serum potassium, low serum calcium and low serum magnesium might be associated factors.

Funding: Government Support - Non-U.S.

PUB311

30-Day Readmissions in ESRD Patients with Heart Failure

Linda-Marie Ustarius, Sandeep K. Mallipattu. Stony Brook Medicine, Stony Brook, NY.

Background: The overall number of hospitalizations for ESRD on hemodialysis in 2013 was 7.1 admissions per patient-year. Rehospitalization rates for Medicare beneficiaries greater than 66 years old without kidney disease compared to those with ESRD are 15.8% and 34.8%, respectively. This study’s objective is to identify the modifiable and non-modifiable risk factors associated with increased readmission rates in ESRD patients.

Methods: 1,534 ESRD patients corresponded to 28,695 encounters with an ICD 9 code for ESRD at a university hospital from 2010-2014. Inclusion criteria: more than one inpatient encounter (admission or ER visit) within a 30-day period. Outpatient, ambulance, and duplicate visits were excluded. Each hospital encounter within 30 days of the last discharge was reviewed for reason for admission: dialysis related (HTN, volume overload, electrolyte abnormality and access complication) or non-dialysis related. Baseline demographics and clinical data were collected, including ejection fraction and the presence of left ventricular (LV) dysfunction on echocardiogram. We calculated the proportion of dialysis related visits within each group. Chi square Fisher’s exact test calculated the p-value.

Results: 1,184 ESRD (445 females, 739 male) patients and 4,358 encounters met the inclusion criteria. Average number of encounters per patient year was 0.73, with an average of 0.57 encounters per patient per year. Rehospitalization rate was 0.56 per patient year.

Conclusions: Our preliminary data suggests that the presence of both systolic and diastolic dysfunction is associated with more dialysis related encounters compared to those without LV dysfunction.

Funding: NIDDK Support
determinants of AAC in HD patients. MPV may be a potential marker for prediction of AAC score was independently associated with MPV level ($\beta$ significantly positive association with age, HD vintage, diabetes, previous cardiovascular (BP) and higher levels of sleep diastolic BP and serum ferritin. AAA score showed a significant association with age, HD vintage, diabetes, and higher intradialytic weight gain. Also, a lower adequacy, treatment time, and body mass index was inversely correlated to walkability scores (all $p<0.05$).

**Methods:** We obtained data on Walk Scores (www.walkscore.com) in 10,000 zip codes in the United States (US) and identified dialysis patients treated at Fresenius Kidney Care (FKC) clinics residing in the same zip codes during June of 2016 to May of 2017. The Walk Score measures neighborhood walkability on a scale of 0 (poorest walkability) to 100 (greatest walkability) based on access to key destinations (e.g. grocery stores, restaurants, retail stores). We calculated the correlation coefficients between the walkability score in the zip code of each patient’s residence and 56 clinical and non-clinical variables.

**Results:** We analyzed data from 89,551 FKC patients living in 8,351 zip codes throughout the US. Of 56 parameters investigated, 17 were positively correlated with higher walkability scores. These included higher KDOQI physical composite scores, albumin, and creatinine levels, and lower rates of infection, rates of hepatitis, potassium levels, a younger dialysis vintage, and others (all $p<0.05$). Black, Asian, and Hispanic patients tend to live in areas with higher walkability. We found 25 parameters negatively correlated with walkability scores, including older age and higher prevalence of cardiac diseases and diabetes, as well as higher intradialytic weight gain. Also, a lower adequacy, treatment time, and body mass index was inversely correlated to walkability scores (all $p<0.05$).

**Conclusions:** These findings indicate that the walkability score where patients reside is related to physical composite scores, disease states, and many clinical markers of optimal patient management. Identification of surrogate measures of physical activity and overall infrastructure could assist in designing geographically specific support systems.

**Funding:** Commercial Support - Fresenius Medical Care North America

**PUB312**

**Correlation Analysis between GNRI and LRV, RDW, and PDV, and AAA in Maintenance Hemodialysis Patients**

**Wenbo Zhao,** 1 Hui-qun Li. 1 The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; 2the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.

**Background:** Malnutrition was a common condition in maintenance hemodialysis patients and increased mortality. The purpose of this study was to investigate the correlation between nutritional risk index (GNRI) and LRV, RDW, PDV and AAA in patients with maintenance hemodialysis

**Methods:** We enrolled 91 cases of maintenance hemodialysis patients (female 42 cases, male 49cases, dialysis time: 3.3±3.34 years). The nutritional risk index (GNRI) was correlated with the red blood cell distribution width (RDW), the platelet distribution width (PDW), the left ventricular mass index (LVM), Osteoporosis self-assessment Tool for Asians (OSTA).

**Results:** GNRI range (93.87 ± 7.92), LRV (0.146 ± 0.015), PDV (11.46 ± 1.65), LVM (145.23 ± 39.50), OSTA, (0.50 ± 3.98), GNRI, with a higher risk of RDW, PDV, LVM, related to the increased of OSTA level ($p<0.05$), AAA score (r=0.317, $p<0.002$), PDV ($r=0.203, p=0.045$), LVM ($r=0.201, p=0.04$), negative correlation, positive correlation with OSTA ($r=0.353, p=0.001$)

**Conclusions:** For maintenance hemodialysis patients, GNRI was closely related to cardiovascular function, blood cell morphology and degree of osteoporosis. It was important to evaluate the nutritional status of routine hemodialysis patients for routine GNRI to improve the survival state.

**PUB313**

**Mean Platelet Volume as a Determinant of ABDOMINAL AORTIC CALCIFICATION**

**Mingjun Jin Cho,1 Jiwon Ryu,1 Eun young No.2 Cheju Halla Hospital, Seoul, Republic of Korea; 2Chuncheon Sacred Heart Hospital, Chuncheon, Republic of Korea.**

**Background:** Mean platelet volume (MPV) is a marker of platelet activation. Increased MPV has been reported with the development of thrombotic events such as coronary artery occlusive disease, cardiovascular mortality and vascular access failure in chronic kidney disease (CKD) patients. However, abdominal aortic calcification (AAC) is also correlated with cardiovascular events in dialysis patients. The effects of MPV on arterial calcification is not known. This study was designed to determine the predictor for AAA in hemodialysis (HD) patients.

**Methods:** Eighty-nine chronic HD patients (age 59.7 ± 10.4 years, male 51.7 %, diabetes 53.9 %, mean dialysis duration 48.7 ± 3.34 years). The nutritional risk index (GNRI) range (93.87 ± 7.92), LRV (0.146 ± 0.015), PDV (11.46 ± 1.65), LVM (145.23 ± 39.50), OSTA, (0.50 ± 3.98), GNRI, with a higher risk of RDW, PDV, LVM, related to the increased of OSTA level ($p<0.05$), AAA score (r=0.317, $p<0.002$), PDV ($r=0.203, p=0.045$), LVM ($r=0.201, p=0.04$), negative correlation, positive correlation with OSTA ($r=0.353, p=0.001$)

**Conclusions:** For maintenance hemodialysis patients, GNRI was closely related to cardiovascular function, blood cell morphology and degree of osteoporosis. It was important to evaluate the nutritional status of routine hemodialysis patients for routine GNRI to improve the survival state.

**PUB314**

**Relationship of Neighborhood Walkability and Dialysis Patient Characteristics and Outcomes**

**John W. Larkin,1 Maggie Han,1 Schantel Williams,1 Xiaoling Ye,2 Len A. Usvyat1 Peter Kotanko,3 Franklin W. Maddux,1 Roberto Pecois-Filho,2 Fresenius Medical Care North America, Waltham, MA; 2Pontificia Universidade Catolica do Parana, Curitiba, Brazil; 3Renal Research Institute, New York, NY.**

**Background:** Higher levels of physical activity are known to be associated with dialysis patients achieving better outcomes. A recent study identified that neighborhood walkability scores are positively correlated with the mean daily steps walked by dialysis patients (Han M et al. 2017). We aimed to investigate whether there are correlations in walkability scores and an array of dialysis patient characteristic and outcomes.
Low Triiodothyronine Syndrome Is Associated with High Beta 2 Microglobulin in Hemodialysis Patients Hong joo Lee, Seoul Red Cross Hospital, Seoul, Republic of Korea.

**Background:** Low circulating triiodothyronine (T3) levels, known as the low T3 syndrome, are the most frequently encountered thyroid functional test derangement in end-stage renal disease (ESRD) patients on hemodialysis. Beta-2 microglobulin (β2M) is a prototypical middle molecule uremic toxin that associate with a higher mortality in hemodialysis patients. Hence, we conducted a study to elucidate the interacting factors between β2M and a low T3 level in ESRD patients on hemodialysis.

**Methods:** All hemodialysis patients in Red Cross Hospital within a period of one year were included in the study. The participants were divided into two groups based on the level of T3. We evaluate relationships between T3 level and the variables showing malnutrition, inflammation, comorbidity, and β2M. Statistical analysis was carried out by using SPSS.

**Results:** Among the 56 cases, 44.6% of the patients had the low T3 syndrome. The patients with the low T3 syndrome had lower weight and body mass index (BMI) than the patients with normal T3 level. In addition, the T3 level was associated significantly with the level of ferritin, total iron-binding capacity (TIBC) and albumin/globulin (A/G) ratio. We observed a negative correlation between the level of T3 and β2M. However, blood urea nitrogen, creatinine, and lipid profiles including total cholesterol, high density lipoprotein and low density lipoprotein cholesterol, and triglyceride were not related to the level of T3.

**Conclusions:** Therefore, the intensive hemodialysis treatment for clearing β2M may have an advantage for normal T3 in hemodialysis patients.

---


**Academic Medical Center, Amsterdam, Netherlands; Ambroise Pare University Hospital and Inserm U1015 Eq5, Boulogne Billancourt/ Paris cedex, France; Arbor Research Collaborative for Health, Ann Arbor, MI; Clinical research center Amiens University hospital and Inserm U1069, Amiens, France; UK Renal Registry and University of Bristol, Bristol, United Kingdom; CHU de Bordeaux, Bordeaux, France.

**Background:** Haemodialysis patients experience a wide variety of intermediate complications, such as anaemia, hypertension and mineral bone disease (MBD). We aimed to compare survival and hospital admissions in patients according to the simultaneous attainment of different guideline targets (hypertension, anaemia and MBD) in a large European cohort of dialysis patients.

**Methods:** EURODOPPS is part of DOPPS, an international, prospective cohort study of adult, in-centre haemodialysis patients, with clinical data extracted from patient records. For this analysis, 6517 patients from seven European countries were included between 2009 and 2011. Quality of guidelines target attainment was considered high if 4 or 5 targets of the 5 evaluated targets were attained, moderate if 2 or 3 targets were attained and low if 0 or 1 target were attained (Table 1). Fully adjusted multivariate Cox models investigated the relationship between quality of guideline targets attainment and mortality or first hospital admission.

**Results:** At baseline, attainment of guidelines was considered as low in 1751 (28%) patients, moderate in 3803 (60%) and high in 763 (12%) patients. In the fully adjusted model using time dependent covariates, low attainment was associated with higher all-cause mortality (Table 2) and with higher risk of hospitalizations (HR = 1.20; 95% CI, 1.11 – 1.30), whereas high attainment was only associated with lower all-cause mortality (Table 2) and not with risk of hospitalization (HR = 1.09; 95% CI, 0.96 – 1.23).

**Conclusions:** Given the large proportion of patients with low attainment, we may argue that amelioration of guidelines application could improve patient outcomes.

---

### Table 1: Definition of clinical targets, clinical biochemical targets

<table>
<thead>
<tr>
<th>Targets</th>
<th>CKD-MBDs</th>
<th>Hyper tension</th>
<th>Anaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Serum phosphate level between 3.5 and 5.5 mg/dl</td>
<td>2 Asat PTH level between 350 and 600 pg/ml</td>
<td>3 Serum calcium level between 9.4 and 10.2 mg/dl</td>
<td>4 Mean of three blood pressure measurements &lt;140/90 mmHg (pre-HD) and &lt;130/80 mmHg (post-HD)</td>
</tr>
</tbody>
</table>

### Table 2: Association between quality of guidelines attainment and mortality during the study follow-up

<table>
<thead>
<tr>
<th>Target attainment</th>
<th>Baseline</th>
<th>Time-keeping covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low attainment</td>
<td>1.07 (0.94, 1.21)</td>
<td>1.18 (1.05, 1.34)</td>
</tr>
<tr>
<td>Moderate attainment</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>High attainment</td>
<td>0.84 (0.71, 0.99)</td>
<td>0.82 (0.68, 0.99)</td>
</tr>
</tbody>
</table>

**Funding:** Private Foundation Support
Relationship Between Vascular Access (VA) Performance Evaluated with a Triage System and Clinical Events in Haemodialysis (HD) 

Background: VA type and performance affect morbidity and mortality in HD. Routine does not allow standard monitoring of VA. We developed a system of VA triage to be implemented as routine practice and to be representative of average monthly performance. We evaluated the relationship between VA triage and clinical events

Methods: In any session of every patient, nurses report weights, BP, HR, Blood flows, VA pressures, symptoms, clots and, monthly, K/VI. Records generate a score that, according to thresholds, triages the VA as Green (G), Yellow (Y) or Red (R). We retrieved clinical events (admissions and deaths) of those patients whose VA had been triaged for >3 months in the period between 1/1/2014 and 12/31/2016. For each patient we considered the average triage during the whole available follow-up.

Results: We followed 131 patients (78 AVF and 52 CVC) for 21±11 months and recorded 18 deaths and 217 hospital admissions lasting 19±30 days. Prevalence of events was greater in CVC vs AVF patients (83% vs 78%, X²=4.6; p<0.05). For statistical purposes, given the unbalanced distribution of triage (70 G; 52 Y; 8 R), we merged the two pathologic classes (Y+R). The incidence rate of events was lower in the G group (1.9/1000 pt/years vs 4.0/1000 pt/years; p<0.001). We developed a system of VA triage to identify patients at increased risk of any clinical event independently of VA type. In patients with CVC VA triage also identifies cases at increased risk of mortality. Our triage is simple and reliable as a sensor of VA performance and labels patients at increased clinical risk.

<table>
<thead>
<tr>
<th>Patients. (n)</th>
<th>Events. (n)</th>
<th>Events incidence rate/1000 pt/years</th>
<th>Follow-up months</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triage Green</td>
<td>70</td>
<td>69±14</td>
<td>281±2</td>
<td>23±11</td>
</tr>
<tr>
<td>Triage Yellow</td>
<td>139</td>
<td>68±14</td>
<td>253±4</td>
<td>19±11</td>
</tr>
</tbody>
</table>

Table 1

Long-Term Competing Risk for ESKD and Death in a Large Austrian Cohort

Background: Knowledge of metabolic risk factors for end-stage kidney disease (ESKD) in the general population is limited, especially when considering the competing event death before ESKD in risk analysis. Aim of our study was to investigate competing risks for ESKD and death in a large general population-based cohort with long-term follow-up.

Methods: In this prospective, longitudinal observational study participants were recruited between 1988 and 2005 within a community-based health monitoring and prevention program (VH&M&PP) in the Austrian state of Vorarlberg. This cohort was linked to the Austrian Dialysis and Transplant Registry and the Vorarlberg Mortality Registry. Every adult above the age of 20 years was invited to participate in the program after providing written informed consent. 177,255 participants (53.8% women; mean age 42.5 (SD 15.8) years) were included. Body mass index, fasting blood glucose, systolic and diastolic blood pressure, total cholesterol, triglycerides and γ-glutamyltransferase (GGT) were determined as continuous and obesity, diabetes mellitus, hypertension, hypertriglyceridemia, hypercholesterolemia and GGT elevation as categorized variables.

We calculated the risk for ESKD and death applying cause-specific Cox proportional hazards models and subdistribution regression models.

Results: Over a mean follow-up of 16.0 years 358 participants reached ESKD (38% women) and 19,512 participants died. In the fully adjusted cause-specific risk models (HR, 95% confidence interval) diabetes mellitus (4.62, 3.54-6.03), hypertension (2.89, 2.22-3.77), hypertriglyceridemia (2.08, 1.32-3.28) and hypercholesterolemia (1.61, 1.29-2.00) were associated with a higher risk for ESKD than for death, whereas elevated GGT was associated with an increased all-cause mortality risk (1.49, 1.44-1.54). Subdistribution models supported cause-specific findings.

Conclusions: Components of the metabolic syndrome are associated with a higher risk for ESKD than for its competing event death in a large general population-based cohort of middle-aged adults, whereas elevated GGT levels indicate a higher risk for all-cause mortality. These findings might help improve the design of renal risk factor modification trials and kidney disease awareness and prevention programs in the general population.

Elevated Outdoor Temperatures Are Associated with Increased Mortality and Hospitalization Events among Hemodialysis Patients in Northeastern US Cities

Background: Few studies have focused on the effects of heat-related stress on populations living with chronic diseases, more specifically end-stage renal failure. In this work, we sought to examine the effects of weather conditions on mortality and hospitalization risks among hemodialysis patients treated at Fresenius Medical Care North America (FMC-NA) clinics in Boston MA, New York, NY, and Philadelphia, PA.

Methods: Time-stratified case-crossover analyses were applied to estimate short-term effects of weather on mortality and hospitalization using maximum air and heat index daily temperatures for each city. We considered same-day and one-day lag (before reported event) exposures on patients receiving treatment between 2001 and 2012. We accounted for varying rate denominators inherent with a dynamic cohort. Extreme heat was categorized with respect to upper percentiles of temperature and tested to determine risk.

Results: One-day lag heat wave events (above 97.5th percentile) exhibited statistically significant (p<0.05) associations with mortality across all three cities (Fig 1A). We estimated a 55- to 98-percent increase in the risk of death among patients within a day of a heat wave event. Same-day extreme heat exposures also had a significant effect on mortality rates in Boston and NYC (Fig 1B). On hospitalization, we found that increasing air temperatures had a positive, however modest, effect in all three cities. Extreme heat events demonstrated a null association with hospitalization events.

Conclusions: Heat effects on the mortality and hospitalization of hemodialysis patients varied among the three urban areas. However, extreme heat may have an effect on hemodialysis patients residing in Northeastern USA. The rate of hospitalization does not appear to be associated with extreme heat. Additional factors such as pre-existing comorbidities and prior infection need to be considered.

Funding: Commercial Support - Renal Research Institute

National Trends in Medicare Advantage Insurance Coverage for ESRD

Background: Nearly all ESRD patients are entitled to Medicare coverage, but they have been restricted to traditional fee-for-service (FFS) and barred from Medicare Advantage (MA) health plans, with the exception of beneficiaries who develop ESRD while already in MA. Outside ESRD, the MA program has grown dramatically over the last decade and now covers almost one in three Medicare beneficiaries. Beginning in 2021, the 21st Century Cures Act will allow ESRD patients to join any MA health plan. This study examines recent trends in MA and ESRD.

Methods: USRDS data were analyzed to identify Medicare beneficiaries who had developed ESRD from 1996-2015. MA enrollment at ESRD onset and at one year was obtained from the Medicare Enrollment Database. Multivariate logistic regression was used to identify predictors of MA at incidence (compared to FFS) and predictors of MA beneficiaries switching from MA to FFS.
**Results:** Out of 1,337,786 patients with Medicare coverage at ESRD onset, 19% were in MA (12% of age >65, 22% of age >65). A 2005 change to the Medical Evidence Form (CMS-2278) added MA as a prior insurance choice but since 2006 only 43% of MA enrollees were reported as MA. Patients in MA were more likely to be older, male, black, Hispanic/Latino, and have diabetes as cause of ESRD. At one year after ESRD onset, 28% of MA patients had died, similar to FFS. Among those still alive, 13% have switched to FFS (15% of age >65, 12% of age >65). Those more likely to switch to FFS were young, female, from racial/ethnic minorities and with diabetes as cause of ESRD.

**Conclusions:** Consistent with increasing use of MA in the general Medicare population, an increasing number of patients have MA at the onset of ESRD. Most patients in MA at ESRD onset who survive to one year remain in MA. Patients in MA differ from patients in FFS, and thus any comparisons will need to be risk-adjusted. Policy changes promote additional use of MA for the ESRD population; future research should examine the effect MA plans can have on access, quality, cost, and health outcomes.

**Funding:** NIDDK Support

---

### PUB325

**Demographics and Hospitalization Rates of Dialysis Patients Prescribed the Ten Most Common Drugs**

**Methods:** We analyzed data on all dialysis patients treated at Fresenius Kidney Care clinics as of December 2016, and located the ten most common drugs. We then characterized patient demographics by analyzing age, body mass index (BMI), vintage, gender, and hospital admission rate in each drug group and compared them to the whole patient population.

**Results:** We studied data from 170,560 dialysis patients. We found that the ten most commonly prescribed drugs were: sevelamer carbonate, aspirin, cinacalcet, calcium acetate, amiodipine, carvedilol, atorvastatin, hydralazine, gabapentin, and furosemide. Patients taking aspirin and atorvastatin were the oldest, with a median age of 66. Patients taking cinacalcet had the longest median vintage (4.8 years, compared to 3.1 in the whole population). Hospital admission rate was the lowest for patients taking carvedilol (2.68 per patient year [ppy]) and furosemide (2.96 ppy), and was the highest for those taking hydralazine (4.06 ppy).

**Conclusions:** Our results indicate that patients on certain medications may have increased hospitalization rates. This worsened morbidity is likely due to indication, yet appears useful for pinpointing patients that might require more attention. More analyses to identify a potential connection between medication utilization and outcomes are warranted.

**Funding:** Commercial Support - Fresenius Medical Care North America

---

### PUB326

**Changing Burden of Comorbidities Over Last 20 Years among Incident US Hemodialysis Patients and Rate of First-Year Mortality**

**Background:** Mortality among HD patients during their first year of renal replacement therapy remains very high, although there is a trend toward declining death rates in recent years. We sought to determine the potential impact of changing patient characteristics and comorbidity burden at initiation of HD on first-year mortality, over the last 20 years.

**Methods:** A total of 1,885,074 first-time incident HD patients between January 1996 and December 2015 were included and analyzed by year of HD initiation. Age, race, ethnicity, sex, and comorbidity conditions were taken from the Medical Evidence Form (MEF), collapsing diabetes and cardiac diagnoses into single variables to align data between the 1995 and 2005 MEF. Cox models, stratified by year, were run to determine the association between each comorbidity condition and mortality. The dot product of these model estimates and the means of each covariate by year were used to calculate the log hazard ratios associated with demographic and comorbid differences, versus the reference year 1996. Follow-up was censored at 1 year.

**Results:** Cardiovascular disease (CVD), stroke, cancer, diabetes (DM), lung disease, and peripheral vascular disease (PVD) showed little change in their impact on mortality over time. Compared to 1996, the aging of the HD population increased the first-year mortality risk 8%, which showed increased after 2002. Although the prevalence of hypertension (HTN) rose from 68% to 88% during this period, this increase was associated with lower log hazards of first year mortality over time (HR=0.67, p<0.0001), which drove the overall mortality trend downward.

**Conclusions:** Increasing age of incident HD patients was associated with an increased risk of first-year mortality, but risk associated with comorbid conditions decreased over time, especially for HTN. The overall risk of first-year mortality decreased from 2010 onwards, suggesting improving health status of incident HD patients over time, which may help explain decreasing first-year mortality rates over the past 2 decades.

**Funding:** NIDDK Support

---

### PUB327

**Sucroferric oxyhydroxide: A Novel Phosphate Binder Only or Something More?**

**Methods:** In this study HD patients with hyperphosphatemia were received PA21 for 10 months. The primary outcome was estimation of serum phosphate concentration at the end of treatment. Secondary outcomes were monitoring of hematocrit, serum calcium, albumin, cholesterol, triglycerides, intact-parathyroid hormone (iPTH) concentrations. Ferritin levels were monitored also. Adverse events were evaluated.

**Results:** 31 HD patients were enrolled with mean age 61. 35 patients (range: 35-87). 9 patients were naïve regarding phosphate medication, 18 were receiving sevelamer before and 4 lanthanum. All of the patients were taken 2-3 pills of PA21. 6 patients were withdrawn. We noticed significant reduction of the phosphate levels from the first month (from 6.3±4.1 to 3.5±1.1 mg/dl, p<0.05). This trend carried out until the end (4.9±0.9 mg/dl beginning vs 2.4±0.1 mg/dl, p<0.05). PTH levels significantly reduced (PTH at first 69±564 pg/ml, 6th month 433±409 pg/ml, p<0.05) which carried out until the end (383±115 pg/ml). Ferritin levels remained stable. 2 months since the beginning we noticed increase of Hct (35.9±37.4, p=0.097) until the end (37.4±7). Cholesterol levels tended to reduce (175±34 mg/dl beginning vs 160±15 mg/dl, at the end, p=0.213). Albumin and triglycerides levels remained stable. Calcium levels had also unremarkable differences.

**Funding:** Private Dialysis Unit "NEFROATRIKI", ATHENS, Greece; Nephrology, 417 Veterans Army Administration Hospital of Athens, Athens, Greece. Group/Team: Private Dialysis Unit "NEFROATRIKI"
Conclusions: In conclusion, sucralfate ooxhydroxyde is a valuable treatment option for the prevention of phlebitasia in CKD patients on dialysis, providing an effective and generally well tolerated non-aluminum based phosphate binder therapy and the potential for improved treatment adherence in MBD in general. Apart from that, it seems that it helps HD patients holistically since it favours stability of both hydration and nutrition improving lipid parameters at the same time.

PUB328

Association between Estimated Glomerular Filtration Rate Equations at Hemodialysis Initiation and Survival in Chinese ESRD Patients

YING LIU, nephrology, The First Affiliated Hospital of Dalian Medical University, Dalian, China. Group-Team: CHINA2DHE study.

Background: Accurate estimating glomerular filtration rate (GFR) is one of the important indicators in assessment of dialysis initiation. There are several commonly used GFR estimating equations, while no equation is considered superior for assessing the initiation of dialysis in Chinese end stage renal disease (ESRD) patients. This study aims to examine the association between estimated GFR (eGFR) at the time of hemodialysis initiation and survival using different estimating equations in Chinese ESRD patients.

Methods: 1997 patients with ESRD, commenced hemodialysis between 2008 and 2015 from 24 hemodialysis centers all around mainland China, were enrolled in the study. The eGFR at the initiation of hemodialysis were calculated by the Cockcroft and Gault (CG), the Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and the Chinese-MDRD (C-MDRD) equation. The cohort was respectively grouped by tertiles according to the eGFR calculated by four equations.

Results: The greatest agreement was between the GFR estimated by the CG and CKD-EPI equations with the difference of 0.6 ml/min/1.73m² (limits of agreement=1.1-2.2 ml/min/1.73m²), and the closest was between the MDRD and CKD-EPI equations, with the difference of 2.6 ml/min/1.73m² (limits of agreement=1.5-6.7 ml/min/1.73m²). The agreement between the GFR estimated by C-MDRD, MDRD and CKD-EPI equations was similar. After adjustment for age, sex, diabetes mellitus, signs and symptoms at the initiation and laboratory data, there were no significant difference in survival between eGFR tertiles calculated by CG, MDRD, CKD-EPI and C-MDRD.

Conclusions: There were differences between GFR estimated by C-MDRD and other three equations for the assessment of hemodialysis initiation. eGFR at the initiation of hemodialysis was not associated with patient survival no matter which estimating equation was used.

Funding: Government Support - Non-U.S.

PUB329

Analysis of Factors Regarding Life Prognosis at the Time of Dialysis Initiation among Late-Stage Elderly Patients Starting Hemodialysis

Tatsuomi Inoue, Ono Atsushi, Koji Tomori, Hirokazu Okada. Saitama Medical University, Iruma-gun, Saitama, Japan.

Background: The life prognosis of elderly patients after the initiation of dialysis is not always favorable. Predictive indicators for prognosis provide valuable information for patients and their families when making decisions regarding the initiation of dialysis. The purpose of this study was to investigate the factors regarding life prognosis at the time of dialysis initiation among late-stage elderly patients aged 75 or over starting hemodialysis.

Methods: A single center, retrospective, observational study was conducted. A total of 91 late-stage elderly patients (the mean age: 80.4±4.14 years; the mean observation duration of dialysis: 34.1±24.7 months) who received hemodialysis at our hospital during the period from April 1, 2011 to March 31, 2014 were included in the study. Examination items included age, sex, blood tests at the time of dialysis initiation, ADL at admission and discharge, family structure, as well as all the physical, social, and medical factors.

Results: During the follow-up, 31 patients died (causes of death by fatalities: sepsis, heart disorder, and cancer). With time to death being taken into consideration, a multivariate analysis was performed to identify factors of death using a Cox proportional-hazards model. The followings were found to be significant independent factors: ADL independence and nutritional status at the time of dialysis initiation and laboratory data, there were no significant difference in survival between eGFR tertiles calculated by CG, MDRD, CKD-EPI and C-MDRD.

Conclusions: There were differences between GFR estimated by C-MDRD and other three equations for the assessment of hemodialysis initiation. eGFR at the initiation of hemodialysis was not associated with patient survival no matter which estimating equation was used.

Funding: Government Support - Non-U.S.

PUB330

Efficacy and Safety of Ferric Citrate in Hemodialysis Patients: A 2-Year Retrospective Cohort Study

Kazanori Yamada,1 Mizuho Wada,2 Minoru Kaneko,3 Toru Shibata,4 Satoshi Hara,4 Ichiro Mizushima,5 Hiroshi Fujii,1 Remon Otake,2 Akira Junichiro,3 Masatsune Hasegawa,2 Mitsuhiro Kawano,3 Mikio Namiki,1 Toru Hasegawa.1 Division of Nephrology, Department of Internal Medicine, Kanazawa University Graduate School of Medicine, Kanazawa, Kanazawa, Japan; 2Division of Rheumatology, Kanazawa University Hospital, Kanazawa, Japan; 3Hasegawa Hospital, Toyama, Japan; 4Kanazawa Graduate School of Medicine, Kanazawa, Japan; 5Kanazawa University Graduate School of Medicine, Kanazawa, Japan.

Background: Long-term effects of ferric citrate (FC) in hemodialysis patients (pts) have not been studied. We evaluated the efficacy and safety of FC in hemodialysis pts.

Methods: We enrolled 132 Japanese hemodialysis pts who underwent HD between July 2014 and October 2016, categorized into two groups: FC group (FCG, n=30) and non-FC group (non-FCG, n=102). All FCG pts discontinued intravenous iron use after FC treatment. Baseline clinical data were obtained between July and September 2014. We retrospectively analyzed serum phosphorus (P), iron, ferritin, hemoglobin (Hb) levels, and the dose of erythropoietin stimulating agent (ESA), which was calculated as darbepoetin a. Bowel movement (BM) disorders were evaluated using Constipation Scoring System (CSS).

Results: Baseline demographics showed that FCG pts were significantly older (60.9 ± 2.7 vs. 60.0 ± 1.3, P = 0.029), had a higher serum P level (6.0 ± 0.3 vs. 5.4 ± 0.1, P = 0.015), and lower ferritin level (63.6 ± 14.6 vs. 113.1 ± 15.4, P=0.008) compared to non-FCG pts. After FC treatment, serum P level did not significantly differ. Serum ferritin level decreased significantly (14 wks): significantly higher in FCG than in non-FCG (104 wks; 158.7 ± 37.1 vs. 86.5 ± 11.8, P<0.001). Baseline Hb level in both groups was almost the same; however, Hb level in FCG became significantly higher than in the non-FCG between 24 and 72 wks, without a change in the non-FCG. The ESA dose in FCG was significantly lower than in the non-FCG after 24 wks (104 wks; 6.8 ± 1.2 vs. 19.7 ± 1.7, P<0.001), indicating that iron supplied by FC improved anemia, and led to dose reduction of ESA. CSS started to improve at 12 wks in FCG. CSS values at 48, and 104 wks in FCG were significantly lower than in the non-FCG (1.6 ± 0.5 vs. 4.4 ± 0.4, P<0.005, 2.4 ± 0.4 vs. 4.3 ± 0.4, P<0.039, respectively). The most frequent adverse event (AE) was loose stool (n=4). No severe AE was seen.

Conclusions: FC lowered P levels and improved anemia and constipation, indicating that pts with iron deficiency and BM disorder may additionally benefit with use of FC.

PUB331

Effects of a Progressive Inspiratory Muscle Training on Pulmonary Function in Hemodialysis Patients

Hsin-Yu Fang, Brett Burrows, Luis M. Perez, Ken Wilund. University of Illinois at Urbana-Champaign, Urbana, IL.

Background: Pulmonary abnormalities are prevalent in hemodialysis (HD) patients and the increased pulmonary capillary permeability associated with fluid overload may be one of the causative factors of impaired respiratory function. Inspiratory muscle training (IMT) helps improve respiratory function in other populations, but there are relatively few studies investigating its treatment effects in patients on HD. This pilot study aimed at assessing the efficacy of a progressive IMT intervention on pulmonary function in HD patients.

Methods: Nine HD patients were recruited from two outpatient clinics in central Illinois with spirometry assessments for pulmonary function at baseline and 8 weeks (immediately post intervention). During the 8-week IMT intervention period participants engaged in thrice weekly training sessions during dialysis by progressively increasing both the training duration and resistance of the IMT breathing device.

Results: All nine patients completed the 8-week intervention for a 100% compliance rate. Baseline patient characteristics were (mean±SD): age = 61±12, BMI = 35.8±12.9 kg/ m², 56% male, 56% AA; 56% smoker. No statistically significant difference was found in patient characteristics from baseline to 8-weeks. For pulmonary function, significant decreases were observed in forced expiratory volume in first second (FEV1, from 2.08 ± 0.506 to 2.01 ± 0.460; P = 0.005) and forced vital capacity (FVC, from 2.60 ± 0.762 to 2.36 ± 0.715; P = 0.005), while a significant increase in peak expiratory flow (PEF, from 3.11 ± 7.83 to 3.39 ± 6.77; p = 0.007) was also shown. The FEV1/FVC ratio increased significantly (from 0.813 ± 0.094 to 0.873 ± 0.085; p = 0.017) post training, which was attributed to a decreased FVC level as the denominator.

Conclusions: The present study showed no favorable effects of the 8-week progressive IMT intervention on several pulmonary function test parameters. Because fluid overload is associated with pulmonary malfunction in HD patients, whether IMT intervention is preferable to HD patients with better fluid control remains to be tested. Further studies are needed.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
**PUB332**

The Impact of Patient-Centered Pharmacist Care on Pharmacoeherence in Hemodialysis (HD) Patients: A Quasi-Experimental Study

**Background:** Pharmacoeherence is a public health problem in patients with chronic illness (WHO 2003). Non-Pharmacoeherence in HD patients varies from 12.5-98.6%, which leads to poor clinical outcomes. There is a paucity of data determining the influence of pharmacist on pharmacoeherence in our setting; therefore we aim to assess the impact of patient-centered pharmacist care to improve pharmacoeherence in HD patients.

**Methods:** The study was conducted at King Abdulaziz Medical City from Oct 2016 - Apr 2017. Ambulatory HD patients were included if age ≥18 years and on HD for at least 3 months and excluded if they have no mental capacity to participate. Primary outcome is change in pharmacoeherence assessed by medications' self-report vs. records and pre-dialysis serum phosphorus before and after intervention. Secondary outcomes include changes in systolic blood pressure (SBP), glycosylated hemoglobin (A1c), serum low-density lipoprotein (LDL) and prevalence of Medication-related problems (MRPs) pre and post intervention.

**Conclusion:** Patient-centered pharmacist care may improve pharmacoeherence in HD patients. Although it was not statistically significant, it’s crucial to identify and mitigate Medication-related problems.

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

**PUB333**

Assessing the Microeconomic and Psychosocial Impact of Dialysis for ESRD in Kerala, India

**Background:** A diagnosis of end-stage renal disease (ESRD) carries with it significant financial and psychosocial ramifications, especially in low and middle-income countries where it can have particularly devastating impact on the individual and their families. In the absence of universal insurance coverage, persons with ESRD often have to resort to extreme measures in order to fund their care, frequently without full understanding of their disease trajectory and prognosis.

**Methods:** We conducted a cross-sectional multi-site study of persons with ESRD on maintenance hemodialysis in Kerala. Using an interview-based questionnaire, we collected data on demographics, dialysis history, understanding of and engagement in treatment, and included information on financial and psychosocial burdens experienced by South Asians with chronic kidney diseases.

**Conclusion:** Patients with ESRD on chronic dialysis were more likely to have had reduced in-hospital mortality risk compared with non-ESRD patients. There was also a significantly reduced hospital charges ($49,815 vs $76,025, p<0.001) and a trend in shorter length of hospital stay (6.83 vs 6.95 days, p=0.054) in female patients.

**Funding:** NIDDK Support, Veterans Affairs Support, Private Foundation Support.
Evaluation of Cognitive Functions in Hemodialysis versus Peritoneal Dialysis Treatment Patients in CKD Aclan Ozder,1 Zeynep I. Yüksel salduz,2 Yelda Deligoz bildaci,1 Rumeyza Kazancioglu.1 ‘Bezmialem Vakif University, Istanbul, Turkey; ‘Bezmialem Vakif University, Istanbul, Turkey.

Background: Chronic kidney disease (CKD) is the disease characterized by the elevation of serum creatinine which had been described in five stages depending of the levels. Renal replacement therapy is required for the patients in last stage which can be done with kidney transplantation, hemodialysis (HD) or peritoneal dialysis (PD). Impaired cognitive function usually accompanies to worsening kidney functions. In this study our aim is to compare cognitive functions of patients which are on either HD or PD versus healthy control groups.

Methods: Our study group was patients who were on renal replacement therapy with either HD or PD in Bezmialem Vakif University Hospital and Haseki Hospital. Patients who did not know reading or writing, who had visial impairment were excluded. Totally 35 (HD:9, PD: 26) patients had Montreal Cognitive Asessement Test (MoCA) with their demographic properties noted as well as their etiology of CKD. Age and gender matched healthy control group also had MoCA test. We compared results renal replacement therapy group vs control group and the differences between dialysis modalities.

Results: Patients on renal replacement therapy showed a rate of mild cognitive impairment (MCI) as 28.57% compared to 8.57 % in control group (p<0.05). There is no difference found between HD versus PD in terms of MCI (p<0.05).

Conclusions: In our study we found that MCI is more often in patients on dialysis therapy compared to patients who are not. There is no differences of MCI scores in between dialysis modalities. We believe that with larger studies to come, our results will be backed up.

Outcomes in Patients with Chronic Renal Disease Undergoing Peritoneal Dialysis versus Hemodialysis Fernando R. Aguilar,2 Ammar Qureshi,3 Mark A. Nader,1 Nesreen Benhamed,5 None, Germantown, DC; ‘Internal Medicine, Marshall University Medical Center, Huntington, WV; ‘Internal Medicine, Marshall University, Huntington, WV.

Background: Renal transplant allows a higher life expectancy for patients with end-stage renal disease(ESRD). However, due to the dearth of renal transplant donors, patients with ESRD are treated with dialysis. The 2 most common modalities for dialysis are peritoneal and hemodialysis. Peritoneal dialysis is cheaper, but its use has declined. Some studies have shown that peritoneal dialysis has a higher adjusted mortality rate than hemodialysis and some have shown otherwise. The aim of this study was to compare the demographics and mortality rates between the patients receiving hemodialysis and peritoneal dialysis.

Methods: Data was extracted from the 2005-2012 nationwide sample (NIS) registries. Patients with a diagnosis of Chronic Kidney Disease and ESRD were included in this study. We compared the comorbidities such as diabetes mellitus and hypertension, all-cause mortality, the length of stay between the 2 groups. Pediatric population and those patients who received both hemodialysis and peritoneal dialysis were excluded. The population with chronic kidney disease was stratified based on their glomerular filtration rates and hence stages based on ICD 9 codes and compared the 2 groups.

Results: The NIS registry showed 2.85 million patients diagnosed with ESRD disease between 2005 and 2012. Out of this, 1.07 million received either hemodialysis or a peritoneal dialysis. Patients who were receiving a hemodialysis had a higher mortality rate (4.69%) as compared to those receiving peritoneal dialysis (4.69%) vs. 3.28%, p=0.0001; OR=1.45 (95% CI 1.37-1.54). Mean length of stay in patients receiving hemodialysis was significantly higher than those receiving peritoneal dialysis (7.85+/- 10.69 vs. 6.40+/- 6.89, p< 0.0001). More patients in the earlier stages of chronic kidney disease (CKD stages 1-4) received hemodialysis, while peritoneal dialysis was seen to administered more in those diagnosed with stages V and ESRD.

Conclusions: Our results clearly showed that the all crude mortality rate and length of stay were significantly higher in those patients receiving hemodialysis as compared to those receiving peritoneal dialysis. However, since it was also seen that patients with a later stage of chronic kidney disease were more likely to receive hemodialysis, it could explain the higher mortality associated with hemodialysis.

Effects of Dialysate Magnesium Concentration on Serum Magnesium Concentrations and Mortality: A Retrospective Cohort Study of the Monitoring Dialysis Outcomes Initiative Xiaoling Ye,1 Adrian M. Guinburg,2 Cristina Marelli,1 Bernard J. Canaud,1 Stefano Stuard,1 Xiaoxi Xu,1 Jeroen Kooman,4 Frank van der Sande,2 Albert J. Power,5 Len A. Usvyat,1 Yuqiong Wang,1 John T. Daugirdas,10 Peter Kotanko,7 Jochen G. Raimann.1 FMC Deutschland GmbH, Bad Homburg, Germany; Fresenius Medical Care, Moron, Argentina; Fresenius Medical Care Argentina, Buenos Aires, Argentina; Fresenius Medical Care Asia Pacific, Hong Kong, China; Fresenius Medical Care North America, Melrose, MA; Maastricht University Medical Centre, Maastricht, Netherlands; Renal Research Institute, New York, NY; Richard Bright Renal Unit, Bristol, United Kingdom; University of California - Santa Barbara, Santa Barbara, CA; University of Illinois College of Medicine, Burr Ridge, IL.

Background: Serum magnesium(SMg) is known to associate with mortality and lower levels, in particular, are associated with a risk of adverse outcomes (Lacson, AJKD 2015). We investigated the relationship between SMg and all-cause mortality in data from the global MONitoring Dialysis Outcomes Initiative.

Methods: For this analysis, we used data from hemodialysis patients between 2000 and 2012 from the international MONDO database initiative. Following the first available data point on SMg we established a 3 month baseline using averages of included parameters for subsequent analyses, and followed outcomes over one year of follow-up. Survival analyses were conducted after stratification of the entire population into tertiles (G1: <1.7, G2 1.7 to 2.7 and G3 >2.7 mEq/L). Kaplan Meier survival curves, Log Rank test and Cox regression analysis adjusted for age, gender, albumin, catheter and dialysis vintage, were employed for the survival analysis.

Results: We studied 20,362 patients (59.0±16.7 years, 58% males, 70% diabetics, 25% catheter. Uni- and multivariate survival analysis showed significant differences in all-cause mortality between the lowest tertile of serum magnesium and the two higher tertiles (Figure 1).

Conclusions: Low SMg associates with worse outcomes as compared to higher levels, even after adjustment for relevant parameters possibly confounding the relationship. Frequent magnesium measurements may be indicated and if levels are found to be low and oral or dialytic magnesium supplementation may be beneficial for some patients. Prospective studies investigating the effects of magnesium supplementation on outcomes are needed.

Difference in Mortality in Diabetic Patients Receiving Peritoneal versus Hemodialysis Fernando R. Aguilar,1 Ammar Qureshi,1 Mark A. Nader,2 Nesreen Benhamed,1 Georgetown University Hospital, Washington, DC; ‘None, Germantown, DC; ‘Internal Medicine, Marshall University, Huntington, WV; ‘in, MUSOM, Barboursville, WV.

Background: Diabetic patients (DM) often develop end-stage renal disease (ESRD) requiring renal replacement therapy in the form of hemodialysis (HD) or peritoneal dialysis (PD). Studies comparing the outcomes and difference in in-hospital mortality between these 2 groups are sparse. We set our objective to determine the dialysis modality with a better in-hospital survival rate among diabetics with ESRD (ESRD-DM).

Methods: Data was extracted from the 2005 to 2012 Nationwide Inpatient Sample (NIS). Using propensity score matching, ESRD-DM patients on PD were matched with patients on HD at a 1:1 ratio. Analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results: Among 586,238 patients with incident ESRD, 568,469(96.97%) and 17,769(3.03%) were initiated on HD and PD, respectively, during the hospitalization. HD-DM patients had a significantly higher in hospital mortality compared with PD, however after matching both groups, it appears PD- DM have a much higher mortality (3.0 % vs 2.52% p<0.0001).
Conclusions: Diabetic patients with ESRD who undergo PD have significantly higher in-hospital mortality, favoring HD as the modality of choice.

**PUB340**

**President Trump’s Executive Order 13769: A Nephrology Perspective**

Scott Reule,1,2 Mark E. Rosenberg,1 Paul E. Drawz,1 Arefe Ishani,1 Robert N. Foley,1 None, Minneapolis, MN; University of Minnesota, Minneapolis, MN; Medicine, Veterans Affairs Health Care System, Minneapolis, MN.

Background: With the recent signing of Executive Order (EO) 13769 restricting travel from 7 designated countries, we set out to describe associations between providers originally from the countries designated (EO providers) and clinical outcomes.

**Methods:** Physician data obtained from AMA Masterfile combined with USRDS and Medicare claims from 2010-2012 was used to determine associations between providers and their countries of origin, listing for, and receipt of kidney transplantation.

Results: A total of 8,025 providers cared for 361,454 patients on renal replacement therapy (RRT), with 7,364 patients receiving care from 174 EO providers compared to 346,451 patients receiving care from the remaining providers. Overall, EO providers were less likely to be female (12.5% vs. 25.5%) and more likely to practice in the Midwest (22.2% vs. 18.8%). EO providers delivered care in less densely populated areas, defined as the highest tertile of population density (32.2% vs. 36.3% for non-EO providers); >3,600.4 people/sq mi. and in populated areas with lower median household incomes ($44,126 vs. $49,443 for non-EO providers). Patients receiving care from EO providers were younger than 65 years of age (37% vs. 39.5%), more likely receive care = 12 months prior to initiation of renal replacement therapy (27.9% vs. 25.1%), and more likely to utilize peritoneal dialysis (8.9% vs. 7.9%) as a primary modality. At a mean follow up of 5.8 years, 31.4% of the cohort died. Overall, no significant differences in mortality (AHR 0.97; CI 0.87-1.08), listing for kidney transplantation (AHR 0.95; CI 0.88-1.02), or receipt of kidney transplantation (AHR 0.97; CI 0.84-1.11) were found.

Conclusions: EO providers are tasked with the care of patients in less populated, lower income areas with no impact on important clinical outcomes.

**Funding:** Clinical Revenue Support

**PUB341**

**Developing an Energy Budgeting Education Program to Improve Fatigue Self-Management in Adults on Chronic Dialysis**

Janine Farragher,1 Sarbjit V. Jassal,1,2 Sara McEwen,1,2 Helene Polatjko,1 1University Health Network, Toronto, ON, Canada; 2University of Toronto, Toronto, ON, Canada; 3Stonybrook Health Sciences Centre, Toronto, ON, Canada.

Background: Fatigue is one of the most common and disabling symptoms found among people with end-stage renal disease on long-term dialysis. Energy budgeting is a novel approach to fatigue self-management, that focuses on strategies such as planning, pacing, and prioritizing to promote optimal use of available energy during everyday tasks. The approach has demonstrated positive effects in other clinical populations, such as multiple sclerosis, but has not yet been tried in the dialysis patient population. The objective of this project is to develop an energy budgeting intervention, that limits the deleterious effects of fatigue on life participation for adults on dialysis with fatigue.

Methods: Energy budgeting principles were combined with an established approach to problem-solving (the Cognitive Orientation to Occupational Performance) to form the theoretical framework of the intervention. Learning principles were applied to make educational material concise, simple and easy to learn. Key informant feedback was sought after initial prototype development to guide further program revisions.

Results: The P.E.P. (Personal Energy Planning) program is a two-part fatigue self-management program for adults on dialysis. In Part 1, patients learn general concepts about fatigue and energy budgeting during two consecutive, self-administered web modules. In Part 2, patients apply the concepts with the guidance of a healthcare professional to create and test personalized energy plans that address their unique goals. The content and design of the program have been largely endorsed by key informants (2 CKD patients, a dialysis nurse coordinator, and a health education specialist), who provided several minor recommendations for further enhancement.

Conclusions: After key informant feedback is implemented, the PEP program will be ready to undergo efficacy testing to explore its effects on fatigue and life participation in adults on chronic dialysis.

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

**PUB342**

**Intra-abdominal Non-Communicating Pseudocyst in a Peritoneal Dialysis Patient**

Devan Makati,1 Sana R. Akbar.1 None, Morgantown, WV; 2West Virginia University, Morgantown, WV.

Background: Introduction: Intrapertoneal pseudocyst formation is a rare complication found in peritoneal dialysis (PD) patients. Thus far the cases reported involve the pseudocyst encasing the Tenckhoff catheter tip (1).

Methods: Case 66 yr old male with a past medical history of Diabetes, cerebral stroke and end stage renal disease on continuous ambulatory PD for 2 years was being treated with various antibiotics for pneumonia. On hospital day 8 due to patient’s abdominal pain CT abdomen pelvis was performed showing a 16.1 x 9.0 cm rim-enhancing loculated fluid collection in the right abdomen. Fluid analysis showed creatinine and urea matching fluid of peritoneal dialysis.

Conclusion: This is the first reported case of an intra-abdominal non-communicating pseudocyst in a PD patient. The finding of pseudocyst formation in our case suggests a rare complication that occurred in PD patients. In our case, the pseudocyst was encasing the catheter tip and the fluid was similar to dialysis fluid.

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

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

Underline represents presenting author.
Conclusions: Remote patient monitoring in APD patients allows early detection of disturbances in filling and drainage patterns during dialysis. An interesting finding is the correlation between the total time of therapy and the UF

PUB345

Difference in Consideration of Patient Eligibility for Peritoneal Dialysis between Nephrologists and Other Medical Staffs — Using a Conjoint Analysis  
Hisako Yoshida,1 Kazuhiko Tsuruya,1 1Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; 2Clinical Research Center, Saga University Hospital, Saga, Japan.

Background: In patients with incident end-stage renal disease, selection of renal replacement therapy (RRT) modality is affected by consideration of medical staffs. Very few studies have investigated the consideration of medical staffs regarding RRT modality selection. Thus, we conducted a web questionnaire to determine the factors for nephrologists (Neph) and other medical staffs (OMS) to elucidate their consideration of RRT modality, especially regarding eligibility for peritoneal dialysis (PD), using conjoint analysis (CA).

Methods: CA is a method for understanding the preferences for such as services over a set of multi-attribute alternatives (Clark MD, et al. NDT 2016). According to CA procedure, 21 simulation cases were created to quantify the relative importance of hypothetical patient attributes as the 6 categories: sex (male, female); age (40, 55, 70, 85 years old); primary diseases (diabetic nephropathy, chronic glomerulonephritis, polycystic kidney disease); abdominal condition (normal, post-surgery, hema, diverticulum); necessary for support (independent or dependent of family support); and self-care status (good, poor dietary control, or poor sanitary control). For each case vignette, the Neph and OMS who were working at the PD clinic of Kyushu University Hospital and its related facilities were asked to indicate whether they would recommend PD for their patients using a five-point scale. This research was performed using a web response system (https://questant.jp). Relative importance rates and partial utility scores were calculated via CA. We compared these values between Neph and OMS using Wilcoxon signed-rank test.

Results: A total of 98 respondents (42 Neph and 56 OMS) answered our web questionnaire. We calculated the relative importance which means the strength of influence for respondents’ evaluation, and the utility score means weight for decision making within each factor. In Neph compared to OMS, the relative importance was higher in “primary diseases” (p=0.002) and lower in “self-care status” (p=0.023). In “age”, the utility score of 85 years old was higher (p=0.023), while in “self-care”, good self-care was necessary for support (independent or dependent of family support); and self-care status between Neph and OMS.

Conclusions: The consideration of eligibility for PD was significantly different in age and self-care status between Neph and OMS.

PUB346

Effectiveness of Chlorhexidine, Mupirocin, and Conventional Exit-Site Care for the Prevention of Peritoneal Dialysis-Related Infections (COSMOS-PD): A Preliminary Result of a Randomized Trial surapon nochawieng,1,6 Chidchanok Rungern,1,6 Kajohnsak Noppakun,1 Kittirakriang Koryatikon,1,6 Chayuthaphong Chaisai,1,6 Ratanaporn -, Awiphan,1,6 Wiilaivan - , Chongrukst,1,8 Sirasak Nanta,1,6 1Chiangmai University, Chiangmai, Thailand; 2Academy Medical Center, 1100 DE Amsterdam, The Netherlands; 3University of Michigan, Ann Arbor, MI. Group/Team: On behalf of INTEGRATED Study Group.

Background: Topical antibacterials, antiseptics, and cleansing agents for exit-site care are the most common method to prevent peritoneal dialysis-related infections (PD-IRIs). However, no comparative study has been conducted to determine the potential effectiveness difference between different topical agents. In order to elucidate the potential differences in effectiveness, we conducted a randomized, double-blind, multicenter trial to study the effectiveness of three exit-site care agents: 2% CHG-impregnated patch, 2% mupirocin ointment, and conventional exit-site care. We compared these three agents with topical CHG-impregnated patch (CHG) in reducing the rate of PD-related infections among incident adult PD patients. Although CHG-impregnated patch has showed to be effective for the prevention of PD-related infections, we were interested in comparing with a conventional exit-site care, especially when the patients were recruited from tertiary PD centers in Thailand, from June 2016 (enrollment is ongoing).

Methods: In a randomized, double-blind, multicenter trial, we study the effectiveness of three exit-site care agents; 2% CHG-impregnated patch, 2% mupirocin ointment, and conventional exit-site care by normal saline solution among adult PD patients. Participants were recruited from three tertiary PD centers in Thailand, from June 2016 (enrollment is ongoing). The primary pre-specified outcome was a composite of PD-related peritonitis and exit-site infection (ESI). Secondary outcomes includes rates of catheter removal, adverse events, and all-cause mortality. The study has been registered as NCT02547103.

Results: Of 215 participants screened, 44, 43, and 43 were randomized to receive CHG, mupirocin, and conventional exit-site care, respectively. No difference of characteristics among groups were observed. With the numbers available, there was no differences of primary and secondary outcomes (all p>0.05) among the study groups, as well as safety profiles.

Conclusions: A preliminary result revealed that no statistically significance in effectiveness and safety of three exitsite care agents. However, results may change as the study reaches closure, longer follow-up is warranted.  
Funding: Government Support - Non-U.S.

Primary and Secondary Efficacy Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Conventional Exit-site Care</th>
<th>Mupirocin Ointment</th>
<th>CHG-impregnated Patch</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Event</td>
<td>HR (95% CI)</td>
<td>No. of Event</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Primary composite PD-related infection</td>
<td>9 Reference</td>
<td>11</td>
<td>1.01 (0.59 - 1.71)</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Peritonitis</td>
<td>7 Reference</td>
<td>1</td>
<td>0.69 (0.19 - 4.37)</td>
</tr>
<tr>
<td>- ESI</td>
<td>4 Reference</td>
<td>4</td>
<td>1.04 (0.28 - 3.93)</td>
</tr>
<tr>
<td>- Infection-associated catheter removal</td>
<td>1 Reference</td>
<td>1</td>
<td>0.69 (0.10 - 4.85)</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio; NA, not applicable

PUB347

Early Mortality in Patients Transferring from Peritoneal Dialysis to Facility Hemodialysis  
Amnie-Claire Nadeau-Fredette,1 Christopher T. Chan,2 Simon J. Davies,1 Kitty J. Jager,2 Mark Lambie,4 Jeffrey Perl,1 Ronald L. Pisoni,2 James A. Sloom,1 Nidhi Sukul,11 Wim Van Biesen,11 David W. Johnson.1 1Academic Medical Center, 1100 DE Amsterdam, Netherlands; 2Arbor Research Collaborative for Health, Ann Arbor, MI; 3Baxter Healthcare Corporation, Deerfield, IL; 4Ghent University, Ghent, Belgium; 5Hôpital Maisonneuve-Rosemont, Montreal, QC, Canada; 6Keele University, Crewe, United Kingdom; 7Princess Alexandra Hospital, Brisbane, QLD, Australia; 8St. Michael’s Hospital, Toronto, ON, Canada; 9Toronto General Hospital, Toronto, ON, Canada; 10University Hospital of North Midlands, Stoke-on-Trent, United Kingdom; 11University of Michigan, Ann Arbor, MI. Group/Team: On behalf of INTEGRATED Study Group.

Background: Transition of patients with end-stage kidney disease (ESKD) between peritoneal dialysis (PD) and hemodialysis (HD) is both common and associated with a heightened risk of adverse events. This study aimed to assess rates and predictors of early death after transfer from PD to facility HD.

Methods: All incident Australian and New Zealand ESKD patients initiated on PD between 2000 and 2014 and with a transition between PD and HD were included. Weekly crude mortality rates were calculated using a Poisson model for the first 26 weeks after the transition and predictors of early death (≤ 50 days after switch to HD) were assessed in an adjusted Cox proportional hazard model, censoring for transplantation, change of modality and end-of-life follow-up.

Results: The study included 5577 patients with a transition from PD to facility HD. Crude mortality rate was highest during the second week after transfer to HD (66 deaths per 100 patient-years, 95% CI 52-84) and stabilized 8 weeks after the switch (Figure 1). Predictors of early death after transition included older age (HR 1.25, 95% CI 1.18-1.32, per 5 years), diabetic kidney disease (HR 1.41, 95% CI 1.01-2.0 compared to glomerulonephritis), and longer dialysis duration (HR 1.16, 95% CI 1.00-1.24, per year). In contrast, male gender (HR 0.68, 95% CI 0.54-0.85), Asian race (HR 0.58, 95% CI 0.35-0.94 compared to Caucasian), and recent era (HR 0.63, 95% CI 0.43-0.91 for year 2010-2014 compared to 2000-2004) were associated with a lower risk of early death after transition.

Conclusions: The first weeks following transition from PD to HD are associated with a high death rate. Further studies should evaluate whether this vulnerability is mostly related to the reason behind PD completion or to the transition process, and target interventions to mitigate transition-associated risks.
Further investigation is warranted to confirm that overweight patients have more catheter-related problems. All efforts should be done in order to preserve renal function and avoid infection.

Methods: The abdomen is scrubbed and cleaned. The PD catheter distal to the exit site is meticulously cleaned, the titanium adaptor and transfer set removed, the former soaked in povidone-iodine. A guide wire is passed through catheter into the peritoneal cavity. After infiltrating skin over the previous healed incision scar with local anesthetic, a 5mm incision is made. The soft tissue is dissected until the deep cuff is visible. With blunt dissection, the cuff is gently separated from the subcutaneous tissue where it had become anchored. Taking care to retain guide wire’s position inside the peritoneum, the intra-peritoneal part of the PD catheter is removed. The external portion of the guide wire is advanced through the PD catheter till free from the catheter. The proximal end of the guide wire is thus in the peritoneum and distal end is free. Occluding clots, which may contribute to catheter malfunction, if present, are gently removed and the catheter flushed with saline. A dilator is advanced along the guide wire to ensure adequate space for the PD catheter at the linea alba and below. The peel-away sheath and dilator are then advanced into the peritoneum. The dilator and guide wire are removed leaving only the sheath in place. The catheter is then re-introduced into the peritoneum through the sheath, which is separated leaving the catheter in place. The peritoneal cavity is filled with PD fluid and good inflow and outflow are ensured. The subcutaneous tissue and skin are closed in layers.

Results: In the 18 patients with PD catheter malfunction in whom percutaneous repositioning was done, we had immediate success in 100% and a month later 12 catheters were functioning well. Six months later, they remained functional but one patient had died due to cardiac disease. In a significant proportion of cases, this novel procedure will help to obviate surgical repositioning, saving money, decreasing hospital stay and not necessitating personnel with surgical expertise. This promises to be exceptionally useful in resource-poor settings of South Asia.

Conclusions: Since peritonitis and membrane failure are the main causes for dropout from PD, all efforts should be done in order to preserve renal function and avoid infection. Further investigation is warranted to confirm that overweight patients have more catheter-related problems.

Case of Encapsulating Sclerosing Peritonitis in a Renal Transplant Recipient

Methods: We report a case of a 49-year-old male, former PD patient of 5 years, with history of HTN, on metoprolol, and a renal transplant recipient. Patient presented 1-2 years after renal transplantation with a month-long history of abdominal discomfort, nausea, and vomiting. CT imaging revealed a small bowel obstruction. Patient received conservative management with an improvement in symptoms and was discharged home. After one week, the patient presented again with similar symptoms. He was again found to have a high-grade small bowel obstruction. Despite the initial conservative treatment, for persistence of symptoms, he underwent surgical treatment. A biopsy then revealed EPS as the cause of his recurrent small bowel obstruction.

Results: Our patient received a diagnosis of EPS, a rare disease which caused him to have SBO. Our patient’s history of long term PD treatment was the main cause leading him to develop EPS. Another known contributor to EPS is the use of betablockers. While the specific mechanism remains unclear, one possible explanation is that betablockers have an inhibitory effect on surfactant release. The role of surfactant in the peritoneum may compare to that of surface-active phospholipids, which prevent intra-abdominal adhesions. Surgical treatment is the exclusive recommendation for patients with EPS. This patient population has a relatively poor prognosis with a mortality rate of 25-55%.
PUB352
Scope and Heterogeneity of Outcomes Reported in Randomized Trials in Patients Receiving Peritoneal Dialysis
Carine E. Manera, Allison Tong, Jonathan C. Craig, Roberto Pecois-Filho, Benedicte Sautenet, David W. Johnson, Pontificia Universidade Catolica do Parana, Curitiba, Brazil; Princess Alexandra Hospital, Brisbane, QLD, Australia; The University of Sydney, Westmead, NSW, Australia; University of Sydney/Children’s Hospital, Sydney, NSW, Australia; Centre for Kidney Research, The Children’s Hospital at Westmead, Westmead, NSW, Australia; Department of Nephrology and Clinical Immunology, University Francois Rabelais, Tours, France. Group/Team: On behalf of SONG-PD Steering Group.

Background: Randomized trials can provide evidence to inform decision-making for improved care and outcomes but this may be limited if the chosen outcomes are not relevant to patients and clinicians, and are reported inconsistently.

Methods: Medline, Embase, the Cochrane Kidney and Transplant Specialized Register and clinicaltrials.gov were searched for RCTs involving adults receiving PD published from 2011 to 2016. All outcome domains and measurements were extracted. The frequency and characteristics of the reported outcome domains and measures were analyzed.

Results: From 85 included trials, 1346 different measurements of 60 different outcome domains were reported, with a median of 5 per trial (interquartile range 3 to 10). Overall, 27 (45%) domains were surrogate, 23 (38%) clinical and 10 (17%) patient-reported. The six most commonly reported domains were PD-related infection (37 [44%]), mortality (32 [38%]), renal function (31 [36%]), dialysis solute clearance (26 [31%]), protein metabolism (25 [29%]) and technique failure (25 [29%]). Quality of life (14%) and fatigue (4%) were reported infrequently. The most frequently reported clinical outcome, PD-related infection, had 69 different outcome measures, with only 11 of these being used in more than one trial.

Conclusions: Trials in PD include important clinical outcomes such as mortality and infection, but these are measured and reported inconsistently, and patient-reported outcomes are infrequently reported. Nearly half of the outcome domains were surrogate or biochemical outcomes.

PUB353
Association between Lipid Profile and Residual Renal Function in Incident Peritoneal Dialysis Patients
Yu Honda, Yukio Maruyama, Masatsugu Nakao, Nanae Matsuo, Yudo Tanno, Takashi Yokoo, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan.

Background: Preserving residual renal function (RRF) is known to be related to mortality in peritoneal dialysis (PD) patients. It has been reported that lipid profile is associated with the incidence and progression of chronic kidney disease, whereas it is not clear whether lipid profile is associated with the decline of RRF in incident PD patients. The aim of this study was to evaluate the association between lipid profile and RRF in incident PD patients.

Methods: This was a retrospective cohort study of 78 patients (58±14 years, male 68%, diabetes 41%) initiating PD between 2006 and 2015 in the three centers. We analyzed the relationship between lipid profile and the alteration of RRF, expressed as renal Kt/V, during 1 year.

Results: The change in renal Kt/V during 1 year was inversely correlated with high-density lipoprotein cholesterol (HDL-C) at PD initiation (rho=−0.28, P<0.05) and positively with the change in HLC-C (rho=0.24, P<0.05) during 1 year. On the other hand, there was no significant correlation between the change in renal Kt/V during 1 year and light-density lipoprotein cholesterol.

Conclusions: Our results demonstrated the association between HDL-C and deterioration of RRF in incident PD patients. Further study is needed to clarify the effect of medication for dyslipidemia on preserving RRF in PD patients.

PUB354
Long-Term PD Patients in Greece: Are There Any Special Characteristics?
Emilios Andrikos, Paraskevi Tseke, Olga Bulafa, George I. Tsirpanlis, Christina Melexopoulou, Vasileios Liakopoulos, Christos Katinas, Chryssostomos Dimitriadis, Marios Theodoridis, Ploumis Passadakis, Nephrology, University Hospital of Ioannina, Ioannina, Greece; Hatzikosta, General Hospital, Ioannina, Greece; MESOGIOI Dialysis Center, ATHENS, Greece; Nephrology, G.Geniaturas, General Hospital Of Athens, Athens, Greece; Nephrology, Bodosakio, General Hospital, Potelemaidia, Greece; Nephrology, Laiko, General Hospital, Athens, Greece; Nephrology, Ippokrateio, General Hospital, Thesaloniki, Greece; Nephrology, University Hospital of Alexandroupolis, Alexandroupolis, Greece; Nephrology, University Hospital of Alexandroupolis, Alexandroupoli, Greece; Nephrology, AXEPA, General Hospital, Thessaloniki, Greece.

Background: The Hellenic Peritoneal Dialysis (PD) Registry started setting up at the beginning of 2017 in order to evaluate the special characteristics of PD patients (pts) in Greece and to enhance the practical experience of PD physicians and nurses.

Methods: A group of nephrologists with great experience in PD in co-operation with biostatisticians designed a database to record all prevalent PD pts in Greece. All PD physicians were informed for the development of the registry and asked to participate.

Results: Until today, 182 prevalent PD patients from 7 centers have been recorded, 39 of whom are on PD for more than 5 years. Long-term PD survivors (23 male and 16 female) have a median time on PD of 72 months (range from 60-145) and their mean age at start of dialysis was 54.5±15.9. The majority of pts was married (76.3%) and was followed by nephrologists prior to PD initiation (half of them for almost 4.5 years). The educational level was low to basic for 57% of these pts and 1 out of 3 of them lived in islands and rural areas. Training on PD was performed by institutional PD nurses or properly educated employees of PD companies. The latter was significantly associated with longer PD training period (mean training time was 11.5 vs 6.4 days, p=0.004) and shorter time on PD (median time on PD was 60 vs 74 months, p<0.05). Initial PD regimen which was CAPD in 75% and APD in 25% did not significantly affect the total time on PD. However, the odds for peritonitis was significantly reduced in those on APD (OR: 0.12, p=0.023). Noteworthy, 37.5% of the total pts had none or 1 episode of peritonitis in a median time of 67 months and overall peritonitis rate was 3.5 episodes per pt-year. 39.5% of these pts are candidates for kidney transplantation, which is strongly associated with the age at the start of PD treatment (p=0.006) and Charlson’s Co-morbidity Index (p<0.008).

Conclusions: As this is the first report of an ongoing study limitations may exist as further findings are expected to fully explore the PD map in Greece.

PUB355
Surgical Outcomes of Tenckhoff Catheter Insertion in a Tertiary Center
Gerard Low, Jia rui Kwan, Gabriel W. Low, Tze tcc Chong, Nanyang Technological University, Singapore, Singapore; National University of Singapore, Singapore, Singapore; Singapore General Hospital, Singapore, Singapore.

Background: Peritoneal Dialysis is a cost-effective form of renal replacement therapy. The initiation of PD requires the insertion of a Tenckhoff catheter and this is most commonly performed by a surgeon in our center. We aim to report the surgical outcomes of Tenckhoff catheter insertion in our center and factors affecting outcomes.
Icodextrin as an Alternative to Glucose to Evaluate Peritoneal Membrane Transport Pattern

Methods: Tenckhoff catheter insertion was successful in all patients with no mortality attributable to surgical mishap. Early complications within 30 days of Tenckhoff insertion include bleeding (3/470 with no requiring operative hemostasis), leak (3/470 with none requiring operation), flow-related issues requiring re-operation (20/470; migration 3.0%, obstruction 0.8%, poor flow 0.4%) and infection (22/470; PD peritonitis 3.2%; Exit-site infection 3.0%; Tunnel tract infection 0.2%; Incision site infection 0.2%). Early complications were not related to the method of catheter insertion, peritoneal characteristics or BMI on multivariate analysis.

Conclusions: Tenckhoff catheter can be successfully inserted in majority of patients. Flow-related complications are the most common indication for re-intervention within 30 days. Further studies of composite endpoints are required to improve Tenckhoff insertion outcomes.

RESULTS:

Significantly higher incidence and prevalence of PD in KPNC was achieved compared to the local community. Multiple factors are likely contributing, including socio-economic, demographic, patient composition and changes in healthcare landscape. We evaluate strategies to sustain growth of our home dialysis population by continuous provider education, ongoing evaluation of operational needs of local medical centers and use of technology to support patient education and engagement.

Conclusions: In a fully integrated health care system, despite continuous organizational efforts to increase PD incidence and prevalence, we observe slowing down of growth in some medical centers. Multiple factors are likely contributing, including socio-economic, demographic, patient composition and changes in healthcare landscape. We evaluate strategies to sustain growth of our home dialysis population by continuous provider education, ongoing evaluation of operational needs of local medical centers and use of technology to support patient education and engagement.

Organizational Performance Improvements in a Successful PD Program

Methods: A 44-year-old female patient started CAPD in August 1994. She used predominantly small solute dextrose dialysate (d/LA) 4.25% glucose solution until one bag of icodextrin per day was started in December 2006. A second was started in December 2009. She had an early cluster of peritoneal complications. Between 31/470 with no requiring operative hemostasis, leak (3/470 with none requiring operation), flow-related issues requiring re-operation (20/470; migration 3.0%, obstruction 0.8%, poor flow 0.4%) and infection (22/470; PD peritonitis 3.2%; Exit-site infection 3.0%; Tunnel tract infection 0.2%; Incision site infection 0.2%). Early complications were not related to the method of catheter insertion, peritoneal characteristics or BMI on multivariate analysis.

Conclusions: Tenckhoff catheter can be successfully inserted in majority of patients. Flow-related complications are the most common indication for re-intervention within 30 days. Further studies of composite endpoints are required to improve Tenckhoff insertion outcomes.

RESULTS:

Significantly higher incidence and prevalence of PD in KPNC was achieved compared to the local community. Multiple factors are likely contributing, including socio-economic, demographic, patient composition and changes in healthcare landscape. We evaluate strategies to sustain growth of our home dialysis population by continuous provider education, ongoing evaluation of operational needs of local medical centers and use of technology to support patient education and engagement.

Conclusions: In a fully integrated health care system, despite continuous organizational efforts to increase PD incidence and prevalence, we observe slowing down of growth in some medical centers. Multiple factors are likely contributing, including socio-economic, demographic, patient composition and changes in healthcare landscape. We evaluate strategies to sustain growth of our home dialysis population by continuous provider education, ongoing evaluation of operational needs of local medical centers and use of technology to support patient education and engagement.

Evolution of Small Solute Transport in a Patient Treated for 18 Years with CAPD Restricting Hyperosmolar Glucose

Methods: A 44-year-old female patient started CAPD in August 1994. She used predominantly small solute dextrose dialysate (d/LA) 4.25% glucose solution until one bag of icodextrin per day was started in December 2006. A second was started in December 2009. She had an early cluster of peritoneal complications. Between 31/470 with no requiring operative hemostasis, leak (3/470 with none requiring operation), flow-related issues requiring re-operation (20/470; migration 3.0%, obstruction 0.8%, poor flow 0.4%) and infection (22/470; PD peritonitis 3.2%; Exit-site infection 3.0%; Tunnel tract infection 0.2%; Incision site infection 0.2%). Early complications were not related to the method of catheter insertion, peritoneal characteristics or BMI on multivariate analysis.

Conclusions: Tenckhoff catheter can be successfully inserted in majority of patients. Flow-related complications are the most common indication for re-intervention within 30 days. Further studies of composite endpoints are required to improve Tenckhoff insertion outcomes.

RESULTS:

Significantly higher incidence and prevalence of PD in KPNC was achieved compared to the local community. Multiple factors are likely contributing, including socio-economic, demographic, patient composition and changes in healthcare landscape. We evaluate strategies to sustain growth of our home dialysis population by continuous provider education, ongoing evaluation of operational needs of local medical centers and use of technology to support patient education and engagement.

Conclusions: In a fully integrated health care system, despite continuous organizational efforts to increase PD incidence and prevalence, we observe slowing down of growth in some medical centers. Multiple factors are likely contributing, including socio-economic, demographic, patient composition and changes in healthcare landscape. We evaluate strategies to sustain growth of our home dialysis population by continuous provider education, ongoing evaluation of operational needs of local medical centers and use of technology to support patient education and engagement.
dwell times of 4 and 0 hours as an index of SST. The D4/D0 ratio actually increased (SST decreased) until 2004; it then slowly decreased, and was ~25 in March 2012, its initial value. There had been a gradual decrease of the effluent volume for both the 1.36% glucose and icodextrin bags since 2010.

Conclusions: This particular case suggests that persistently avoiding exposure to hypertonic glucose may prevent for up to 10 years the increase in SST linked to vascular proliferation.

PUB360
Evaluation of the Nutritional Status in Peritoneal Dialysis Patients: Interactions with Mental Psychological State and Appetite

Valerio Vizzardi, Scilla Maghella, Massimo Sandrini. 1 ASSFT-Spedali Civili, Brescia, Italy; 2University of Brescia, Brescia, Italy.

Background: Malnutrition (MN) is a risk factor in peritoneal dialysis (PD) patients and it’s correlated with a major risk of morbidity, mortality and a worsening of quality of life.

Methods: 41 prevalent PD patients were included. The aim was to evaluate nutritional status (NS) testing Malnutrition Inflammation Score (MIS) and correlated it with appetite and mental psychological state (MPS); appetite was assessed by the Council Nutritional Assessment Questionnaire (CNAQ), NS was assessed by the Mental Component Scale.

Results: The percentage of malnourished depended on the method used for the evaluation both at T0 and T1, MIS was negatively correlated with nephelometric albumin and cholesterol at T0 (p<0.001, p=0.01) and T1 (p=0.001, p=0.05) and with triglyceride at T0 (p<0.05). MIS was positively correlated with C-Reactive Protein (CRP) at T1 (p<0.05).

Conclusions: This study demonstrates that MIS can be used to evaluate the NS of PD patients which resulted influenced by inflammation, appetite and MPS. The latter influenced also the appetite.

PUB361
The Effect of Core Fucosylation on Rat Peritoneal Fibrosis

Longkai Li. First affiliated hospital of Dalian Medical University, China, Dalian, China.

Background: To investigate the effect of core fucosylation (CF) on rat peritoneal fibrosis.

Methods: SD rats were divided into control, peritoneal fibrosis, Ad-Fut8shRNA, Ad-con and imatinib (PDGFR inhibitor) group. We used peritoneal fibrosis rat model induced by peritoneal dialysate. Fut8shRNA recombinant adenovirus was used to inhibit CF. We detected pathologic lesion, observed Collagen I and III, and examined TGFβ and PDGF signaling. We also compared the difference between inhibition of CF and imatinib.

Results: There is increased CF expression in rats with peritoneal fibrosis. After inhibition of CF, pathological lesion and functional changes in Fut8shRNA group were alleviated, compared with peritoneal fibrosis and Ad-con group. Collagen I and III in Fut8shRNA group were also alleviated. In TGFβ signaling, TGFβ receptor I and II and Smad were all increased, p-Smad was significantly decreased in the Fut8shRNA group. In PDGF signaling, PDGF receptor and p-ERK were all increased, p-ERK was significantly decreased in Fut8shRNA group. Compared with imatinib group, pathological and functional changes, and Collagen I and III were all alleviated in Fut8shRNA group.

Conclusions: Blockage of CF inhibited PF, its effect is better than imatinib.

PUB362
Physical Activity in Patients Treated with Peritoneal Dialysis: A Systematic Review

Tharshika Thangarasa, 1 Rameez Imtiaz, 3 Swapanl Hiremath, 1 Deborah Lynn Zimmerman, 2 Ottawa Hospital Research Institute, Ottawa, ON, Canada; 2Medicine, Ottawa Hospital, Ottawa, ON, Canada; 3University of Ottawa, Ottawa, ON, Canada.

Background: End-stage kidney disease (ESKD) treated with peritoneal dialysis (PD) are less active than sedentary individuals in the general population. The actual effects of physical activity with or without structured exercise programs for these patients remain unclear. Our objective was to more completely define the risks and benefits of physical activity in the ESKD population treated with PD.

Methods: With the help of a skilled librarian, a search was conducted using MEDLINE, EMBASE, CINAHL and Cochrane Central Register of Controlled Trials for randomized trials and observational studies to identify research articles examining the effects of physical activity on ESKD patients treated with PD. The primary outcomes of interest were improvements in mental health, physical function, fatigue, quality of life (QOL) and adverse events. Studies reporting adult end-stage kidney disease patients

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
treated with peritoneal dialysis that have participated in an exercise training program or had their level of physical activity assessed directly or by self-report were included.

**Results:** A total of 1828 manuscripts were identified; 13 were found to fit the inclusion criteria. Eight of the studies were observational (6 used an accelerometer/ pedometer, 1 used self-reported measures of physical activity and 1 used occupation type as a measure of physical activity), the remaining studies were interventional. Most of the interventional studies assessed aerobic exercise programs. There was evidence from 3 studies to suggest that physical activity resulted in increased levels of physical functioning. I study suggested an increased quality of life, and 1 study provided evidence for decreased mortality rates. Biochemical markers improved in majority of studies in which they were measured. However in 1 study, physical activity did not affect fatigue or physical performance.

**Conclusions:** There is limited evidence to suggest that physical activity in PD patients is associated with important benefits. Most of the studies is small and have important methodological limitations. There is a need for future randomized control trials examining the impact of exercise programs (both aerobic and resistance) in PD patients.

**Funding:** Clinical Revenue Support

**PUB363**

**Peritonitis in Mexico: Comparison of CAPD and APD Population Ruben G. Roldan, Instituto Nacional de Cardiología Ignacio Chávez, Mexico city, Mexico.

**Background:** Peritonitis is the major cause of morbidity and mortality in patients on PD. PD infection is associated with peritoneal membrane damage and technique failure. Following a single episode of peritonitis, the risk of further peritonitis episodes, haemodialysis transfer and death are greatly increased and remain significantly elevated for up to 6 months.

**Methods:** In this retrospective study we aimed to evaluate patients with peritonitis episode between October 2014 to December 2016 catered in the “National Institute of Cardiology Ignacio Chávez” in Mexico city under continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD). Using electronic database we found 71 patients with peritonitis. Clinical and biochemical data were evaluated.

**Results:** 36 (50.7%) patients were female sex with a median age of 50 years, 54 (76.1%) on CAPD and 17 (23.9%) on APD. The principal etiology of CKD were diabetic nephropathy in 34 (45.1%), 17 (23.9%) with chronic kidney disease of unknown origin and 6 (8.5%) with focal segmental glomerulosclerosis. 28 patients (39.4%) with no history of peritonitis and the principals comorbidities were chronic hypertension (47.9%), isquemic heart disease (16.9%) and chronic heart failure (8.5%). The principal organisms identified on cultures were S aureus in 23 (32.4%) of patients, E coli in 7 (9.9%), S marcescens in 5 (7%), S epidermidis with 5 (7%) cases and Candida in 5 patients (7%).

**Conclusions:** The results demonstrate a less commonly cases of peritonitis in the APD population, with the highest number of cases caused by S. aureus (39.4%). From the patients with mechanical dysfunction (10) only 1 correspond to the APD population, and from the deads recorded (5) only 1 was part of the APD modality. We emphasize the results above-mentioned, were the level of albumin and BUN demonstrated a statistical significance. Possible related to a properly nourished population, whom presented the less mortality and better outcome, in relation to a close follow up in the course of the treatment.

**PUB365**

**A Prospective Observational Study on Prevalence of Hepatitis C Virus Infection and Its Risk Factors in CKD Patients on Hemodialysis at Faridabad, Delhi NCR, India Harisharan R. Munganda, Jitenendra Kumar, Punit Pruthi. Asian institute of medical sciences, Faridabad, Haryana, India; internal medicine, Asian Institute of Medical Sciences, Faridabad, India.

**Background:** Chronic renal disease patients on haemodialysis are at increased risk of infection by hepatitis C virus (HCV). Subjects undergoing treatment in dialysis centres without nephrologists and improper viral marker screening, dialysis at more than one centre and no separate dialysis machine for HCV positive patients, unscreened blood transfusion are at risk of cross contamination. Thus, there is a need to screen these subjects for prevalence of HCV seropositivity and study the impact of HCV positivity on clinical course of the disease.

**Methods:** Aim of our study was to assess prevalence of HCV positivity in CKD on hemodialysis subjects. Also to assess various characteristics of HCV positive subjects compare them with HCV negative CKD subjects. **Methodology:** In our Asian tertiary care hospital dialysis unit a total of 100 CKD subjects were recruited for the study and after informed written consent, further detailed history, socioeconomic and clinical parameters including dialysis related parameters were analysed and compared between the Hepatitis C seropositive and Seronegative subjects. Hepatitis C positivity was assessed using chemoluminescence.

**Results:** Prevalence of seropositivity was found to be 16% in CKD subjects. Only 2% of the subjects have turned HCV positive from contaminated blood transfusion and dialysis at multiple centres while 14% have acquired HCV infection from same dialysis centre and by usage of same dialysis machine.

**Conclusions:** High prevalence of HCV infection exists in CKD subjects. Though CDC doesn’t recommend HCV patient isolation/segregation, we in our study strictly recommend use of separate dialyzer for HCV positive patients under expert nephrologists supervision to contain the HCV infection. **References:** 1) CDC may call for HCV screening in hemodialysis, But not likely to recommend patient isolation, Suzanne Cotter, MD, medical epidemiologist in the CDC; https://www.aemedia.com/articles/44946-cdc-may-call-for-hcv-screening-in-hemodialysis 2) Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. Centers for Disease Control and Prevention. MMWR Recomm Rep. 1998 Oct 16

**PUB366**

**Tracheostomy Dependent Long Term Dialysis Patients Jack Rubin, Jacqueline Bogo, None, Long Beach, CA; *none, Los Alamitos, CA.**

**Background:** Since April 2014 we have been treating tracheostomy dependent patients at our dialysis unit (ventilator and former continous ventilator). We wish to report our experiences of our experiment.

**Methods:** Data were retrieved from the dialysis charts. The data from the last available chart entry are presented. All data are presented as mean ± sd unless stated otherwise. Differences between groups were evaluated by 2 tailed t test with Bonferroni correction for multiple comparisons.

**Results:** There were 35 pts (18F/20M) Their mean age was 68 ± 14 years with a mean time on dialysis at our unit of 171 ± 219 days (median 92). These pts were on dialysis prior to coming to us. They had suffered a medical catastrophe or transferred from a long term acute facility after developing renal failure that did not resolve. KTV 1.4 ± 0.3, hgb 9 ± 0.8, albumin 3.1 ± 0.6, glicemia 9.3 ± 0.9 mg/dL and phosphorus 4.3 ± 2.2 mg/dL. Ten (9F, 1M) (A) are on dialysis 185 ± 300 (median 185) days and 28 have deceased (D) after 112 ± 148 days (median 50). By 2 tailed t test creatinine mg% (A 6.7 ± 1.1; D 4.8 ± 1.4) was significantly lower in those who died (p<0.007). Cholesterol mg% (A 128 ± 50; D 88 ± 31 P<0.009) and albumin g% (A 3.3 ± 0.6; D 2.9 ± 0.5) P<0.05 almost reached significance (negative after Bonferroni correction). KTV (A 1.6 ± 0.3; D 1.4 ± 0.3), bun mg% (A 88 ± 39; D 100 ± 34), hemoglobin g% (A 9.9 ± 1.1; D 8.9 ± 1.2), prealbumin mg% (A 20 ± 8; D 16 ± 9), calcium mg% (A 9.5 ± 1.1; D 9.4 ± 0.8), phosphorus mg% (A 4.6 ± 1.5; D 4.4 ± 2.4) and hgb A1c % (A 5.8 ± 1.1; D 6.1 ± 0.9) were not significantly different.

**Conclusions:** The laboratory differences observed between Alive and Deceased pts may reflect diminished muscle mass (lower creatinine) and malnutrition (lower albumin and cholesterol) as heralds of clinical deterioration prior to death. Upon taking on treatment of this group of pts one must expect a lower star rating as most require catheters and are frequently admitted for infection, bedsores or pulmonary complications. The logistics of transporting patients and ensuring ambulance traffic can be challenging. Funding may be a problem for ambulance service companies. To sustain these selected pts requires a dedicated staff of nurses, respiratory technicians and ambulance services.
Reporting Feasibility of the Use of a Real-Time Data Reporting Tool to Improve Outcomes of Haemodialysis Catheter Complications across Australia (REDUCTION) Sradha S. Kotwal,1,2 Girish S. Talaulikar,3 Nicholas A. Gray,3 Kevan Polkinghorne,3 Stephen P. McDonald,3 Alan Cass,3 Martin P. Gallagher,4,5 ANZDATA Registry, Adelaide, SA, Australia; 3Monash School of Health Research, Darwin, NSW, Australia; 4Monash Medical Centre and Monash University, Melbourne, VIC, Australia; 5None, Sydney, NSW, Australia; 6SUNSHINE COAST University Hospital, Birtinya, NSW, Australia; 7Renal and Metabolic, The George Institute of Global Health, Sydney, NSW, Australia; 3Prince of Wales Clinical School, UNSW, Sydney, NSW, Australia.

Background: Patients with kidney disease are susceptible to healthcare associated infections, especially in association with dialysis catheter use. These catheters are a major driver of blood stream infection and the higher mortality in dialysis patients. Dialysis catheter care in Australia is managed by individual renal units, without real-time reporting and limited national benchmarking. Tools to analyse clinical variation and mount an effective timely response are lacking. Data on the total extent of catheter use and outcomes is limited.

Methods: This project has developed standardised definitions around dialysis catheter usage and complications, validated for accuracy by a central committee. Development of a custom-designed data collection tool used by clinical staff has enabled real-time data collection. The data collection tool was designed and developed using an iterative consultative process with participating renal units. Regular feedback meetings have been conducted since the launch of the data collection tool with changes/updates made using the feedback.

Results: The first phase of this study has involved the design, implementation and uptake of the data collection tool. Of the 36 units involved in the study, 28 are currently entering data. We have data on 696 participants, 427 active catheters with 41033 total catheter days. We expect data on approximately 9000 participants by the end of the study.

Conclusions: Early involvement of renal units, with regular feedback sessions, is invaluable when pursuing an implementation project at this scale. Meaningful representation with effective engagement from each state is essential to implement change nationally.

PUB368

Hepatitis C Virus Outbreak in a Primary Hospital: Infection Investigation and Treatment Follow-Up Hua Liu,1 Jinhong Xue,1 Hongli Jiang,1 1Dialysis Center of First Affiliated Hospital of Medicine School, Xi’an Jiaotong University, Xi’an, Shaanxi, China; 2First Affiliated Hospital of Medical College of Xi’an Jiaotong University, Xi’an, China.

Background: To investigate the status of hepatitis C virus (HCV) infection, related factors and treatment follow-up in MHD patients in a primary hospital.

Methods: We investigated the prevalence of hepatitis C virus infection in 47 patients with positive anti-HCV antibody. The epidemiological investigation, infection risk factors were analyzed, and treatment response and tolerance of different patients were followed up.

Results: From the analysis of various aspects of HCV transmission in hemodialysis: 1) Regulations on the use of disposable articles are not strictly enforced; 2) The infection consciousness of medical staff is dim, and the conception of asepsis is not strong; 3) the hospital system is not perfect; 4) Infection index monitoring is defective. In the 47 patients, 2 patient were not detected HCV-RNA. The genotype 2a were 32 cases (68.1%), 1b were 9 cases (19.1%), and 2a mixed 1b were 4 cases, 2 (4.25%) patients did not use interferon and ribavirin (PR protocol) in the beginning, but 21 patients of those were changed to the DAA protocol (Sofobuvir and Dacabavir) because of the side effect. 20 cases used the DAA protocol at the beginning. All of the patient used the DAA protocol not only first using but also the replacement, there were no patient exiting because of the intolerance.

Conclusions: Strengthen the control measures, and strictly implement the infection control system is an important measure to prevent hemodialysis patients from HCV infection. DAAs scheme for MHD patient with HCV-infection has better tolerance, which is a good choice for patients with intolerance of PR protocol, and have better antiviral effect, but also need a lot of guidance for clinical use in clinical data support.
Intra-Abdominal Collection and Catheter Removal as a Complication in Mexican Peritoneal Dialysis Patients Guadalupe R. Rodriguez-Luis I. Bonilla,1 Diego E. de la fuente,2 Elisa M. Guerrero Gonzalez.1 Nephrology, University Hospital Dr. José Eleuterio Gonzalez, Monterrey, Mexico; Facultad de Medicina UANL, Monterrey, Mexico.

Background: Peritonitis continues to be the most frequent cause of Peritoneal dialysis (PD) failure. All dialysis treatments include a certain risk of infection because dialysis patients are often admitted to hospitals with a high risk of infection of the peritoneum, subcutaneous tunnel and exit site. PD patients with severe peritonitis require catheter removal. It is often assumed that this approach, together with antibiotics, would eradicate the infection; however, some patients present further complications despite catheter removal. It is broadly known that developing countries, such as Mexico, are still using proportionally more PD than the rest of the world.

Methods: This was a Retrospective descriptive study about peritonitis on peritoneal dialysis patients. In a period of 40 months nephrology service implanted 238 peritoneal catheter in patients following a protocol for PD education. In this study authors describe the characteristics of the study cohort are described using medians ranges, and moans ranges for the continuous variables and proportions for the categorical variables. The differences between the groups were calculated using chi-square test.

Results: 238 patients were included. The median age was 50.3 years. 12 (52.2%) were male. 62 % were diabetic, 17 (70.8%) had I episode and 6 (25%) had 2 episodes of peritonitis. During the study period, 44.1% required catheter removal and 25% developed recurrent peritonitis collection that required percutaneous drainage. In most of cases (88%) the cause of removal catheter was the presence of abdominal collections and I patient had several hypocalbuminemia and associated shock, X2[2]= 3,489 p <0.077. Pseudomonas species were the microbiological causes of the peritonitis episodes in most of cases (20%). Of the 238 patients, 2 patients died within 24 months, 1 due to pneumonia and 1 due to myocardial infarction.

Conclusions: The formation and the persistence of intra-abdominal fluid collections of different sizes and localizations is not a rarely encountered phenomenon in peritoneal dialysis patients. Catheter removal represents high cost in developing countries, and implies a low chance of successful return to peritoneal dialysis. Effective education and training in pre - dialysis should improve outcomes and avoid catheter removal.

PUB371
Gram-Negative Bacteraemia (GNB) in Hemo dialysis Patients with Tunnelled Dialysis Catheters (TDCs) Quan Yao Ho, Tan Tock Seng Hospital, Singapore, Singapore.

Methods: The clinical, microbiological characteristics and management of Gram-negative bacteremia (GNB) in hemodialysis patients with tunnelled dialysis catheters (TDCs) has not been clearly defined.

Methods: Patients who underwent TDC-related procedures from 2014 to 2016 were reviewed and patients who developed GNB while on hemodialysis via TDCs were included.

Results: 599 patients were either newly initiated on dialysis via a TDC (n=424) or converted to hemodialysis via a TDC – either due to failed arterio-venous access (n=138) or conversion from peritoneal dialysis (n=37). On follow-up to 31 March 2017, 121 episodes of GNB developed in 99 patients while on dialysis via TDCs, including 16 episodes of polymicrobial bacteraemia. The attributed sources of GNB were TDC (66.9%,n=81), musculoskeletal (6.6%,n=8), respiratory (5.8%,n=7), hepatobiliary (5.0%,n=6), urinary (5.0%,n=6), other gastrointestinal sources (4.1%,n=5) and others (6.7%,n=6). The principal organisms isolated were Pseudomonas (22.4%,n=31), Klebsiella (17.4%,n=24), Escherichia coli (15.9%,n=22), Enterobacter (11.5%,n=16) and Acinetobacter (7.2%,n=11). Among the all isolates tested, 29.1% were resistant to ceftiraxone, 12.6% to cefadiazem, 16.5% to cephaline, 15.6% to pipercillin/tazobactam, 14.1% to carbenapenems, 22.7% to gentamicin, 13.6% to amikacin, 23.4% to ciproflxicin, 32.0% to co-trimoxazole. 82.6%(n=100) of the cases had abnormal imaging (Computer tomography or ultrasound) performed, of which 19.8%(n=24) revealed at least 1 infective focus. 90-day mortality was 17.4%(n=21). 17.4%(n=21) of the cases required Intensive Care Unit (ICU) care; amongst these cases the 90-day mortality rate was 76.2%(n=16). 90-day day mortality was associated with ICU admission (OR=15.2, 95%CI 6.28-37.0, p<0.01); a higher median Pti Bacteraemia Score (3 vs 1; p<0.01); hospital-acquired (>48hours from admission) GNB (OR<3.0, 95%CI 2.13-5.42); source not attributed to TDC (OR=2.38, 95%CI 2.08-4.85, p=0.01) and at least 1 infective focus on imaging (OR=2.83, 95%CI 1.48 to 5.41, p<0.01) and management without a line-free period (TDC exchange or no line removal) (OR=1.78, 95%CI 1.18-2.70, p=0.05).

Conclusions: GNB in patients on hemodialysis via TDCs is associated with high morbidity and mortality. Abdominal imaging may be useful in prognostication and TDC removal may be associated with improved survival.

PUB372
Diabetic “MALA”-dy: A Tale of a Patient with Diabetes Who Survived Metformin Associated Lactic Acidosis Twice Krishna K. Manda, Sameer Ansar. OSF St Anthony Medical Center, Rockford, IL.

Background: We present a case of a 54 y/o man with a h/o Type 2 Diabetes mellitus and hypertension who was fortunate enough to survive Metformin Associated Lactic Acidosis (MALA). He was admitted in June ’16 with weakness, nausia and vomiting. Initial investigations revealed Acute Kidney Injury (AKI) with Creatinine (Cr) of 7.3 mg/dl, severe acidosis with Lactic acid greater than 13.3 mmol/L and pH was 7.01. He was on Metformin, this was thought to be related to MALA amongst other etiologies. He was urgently started on hemodialysis. Renal functions improved and Cr was 1.33 at the time of discharge in July ’16. He was again admitted in Feb ’17 with increasing lethargy. Labs were notable for AKI with a Cr of 7.1 mg/dl, severe Lactic acidois >13.3 mmol/L and pH was <6.8. Hemodialysis was emergently initiated. Metformin level was checked which was later found to be elevated at 31 mcg/ml (therapeutic range 1-2). Renal functions gradually recovered and Cr was 1.79 at the time of discharge in March ’17.

Methods: Metformin is one of the most commonly used oral agents in Diabetes. It decreases insulin resistance, decreases hepatic glucose output and increases peripheral glucose uptake. The elimination half-life of Metformin in patients who take multiple doses and have good renal function is approximately 5 hours. Metformin is actively excreted, unmetabolized, via transporters in the proximal tubules of the kidneys and may accumulate in renal failure. The mechanism of MALA is complex. Metformin promotes the conversion of glucose to lactate in the splanchic bed of the small intestine. Metformin also inhibits mitochondrial respiratory chain complex 1, leading to decreased hepatic gluconeogenesis from lactate, pyruvate, and alanine. This results in additional lactate production. Metformin plasma concentrations exceeding 5 mcg/ml are generally associated with MALA. Multiple case series have reported a high rate of mortality with MALA, some approaching 45%. Hemodialysis is indicated if lactate level ≥20 mmol/L or severe metabolic acidosis (pH≤7.0).

Conclusions: As Metformin usage in renal impairment has increased since the removal of rigid serum Cr levels, careful consideration of ongoing usage should be done in order to prevent this potentially life threatening “MALA”-dy.
Methods: A 79-year-old female with history of anxiety, depression, and COPD was admitted with frank acetone odor. She started on scheduled acetaminophen 650 mg PO every six hours for pain. Hospital course was complicated by respiratory failure and hemodynamic instability. Shortly after admission her serum bicarbonate (CO2) level began to fall: from 24 mg/dl, it decreased daily to a nadir of 14. At the time of consultation, 14.9 g of acetaminophen were administered to the patient over 7 days. ABG: 7.26/35/101; serum chemistry (mEq/L): sodium 137, potassium 4.1, chloride 109, CO2 14, BUN/creatinine 16/0.74 mg/dl (within her baseline), glucose 169 mg/dl, anion gap 17, albumin 2.7 g/dl, lactate normal, no ketones. With negative work-up for common causes of acidosis, discontinuation of acetaminophen was recommended and urine oxoacids were ordered. Urine 5-OH level was 17 mmol/mmolCr. One day after stopping acetaminophen her CO2 improved to 18 and normalized within 72 hours.

Results: Conclusions: 5-oxoproline acidosis remains a rare cause of AGMA. While mainly diagnosed in women with chronic use of acetaminophen, hospital-acquired cases have been reported. Given the transient nature of the elevation of 5-OH levels and the delay in obtaining confirmatory results, laboratory confirmation should not delay treatment when suspected clinically. In our case, clinical characteristics like gender, age, nutritional status, critical illness, and morbidities such as temporal correlation between acetaminophen intake and increase in anion gap provided a strong evidence for causality. The resolution of the acidosis after discontinuation of the drug also supports our diagnosis. Even when 5-OH levels in urine were not significantly elevated, its presence represents a pathological condition as it is rarely seen in healthy controls.

PB377

Acidosis Measurement

Gillespie.

Pharmaceutical university

Proteomic Analysis of the Liver with Vacuolar Degeneration from

Columbus, OH

Conclusions: Our study provides new insight into the pathogenesis of AQP11 deficiency in the setting of ADPKD and also in patients with other causes of tubular dysfunction. Further studies are needed to fully understand the role of AQP11 in ADPKD and other tubular diseases.

Introduction: ADPKD is an autosomal dominant disorder caused by mutations in the PKD1 or PKD2 genes. The condition is characterized by the progressive enlargement of the kidneys due to the accumulation of fluid-filled cysts. AQP11 is a water channel expressed in the proximal tubule of the kidney, and its dysfunction has been associated with the development of ADPKD.

Aim: To investigate the expression and function of AQP11 in the liver of ADPKD patients.

Materials and methods: We performed proteomic analysis of the liver from a patient with ADPKD and from a healthy control. The tissues were homogenized, and the proteins were extracted. The samples were then fractionated by C18- and TMT labeling with tandem mass tag (TMT) 6-plex, mixed samples were fractionated by C18- and 5-oxoproline acidosis remains a rare cause of AGMA. While mainly diagnosed in women with chronic use of acetaminophen, hospital-acquired cases have been reported. Given the transient nature of the elevation of 5-OH levels and the delay in obtaining confirmatory results, laboratory confirmation should not delay treatment when suspected clinically. In our case, clinical characteristics like gender, age, nutritional status, critical illness, and morbidities such as temporal correlation between acetaminophen intake and increase in anion gap provided a strong evidence for causality. The resolution of the acidosis after discontinuation of the drug also supports our diagnosis. Even when 5-OH levels in urine were not significantly elevated, its presence represents a pathological condition as it is rarely seen in healthy controls.

PB375

Easy to Miss but Treatable: A Cause of High Anion Gap Metabolic Acidosis

Priyamvada Das,1 Jean M. Francis,1 Craig E. Goodwin,2 Boston University Medical Center, West Roxbury, MA; 2None, Natick, MA; 3Renal, Boston University, Boston, MA.

Background: Acquired 5-oxoprolineuria secondary to excessive acetaminophen ingestion is a rare, and underdiagnosed cause of anion gap metabolic acidosis.

Methods: A 59-year-old female with CKD stage 3 (baseline creatinine 1.3 mg/dl, eGFR 41ml/min/1.73m2), diabetes, hypertension, and ischemic heart disease was admitted for bilateral foot gangrene and underwent left saphenofemoral endarterectomy. Her hospital course was complicated by delirium, Clostridium difficile colitis, AKI (peak creatinine 1.6mg/dl), and high anion gap metabolic acidosis (AGMA). AKI was attributed to ATN in the setting of high vancomycin levels and hypotension. She was treated with acetaminophen during the hospital course (total 56 grams). Apart from AKI, she was frail, lethargic, behaving unusually; oriented to only person and place. She was referred for neurological consultation. On exam, she drank Bay Rum. A week prior, the patient had been admitted for a fall related to beer potomania. Her son took away her alcohol so she ingested Bay Rum. We describe a case of mistaken ingestion of Bay Rum, a well-known aromatic plant oil (products marketed as Bay Rum). Current packaging of Bay Rum often resembles that of common ethanol containing rums. A 59-year-old female with CKD stage 3 (baseline creatinine 1.3 mg/dl, eGFR 41ml/min/1.73m2), diabetes, hypertension, and ischemic heart disease was admitted for bilateral foot gangrene and underwent left saphenofemoral endarterectomy. Her hospital course was complicated by delirium, Clostridium difficile colitis, AKI (peak creatinine 1.6mg/dl), and high anion gap metabolic acidosis (AGMA). AKI was attributed to ATN in the setting of high vancomycin levels and hypotension. She was treated with acetaminophen during the hospital course (total 56 grams) over 1 month. We recommended discontinuation of acetaminophen which resulted in improvement in her AGMA and delirium.

Results: Conclusions: An under-recognized cause of high AGMA is acquired pyroglutamyl (5-oxo)proline acidosis due to excessive acetaminophen ingestion. Acetaminophen disrupts the gamma-glutamyl cycle causing depletion of glutathione stores, and leading to accumulation of 5-oxoproline. Normally, glutathione results in a negative feedback by inhibiting gamma-glutamyl cysteine synthetase. With glutathione depletion, the negative feedback is disrupted. As a result, the enzyme leading to increased gamma-glutamyl cysteine, a precursor to 5-oxoproline. Acquired 5-oxoproline acidosis is more common in elderly women with multiple comorbidities, in whom baseline glutathione levels may already be low. This likely is an underdiagnosed condition because measurements of serum and/or urinary 5-oxoproline levels are not readily available. Usually, treatment of the condition is to discontinue acetaminophen. Also, N-acetyl cysteine is shown to be of some benefit likely as it augments glutathione levels. Our case thus illustrates the need for keeping a high clinical suspicion and checking 5-oxoproline levels regularly in patients with unexplained AGMA as it is an easily treatable condition.

PB376

The Bay Rum Diaries: False Assumptions about Rum and Kidney Function in a Case of Isopropyl Alcohol Ingestion

Daniel Corbally, Avrum Gillespie. Temple Medical School, Philadelphia, PA.

Background: Isopropyl alcohol ingestion presents with a unique array of clinical and laboratory findings that challenge the understanding of both physiology and clinical chemistry. Isopropyl alcohol is a common alcohol that is commonly found in products marketed as Bay Rum. Current packaging of Bay Rum often resembles that of common ethanol containing rums. A 59-year-old female with CKD stage 3 (baseline creatinine 1.3 mg/dl, eGFR 41ml/min/1.73m2), diabetes, hypertension, and ischemic heart disease was admitted for bilateral foot gangrene and underwent left saphenofemoral endarterectomy. Her hospital course was complicated by delirium, Clostridium difficile colitis, AKI (peak creatinine 1.6mg/dl), and high anion gap metabolic acidosis (AGMA). AKI was attributed to ATN in the setting of high vancomycin levels and hypotension. She was treated with acetaminophen during the hospital course (total 56 grams) over 1 month. We recommended discontinuation of acetaminophen which resulted in improvement in her AGMA and delirium.

Results: Conclusions: An under-recognized cause of high AGMA is acquired pyroglutamyl (5-oxo)proline acidosis due to excessive acetaminophen ingestion. Acetaminophen disrupts the gamma-glutamyl cycle causing depletion of glutathione stores, and leading to accumulation of 5-oxoproline. Normally, glutathione results in a negative feedback by inhibiting gamma-glutamyl cysteine synthetase. With glutathione depletion, the negative feedback is disrupted. As a result, the enzyme leading to increased gamma-glutamyl cysteine, a precursor to 5-oxoproline. Acquired 5-oxoproline acidosis is more common in elderly women with multiple comorbidities, in whom baseline glutathione levels may already be low. This likely is an underdiagnosed condition because measurements of serum and/or urinary 5-oxoproline levels are not readily available. Usually, treatment of the condition is to discontinue acetaminophen. Also, N-acetyl cysteine is shown to be of some benefit likely as it augments glutathione levels. Our case thus illustrates the need for keeping a high clinical suspicion and checking 5-oxoproline levels regularly in patients with unexplained AGMA as it is an easily treatable condition.

PB376

The Bay Rum Diaries: False Assumptions about Rum and Kidney Function in a Case of Isopropyl Alcohol Ingestion

Daniel Corbally, Avrum Gillespie. Temple Medical School, Philadelphia, PA.

Background: Isopropyl alcohol ingestion presents with a unique array of clinical and laboratory findings that challenge the understanding of both physiology and clinical chemistry. Isopropyl alcohol is a common alcohol that is commonly found in products marketed as Bay Rum. Current packaging of Bay Rum often resembles that of common ethanol containing rums. We describe a case of mistaken ingestion of Bay Rum, a well-known aromatic plant oil (products marketed as Bay Rum). Current packaging of Bay Rum often resembles that of common ethanol containing rums. We describe a case of mistaken ingestion of Bay Rum, a well-known aromatic plant oil (products marketed as Bay Rum). Current packaging of Bay Rum often resembles that of common ethanol containing rums. We describe a case of mistaken ingestion of Bay Rum, a well-known aromatic plant oil (products marketed as Bay Rum). Current packaging of Bay Rum often resembles that of common ethanol containing rums.
Nattawat Klomjit, Cholangiocarcinoma
Publication-Only
permeation of AQP11 as some AQPs permeate metals.

In cancer patients who present with hypercalcemia and hypophosphatemia, more commonly seen in Asia, is Chinese herbal medicine nephropathy. Although identified in all main ethnic groups, it is less common in African Americans. Because Fanconi syndrome is a rare disorder with multiple etiologies that is characterized by generalized proximal renal tubular dysfunction. Patients could develop hypophosphatemia, hypokalemia, tubular proteinuria, non-anion gap metabolic acidosis with bicarbonaturia. A potential cause of Fanconi syndrome, more commonly seen in Asia, is Chinese herbal medicine nephropathy.

Patients were not able to tolerate the low salt diet and urine sodium of 245. Her TSH and T4 were normal. A diagnosis of SIADH was made and patient started on fluid restriction, Lasix and salt tablets with no improvement in her sodium level. Patient was started on 3% hypertonic saline with correction of her sodium. Given the patients abdominal pain, hypertension and SIADH, the diagnosis of acute intermittent porphyria was suspected. A 24 hour urine sample was collected and she was found to have increased levels of δ-aminolevulinic acid and porphobilinogen. Hypercalcemia was treated with blood pressure control and advised to avoid medications that precipitate an acute attack. Two years later, the patient had another episode of hypophosphatemia consistent with SIADH and which responded to Lasix and salt tablets. She has experienced a progressive decline in her renal function, her last estimated glomerular filtration rate was 40ml/min with a serum creatinine of 1.8mg/dL and her urinary tract had mild proteinuria, a finding consistent with tubular damage possibly from porphyrin precursors that result in endoplasmic reticulum stress and apoptosis.

Results:
Conclusions: As there is a low prevalence of acute intermittent porphyria in the United States, the diagnosis should be considered in young females who presents with abdominal pain and SIADH of unclear etiology.

PUB8382
An Asian Woman with Chinese Herbal Medicine Induced Transient Fanconi Syndrome Resulting in Rhabdomyolysis and Complicated by Severe Hyponatremia Nattawat Klomjit, Noah M. Solomon, Rick Y. Hayashi, Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI; Nephrology, Straub Clinics and Hospital, Honolulu, HI; Nephrology, Pall Malo Medical Center, Honolulu, HI.

We reported a rare case of transient Fanconi syndrome associated with severe hyponatremia and rhabdomyolysis. Methods: A 21 year old African American female with no previous medical history presented to the emergency department with severe abdominal pain and nausea. She had been taking Chinese herbs for the treatment of weight loss starting 1 year prior to the admission. Serum phosphorus and potassium had been improved and were normalized prior to discharge. Sodium level was appropriately improved after 3% NaCl infusion. It is uncommon for Fanconi syndrome to present with severe hyponatremia. Although pain and nausea might contribute to appropriate increased ADH production causing hyponatremia. The temporal relationship between the electrolytes recovery and discontinuation of the Chinese herbs suggests a possible causal role in the patient’s transient Fanconi syndrome.

Results:
Conclusions: We reported a rare case of transient Fanconi syndrome associated with Chinese herbal medicine use. Chinese herbs containing aristolochic acid have been known to cause aristolochic nephropathy which could present with Fanconi syndrome.

PUB381
Acute Intermittent Porphyria as a Cause of Syndrome of Inappropriate Anti-Diuretic Hormone in a Young African American Woman Serena Bhela, Dheeraj Kaul, Gary R. Briefel, Mary C. Mallappallil, Moro O. Salifu, Medicine, SUNY Downstate, Brooklyn, NY; Medicine, SUNY Downstate Medical Center, Brooklyn, NY; Medicine, SUNY Downstate, Brooklyn, NY.

Background: Acute intermittent porphyria (AIP) is a rare genetic disorder of the synthesis of heme caused by a deficiency in hydroxymethylbilane synthase (HMBS), resulting in the overproduction of the porphyrin precursors δ-aminolevulinic acid and porphobilinogen. When present it can result in hyponatremia and chronic kidney disease. Although identified in all main ethnic groups, it is less common in African Americans.

Results:
Conclusions: We reported a rare case of transient Fanconi syndrome associated with Chinese herbal medicine use. Chinese herbs containing aristolochic acid have been known to cause aristolochic nephropathy which could present with Fanconi syndrome.
When the Hospitalist Meets the Nephrologist: A Case of a Mixed Acid-Base Disorder in the Ward

Alexander C. Bell,1 Amir E. Mohamed,1,2 Javier A. Neyra,3 Fabrizio Canepa-Escaro.2 1University of Kentucky College of Medicine, Lexington, KY; 2University of Kentucky, LEXINGTON, KY; 3University of Kentucky Medical Center, Lexington, KY.

**Background:** Mixed acid-base disorders are often found in hospitalized patients. We report a case of non-anion gap metabolic acidosis (NAGMA) resulting from rapid correction of severe metabolic alkalosis in a patient with acute kidney injury (AKI) receiving total parenteral nutrition (TPN).

**Methods:** A 37-year-old woman with TPN dependency after total small bowel resection and chronic percutaneous gastrostomy (PEG) tube presented with altered mental status. On admission, she had severe metabolic alkalosis with concomitant respiratory acidosis and AKI. Urine electrolytes were obtained after fluid resuscitation with 2.5 L of 0.9% NaCl and a dose of Diamox (250 mg) in the ED. History revealed her PEG tube was placed to continuous drainage for several days. On the wards, the patient continued to receive IV 0.9% NaCl and was briefly on BIPAP. Her mental status, kidney function and metabolic alkalosis improved after IV fluids. Home TPN (amino acids 1.6 g/kg/day) was then resumed without adjustments. Subsequently, the patient’s serum HCO3- trended down with a normal serum anion gap and positive urine anion gap. The patient was diagnosed with post-AKI tubulopathy impairing the ability of the kidney to excrete HCO3 from amino acid metabolism in the context of high-protein TPN and relative dilutional hyperchloremic metabolic acidosis from aggressive administration of chloride-rich solutions. Patient was discharged on Bicitor and follow-up in Renal Clinic.

**Results:**

**Conclusions:** Post-AKI tubulopathy may affect acid-base homeostasis in patients exposed to high-protein TPN. Recognition of mixed acid-base disorders is critical for the management of patients with PEG tubes and TPN.

---

**Prostate Cancer Leading to Severe Hypokalemia**

Victoria Grogurt,1 Ilya Glezerman.1 1Memorial Sloan Kettering Cancer Center, New York, NY; 2Nephrology, Weill Cornell, New York, NY.

**Background:** The most common cause of hypokalemia in hospitalized patients is syndrome of inappropriate antidiuretic hormone (SIADH). In older male patients, the etiology may be related to urinary obstruction, with improvement in serum sodium seen after relief of the obstruction.

**Methods:** Case 1: 63 year old man with prostate cancer and brachytherapy implantation three days prior to admission for altered mental status and penile swelling. He had no focal neurologic deficits on exam. Blood work showed serum osmolality of 243 mOsm/L and sodium of 136 (134-144) mEq/L. Random serum sodium was 114.4 pg/mL, and 24 hour urine free cortisol 1772 ug. Lack of cortisol suppression after high dose dexamethasone administration confirmed EAS. Ketoconazole was added to potassium supplementation and spironolactone therapy. Paralysis resolved and potassium normalized in just over 24 hours. Ketoconazole was discontinued due to worsening liver function and changed to octreotide. He was discharged on hospice and died 6 weeks after initial evaluation.

**Conclusions:** EAS is a clinical state due to prolonged, inappropriate exposure to excessive endogenous secretion of cortisol and excess circulating free cortisol, with loss of the normal feedback mechanisms of the hypothalamo-pituitary-adrenal axis and the normal circadian rhythm of cortisol secretion. Advanced prostate cancer has been shown to dedifferentiate leading to a paraneoplastic syndrome. Inappropriate repression or inactivation of certain genes, presumably similar to those in normal pituitary corticotropes, can cause tumors to secrete ACTH. Treatment options include ketoconazole, which inhibits adrenal corticosteroid production, and octreotide which has a direct effect on tumor production of ACTH. Despite aggressive therapy, prognosis is poor for unresectable disease.

**Funding:** Veterans Affairs Support

---

**Surreptitious Alcohol Intake in a Hospitalized Patient**

Victoria Grogurt,2,3 Ilya Glezerman.1 1Memorial Sloan Kettering Cancer Center, New York, NY; 2Nephrology, Weill Cornell, New York, NY.

**Background:** The serum osmolar gap is a useful tool to evaluate for additional solutes in the blood apart from sodium, glucose, and urea. If the difference between measured and calculated osmolality exceeds 10 mosmol/L, an alternative solute should be considered. Common causes include ethanol intoxication, methanol, ethylene glycol, or isopropyl alcohol. An anion gap can be calculated to differentiate these causes.

**Methods:** 30 –year-old gentleman with a history of Hodgkin’s Lymphoma, Myelodysplastic syndrome, and allogenic stem cell transplant one year ago, presented with bilateral upper extremity up revealed diaphoresis for three days. Torem was initially thought to be a side effect of cyclosporine, but despite dose reduction and lower serum levels of the cyclosporine, the tremor persisted. Hospital course was complicated by hypernatremia and nephrology was consulted for further evaluation on day 4 of admission. Patient complained of feeling thirsty, and drank two bottles of water daily. He was normotensive, not tachycardic, and afebrile. Physical exam was notable for an essential tremor of the bilateral upper extremities. Otherwise, patient was alert and oriented to person, time, place, but slow to answer and tangential. Recorded urine output was 1.3 liters in 24 hours but patient reported non-compliance with measurement of the output. Blood work was significant for a serum sodium of 154 (136-144) mEq/L and a serum osmolality of 397 (280-295) mosmol/L. The calculated serum osmolality was 326 mosmol/L with serum osmolal gap of 71. An anion gap was not present. A more thorough social history was reviewed but patient denied use of alcohol, ingestion of antifreeze, methanol, or alcohol derivatives. Upon further investigation, patient was found to have several empty alcohol containers under his bed.

**Conclusions:** Ethanol is the most common cause of an elevated serum osmolal gap. When presented with an elevated serum osmolality, it is important to calculate the osmolality to investigate whether an osmolar gap is present. Hypernatremia is another clue to ethanol use, since it can cause diabetes insipidus through a transient inhibitory effect on anti-diuretic hormone (ADH) release. When presented with this scenario, a thorough social history and search need to be performed in order to effectively rule out a hazardous cause.

---

**Posts ED fluid resuscitation and Diamox**

---

**Cases of Obstructive Uropathy Causing Hyponatremia**

Victoria Grogurt,2,3 Ilya Glezerman.1 1Memorial Sloan Kettering Cancer Center, New York, NY; 2Nephrology, Weill Cornell, New York, NY.

**Background:** The most common cause of hyponatremia in hospitalized patients is syndrome of inappropriate antidiuretic hormone (SIADH). In older male patients, the etiology may be related to urinary obstruction, with improvement in serum sodium seen after relief of the obstruction.

**Methods:** Case 1: 63 year old man with prostate cancer and brachytherapy implantation three days prior to admission for altered mental status and penile swelling. He had no focal neurologic deficits on exam. Blood work showed serum osmolality of 243 mOsm/L and sodium of 116 (134-144) mEq/L. Random urine sodium was 160 mEq/L and osmolarity 500mOsm/L. A urinary catheter was placed and 1600 ml of urine drained. The patient was volumetraic and improved, but patient required 5% continuous dextrose infusion to avoid overcorrection. His mental status improved and returned to baseline. Patient was discharged with indwelling urinary catheter and plan for future trial of void. Case 2: 60 year old man with invasive urethral cancer who underwent radical cystoprostatectomy, bilateral ureterorectal ureterostomy and creation of neobladder two weeks prior to hospital admission. Patient was brought in for lethargy and poor oral intake. On exam, he was normotensive, lethargic but oriented, and had a urinary catheter draining yellow urine. Blood work notable for serum sodium of 99 mEq/L and creatinine of 4.4 (0.6-1.3) mg/dl from baseline of 9.9mg/dl. Urine studies showed random urinary sodium of 26 mEq/L and osmolality of 135mOsm/L. Further imaging revealed a large pelvic fluid collection causing displacement of the neobladder and ureteric anatomy anteriorly. Drainage of the collection improved renal function to 1.3mg/dl with normalization of serum sodium.

**Results:**

**Conclusions:** In both cases, urinary retention, either secondary to recent prostate instrumentation or extrinsic compression of the bladder from a pelvic collection, was the direct cause of hyponatremia. Relief of the obstruction with placement of a urinary catheter or drainage of the pelvic collection, respectively, caused improvement in serum sodium. The possible mechanism of SIADH involves antidiuretic hormone release from pain related to distention of the bladder exacerbated by excessive free water intake to counter low urine output. Obstructive uropathy is a reversible cause of hyponatremia that should be considered as part of investigations particularly in the setting of recent urologic procedures.
period of time. He was diagnosed with rhabdomyolysis and was treated with intravenous fluids (CK 28,000 units/L). Despite appropriate interventions, CK continued to increase, hyperkalemia ensued and calcium decreased to 6.5 mg/dL with an ionized calcium 0.91 mmol/L. Intermittent hemodialysis was initiated for progressive renal insufficiency with hyperkalemia and oliguria. After three days of persistently low calcium, the calcium levels started to increase and was within the normal range at day six. However, over the following two weeks, serum calcium elevated to a peak level of 15.8mg/dL. He underwent further investigation. PTH was found to be elevated at 108 pg/mL. 25-OH Vitamin D was 35 ng/mL and 1, 25 Vitamin D was 13 pg/mL. PTHrP was elevated at 5.2pmol/L. Serum and urine were negative for paraprotein. The patient was given calcitonin, cinacalcet, and denosumab and calcium levels improved. In addition, his renal function recovered, and dialysis was discontinued. A tumor evaluation was conducted with a whole body PET scan that revealed increased metabolic activity at the site of muscle injury and ensuing calcinosis. Further review of his chart revealed a previous diagnosis of hyperparathyroidism due to a right inferior parathyroid adenoma seven years before. He declined surgery then and was lost to follow up.

Results: Conclusions: This case illustrates the difficulties involved in the interpretation and management of calcium levels during acute rhabdomyolysis and ensuing shift of calcium between the muscle and the vascular compartments. Management principles include supportive fluid and calcium management along with renal replacement therapy. In this case, an underlying cause became apparent following correction of the acute metabolic sequela of rhabdomyolysis. We believe the elevation of PTHrP is unexplained and likely false positive finding.

**PUB389**

**Assessment of PROPKD Score in Chilean ADPKD Patients to Predict Renal Outcome**

**Paola Kralj,1 Daniela Ubilla,2 Daniela P. Nualart,3 Rocío P. Saenz,4 Claudio A. Flores,2 Patricio Downey,1 Leopoldo G. Ardiles,5 Sergio A. Mezzano.1** 1Centro de Diálisis Dialis, Osorno, Chile; 2Pontificia Universidad Catolica, Santiago, Chile; 3Universidad Austral de Chile, Valdivia, Chile.

**Background:** ADPKD is a genetic kidney disease with a highly variable clinical presentation between individuals, even if they share the same mutation within a family. A clinical-genetic prognostic model, PROPKD score, is available to predict renal outcomes in ADPKD patients that needs to be assessed in developing countries with low health care resources.

**Methods:** 20 unrelated Chilean families with clinical ADPKD diagnosis were recruited between 2015 and 2017. Genetic analysis of PKD1/ PKD2 was performed in the index case and offered to relatives after identification of a pathogenic variant. Clinical data were collected in individuals carrying a pathogenic variant and scored: being male (1pt), hypertensive or first urologic event < 35 years (2 pt each one), non-truncating (4 pt) or truncating (4 pt) PKD1 mutation. Relationship between risk categories (low, intermediate or high) of progression to ESRD and age of ESRD was analyzed. Association between position of truncating mutations and hypertension was evaluated.

**Results:** A genetic basis was confirmed in 18 out of 20 Chilean families. 16 different pathogenic PKD1 mutations were identified that predicted protein truncation (n=11), in frame-deletion (n=1) or missense changes (n=4). PROPKD score was estimated in 51 participants (median ESRD age = 49 years) that resulted with low, intermediate or high-risk, with median ages for ESRD of 56, 49 and 48 years, respectively (p=NS). 53% (11/21) of patients carrying truncating before 35 years, whereas only 21% (4/19) of patients carrying truncating mutations after exon 26 had this condition, suggesting that early truncating mutations are associated with early hypertensive phenotype (p=0.048; OR 4.58; 95% CI 1.12-18.81).

**Conclusions:** Our findings indicate that PROPKD score seems to predict renal outcome in Chilean ADPKD patients, with the same tendency as described in other cohorts. GANAB might be considered as third candidate gene in the two families with negative results. Truncating mutations before the first PKD1 TM domain (exon 26) are associated with hypertension and, secondarily, might be important for renal outcome. We expect to recruit more ADPKD families and monitor young affected relatives to be able to predict ESRD with this highly predictive model. FONDECYT #11140242

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

---

**PUB390**

**Overweight and Obesity Are Predictors of Progression in Early Autosomal Dominant Polycystic Kidney Disease**

**Kristen L. Nowak,5 Zhiting You,5 Bernice Y. Gitomer,8 Godela M. Brossnaham,8 Vicente E. Torres,1 Arlene B. Chapman,1 Ronald D. Perrone,4 Theodore I. Steinman,1 Kaleab Z. Abebe,5 Frederic F. Rahbabi-Oskouji,2 Alan S. Yu,8 Peter C. Harris,9 Kyongtae T. Bae,3 J. Keck School of Medicine of USC, Los Angeles, CA; 2Tufts Medical Center, Boston, MA; 3University of Maryland School of Medicine, Baltimore, MD; 4University of Maryland School of Medicine, Baltimore, MD; 5University of Pittsburgh, Pittsburgh, PA.

**Background:** Preclinical studies suggest that metformin may be efficacious for preventing progression in ADPKD by activating the sensor AMP-activated protein kinase (AMPK). However, the effect of metformin on disease progression in human patients with ADPKD, and the long-term tolerability of this medication in these patients, is unknown.

**Methods:** This is a phase 2 double-blind placebo-controlled multicenter randomized clinical trial to evaluate the safety, efficacy, and tolerability of metformin in ADPKD patients over a two-year treatment period. Participants (N=96) are adults with ADPKD with estimated GFR ≥ 50 ml/min/1.73m2, without contraindication to MRI or metformin treatment. Participants are randomized in 1:1 ratio to metformin - beginning at 500mg daily and titrating over 6 weeks to maximally tolerated dose up to 1 gram twice daily - or matching placebo. Follow-up evaluations occur every 2 weeks for 2 months, monthly for 4 more months, and then every 3 months for 24 months total. Metformin dose will be reduced to 500mg twice daily if eGFR declines <45 ml/min/1.73m2, and will be discontinued if eGFR declines <30 ml/min/1.73m2 or if increased serum lactate occurs. The primary safety/tolerability outcomes are: proportion of participants experiencing serious adverse events; gastrointestinal symptom rating scale severity; and maximally tolerated dose of study medication. Treatment efficacy is assessed by comparing the annual rate of change in a) height-adjusted total kidney volume on MRI performed every 6 months (CK); b) eGFR. Diagnostic outcomes include the changes in activity of key glycolytic pathway enzymes, metabolite concentrations, and activity of AMPK pathway enzymes measured in urine. An independent Data Safety Monitoring Board provides study oversight.

**Results:** Through May 2017, 57 participants have completed screening, of whom 55 were eligible. Of these, 48 were randomized, and 45 remain in active follow-up for a median 4.5 months.

**Conclusions:** Results of this phase 2 multicenter clinical trial will provide important evidence on the safety, tolerability, efficacy and effects on renal metabolic biomarkers of metformin in patients with ADPKD. Such evidence will be crucial to support and plan a phase 3 multicenter efficacy trial.

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

---

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

**Underline represents presenting author.
Adaptations to Increased Flow in Polycystic Kidney Disease
Elizabeth Y. Chen,1 Marcelo F. Cassidy,1 Vijayakumar R. Kakade,1 Richard Torres,2 Lloyd G. Cantley,1 Yale University School of Medicine, New Haven, CT.

Background: Previous studies have demonstrated that the loss of polycystins results in unopposed cilia dependent cyst activating signaling, which leads to pathologic tubule remodeling. Because it has been hypothesized that the polycystin complex can function as a flow sensor in cilia, we evaluated the effect of increased GFR on tubule diameter in mice with either normal PC1 expression or Pkd1 haploinsufficiency.

Methods: We employed a nephrectomy model to induce compensatory hyperfiltration in the remaining kidney in both wild-type and Pkd1 heterozygous mice (which have approximately a 50% reduction of PC1 expression). To analyze tubule morphology, we used multiphoton confocal microscopy and optimized the Z-stack image analysis techniques to accurately detect morphological changes in response to hyperfiltration.

Results: One week after unilateral nephrectomy, wild-type mice exhibited a 18.02% increase in tubule diameter (718.84 ± 118.06 um vs. 848.37 ± 190.06 um, p<0.01, n=20 tubules). Similarly, Pkd1 heterozygous mice exhibited a 20.45% increase in diameter at the same time point (688.48 ± 102.58 um vs. 829.30 ± 153.41 um, p<0.01, n=20 tubules).

Conclusions: These studies support a model of tubular adaptation to increased flow, but demonstrate that Pkd1 haploinsufficiency does not impact the magnitude of external remodeling.

Funding: Private Foundation Support

PUB392

Background: Tuberous Sclerosis(TS) is a rare genetic disorder affecting multiple organ systems including kidneys, where it presents as Angiomyolipoma(AML) and Cysts. With the advent of mTOR inhibitors, the management of this condition has taken a new dimension. As our institution is a tertiary renal and neurological centre, we have a growing cohort of TS patients followed-up in our multi-speciality and multi-disciplinary(MDT) TS clinic.

Methods: A cross-sectional observational study of all patients registered in our TS database. Clinical characteristics and Management strategies were reviewed.

Results: Currently 25 patients are registered in our study database. Mean age of our cohort is 40 with 14 males and 11 females. So far 22/25 had some form of imaging (MR or CT Scan) of their Abdomen/Kidneys. Of these 22 patients, 13(59%) had a size of AML>3cm and qualified for mTOR inhibitor therapy based on current international guidelines. 5 had AML size<3cm and 4 with no renal involvement. Mean eGFR of the sample was 74.6ml/min/1.73m² with the mean haemoglobin 130g/ml. eGFR did not correlate with the number of AMLs. There a linear increasing trend noted in the size of AMLs with age. Of the 13 eligible for mTOR inhibitor treatment, eight are on sirolimus, one on everolimus and rest under assessment. On review of neurological manifestations, 84%(16 of the available 19) had radiological evidence of cortical tubers in the brain, in 11 had Sub Ependymal Nodules, 7 had SEGAs(Astrocytoma). Phenotypically, 14 of 25 had an intellectual disability with 23 of the 25 patients having active epilepsy; generalised onset in 18 with co-existent focal onset in 17. The seizure type was unclassified in 5 patients. All 25 were on at least two antiepileptic medications.

Conclusions: Our study and database have given a better insight of our patient characteristics and management strategies. Including a plan for timely imaging. With expanding indications of the use of mTOR inhibitors an MDT approach would be the appropriate management strategy. Plans also include the use of Physiologically Based Pharmacokinetic Modelling(PBPK) in guiding mTOR inhibitor dosing to overcome appropriate management strategy. Plans also include the use of Physiologically Based Pharmacokinetic Modelling(PBPK) in guiding mTOR inhibitor dosing to overcome appropriate management strategy. Plans also include the use of Physiologically Based Pharmacokinetic Modelling(PBPK) in guiding mTOR inhibitor dosing to overcome appropriate management strategy. Plans also include the use of Physiologically Based Pharmacokinetic Modelling(PBPK) in guiding mTOR inhibitor dosing to overcome appropriate management strategy. Plans also include the use of Physiologically Based Pharmacokinetic Modelling(PBPK) in guiding mTOR inhibitor dosing to overcome appropriate management strategy. Plans also include the use of Physiologically Based Pharmacokinetic Modelling(PBPK) in guiding mTOR inhibitor dosing to overcome appropriate management strategy.

Funding: None

PUB393
The Effect of Hydration Advice on Urine Specific Gravity as a Marker of Vasopressin Suppression in Polycystic Kidney Disease Ragada El-Damanawy,1,2 Anaia Sarker,1 Caroline M. Robinson,3 Richard N. Sandford,3 Fiona E. Karet,1,2 Thomas F. Hiemstra1,3,4 "Clinical Biochemistry, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; 1Medical Genetics, University of Cambridge, Cambridge, United Kingdom; 1Renal Medicine, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; 1Clinical Trials Unit, Cambridge, United Kingdom; 3Clinical Trials Unit, Cambridge, United Kingdom; 4Renal Medicine, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom.

Background: Patients with Autosomal Dominant Polycystic Disease (ADPKD) have a 50% chance of transmitting the disease to their offspring. Preimplantation genetic diagnosis (PGD) reduces this risk to 1-2%. We hypothesized ADPKD patients of childbearing potential who are at high risk of clinical progression are likely to pursue PGD to conceive. Common clinical features that may predict high risk of clinical progression to end stage renal disease (ESRD) in ADPKD patients include genotype, early onset of hypertension, and large kidneys or increased total kidney volume (TKV). In addition, patients may have a family history of intracranial aneurysms or complications of hepatic cysts which may cause a truncating mutation, 1 patient had predicted pathogenic mutation in an intronic region. All 8 patients were at high risk of clinical progression, and considered and/or underwent PGD with IVF to conceive.

Methods: After IRB approval, we performed a retrospective medical record review of eight patients diagnosed with ADPKD who attempted PGD with IVF. We collected family history and patient characteristics and, including genotype, presence of hypertension, extra-renal manifestations of PKD, and TKV when available.

Results: See table.

Conclusions: 7 patients had novel mutations, 4 patients had truncating PKD1 mutations, and 4 patients required additional testing of family members to determine disease associated short tandem repeats (STRs). 1 patient had a mutation near an exome splice site which may cause a truncating mutation, 1 patient had predicted pathogenic mutation in an intronic region. All 8 patients were at high risk of clinical progression, and considered and/or underwent PGD with IVF to conceive.

PUB394
Clinical Characteristics of ADPKD Patients Requesting Pre-Implantation Genetic Diagnosis Erin L. Murphy, Madeline Droher, Neera K. Dahl. Yale School of Medicine, New Haven, CT.

Background: Patients with Autosomal Dominant Polycystic Disease (ADPKD) have a 50% chance of transmitting the disease to their offspring. Preimplantation genetic diagnosis (PGD) reduces this risk to 1-2%. We hypothesized ADPKD patients of childbearing potential who are at high risk of clinical progression are likely to pursue PGD to conceive. Common clinical features that may predict high risk of clinical progression to end stage renal disease (ESRD) in ADPKD patients include genotype, early onset of hypertension, and large kidneys or increased total kidney volume (TKV). In addition, patients may have a family history of intracranial aneurysms or complications of hepatic cysts which may cause a truncating mutation, 1 patient had predicted pathogenic mutation in an intronic region. All 8 patients were at high risk of clinical progression, and considered and/or underwent PGD with IVF to conceive.

Methods: After IRB approval, we performed a retrospective medical record review of eight patients diagnosed with ADPKD who attempted PGD with IVF. We collected family history and patient characteristics and, including genotype, presence of hypertension, extra-renal manifestations of PKD, and TKV when available.

Results: See table.

Conclusions: 7 patients had novel mutations, 4 patients had truncating PKD1 mutations, and 4 patients required additional testing of family members to determine disease associated short tandem repeats (STRs). 1 patient had a mutation near an exome splice site which may cause a truncating mutation, 1 patient had predicted pathogenic mutation in an intronic region. All 8 patients were at high risk of clinical progression, and considered and/or underwent PGD with IVF to conceive.

PUB395
The Effect of Hydration Advice on Urine Specific Gravity as a Marker of Vasopressin Suppression in Polycystic Kidney Disease Ragada El-Damanawy,1,2 Anaia Sarker,1 Caroline M. Robinson,3 Richard N. Sandford,3 Fiona E. Karet,1,2 Thomas F. Hiemstra1,3,4 "Clinical Biochemistry, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; 1Medical Genetics, University of Cambridge, Cambridge, United Kingdom; 1Renal Medicine, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; 1Clinical Trials Unit, Cambridge, United Kingdom; 3Clinical Trials Unit, Cambridge, United Kingdom; 4Renal Medicine, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom.

Background: Patients with Autosomal Dominant Polycystic Disease (ADPKD) have a 50% chance of transmitting the disease to their offspring. Preimplantation genetic diagnosis (PGD) reduces this risk to 1-2%. We hypothesized ADPKD patients of childbearing potential who are at high risk of clinical progression are likely to pursue PGD to conceive. Common clinical features that may predict high risk of clinical progression to end stage renal disease (ESRD) in ADPKD patients include genotype, early onset of hypertension, and large kidneys or increased total kidney volume (TKV). In addition, patients may have a family history of intracranial aneurysms or complications of hepatic cysts which may cause a truncating mutation, 1 patient had predicted pathogenic mutation in an intronic region. All 8 patients were at high risk of clinical progression, and considered and/or underwent PGD with IVF to conceive.

Methods: After IRB approval, we performed a retrospective medical record review of eight patients diagnosed with ADPKD who attempted PGD with IVF. We collected family history and patient characteristics and, including genotype, presence of hypertension, extra-renal manifestations of PKD, and TKV when available.

Results: See table.

Conclusions: 7 patients had novel mutations, 4 patients had truncating PKD1 mutations, and 4 patients required additional testing of family members to determine disease associated short tandem repeats (STRs). 1 patient had a mutation near an exome splice site which may cause a truncating mutation, 1 patient had predicted pathogenic mutation in an intronic region. All 8 patients were at high risk of clinical progression, and considered and/or underwent PGD with IVF to conceive.
PUB395

Thermal Radiofrequency Ablation (RFA) in Renal Cancer of Von Hippel Lindau (VHL) Patients: A Case for Renal Mass Preservation in a Multiple Renal Tumor Setting

**Javier De Arteaga,**1,4 Pehuén Fernández,2,4 Jorge De la fuente,1,2 Walter Douthat,1 1Hospital Privado Universitario, Córdoba, Argentina; 2ITAL PRIVADO DE CORDOBA, BUENOS AIRES, Argentina; 3Hospital Privado Universitario de Córdoba, Córdoba, Argentina; 4Universidad Catolica de Cordoba, Cordoba, Argentina.

**Background:** VHL can present with a devastating clinical picture that may include ESRD for surgical procedures of multiple renal carcinoma. Until not far, open or laparoscopic surgery has been the only therapy considered. Teral RFA is a percutaneous less invasive procedure that allows targeting small nodules (less than 3.5 cm usually). Objective: to perform thermal RFA in VHL patients to avoid open surgery with unnecessary loss of renal tissue.

**Methods:** 3 VHL patients with renal nodules between 2.5 (smallest) and 4.2 cm (largest) were subjected to thermal RFA under light sedation and local anaesthesia. A percutaneous tumor biopsy was realized during the procedure. 2 patients had a previous unilateral nephrectomy for renal cancer.

**Results:**

**Conclusions:** Thermal RFA is a valuable and non-aggressive alternative therapy to open surgery in the setting of multiple and bilateral kidney cancer of VHL. Three patients with small nodules between 2.5 and 4.2 cm were treated successfully and without complications with this modality. Follow-up time was of 2.5 years (pt 1), 9 months (pt 2) and a 3rd one with an extremely fragile condition were treated successfully and without complications with this modality. Follow-up time was of 2.5 years (pt 1), 9 months (pt 2) and a 3rd one with an extremely fragile condition were treated successfully and without complications with this modality.

**Patients**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Temperature</th>
<th>Procedure</th>
<th>Tumor Size (cm)</th>
<th>Tumor Site</th>
<th>Post-ablation</th>
<th>Follow-up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>F</td>
<td>Yes</td>
<td>Percutaneous Tumor biopsy</td>
<td>2.5</td>
<td>Right</td>
<td>122.7</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>M</td>
<td>No</td>
<td>Percutaneous Tumor biopsy</td>
<td>3.5</td>
<td>Right</td>
<td>108.6</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>M</td>
<td>Yes</td>
<td>Percutaneous Tumor biopsy</td>
<td>4.2</td>
<td>Left</td>
<td>66.9</td>
<td>54</td>
</tr>
</tbody>
</table>

RFA: Radiofrequency ablation

---

PUB396

Urine Citrate Excretion, a Renal Bioenergetic Source, Is Reduced in Autosomal Dominant Polycystic Kidney Disease

Matthew Lanktree.1 Peli Chen,2 Anna L. Zisman,2 Bharathi V. Reddy,2 Kristin J. Bergslund,2 Fredric L. Coe,2 Elaine M. Worcester,2 Arlene B. Chapman.2 Nephrology division, McMaster University, Hamilton, ON, Canada; 1University of Chicago, Chicago, IL.

**Background:** Increased renal metabolism is a feature of autosomal dominant polycystic kidney disease (ADPKD). Hypocitraturia occurs in ADPKD and has been ascribed to reduced glomerular filtration rate (eGFR) and defects in renal tubular acidification. We hypothesize that ADPKD patients have hypocitraturia independent of these abnormalities.

**Methods:** 16 APDKD and 16 age-, sex-, and eGFR-matched controls with relatively intact kidney function (mean eGFR=64 ml/min/1.73m²) provided a 24-hour and a fasting morning urine and plasma sample in a Clinical Research Center setting. Serum creatinine, electrolytes and citrate, and urine pH, creatinine, electrolytes, and citrate were obtained, and eGFR, fractional excretion of citrate (FECit), gastrointestinal alkali absorption (GIAA), net endogenous acid production (NEAP), and net acid excretion (NAE) were calculated.

**Results:** Unadjusted urinary citrate and FECit were significantly lower in ADPKD vs. controls (327 ± 221 vs. 548 ± 199 mEq/day, P=0.006; 4.6 ± 2.4 vs. 11.5 ± 5.4 %, P=0.002). No difference in plasma citrate, GIAA, NEAP, or NAE were observed between ADPKD and controls (3.8 ± 1.1 vs. 3.9 ± 1.2 mmol/L, P=0.9; 18.5 ± 24.7 vs. 26.2 ± 19.6 mEq/day, P=0.4; 38.5 ± 19.5 vs. 28.8 ± 15.1 mEq/day, P=0.3). No difference in 24-hour urine pH or bicarbonate (5.8 ± 0.5 vs. 6.1 ± 0.5, P=0.2; 3.5 ± 4.8 vs. 3.1 ± 2.7 mEq/L, P=0.3), serum bicarbonate or potassium concentration (25.0 ± 2.1 vs. 25.2 ± 1.9 mmol/L, P=0.3; 4.2 ± 0.3 vs. 4.3 ± 0.9 mmol/L, P=0.5) were observed. Linear regression modelling demonstrated that ADPKD status contributed independently to 24-hr urinary citrate excretion and FECit beyond eGFR, GIAA, NEAP, and urinary potassium, chloride, and ammonium excretion (R² = 0.56, F-statistic = 10.0, P<0.001).

**Conclusions:** ADPKD status associates with decreased urinary citrate excretion. Decreased FECit in the setting of unchanged plasma citrate concentration indicates an enhanced proximal tubule uptake of citrate. Citrate provides 10% of energy for renal metabolism under normal conditions. Given epithelial proliferation, cyst growth, expansion, and the increased metabolic demands of kidneys in ADPKD, urinary citrate uptake may provide additional epithelial energy substrate.

**Funding:** NIDDK Support
Clinical Outcome of Patients with Autosomal Dominant Polycystic Kidney Disease Receiving Renal Replacement Therapy Seong Sik Kang,1,2 Hayeon Park,1 Sang Mok Yeo,1 Yoong Yeong Park,1,2 Kyubok Jin,1 Sung Bae Park,1 Seungyeung Han,1,2 Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Republic of Korea; Keimyung University Kidney Institute, Daegu, Republic of Korea.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic cause of kidney disease in patients receiving renal replacement therapy (RRT). However, there are few reports of clinical outcomes of patients with ADPKD receiving RRT. Herein, we evaluated clinical characteristics and outcomes of patients with ADPKD.

Methods: We retrospectively reviewed the medical records of 253 patients with ADPKD at Keimyung university hospital between January 1989 and January 2017. We analyzed risk factors for renal disease progression and survival rates in patients with ADPKD receiving RRT.

Results: The mean age at diagnosis was 43.2 ± 13.2 years (range, 10-75). Males were 129 (51%) and patients with a family history of ADPKD were 93 (37%). Average duration of follow-up was 76 ± 74.5 months (range, 1-280). Among the 253 patients, 125 (49%) progressed to CKD stage 5 and 100 (40%) received RRT. The mean duration from diagnosis to renal replacement therapy was 8.8 ± 7.8 years (range, 0-32). In a multivariate analysis, hypertension (HR 2.154, P = 0.016), cardiovascular disease (HR 4.325, P = 0.023), cyst infection (HR 5.317, P < 0.001) were independent risk factors for progression to end-stage renal disease (ESRD). The number of patient receiving hemodialysis, peritoneal dialysis, and kidney transplantation (KT) was 72, 2, and 26, respectively. Twelve (40%) of the 26 KT recipients (KTRs) were treated prior to transplantation. Four underwent simultaneous bilateral nephrectomy and 8 underwent renal artery embolization. The 5-year survival rate of patients without RRT and KTRs was 94.3 ± 2.3% and 96 ± 3.9%, respectively, which was higher than that of 82 ± 5.2% in hemodialysis patients (P = 0.021). The 5-year survival rate of allograft kidney in KTRs was 88 ± 8.1%. The prevalence is calculated considering alive ADPKD patients at the diagnosis of at risk patients without clinical information was predicted on a 6 part small feeding diet and has been followed for 6 months with stable weight and no hospitalizations.

Conclusions: Hypertension, cardiovascular disease, and cyst infection were independent risk factors for progression of renal disease in ADPKD. In order to slow the progression to ESRD, best efforts to properly manage hypertension and cardiovascular disease are required. Nevertheless, when progressing to ESRD, KT can be recommended as treatment of choice.

ADPKD Prevalence in the Italian Province of Modena Suggests That Is a Rare Condition Francesca Testa,1 Andrea Solazzo,2 Marco Busutti,2 Luciana Furci,1 Silvia Giovanella,1 Giulia Ligabue,1 Giacomo Mori,1 Gianni Cappelli,3 Marco Leonelli,1 Riccardo Magistrini,1 Division of Nephrology, Dialysis and Transplant, Azienda Ospedaliero-Universitaria Policlinico di Modena, Modena, Italy; 2UO Nefrologia, Dialisi e Trapianto, Dipartimento di Medicina Specialistica e Sperimentale, Ospedale Sant’Orsola-Malpighi, Alma Master Studiorum Università di Bologna, Bologna, Italy.

Background: The population of the Province of Modena is 701,642 inhabitants (ISTAT, 2016). The prevalence is calculated considering alive ADPKD patients at the date of 31/Oct/2016. All possible sources of information, including electronic databases, clinical notes of nephrology clinics, registry of RRT patients, have been checked. Index cases were asked to sign the consent and have been clinically evaluated. At risk subjects were identified using specific algorithms in the study as well. Missing data were managed through a mixed linear model. The diagnosis of at risk patients without clinical information was predicted through a binary logistic regression. The risk curve was modeled on the population characteristics of the province of Modena extracted from the last census (ISTAT, 2016).

Results: The population of the Province of Modena is 701,642 inhabitants (ISTAT, 2016). 254 affected subjects were identified. The point prevalence of ADPKD subjects is 3.63:10,000 (IC 95% = 3.010-3.758). Estimated prevalence adjusted for missing diagnosis is 4.82:10,000 (IC 95% = 4.640-4.987). 81% of patients are in renal replacement therapy (41.9% hemodialysis, 11.6% peritoneal dialysis, 46.5% transplant). 42 subjects underwent to a molecular genetic evaluation that showed the involvement of PKD1 in 83% of cases and PKD2 in the remaining 17%. Renal survival is worse in patients with truncated PKD1 mutations (25 survival age 48 years), followed by PKD2 mutations (25 survival age 59 years) and finally by PKD1 missense mutations (25 survival age 64 years).

Conclusions: The prevalence of ADPKD in the Province of Modena is lower than frequently reported in the literature. In our analysis the point prevalence is 3.63:10,000, inhabitants, while predicting missing ADPKD subjects in the cohort of at risk subject produces an estimated prevalence of 4.82:10,000. These estimates are compatible with the definition of rare disease adopted by the European Medicines Agency and FWA and FDA.

Gastropareis in Polycystic Kidney Disease – Emphasis on Early Diagnosis Rhea Bhargava,1 Shradha Gupta,2 Theodore I. Steinman,1 Beth Israel Deaconess Medical Center, Boston, MA; 2Saint Vincent Hospital, Worcester, MA, Worcester, MA.

Background: Malnutrition can lead to poor outcomes in renal patients. Early satiety is a well known symptom of polycystic kidney disease. Most of these cases do not undergo an extensive outpatient workup for their GI symptoms and this can lead to unnecessary hospital visits.

Methods: 42 year old male who was diagnosed with polycystic kidney disease at 17 years of age after undergoing a renal ultrasound because of high blood pressure and a history of PKD in the family. His mother developed renal failure and underwent a transplant in 2001. His sister, 2 years older than him is presently on hemodialysis and was also diagnosed with PKD. He has a diagnosis of hypertension since childhood, which has been managed with lisinopril 20 mg daily. Reports decreasing energy levels for the past 2-3 years with associated early satiety and loss of appetite. He was unable to tolerate full meals and was nauseated after even by several plates. He was also diagnosed with hypokalemic nephropathy for hypovolemia leading to acute kidney injury. No history of hematuria, dysuria, increase in abdominal girth, fever or chills. He has never had any stones or UTIs. He has associated polycystic liver disease as well. Several EGD studies did not reveal any pathology and systemic examination is unremarkable except pallor. He has lost 8 kg over 3 years. Cr has been stable at 1.2 mg/dl for the past 5 years. No other laboratory abnormalities were noted except anemia with a Hb of 11 g/dl. Gastric emptying study showed delayed gastric emptying. Further workup with a CT scan was pursued and this was significant for several right renal cysts providing extrinsic compression on the descending portion of the duodenum. This was thought to be the cause of early satiety. The patient was started on a 6 part small feeding diet and has been followed for 6 months with stable weight and no hospitalizations.

Results: Conclusions: Mechanical complications of PKD have not been well described and sometimes are undiagnosed. Early screening and close monitoring of these patient with extrinsic bowel compression from cysts can avoid unnecessary procedures and prolonged hospital stays. This can also lead to early management and prevent mortality in these patients. Working in conjunction with urologists to relieve severe symptomatic compression by unreoofing cysts has been described.

A Rare Case of Distal Renal Tubular Acidosis Complicated with Hypokalemia Nephropathy Xiaoyu Liu, Xuhui Zhong, Jie Ding, Peking University First Hospital, Beijing, China.

Background: To report a rare case of distal renal tubular acidosis boy complicated with hypokalemia nephropathy, and analyze the association of hypokalemia, renal tubular acidosis and renal cysts. Detailed clinical data were collected and analyzed. Renal ultrasound and MRI were detected to follow up the change of renal cysts.

Methods: A 9 years old boy, first presented to hospital with a complaint of poor growth and motor retardation at 9 months old. Initial blood investigations showed hypokalemia, hyperchloremic acidosis, with urine PH >5.5. Renal ultrasound showed calcinosis. Renal tubular acidosis and inborn metabolic error were suspected, but no positive was result shown in metabolic screening test. Treatments of sodium bicarbonate, potassium citrate were started, but the follow-up was irregular and the treatment of potassium citrate was not persistent. Other problems, such as growth retardation, rickets, consistent muscle weakness, polyuria and polydipsia developed, and he had experienced several episodes of paralysis which could be relieved by potassium chloride infusion. At the age of 8, urine analysis showed alkalinuria, low titratable acid and FeHC03. Urine anion gap was 37.39mmol/L. So the diagnosis was type I renal tubular acidosis. But the lab investigation also showed small molecular proteinuria, aminoaciduria and increase of calcium, phosphorus and potassium in urine. Multiple cysts were found in a latest renal ultrasound. In consideration of his long term hypokalemia, a diagnosis of hypokalemic nephropathy was made. After treatment of sodium bicarbonate, potassium citrate and phosphorous salts, his symptom improved with correction of hypokalemia and metabolic acidosis. After 6 months follow-up, his urine protein was negative and the size of renal cysts was decreased.

Results: Conclusions: Persistent hypokalemia might induce to hypokalemic nephropathy, which manifest as renal tubular acidosis as well as renal cysts. Doctors should pay attention to hypokalemia and correct it as soon as possible.


Background: For the adequate therapeutic strategy, especially decision of Tolvaptan indication, prognostic assessment of autosomal dominant polycystic kidney disease (ADPKD) is very important. At present, there is no effective way to predict and had a hospital staff as most reliable parameter in this regard, however, repeated CT/MRI scanning with one year

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
interval is required to assess KGR. This study aimed to investigate the prognostic efficacy of using N-acetylglucosaminidase-to-Cr ratio (NAG index), conventional parameter for tubulo-interstitial nephropathy (TIN), in patients with ADPKD.

Methods: Clinical data of ADPKD patients who received CT scanning twice or more, before beginning to use Tolvaptan in our facility (n=60) were studied by the prospective analysis based on the medical record. Prediction model for TIN was prepared by focusing clinical data sampled one year prior to the latest CT scanning. In one year prior to the latest CT scanning based on the analytical approach of prospective observation from the past.

Results: Average or median value of age, total kidney volume (TKV), KGR, eGFR and NAG index were 50.2 of age, 1351.7 ml of median value, 5.4% per year of median growth, 47.4±20.3 ml/min and 5.47 IU/mgCr. Stratified analysis by the median value of KGR showed the significant difference in NAG index, but not TKV and eGFR. Univariate analysis showed that NAG index, but not TKV nor eGFR, significantly correlated with KGR (R=0.46, p=0.016), and multivariate analysis also showed that the NAG index would be a predictor of future KGR (partial regression coefficient=0.46, standard error=0.76, p=0.015). In addition, ROC analysis showed that the cut-off value of NAG index for the prediction of a 25%/year of KGR was 5.08 U/mgCr which is almost equivalent to the upper limit of generally accepted normal range of the NAG index (AUC 0.670, 95% CI 0.461 - 0.880, sensitivity 76.9%, specificity 57.1%)

Conclusions: NAG index might be a useful clinical parameter for the assessment of ADPKD prognosis and indication of Tolvaptan, which might be reasonable when it would be considered that ADPKD is a typical disease setting causing TIN.

PUB402
A Japanese Patient with Autosomal Dominant Polycystic Kidney Disease Suffering Sustained Liver Injury by Tolvaptan - Misaki Yoshida,1 Kazunori Yamada,2 Kiyoshi Ito,3 Nobuhiro Suzuki,4 Takahiro Matsunaga,5 Takeshi Yoshima,5 Satoshi Hara,3 Ichiro Mizushima,4 Hiroshi Fujii,3 Takeshi Sawada,5 Mitsuhiro Kawano,1 Division of Rheumatology, Department of Internal Medicine, Kanazawa University Graduate School of Medicine, Kanazawa, Kanazawa, Japan; Division of Rheumatology, Kanazawa University Hospital, Kanazawa, Japan; Kanazawa Graduate School of Medicine, Kanazawa, Japan; Kanazawa University Graduate School of Medicine, Kanazawa, Japan; Kanazawa University Hospital, Ishikawa, Japan; Kanazawa University hospital, Kanazawa, Japan; Kanazawa university, Kanazawa, Japan; Department of Advanced Research in Community Medicine Kanazawa University Graduate School of Medical Sciences, Kanazawa, Japan.

Background: The TEMPO 3-4 trial described that the elevation of AST and ALT were 3.2% and 4.9%, respectively. However, the whole picture of liver injury by tolvaptan has not been well understood, and the liver biopsy is ordinary liver function ameliorated. Conclusions: The detail mechanism and the clinical course of liver injury by tolvaptan has not been well clarified. Here, we reported an autosomal dominant polycystic disease with acute hepatitis due to tolvaptan. Corticosteroid (30 mg/day) was initiated and her hepatic enzymes had been increasing for two weeks. She was consulted to gerontologist and close examinations were performed. Blood tests showed that hepatits viruses and auto antibodies were also all negative in addition of normal value of C-reactive protein. Computed tomography showed only a few liver cysts. DILI due to tolvaptan was suspected, although drug lymphocyte stimulation test was negative. Ursodeoxycholic acid was started, but her liver injury did not ameliorate four weeks after discontinuation of tolvaptan (ALT 302 IU, AST 180 IU). We noted our hospital to perform liver biopsy to exclude other disease such as acute onset autoimmune hepatitis. Liver biopsy showed that lymphocytes, neutrophils, a few eosinophil infiltrations were existed. Necrosis with many pigment-phagocyte cells were seen around centriflobular zone. She was diagnosed with acute hepatitis due to tolvaptan. Corticosteroid (30 mg/day) was initiated and her liver function ameliorated. Conclusions: The detail mechanism and the clinical course of liver injury by tolvaptan has not been well understood, and the liver biopsy is ordinary difficult due to liver cysts in ADPKD patients. Therefore, this patient could give some important information to clarify the pathogenesis of liver injury by tolvaptan.

Results: Conclusions:

PUB403
Experience with Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease - Eiichi Sato,1,2 Tsukasa Nakamura,1 Takao Ono,2 Manaka Degawa,2 Hongmei Lu,2 Daisuke Matsumura,3 Mayumi Nomura,3 Mayuko Amaha,4 Akiko Fujii,5 Yuko Ono,1 Yoshikiko Ueda,1 Dokkyo Medical University, Koshigaya Hospital, Koshigaya, Saitama prefecture, Japan; Shimotsudo Central General Hospital, Matsudo City, Japan.

Background: The aim of this study was to demonstrate the treatment of autosomal dominant polycystic kidney disease (ADPKD) with Tolvaptan. We identified 496 patients using the ADPKD computable phenotype. we identified 496 patients using the ADPKD computable phenotype. We performed chart reviews of a random sample of 283 patients to determine if they had ADPKD or not. ADPKD was confirmed in 236 out of 283 charts reviewed. The ADPKD computable phenotype utilizes ICD9 codes 753.12 and 753.13, and ICD10:Q61.2 and Q61.3. This algorithm was developed through an iterative process by expert clinical nephrologist at KUMC. We used a de-identified patient information in i2b2 data access platform to search for patients with the potential diagnosis of ADPKD. Two reviewers independently determined whether patients had ADPKD or not using strict established criteria.

Results: We identified 496 patients using the ADPKD computable phenotype. We performed chart reviews of a random sample of 283 patients to determine if they had ADPKD or not. ADPKD was confirmed in 236 out of 283 charts reviewed. The ADPKD computable phenotype utilizes ICD9 and 10 codes provides a positive predictive value (PPV) of 83.4% (95% confidence interval 78%-88%). In four charts the diagnosis of ADPKD was unclear due to missing information. A sensitivity analysis was performed to determine whether classifying the excluded patients as having ADPKD, or as not having ADPKD, and it did not meaningfully change the results.

Conclusions: Identifying ADPKD patients using ICD 9 and 10 code has reasonable PPV. We are in the process of assessing the accuracy of the computable phenotype on a
sample of all patients at KUMC which will allow us to determine other accuracy measures including Sensitivity, Specificity and Negative Predictive Values of the computable phenotype. We also plan to validate the computable phenotype in other electronic medical record systems. In a condition like ADPKD, future research should focus on developing probabilistic phenotyping which may allow for consideration of radiology reports and/or family history that can enhance and improve the accuracy of the computable phenotype.

Criteria for diagnosing ADPKD

PUB406
Rapid Loss of Kidney Function Due to MYH9 Nephropathy: A Case Report
Felfely C. Barreto, Gabriela Sevgianni, Silke S. Milano, Giovanna M. Pavanelli, Maria A. Pachaly, Mauricio Carvalho. Universidade Federal do Paraná, Curitiba, Brazil.

Background: Mutations in the non-muscle myosin heavy chain gene (MYH9) are characterized by congenital macrothrombocytopenia, hearing loss, cataracts and glomerulonephritis. We sought to describe a case of rapid loss of kidney function in a young male patient due to MYH9 nephropathy.

Methods: Data were extracted from medical records.

Results: A 20-year-old male has been followed up at the Clinic Hospital of Federal University of Paraná due to medical history of epistaxis, ecchymoses and petechiae since infancy. At first, Bernard-Soulier Syndrome was suspected due to macrothrombocytopenia and tendency of bleeding. When he was 17 years old, hearing loss and hypertension were detected along with mild renal failure [creatinine: 1.2 mg/dl; CKD-EPI estimated glomerular filtration rate (eGFR): 88 ml/min/1.73m²]. Microhematuria and nephrotic-range proteinuria (7.5g/24h). Renal biopsy could not be performed due to the risk of bleeding (platelets: 7000/μl). Cataracts were excluded by ophthalmological evaluation. Due to the clinical suspicion of MYH9 nephropathy, genotyping of the patient and of his parents was performed: a de novo missense mutation in exon 1 of MYH9 [c.287C>T; p.Ser(TCG)96(TTG)Leu] was detected. Enalapril was initiated for renoprotection. The patient did not adhere to treatment and lost follow-up. Two years later, he returned to the Nephrology outpatient clinic complaining of foamy urine, peripheral edema and hypertension (160/120 mmHg). Laboratory tests detected worsening of renal function (creatinine: 3.2 mg/dl; eGFR: 36.4 ml/min/1.73m²) and persistent proteinuria (9.6g/24h).

Table shows the evolution of proteinuria and eGFR.

<table>
<thead>
<tr>
<th></th>
<th>March/2013</th>
<th>June/2015</th>
<th>March/2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.2</td>
<td>1.7</td>
<td>3.2</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>90.5</td>
<td>65.4</td>
<td>36.4</td>
</tr>
<tr>
<td>Proteinuria (g/24h)</td>
<td>7.5</td>
<td>5.5</td>
<td>3.6</td>
</tr>
</tbody>
</table>

eGFR - based on CKD-EPI formula

PUB407
Molecular Inversion Probes (MIPs) Are a Highly Scalable, Lower Cost Method for Targeted Sequencing of Kidney Disease Genes
Brendan Crawford, V Vega-Warner, D Fermín, Rasheed A. Ghadgesia, Simone Sanna-Cherchi, Jacob O. Kitzman, Matt G. Sampson, Columbia University, New York, NY; Duke University Medical Center, Durham, NC; University of Michigan, Ann Arbor, MI.

Background: Targeted sequencing is being used to diagnose patients with putative Mendelian forms of kidney disease. As the number of target genes & patients available for sequencing grows, we are challenged to use affordable and accurate sequencing strategies. Molecular inversion probes (MIPs) is a relatively new method that uses oligonucleotides to perform hybridization-based target capture for subsequent sequencing. MIPs can be massively multiplexed and do not require proprietary technology, thus reducing cost and enhancing scalability. But its performance versus other established methods is less understood. Here, we describe our experience establishing MIPs to screen implicated & candidate Mendelian nephrotic syndrome (NS) genes in a patient cohort.

Methods: We designed an array of 12,000 MIPs for 115 genes (55 previously implicated & 60 candidates). We did a pilot study of 192 NS patients (including 56 previously sequenced) & two 1000 Genomes (1000G) reference samples. Sequences underwent alignment, variant calling, and pathogenicity filtering; Sanger confirmation of qualifying variants was used. We assessed the depth of coverage achieved across the targets, sensitivity in detecting known variants, and depth of coverage needed for acceptable accuracy. We also identified factors impacting acceptable genomic coverage.

Results: The estimated cost was $30/patient, ~5x less expensive than microfluidic based amplification strategies. Sensitivity to detect known variants was 89-94% for 1000G and 100% for previously discovered mutations in NS cases (17/17). Overall, 3.8% of the target region (~23,000 bp) had low coverage, defined as <8X read depth in >10% of samples. Of these regions, 29% also had poor coverage in the Exome Aggregation Consortium dataset, suggesting these are, in general, challenging areas for sequencing. Capturing 1500 “escape” probes resulted in recovery of over 50% of low-coverage regions.

Conclusions: MIPs can be massively multiplexed on arrays, and incorporation of single-molecule tagging permits analysis of unique capture events, reducing the depth necessary at each site to achieve acceptable sensitivity. Provided that there is good DNA quality and rescue of poorly performing regions, MIPs is an accurate and cost-effective method for targeted sequencing studies.

Funding: NIDDK Support

PUB408
LMX1B Associated Nephropathy with Type III Collagen Deposition in Glomerular and Tubular Basement Membranes
Nicole K. Andeen, Jennifer Schleit, Christopher D. Blasser, Fuki M. Hisama, Kelly D. Smith. University of Washington, Seattle, WA.

Background: Variants in LIM homeobox transcription factor 1 beta (LMX1B) gene cause Nail-Patella Syndrome (NPS). Renal involvement is characterized by incorporation of thick bundles of collagen resembling type III collagen into glomerular basement membranes (GBMs). Recently, variants in LMX1B have been associated with renal-limited disease lacking skeletal, joint and nail findings of NPS.

Methods: The patient is a 39 year old man with a family history of kidney disease who presented for transplant evaluation. A kidney biopsy performed 10 years prior when he presented with hypertension, nephrotic syndrome of 5-6 years, and no other physical abnormalities revealed focal and segmental glomerulosclerosis (FSGS). Ultrastructural examination revealed aggregates of electron dense fibrils within thickened GBMs (image) and infrequently in mesangial regions. Some fibrils demonstrated a regular periodicity of 60 nm. Uninvolved GBMs had normal architectural organization and thickness. Several tubular basement membranes were thickened and contained similar fibrils. Immunofluorescence studies were negative. Next generation exome sequencing was performed 10 years later. A total of 66 genes associated with FSGS and steroid resistant nephrotic syndrome were examined. A pathogenic variant in one allele of LMX1B (c.717G>A(p.Arg246Gln)) was identified.

Results:

Conclusions: This case highlights the importance of clinical, pathologic, and genomic correlation, and has the novel finding of type III collagen deposition in tubular basement membranes in LMX1B associated nephropathy. LMX1B variants should be considered as a potential cause of sporadic and hereditary forms of FSGS and steroid resistant nephrotic syndrome, especially in cases where electron microscopy studies reveal incorporation of bundles of type III collagen into basement membranes, regardless of the presence or absence nail or skeletal findings associated with NPS.

Funding: NIH/NEI R01 EY021773

PUB409
Autosomal Dominant Interstitial Disease of Kidney – Father and Son Underwent Transplantation
Pradeep P. Deshpande. Hyderabad, India.

Background: In a village, in India, with 5000 population, around 500 people are suffering from kidney disease. Out of which 100 are on Hemodialysis and 35 underwent kidney transplantation. One family of the same village, in which 6 of the family members are suffering from kidney disease. Father underwent kidney transplantation in 2006 and son underwent kidney transplantation in 2013. Genetic analysis was done for family

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Modulation of Angiotensin II Binding and AT1 Receptor Expression in Experimental Alport Mouse Kidney

Christopher Neagra, 2 Hong weng Pang, 2 Andrea Linares Lopez, 2 Judith T. Molina David, 3 Alessia Fornoni, 3 Robert C. Speth, 4 Palmetto General Hospital, Hialeah, FL; 2College of Pharmacy, Nova Southeastern University, Fort Lauderdale, FL; 3Katz Family Drug Discovery Center and Division of Nephrology, University of Miami, Miami, FL; 4Dept. Pharmacology and Physiology, Georgetown University, Washington, DC.

Background: Alport Syndrome (AS) is a progressive renal glomerular disease that causes kidney failure and hearing and visual impairment, affecting as many as 3% of children and 0.2% of adults with end-stage renal disease (ESRD). It is caused by mutation of a Type IV collagen gene. Angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) are currently the only treatments that slow progression of ESRD in AS.

Methods: Eight-week-old Col4a3 -/- (KO) and wild-type (WT) mice were utilized. AT1 receptors were assayed using 125I-sarcosine (1, isoleucine8 I-SI Ang II) by saturation binding, and receptor autoradiography to determine receptor density, distribution and binding affinity.

Results: There was a significant 48% decrease (p = 0.01) in AT1 receptor binding in KO compared to WT mouse kidneys (fmole/mg initial wet weight). However, when expressed as fmol/mg protein, the decrease in the Bmax for AT1 receptor was 31%, which was not significant (p = 0.11). Interestingly, there was a 24% decrease in mg protein/g expressed as fmol/mg protein, the decrease in the Bmax for AT1 in KO compared to WT mouse kidneys (fmole/mg initial wet weight). However, when expressed as fmol/mg protein, the decrease in the Bmax for AT1 receptor was 31%, which was not significant (p = 0.11).

Conclusions: The density and affinity of AT1 receptors in the whole kidney cortex are reduced or not altered in experimental AS. This suggests that ERT alone and ACEI-ARB in AS is not linked to overexpression of AT, receptors in the kidney or to increased receptor binding. If and how the different distribution of AT1R may contribute to disease progression remains to be established.

PUB411
Renal Manifestations of Deficiency of Adenosine Deaminase

Marika Manolopoulou, Ed Gould, Julia Lewis. Vanderbilt University Medical Center, Nashville, TN.

Background: First described in the literature three years ago, deficiency of adenosine deaminase (DADA2) has since been appreciated to have a myriad of clinical phenotypes. DADA2 is a disease defined by loss of function mutations in the CEUR1 gene, leading to inflammatory activation and early-onset vasculopathy. To date, the renal phenotypes observed in this genetic disease have yet to be fully described in the literature. Here, we introduce one patient diagnosed with DADA2 and characterize her renal phenotype.

Methods: An 18-year-old Caucasian female with DADA2 was referred to renal clinic for evaluation of mildly elevated serum creatinine and low serum bicarbonate. She initially developed manifestations of cutaneous polyarteritis nodosa with livedo reticularis at age two. Despite successful remission with methotrexate, she had several periods of disease relapse over the following decade. Her pre-pubertal serum creatinine (sCr) was 0.3 - 0.4 mg/dL. Between the ages of 8 and 10, her sCr rose to 0.8 - 0.9 mg/dL. At age 14 she was recognized to also have neutrophilic abacterial, cytophenias and relative immunodeficiency; she was managed with non-susorpic based IVlg. This constellation of signs and symptoms prompted referral to the NIH for evaluation. At age 17, shortly after DADA2 was described in the literature, she underwent confirmatory genetic testing. Given the complexity of her case, we referred to renal clinic to consider possible disease manifestations in her kidney. Her renal workup in our clinic – which has been conducted during a period of relative disease quiescence – has demonstrated a stable sCr (0.9 -1.0 mg/dL), an inactive urinary sediment, and a mild metabolic acidosis (serum bicarbonate 18-20 mmol/L) likely driven by a distal renal tubular acidosis.

Results: Conclusions: Adenosine deaminase 2 is primarily active in the extracellular space and seems to have a variety of roles, including serving as a modulator of the extracellular inflammatory milieu. The vasculopathy observed with DADA2 deficiency likely also manifests in the renal vasculature. In our patient, we suspect that her mild renal insufficiency stems from renal vasculopathy during periods of disease activity in her youth. Given the rarity of this disease, we support centralizing a patient database for additional investigation and characterization of the renal specific phenotypes that can be observed.

PUB412
Long Term Renal Function in Patients with Fabry Disease

Ricardo M. Heguielén, 1 Juan Politi, 2 Gustavo H. Cabrera, 2 Amelia R. Bernasconi, 2 Del Viso Medical Group, Buenos Aires, Argentina; 2Hospital Fernandez, Buenos Aires, Argentina; 3Hospital Juan A Fernandez, Buenos Aires, Argentina; 4Department of Neurology, Laboratorio Chamoles, Buenos Aires, Argentina.

Background: Proteinuria and progressive renal dysfunction, along with cardiovascular and neurological conditions are major findings in patients with Fabry disease (FD). In order to prevent progressive organ failure, enzyme replacement therapy (ERT) should be started early to remove substrate deposition in target tissues. In this study we analyze the renal outcome of a cohort of individuals followed-up throughout a period of almost 15 years from the diagnosis of FD.

Methods: Prospective cohort study analyzing the time until an increase in serum creatinina (Screat) 1.5 times from baseline. Proportional hazard (Cox) regression was used to determine whether such outcome was a dependent variable on the following potential covariates: gender, age, hypertension (HTN), diabetes, tobacco use, overweight (OW) or the presence of dyslipemia. Odds ratios with the appropriate 2-sided 95% CI were reported. Kaplan-Meier and the Log-Rank test were used to compare survival curves. All tests were 2 sided, and p values < 0.05 were considered statistically significant.

Results: 44 individuals (13 male) fulfilling the inclusion criteria were followed-up for a mean period ranging from 1 - 15 years; most of them (80%) receiving ERT from 1 through 13.5 years. The age at diagnosis of FD was 35 ± 2.1 y, baseline creatinine (SCr) was 0.9 ± 0.1 and GFR 89.5 ± 5.0. Ten individuals (6 M) developed the outcome; the median time until the occurrence of the main outcome was 4.6 y, (p< 0.01 for gender difference). Male gender (OR 8.9 - 95% CI 1.2-66.8), HTN (10.2; 1.1 – 95.5) and OW (28.7; 1.6 – 50.6) were associated with worsening renal function.

Conclusions: Renal involvement in FD is frequent, and the main findings are proteinuria, decreased GFR and tubular dysfunction. ERT may be important to lessen the burden of the disease but is also mandatory to remove other modificable risk factors that play a major role in the progression of renal involvement.
Familial Neurohypophyseal Diabetes Insipidus (FNDI) Spanning Five Generations

Background: FNDI is a rare genetic mutation in the AVP gene on chromosome 20p13, resulting in misfolded AVP precursors within the endoplasmic reticulum of hypothalamic neurons, causing cell death. Progressive neuronal degeneration can delay onset of symptoms, however polyuria and polydipsia usually manifest before age 6. Inheritance is autosomal dominant (AD), although autosomal recessive (AR) and X-linked inheritance have been reported. We present a middle-aged patient diagnosed with FNDI, unveiling 5 generations of affected individuals in her family.

Methods: A 56 year old woman with polyuria and nocturnal enuresis since infancy consulted nephrology following a diagnosis of FNDI in her daughter during pregnancy complicated by dehydration, hypokalemia, and congestive heart failure. Our patient recalled headaches, dizziness, nausea and fatigue with decreased water intake. She had exacerbation of symptoms with limitation of oral intake at the time of a cholecystectomy and ovarian cystectomy. Family lax was positive for polydipsia (siblings) and nocturnal enuresis (daughters). Of note, despite a BMI of 28.8, and full term pregnancies, the patient delivered low birth weight babies (3.5b 13.3 lbs). Initial labs: Cr 0.6 mg/dL, Na 138 meq/L, Ur SG <<1.005. Overnight water deprivation test revealed a Ur osmolality of 398, Sr osmolality 297, serum Na 146 meq/L. Intranasal desmopressin was initiated, Ur SG increased to 1.015, consistent with central DI. Panel gene sequencing of the AQ2 and AVP genes was negative while the patient was heterozygous in the AVP gene for a sequence variant (c.232_234delGAGG), which results in the deletion of one amino acid (p.Glu78del). This mutation is pathogenic for AD FNDI.

Results:

Conclusions: Patients with Central DI have an inability to conserve free water, and FNDI can present with chronic bedwetting, polydipsia and polyuria resulting in growth retardation in childhood, or insidious symptoms with severe electrolyte disturbances during stress (e.g. pregnancy). Genetic screening is essential in patients with Central DI as FNDI affects multiple generations and can have AD, AR or X-linked inheritance.

Late Onset Variant N215S GLA Mutation Associated with Fabry Nephropathy

Background: Fabry disease (FD) is a heterogeneous condition with >700 GLA gene mutations/variants. Characterization of phenotype severity can guide FD treatment. Late onset variants are believed to cause milder phenotypes compared with classical mutations. We compared glomerular lesions, renal function and structural-functional relationships (SFR) in Fabry patients with late onset N215S vs. classical GLA mutations.

Methods: 7 (MF=4:3) Fabry patients with N215S mutations, age 39-7(5), median (range) years were compared with 7 age and sex matched patients with classical mutations. Fractional volumes of globotriaosylceramide (GL3) inclusions per endothelial [Vv(GL3/Endo)] and mesangial cells [Vv(GL3/Mes)] and podocytes [Vv(GL3/Podo)] were estimated using electron microscopy stereology. Renal function data included urine albumin and protein creatinine ratios (Acr and Pcr) and GFR.

Results: All patients had microalbuminuria. GFR, Acr or Pcr were not different between classical and N215S patients. N215S was associated with lesser Vv(GL3/Endo) (r=0.03) and Vv(GL3/Mes) (p=0.03). Vv(GL3/Podo) was numerically greater (0.35±0.16) than in N215S mutations (0.20±0.21) regardless of sex, but the difference was not significant. There was marked variation in Vv(GL3/Podo) among N215S patients regardless of sex, but in patients with classic mutations, variation in Vv(GL3/Podo) was restricted to females. While PCR was strongly associated with Vv(GL3/Podo) (r=0.78; p=0.04) and Vv(GL3/Endo) (r=0.86; p=0.01) in the classical group, such SFRs were not seen in the N215S group. Among the clinical symptoms, corneal opacities and gastrointestinal complications were more frequent in the classical compared with the N215S groups.

Conclusions: Late onset N215S variant, typically associated with residual enzyme activity, is associated with less GL3 inclusions in endothelial and mesangial cells, and shows remarkable variation in GL3 content in podocytes compared with classical mutations. This study suggests, despite delayed onset and milder symptoms with the N215S mutation, these patients may develop substantial Fabry nephropathy with podocyte injury and microalbuminuria.

Funding: Other NIH Support - NINDS, Commercial Support - Sanofi

The Distribution Characteristic of Monoclonal Antibody against Triple Helix of Type IV Collagen α Chain in Epidermal and Renal of X-Linked Alport Syndrome Patients with Different Genotypes

Background: To investigate the distribution characteristic of monoclonal antibody against triple helix of type IV collagen α chain in epidermal and renal basement membranes of X-linked Alport syndrome boys with different genotypes.

Methods: Indirect IF staining of monoclonal antibody against type IV collagen α5(IV) on the skin and kidney sections of X-linked Alport syndrome boys with different genotypes were analysed.

Results: In 10 X-Linked Alport syndrome boys whose staining of α5(IV) was negative on the EBIM, the staining pattern of monoclonal antibodies against triple helix of type IV collagen α5(IV) on the EBIM was negative in 5 patients but positive in the other 5 patients. A significant relationship between genotype and the staining pattern was found. In 5 X-Linked Alport syndrome boys whose staining of α5(IV) was positive on their EBIM and GBM, the staining pattern of monoclonal antibodies against triple helix of type IV collagen α5(IV) was positive.

Conclusions: Mutations in the COL4A5 gene product abnormal α5(V) chain, and the abnormal α5(V) chain can assemble triple helix type IV collagen protomers with other chains. But the mechanism of how the abnormal protein distribute to the basement membranes and assemble triple helix type IV collagen protomers was still unknown.

Funding: Government Support - Non-U.S.

Diffusion Restriction of Kidney Medulla in Gitelman Syndrome Patients Detected by the New Diffusion Kurtosis Imaging of MRI

Background: Gitelman syndrome (GS) is an inherited tubulopathy with Na+-K+ cotransporter (NCC) dysfunction. Regular imaging techniques including magnetic resonance imaging (MRI) could not detect any changes in kidney of GS. Diffusion kurtosis imaging (DKI) is a new method of MRI which could disclose more precise tissue structure and non-Gaussian water diffusion. This study first applied this novel technique in GS patients to observe the potential biostuctural and functional abnormality of the kidney.

Methods: Sixteen genetically diagnosed GS patients and 24 healthy subjects were enrolled and underwent Diffusion-Weighted imaging of the kidney at a 3 Tesla. Region-of-interest measurements were performed to determine apparent diffusion coefficient (ADC), kurtosis (K) and diffusivity (D) value of the kidney cortex and medulla. Pearson or Spearman correlation was used to evaluate the association between DKI-derived parameters and clinical data, including serum and urine electrolyte levels, plasma upright RAAS levels, and the in vivo NCC function evaluated by the thiourea test.

Results: The mean age of GS patients was 30±10.8y and 50% were males, with a mean onset age of 25±12.7y. At admission, the median duration of hypokalemia was 24(12, 126) months and the mean serum K+ was 3.25±0.6 mmol/L, the urinary K+ excretion was up to 91±32.9 mmol/L. Compared to healthy subjects, lower ADC (1.4±7.0±189 vs. 1.5±7.0±115, P=0.022) indicating greater diffusion restriction was observed in the renal medulla of GS, but ADC was similar in the cortex. ADC of the cortex was associated with plasma Angiotensin (r=0.529, P=0.035) and mean blood pressure (r=-0.598, P=0.014). Among GS patients, D indicating the observed non-Gaussian behavior and K reflecting the more prominent distribution of tissue diffusivities correlated well with serum Cl- (r=-0.733, P=0.001; K: r=-0.664, P=0.005), HCO3- (D: r=-0.603, P=0.014; K: r=-0.621, P=0.010) and actual base excess. In the medulla, only K value associated with serum Cl-(r=-0.562, P=0.023). No correlations were observed between DKI-derived parameters and serum potassium or urinary electrolytes excretion.

Conclusions: In GS patients, diffusion restriction of water molecule in kidney medulla was observed by the novel DKI-MRI and associated well with hypokalemia and metabolic alkalosis.
Erdheim-Chester: A Rare Multi-System Disease

**Background:** A case of Erdheim-Chester disease which demonstrates the classic features of the disease including BRAF gene mutation. We have followed up the patient for over 8 years. We aim to demonstrate the challenges in diagnosis and management of a rare disease.

**Methods:** 55 year old normally fit and well man presented with tiredness and weight loss and underwent investigations for anaemia. Geneticai studies did not find any abnormalities. Upper gastrointestinal biopsies only showed metaplastic changes. He was found to be in acute kidney failure with a Creatinine of 199 µmol/l but no significant proteinuria or microscopic haematuria. A CT scan of abdomen demonstrated retroperitoneal disease, mesenteric soft tissue mass, left adrenal mass and bilateral hydronephrosis. A laparoscopic biopsy of peritoneal tissue confirmed the suspicion of retroperitoneal fibrosis. Vascularic screening has been negative. Patient underwent bilateral ureteric stents for urinary obstruction due to fibrosis and kidney function remained stable during this time. Two years after initial presentation, patient developed bilateral exophthalmos with associated double vision. A biopsy of retro-orbital mass was not diagnostic but excluded malignant causes. Patient received various different immune suppression treatment including rituximab, but showed no response. A diagnosis of IgG4 was excluded from the differentials and Erdheim-chester disease was considered as a possible differential diagnosis. Based on this, X-rays of limbs showed diffuse medullary and cortical sclerosis within the long bones that is classical of Erdheim-chester disease. An MRI of heart showed a cardiac pseudo-tumour. Since a diagnosis of Erdheim-chester was made, patient was started on treatment with Pegylated Interferon therapy for which a good response was shown clinically and on imaging. Unfortunately this had to be discontinued due to drug related hepatitis. Genetic testing came positive for BRAF g600E mutation that has been associated with Erdheim-chester disease. At present he is off treatment and awaiting funding for Vemurafenib.

**Results:** Conclusions: Erdheim-chester is an extremely rare multi-system disease. A little is known about the disease and reported cases in literature is limited. There has been significant challeges in diagnosis. Awareness and high index of clinical suspicion of disease is helpful in diagnosis and timely management.

**PUB417**

Erdheim-Chester: A Rare Multi-System Disease

**Background:** A four years old girl presented with microhematuria at 25 months old, The Lyso GB3 value was within normal ranges 0.6 ng/ml (normal range 0.00 -3.5). A request for genotyping was made and no mutations were found in the GLA gene.

**Conclusions:** In this study, 51 patients in HD have been included in the study after signing their informed consent. This is a single prospective study. This cohort consisted of 31 male patients aged between 27 and 65 years and 20 female patients aged between 35 and 65 years. 4 patients had past history of renal transplantation (1 male; 3 female). The median time of dialysis for male patients ranged from 3 to 97 months and from 6 to 159 months for female patients. Residual enzyme activity of α-GAL was tested in men. For women α-GAL activity combined with testing for Lyso GB3 levels was performed. The genetic test will be performed if the enzyme activity and/or if the Lyso GB3 value is reduced.

**Results:** No patient among 51 was diagnosed with FD. In a female patient the α-GAL enzyme activity was extremely low: 1.4 µmol/l/h (cut-off < 2 µmol/l/h). The Lyso GB3 value was within normal ranges 0.6 ng/ml (normal range 0.00 -3.5). A request for genotyping was made and no mutations were found in the GLA gene.

**Conclusions:** In this study, 51 patients undergoing HD were included to test for Fabry's disease although no patients were diagnosed. A review of the international literature suggests a prevalence of FD in patients with end-stage renal failure (ESRF) near 15%. Several large studies reported a prevalence of 0. It is important to change our practice and routinely investigate for Fabry's disease in patients in ESRF of indeterminate cause. Multi-disciplinary care is required and particularly a medical visit with geneticists and genetic counsellors in order to establish a family pedigree to screen other members of the family. A total of 51 patients in HD have been included in the study after signing their informed consent. This is a single prospective study. This cohort consisted of 31 male patients aged between 27 and 65 years and 20 female patients aged between 35 and 65 years. 4 patients had past history of renal transplantation (1 male; 3 female). The median time of dialysis for male patients ranged from 3 to 97 months and from 6 to 159 months for female patients. Residual enzyme activity of α-GAL was tested in men. For women α-GAL activity combined with testing for Lyso GB3 levels was performed. The genetic test will be performed if the enzyme activity and/or if the Lyso GB3 value is reduced.

**Results:** No patient among 51 was diagnosed with FD. In a female patient the α-GAL enzyme activity was extremely low: 1.4 µmol/l/h (cut-off < 2 µmol/l/h). The Lyso GB3 value was within normal ranges 0.6 ng/ml (normal range 0.00 -3.5). A request for genotyping was made and no mutations were found in the GLA gene.

**Conclusions:** In this study, 51 patients undergoing HD were included to test for Fabry's disease although no patients were diagnosed. A review of the international literature suggests a prevalence of FD in patients with end-stage renal failure (ESRF) near 15%. Several large studies reported a prevalence of 0. It is important to change our practice and routinely investigate for Fabry's disease in patients in ESRF of indeterminate cause. Multi-disciplinary care is required and particularly a medical visit with geneticists and genetic counsellors in order to establish a family pedigree to screen other members of the family.
Jihyen Arabia showed 0.04% in hemodialysis patient of Jeju island. More accurate diagnostic tool their presumptive clinical cause of renal failure was DM in one of the 3 patients, the gene analysis was performed in all patients with low

IL-4 Receptor Gene Polymorphism in Childhood Idiopathic Nephrotic Syndrome Amal A, Al-eisa, Pediatrics, Kuwait University, Kuwait, Kuwait.

Background: Idiopathic Nephrotic syndrome (INS) is an immune-mediated disease with a well-documented association with atopy. IL-4 is a vital cytokine involved in atopic symptoms mediated through its receptors (IL-4R). Gene polymorphism of IL-4 receptor (IL-4R) plays an essential functional role of IL-4R, and therefore might have a role in the pattern of INS. The aim of this study is to determine the frequency and the association of IL-4R gene polymorphisms with idiopathic nephrotic syndrome (INS) and its effect on the disease pattern in Kuwaiti children.

Methods: Genotypes of the IL-4R gene polymorphisms were analyzed using PCR-RFLP in 151 INS patients and 59 age and sex-matched controls. Clinical data of all subjects were reviewed. Results: A total of 151 INS (129 steroid-sensitive and 22 steroid-resistant) patients with a mean age was 7.6±4.3 years were studied. Male: Female ratio was 2:1. The CC genotype of IL-4R gene polymorphism was detected in 64% of the INS patients compared to 69.5% of the controls (P=0.57). The heterozygous CT genotype was detected in 30% of INS patients compared to 25.5% of the controls (P=0.61). The TT-genotype was detected in 6% of INS patients and 5% of the controls (P=1.00). The C-allele frequency in homozygous and heterozygous forms was found in 94% of INS patients compared to 95% of the controls (P=1.00). The T-allele frequency in homozygous and heterozygous forms was found in 35.7% of INS patients compared to 30.5% of the controls (P=0.57). No significant difference was found in any of the allele frequencies between SS and SR sub-groups when compared with each other or when compared to the controls.

Conclusions: Our data shows no role of IL-4 receptor gene polymorphisms on the clinical pattern or response to steroids in Kuwaiti children with INS

Funding: Government Support - Non-U.S.

PUB423

The Prevalence of Fabry Disease in Hemodialysis Patients of Jeju Island So Mi King, Jong tae Cho, Chang hyun Park, Eun kyong Lee, Ji hyeon Jeon, Division of Nephrology, Department of Internal Medicine, Dankook University Hospital, Dankook University College of Medicine, Cheonan, Chungnam, Republic of Korea.

Background: Fabry disease (FD) is an X-linked genetic disorder, caused by mutation in the GLA gene which encodes lysosomal enzyme, a-galactosidase A (a-Gal A). The deficiency of a-Gal A could cause renal failure, but its diagnosis is completely missed at times. Although the prevalence of FD in dialysis patients is known to be between 0.16% and 1.2%, the higher prevalence was expected in island area in terms of genetic disorder. Therefore, we tried to investigate the prevalence of FD in hemodialysis patients of Jeju island.

Methods: A total of 9 artificial kidney units participated in the study. We measured plasma a-Gal A activity before starting hemodialysis. In patients with low level of plasma a-Gal A activity, we analyzed the GLA gene, under patient's agreement.

Results: A total of 663 patients with hemodialysis were enrolled in the study. The mean age of the patients was 57.6 years, and the male was 64.5%. Among them, the 39 (5%) patients showed the low a-Gal A activity with < 0.45 nmol/min/mg protein. The gene analysis was performed in all patients with low a-Gal A activity. In genetic analysis, no definitive GLA mutation was found. But E66Q mutation, controversial whether it is a functional variant or FD, was found in 3 female patients. Although their presumptive clinical cause of renal failure was DM in one of the 3 patients, unknown etiology in other 2 patients, the kidney biopsy was not performed.

Conclusions: Although the prevalence of FD was 0%, the E66Q mutation showed 0.45% in hemodialysis patient of Jeju island. More accurate diagnostic tool for FD and follow-up of prognosis of patient with E66Q mutation are needed.

PUB424

Saudi Children Have High Prevalence of Genetic Related Atypical Hemolytic Uremic Syndrome and Better Recovery with Eculizumab Therapy Li Q,4 Dr. NajlaA,1 AbeerAl,1 AbdullaAl,1 AhmadAl1, Pediatric Nephrology Department, king Fahad medical city, Riyadh, Saudi Arabia.

Background: Atypical hemolytic uremic syndrome (aHUS) is ultra-rare disease, characterized by microangiopathy hemolytic anemia, thrombocytopenia and renal impairment. Genetic defects that determine uncontrolled activation of the alternative complement pathway have been well documented, it accounts for 40%-60% of the cases. Recent studies demonstrate the effectiveness of Eculizumab in the treatment of aHUS. In Saudi Arabia, there is up to 56% of consanguinity marriage resulting in higher prevalence of genetic diseases. We are reporting the experience of a tertiary care center in Saudi for children with aHUS who were treated with plasma therapy and or Eculizumab, their outcomes and genetic background.

Methods: This is a retrospective study, from January 2010 till May 2017 in a tertiary care center comparing children with aHUS who had received plasma therapy to those received Eculizumab therapy which was introduced at our center in 2014. We report our data in terms to demographic, clinical presentation, the length of hospital stay, need for dialysis, renal recovery and genetic mutations.

Results: 21 Saudi children who have similar demographic background diagnosed with aHUS, 12 (57%) of them showed complete renal and hematology recovery (67% in the Eculizumab group versus 33% in plasma therapy group). Six cases (29%) reached End Stage Renal Disease (ESRD), four patients (67%) of these cases from the plasma therapy group; two patients (33%) from Eculizumab group reached ESRD, their genetic mutations were not related to complement dysregulation system. Two of the 21 cases (41%) developed disease recurrence while receiving plasma therapy but no recurrence developed after using Eculizumab. Hospitalization was reduced by 10.6 days in Eculizumab group. 11 (69%) of the 16 cases who underwent genetic testing have identified gene mutations.

Conclusions: In our 21 cases with aHUS, Eculizumab was superior to plasma therapy in inducing, maintaining remission, and associated with better renal recovery. Genetic mutations detected among our patients were higher than reported for this ultra-rare disease, most probably related to the high prevalence of consanguinity marriage.

PUB425

Prohibitin-2 Gene Polymorphism and ROS Tolerance in Frequent Relapsing Nephrotic Syndrome Keisuke Sugimoto,1 Kohei Miyazaki,4 Tomoki Miyazawa,1 Takuki Enya,1 Hidehiko Yanagida,2 Mitsuru Okada,2 Tsukasa Takeurna,2 1Pediatrics, Kindai University Faculty of Medicine, Osaka, Japan; 3Tondabayashi Hospital, Tondabayashi, Japan; Pediatrics, Kindai University Faculty of Medicine, Osaka, Japan; 2Pediatrics, Kindai University Faculty of Medicine, Osaka, Japan.

Background: Patients with minimal change nephrotic syndrome (MCNS) often also have allergic diseases. Imbalances between reactive oxygen species (ROS) and antioxidants have been implicated in MCNS and progression of atopic dermatitis (AD). ROS, produced mainly within mitochondria, subject cells to oxidative stress, while prohibitin 2 protects mitochondria by increasing tolerance to ROS.

Methods: An 18-year-old male patient who developed nephrotic syndrome at 3 years of age subsequently was diagnosed with MCNS by histologic examination. Disease manifestations have recurred 12 times. He had given the various immunosuppressants. All of the ADRs of the treatment had been controlled except for rosacea. After rosacea had healed, Eczema on the patient’s face, trunk, and limbs, beginning at 2 months after birth, and worsening of intractable skin eruptions has accompanied or preceded increases in proteinuria. The serum IgE concentration was 18670 IU/L, representing a marked increase. Sensitive to fungi and staphylococcal enterotoxin was detected by ImmunoCAP-specific IgE. Among Th2 cytokines, increases in IL-4 and IL-13 were marked. High value of the dROM represent high oxidative stress and slight reduction of BAP, indicating low antioxidant activity. On exome sequencing analysis detected a heterozygous probitin 2 polymorphism, c.873-3_873-2 delCA (rs111523336). This mutation in exon 9 located on chromosome 12 caused framenhift in regions connected to splicing sites, where they could disrupt transcription of prohibitin 2. Frequency of this polymorphism in exon 9 is 7.3% among Japanese.

Results: Conclusions: Increase in peripheral blood ROS even MCNS remission state suggests the heterozygous prohibitin 2 variant may contribute to give more susceptibility towards the recurrence of MCNS as well as AD. This increase may have progression of AD, which is related to 2 polymorphism. The effect of Eculizumab on ROS tolarence in glomerular epithelium and led to high local exposure to ROS, increasing permeability of the GBM to result in proteinuria. Imbalance between ROS and antioxidants together with failure of signal transduction in the glomerular slit membrane caused by prohibitin 2 abnormality could have contributed to NS patients. Prohibitin 2 analysis is needed in additional MCNS patients with concomitant allergic disease.

PUB426

The Interaction Effect of rs4077515 and rs71019602 Increases the Susceptibility to IgA Nephropathy Changwei Wang,2 Li Wang,4 Guisen Li,1 1Renal Division and Institute of Nephrology, Sichuan Academy of Medical Sciences and Sichuan Provincial People’s Hospital, Chengdu, China; 2Sichuan Provincial People’s Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China.

Background: Immunoglobulin A nephropathy (IgAN), the most common form of primary glomerular diseases worldwide, is a complex multifactorial disease. Previous genome wide association studies (GWAS) reported that variants CARD9 and VAV3 genes were associated with immunoregulation and susceptibility to IgAN.

Methods: In this study, we further validated the associations and explored the interaction effect of rs4077515 and rs71019602 in IgAN patients.

Results: There was no significant correlation between the two variants and IgAN (P>0.05). The analysis of disease risk score showed that rs4077515 and rs71019602 have interaction effect on the susceptibility to IgAN, and the more the number of risk alleles, the higher the risk of IgAN. For additive interaction, the CT or TT of rs4077515 and GG of 17009602 genotype combination conferred a 2.556-fold risk of IgAN reference to CC.
related to hypertension treatment in the community. Awareness of the importance of sick-day rules in primary care merits emphasis.

PUB427

The Association Between Frailty and Quality of Life in CKD Andrew Nixon,1,2 Theodoros M. Bampouras,3 Alastair R. Petrie,4 Atinuke J. Afolabi,5 Neil Pendleton,6 Sandip Mitra,7 Ayaj P. Dhaygude,8 1University of Manchester, Manchester, United Kingdom; 2Lancashire Teaching Hospitals NHS Foundation Trust, Preston, United Kingdom; 3University of Cumbria, Lancaster, United Kingdom; 4Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom.

Background: Frailty is associated with an increased mortality in chronic kidney disease (CKD). Smaller studies that used modified versions of the frailty phenotype have demonstrated that frailty is also associated with a worse quality of life (QoL) in CKD. Further studies are needed to validate this association.

Methods: Fifty-eight patients with dialysis-dependent CKD and pre-dialysis stage 4 and 5 CKD were recruited. Frailty was assessed using the original frailty phenotype (FP). Patients were categorised as robust, pre-frail or frail. QoL was assessed using the 36-Item Short Form Survey (SF36). Between group differences in SF36 scores were assessed using the Kruskal–Wallis test. A p value of <0.05 was considered statistically significant.

Linear regression analysis was performed to assess the magnitude of associations between FP scores and SF36 domains.

Results: Median age was 70 years old (IQR: 58.75-77.70) with 28 male participants. Half were receiving haemodialysis. Mean Charlson Comorbidity Index (CCI) score was 3.12 (SD: 1.29). Frailty and pre-frailty prevalence was 24% and 47%, respectively. The frail group had the lowest median scores across all SF36 domains. There were significant differences between FP categories for all SF36 domains except ‘emotional well-being’. Table 1 demonstrates linear regression coefficients. Adjusting for age, CCI score and CKD stage did not substantially alter coefficients. An increase in frailty score by 1 point had the greatest effect on the ‘physical functioning’, ‘role limitations due to emotional problems’ and ‘pain’ SF36 domains.

Conclusions: Frailty is associated with a worse QoL in CKD and influences both physical and emotional aspects of QoL. Nephrology services should routinely assess frailty and offer additional support for those considered frail.

Table 1. Frailty and Quality of Life: Linear Regression Analysis.

<table>
<thead>
<tr>
<th>SF36 Domains</th>
<th>Regression Coefficients</th>
<th>95% Confidence Interval</th>
<th>p value</th>
<th>Adjusted Regression Coefficients</th>
<th>95% Confidence Interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Functioning</td>
<td>-1.05</td>
<td>(1.75 to -2.22)</td>
<td>0.01</td>
<td>-1.05</td>
<td>(1.75 to -2.22)</td>
<td>0.01</td>
</tr>
<tr>
<td>Role Limitations due to Physical Health</td>
<td>-1.10</td>
<td>(0.10 to -2.20)</td>
<td>0.03</td>
<td>-1.10</td>
<td>(0.10 to -2.20)</td>
<td>0.03</td>
</tr>
<tr>
<td>Emotional Well-Being</td>
<td>-0.97</td>
<td>(0.20 to -2.22)</td>
<td>0.03</td>
<td>-0.97</td>
<td>(0.20 to -2.22)</td>
<td>0.03</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>-1.06</td>
<td>(0.10 to -2.20)</td>
<td>0.03</td>
<td>-1.06</td>
<td>(0.10 to -2.20)</td>
<td>0.03</td>
</tr>
<tr>
<td>General Health</td>
<td>-0.90</td>
<td>(0.10 to -2.20)</td>
<td>0.03</td>
<td>-0.90</td>
<td>(0.10 to -2.20)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

PUB428

RAAS Blockade in Community Dwelling Elders and the Importance of “Sick Day Rules” Donal J. Sexton,1,2 Mark Canney,3 Rose Anne M. Kenny,3 Mark A. Little,4 Conall M. O’Scaghdha,5 1Nephrology Department, Beaumont Hospital, Dublin, Ireland; 2The Irish Longitudinal Study on Ageing (TILDA), Trinity College Dublin, Dublin, Ireland; 3Trinity Health Kidney Center, Trinity College Dublin, Dublin, Ireland.

Background: Acute kidney injury contributed to by continued RAAS blockade contributed to 1073 hospital admissions and 52 deaths in Ireland in 2012. There is a paucity of data on the use of RAAS blockade in community dwelling elderly patients. “Sick Day Rules” are protocols in primary care where RAAS blockade is stopped if patients are unwell. The aim of this study was to assess the use of RAAS blockade and determine if patients have “Sick Day Rules”.

Methods: We prospectively recruited 46 elder patients with incident ESRD in a dialysis center of tertiary hospital between May 2013 and March 2015. Frailty was assessed using the original frailty phenotype (FP) defined as 8 of the 21 are pts who came to dialysis after medical catastrophes requiring feeding tubes and tracheostomies, 1 patient is noncompliant with dialysis, 1 has short bowel and cardiomyopathy and 2 had hematologic illness. The remaining 13 were excluded. We wish to report on the pts with hematologic illness.

Methods: Mr. Y, aged 75 developed membranous nephropathy and eventually required dialysis. He was started on peritoneal dialysis and converted to hemodialysis after he developed an inguinal hernia (9/12-3/15). He has coronary artery disease with previous bypass surgery and a recent stent placement. His main complaint is the sensation that he is cold all the time and has no energy, especially when his hgb is less than 9 g %. He remained throughout the course requiring large doses of erythropoietin up to 10000 units thrice weekly. For 4 years we requested a hematology consult because he developed thrombocytopenia. Bone marrow found myelodysplastic syndrome with a 20q deletion. Chemotherapy was started with Decocen. After 2 cycles of treatment hgb and platelet count improved. Mrs. X, An 82 year old pt with renal insufficiency secondary to diabetes mellitus and congestive heart failure started hemodialysis 9/2015 initially to control congestive heart failure. Within a month she developed facial zoster. She has been maintained on dialysis twice weekly. She remained anemic. After 18 months she had a sudden marked drop in hemooglobin from 9 to 6 g% with associated rectal bleeding. A gastrointestinal workup was unrevealing. A hemolytic anemia was eventually diagnosed and thrombocytopenia noted culmination in a bone marrow biopsy diagnosing mantle cell lymphoma. Chemotherapy was started with single agent Rituxin and after 4 doses she is in remission.

Results: In summary 17% of our pts (21/123) failed to respond to increasing doses of epo. Of these 21 pts a satisfactory explanation could be found for 11 of the 21 pts. When pts are found to have epo resistance differential diagnosis needs to be broadened beyond iron deficiency, bleeding without a source or an “inflammatory state” causing anemia of chronic disease.

PUB430

Frailty Is Predictive of Future Adverse Outcome in Incident Elder Patients with ESRD: A Prospective Cohort Study in Korea Soonjo Lee,1 Sung Woo Lee,2 Anna Lee,3 Ho Jun Chin.4 1Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea; 2Eulji General Hospital, Seoul, Republic of Korea; 3Seoul National University Bundang Hospital, Seongnam, Republic of Korea.

Background: Little is known for the clinical significance of frailty in elderly patients with end stage renal disease (ESRD).

Methods: We prospectively enrolled 46 elder patients with incident ESRD in a dialysis center of tertiary hospital between May 2013 and March 2015. Frailty was assessed using comprehensive geriatric assessment protocol and was defined as a total of the multidimensional frailty score. The main outcome was composites of all-cause death or cardiovascular hospitalization determined at June 2016.

Results: Of 46 participants, median age was 71.5 years and 63.0% was men. During median 17.7 months' follow-up, the rate of composite outcome was 17.4%.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
multivariate logistic regression analysis, after adjusting for age, sex, diabetes, body mass index (BMI) and time of pre-dialytic nephrologic care, frailty was significantly associated with composite adverse outcome. In rejected frailty assessment, the multidimensional frailty score was significantly improved 12 months after dialysis initiated, which was largely relied on the improved alimentation.

**Conclusions:** Frailty is associated with increased risk of adverse outcome in elder patients with incident ESRD. Dialysis may improve frailty, particularly relying on the improved alimentation in elderly ESRD patients. Future large studies need to confirm our study results.

**PUB431**

**Coordinating Values for Shared Decision Making in Dialysis: Patient and Provider Perspectives**

---

**Background:** Patient values are a core component of shared decision making (SDM). Less often identified, provider values also influence SDM. Little is known about dialysis patient or provider values. As part of the development of a report on dialysis patient functional status using geriatric assessments to facilitate SDM, we examined patient and provider values with respect to dialysis care.

**Methods:** Four-month focus groups were conducted, two with patients (n=17, patient group) and two with providers (n=9, MD group – physicians and physician-extenders; n=8, non-MD group – social workers, registered nurses, and dietitians).

Transcripts were analyzed within and across stakeholder groups for concordance and discordance of expressed values.

**Results:** All groups shared the values of patient function, individualized care, social security, and family/patient responsibility and patient/patient responsibility in treatment. All attributed the value of efficiency to other groups to explain a streamlined, non-individualistic approach to dialysis care. The patients and the non-MD group shared many values, including access to quality patient-provider meetings, family support in care, cost-savings within the medical system, and patient family responsibility, work, independence, effort, and hope. Hope, or focusing on possibilities rather than limitations in function, was repeatedly expressed by both patient groups. Patients but not providers emphasized the importance of their own physical comfort within and outside the clinic; using knowledge of their own body to inform treatment, including medication adherence; and freedom to choose from dialysis. Providers but not patients valued objectivity in functional assessment and biomedical knowledge (i.e., lab results, medications) for treatment decisions. The MD group attributed the value of body knowledge to patients and saw it as a barrier to patient adherence to treatment recommendations.

**Conclusions:** These findings may facilitate SDM by informing dialysis providers about the presence of and allegiance to values across stakeholder groups in dialysis clinics. By attending to the values of patient hope, effort, and family responsibility, nephrologists might increase their persuasiveness with patients with regard to the shared value of personal responsibility in adhering to treatment recommendations.

**Funding:** Commercial Support - Satellite Healthcare

---

**PUB433**

**Effects of Global TRPC6 Knockout on Passive Anti-GBM Nephritis in Sprague-Dawley Rats:**

---

**Background:** Commercial Support - Satellite Healthcare

**Funding:** None of the manipulations in this study affected TRPC5 channels.

**Methods:** TRPC6 channels have been implicated in familial forms of FSGS. Here we examined this question in a global constitutive TRPC6 knockout in Sprague-Dawley rats using a model of immune complex nephritis.

**Results:** Rats injected with nephrotoxic serum had robust IgG and complement deposition within glomeruli measured 28 days after injection. This was the same in TRPC6+/- and TRPC6-/- littersmates. We found no effect on 24-hr protein excretion measured 4, 18 or 28 days after immunization. At 28 days after immunization, TRPC6 knockout had no effect on serum creatinine, BUN or circulating procoagulation type 1 peptide, all of which were significantly elevated in immunized animals, and which reflected a decline in renal function and an ongoing fibrotic process. TRPC6 knockout also had no effect on the abundance of CD68, vimentin, or θ-smooth muscle actin in renal cortex, or on kidney weight: body weight ratio. Tubulointerstitial fibrosis as assessed by PAS and Masson’s trichrome staining was severe in this model, and there was no difference between TRPC6+/- and TRPC6-/- rats compared to normal controls.

**Conclusions:** TRPC6 knockout had a partial protective effect on glomeruli in Sprague-Dawley rats during anti-GBM glomerulonephritis. However, it failed to reduce tubulointerstitial fibrosis and did not have any effect on the decline of overall renal function in this model.

**Funding:** NIDDK Support

---

**PUB434**

**Detection of Convertase-Stabilizing Factors in Patients with Complement-Mediated Renal Disease**

---

**Background:** The autoantibody C3 nephritic factor (C3NeF) plays a pathogenic role in C3 glomerulopathy (C3G) by stabilizing the key enzyme of complement activation, the C3 convertase. However, reliability of currently used assays to detect C3NeF is limited. Recently, we developed a method to measure convertase stability in human serum. We now optimized the method for simple detection of convertase-stabilizing factors such as the C3NeF in large patient cohorts.

**Methods:** Convertase stability was measured in a hemolytic assay using the C5- blocking agent ecuzumab to separate the alternative pathway (AP) into two steps: formation of C3-C5 convertases by test sera in a time-variable step 1 and formation of the AP attack complex, TRPC6 knockout had no effect on 24-hr protein excretion. Samples of 15 controls and 29 patients with C3G were analyzed. In addition, convertase stability was assessed in a family with complement Factor B (FB) mutation (p.Lys323Gln) and atypical hemolytic uraemic syndrome (aHUS), a complement-mediated disease not associated with C3G.

**Results:** Healthy controls were tested to define the normal convertase activity profile: maximal convertase activity was observed after 10-15 min and after 30 min the activity of all controls had returned to background levels. When serum or purified Ig fraction from C3NeF was added to control serum, convertase activity was increased close to t=30 (P=0.001). Thus, detectable convertase activity at t=30 min or later was chosen as a marker for presence of convertase-stabilizing factors such as C3NeF. In our cohort, 16 out of 29 (55%) patients showed increased convertase stability. Interestingly, prolonged convertase activity was also seen in an aHUS family and segregated with the FB mutation in affected and non-aFFECTed family members.

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

Underline represents presenting author.

---

1074
Conclusions: We present optimization of a simple, reliable, and cost- and time- effective assay for detecting convertase-stabilizing factors (C3NeF and some mutations) in patients with various complement-mediated renal diseases. This study may give insight in disease pathogenesis and treatment strategies in these patients.

PUB435

Alterations in Circulating Lymphoid Cell Populations in Systemic Small Vessel Vasculitis Are Non-Specific Manifestations of Renal Injury
Barbara Fazekas,1 Ana D. Moreno,2 Yvelyne P. Kelly,3 Paul O’Hara,1 Susan L. Murray,4 Alan Kennedy,5 Niall P. Conlon,1 Dearbhaille Dooley,2 Éoin O’Brien,6 Sarah M. Moran,7 Derek G. Doherty,2 Mark A. Little,5 Beaumont Hospital, Dublin 9, Co. Cork, Ireland; 2St. James’ Hospital, Dublin, Ireland; 3HSE, Limerick, Ireland; 4None, Dublin 8, Ireland; 5St. James’s Hospital, Dublin, Ireland; 6Trinity College Dublin, Dublin, Ireland; 7Trinity Health Kidney Centre, Trinity College Dublin, Dublin 8, Ireland; 8Trinity Health Kidney Centre, Trinity College Dublin, Dublin, Ireland.

Background: Innate lymphocyte populations, such as innate lymphoid cells (ILCs), γδ T cells, invariant natural killer T (iNKT) cells and mucosal associated invariant T (MAIT) cells are emerging as important effectors of innate immunity and are involved in various inflammatory and autoimmune diseases. The aim of this study was to assess the frequencies and absolute numbers of innate lymphocytes in peripheral blood from a cohort of ANCA associated vasculitis (AAV) patients.

Methods: Flow cytometry was used to enumerate circulating ILC subsets (ILC1, ILC2, ILC3, Ei), γδ T cell subsets (VH1, VH2, VH3), iNKT cells, MAIT cells, CD45++, CD8- and CD45CD8 T cells, B cells, natural killer (NK) cells and monocytes in 29 AAV patients and 19 healthy and disease controls. Recruited patients with AAV were sampled both with and without immunosuppressive treatment, and in the setting of both active and remission disease.

Results: The frequencies of MAIT and ILC2 cells were significantly decreased in all disease groups, including the disease control group, compared to healthy controls. These reductions in the AAV patients remained during remission. B cell numbers and frequencies were significantly lower in AAV in remission compared to patients with active disease and disease controls. Despite the strong Th2 preponderance of eosinophilic injury, Alterations in Circulating Lymphoid Cell Populations in Systemic Small Vessel Vasculitis Are Non-Specific Manifestations of Renal Injury can be seen in patients with AAV and are not specific to disease activity, but are more likely to be due to non-specific manifestations of renal impairment and chronic illness. Reduction in B cells in remission AAV is almost certainly therapy related.

Funding: Government Support - Non-U.S.

Figure 1. ILC2 and MAIT cells are persistently depleted in AAV patients and disease controls.

PUB436

Renal CD141+ Dendritic Cell Infiltration in Crescentic Glomerulonephritis in Humans and Mice Titi Chen.67 Qi Cao.1 Padmarshree Rao.3 Guoping Zheng.47 Yiping Wang.2 David C. Harris.51 ‘Centres for Transplant and Renal Research, Westmead Millennium Institute, University of Sydney, Sydney, NSW, Australia; 2Centre for Transplantation and Renal Research, Westmead Millennium Institute, The University of Sydney, Westmead, NSW, Australia; 3Sydney Medical School - University of Sydney, Sydney, NSW, Australia; 4The University of Sydney, Sydney, NSW, Australia; 5Westmead Millennium Institute, University of Sydney, Westmead, NSW, Australia; 6School of Medicine, University of Sydney, Westmead, NSW, Australia; 7Centre for Transplant and Renal Research, Westmead Institute for Medical Research, Westmead, NSW, Australia.

Background: CD141+ dendritic cells (DCs) have recently been identified as a unique myeloid DC subset that play a significant role in immune regulation. CD103+ DCs, their murine homologue, have been shown to play an important role in murine crescentic glomerulonephritis (mGN). However, little is known about the presence of CD141+ DC in human crescentic GN. We aim to investigate the relationship between CD141+ DC infiltration and clinicopathologic features in human crescentic GN, and to investigate possible underlying mechanisms of injury in a murine model.

Methods: Adult patients with a sole criterion of crescentic GN were enrolled in the study. Patients were excluded if they received immunosuppressant therapy before renal biopsy. Anti-GBM disease was induced in C57BL/6 mice by injection of sheep anti-mouse glomerular basement membrane. Mice were examined at week 1 and week 3.

Results: In normal human kidney, CD141+DCs were rarely present. However, the number significantly increased in patients with crescentic GN (P = 0.021). Higher CD141+ DC density was associated with worse serum creatinine (P = 0.029) and proteinuria (P = 0.038). In contrast to previous studies, which showed myeloid DCs were mainly present in the interstitium, we found that a high number of CD141+ DCs in glomeruli. Similar to humans, we found CD103+ DCs constituted only 2% of total leukocytes in normal murine kidneys. In murine anti-GBM disease, the number and proportion of kidney CD103+ DCs was significantly increased (P = 0.021), and CD103+ DCs were more present in the interstitium. We are examining pathological correlations and pathogenic mechanisms of CD103+ DCs in this model.

Conclusions: Our data suggest that CD141+ DCs may play an important role in crescentic GN.

PUB437

Urinary Cytokines/Chemokines as Prognostic Markers in Crescentic Glomerulonephritis Patients Receiving Immunosuppressive Therapy
Jungmin Jeon,2 Minjung Kim,1 Do Hee Kim,2 Jung eun Lee,1 Wooseong Huh,2 Jae Joong Kim,1 Yoon-Goo Kim,1 Ha Young Oh,1 Hye Ryoun Jang.1 Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; 2Chungbuk National University College of Medicine, Cheongju, Republic of Korea.

Background: Immunosuppressive therapy is considered to be the standard treatment for crescentic glomerulonephritis (CGN). However, timely kidney biopsy and initiation of aggressive immunosuppressive therapy is not always feasible in cases such as very old age or serious comorbidities. In this study, we investigated the clinical usefulness of urinary cytokines / chemokines as non-invasive prognostic markers for predicting the treatment response in patients with CGN.

Methods: A total of 87 patients with biopsy-proven CGN from 2002 to 2015 were included. In 38 patients, both urine and serum samples were collected on the day of kidney biopsy. A panel of cytokines / chemokines were measured as follows: regulated on activation, normal T cell expressed and secreted (RANTES), fractalkine, interferon-γ, interleukin (IL)-4, IL-6, IL-10, monocyte chemotactic protein-1 (MCP-1), tumor necrosis factor-α (TNF-α) and vascular endothelial growth factor (VEGF). Urine cytokine / chemokine levels were adjusted with urinary creatinine levels. Baseline and the proportion of non-albuminuria proteinuria were also analyzed in all patients. The primary outcome was uPCR and renal function at 1 year after kidney biopsy. Good response was defined as a decrease in proteinuria to < 50% without significant renal function deterioration. Mann Whitney U-test and logistic regression analysis were used as appropriate.

Results: The median age of patients was 65 years and 47% were male. Baseline eGFR was 18.7 ml/min/1.73m² and uPCR was 1.87 mg/mg Cr. The proportion of the good response group was 50%. In all patients, baseline eGFR was identified as a predictor of good response to immunosuppressive treatment. In 38 patients whose urinary and serum cytokines / chemokines were analyzed, baseline urinary RANTES (P = 0.016), fractalkine (P = 0.044), and MCP-1 (P = 0.041) levels were higher in the good response group.

Conclusions: Our study demonstrated the importance of early initiation of immunosuppressive treatment before renal function deterioration in patients with CrGN for improving renal outcome. Urinary MCP-1, RANTES and fractalkine may be prognostic value as non-invasive markers predicting treatment response.

PUB438

Cross-Reactivity of Neutralizing Anti-Rituximab Monoclonal Antibodies and New Anti-CD20 Monoclonal Antibodies: An Alternative Therapy in Primary Membranous Nephropathy?
Sonia B. Boyer,1 Sylvia Benzaken,2 Ghislaine Bernard,1 Vincent L. Enault,1 Barbara Setz-Polski.2,1 Nephrology, Nice University Hospital, Nice, France; 2Immunology, Nice University Hospital, Nice, France.

Background: Rituximab (RTX) is a murine / human chimeric monoclonal antibody (mAb) directed against CD20, a surface marker expressed on B cells (BC); RTX induced clinical remission in 60 to 80% of patients with primary membranous nephropathy (MN) in several non-randomized studies. However, mAb as RTX can elicit an unwanted antibody response in a substantial number of patients, resulting in a loss of efficacy of treatment. In MN, we showed that some patients develop neutralizing anti-RTX antibodies. We therefore investigated whether a cross-reactivity existed with new anti-CD20 mAb (humanized or fully human).

Methods: We studied complement-mediated cytotoxicity of anti-CD20 mAb on BC in the presence or absence of anti-RTX antibodies. Tested anti-CD20 mAb were: RTX with increasing concentrations, ocrelizumab (OCR) and obinutuzumab (OHB) (humanized anti-CD20 mAb), ofatumumab (OFA) (fully human anti-CD20 mAb).

Results: In presence of anti-RTX antibodies, RTX cytotoxicity is close to zero, demonstrating the neutralizing character of these antibodies. We observe a dose-response effect in RTX cytotoxicity, related to anti-RTX antibodies saturation. In the case of OCR, OBI and OFA, cytotoxicity is evaluated above 80-100% in the presence of anti-RTX antibodies. There is no neutralizing effect of anti-RTX antibodies on the three new anti-
CD20 mAb tested, even for low dose tested. Our work demonstrates the absence of cross-reactivity with three of the CD20 mAbs currently studied: OCR, OBI and OFA. Moreover, these third-generation mAbs might be less immunogenic and less responsible for treatment resistance.

**Conclusions:** We find no cross-reactivity of anti-RTX antibodies with last-generation of anti-CD20 mAbs. These humanized or fully human anti-CD20 mAb could be an alternative therapy to RTX in MN for patients with anti-RTX antibodies. Searching for neutralizing anti-RTX antibodies could also be extended to other autoimmune diseases.

---

**Zebrafish Embryos and ANCA-Associated Glomerulonephritis: Initial Steps towards a New Animal Model

**Background:** The title of Antineutrophil Cytoplasmic Autoantibodies (ANCAs) in the serum of patients with ANCA associated vasculitis (AAV) does not always correspond to clinical disease activity, although a pathogenic role for these antibodies has been described in several studies. Currently, there is no model available to predict the disease activity in patients with AAV. The zebrafish (Danio rerio) embryo model has been used successfully to study leukocyte migration and inflammatory processes in vivo. Here, we report our initial proceedings into investigating whether the zebrafish embryo model can be used to predict disease activity in patients with AAV.

**Methods:** Frozen sections of 4dpf zMPO:GFP transgenic zebrafish embryos were stained with polyclonal anti-human MPO antibody. 4dpf zMPO:GFP transgenic zebrafish embryos were injected with sera from AAV patients with high anti-MPO levels. Zebrafish embryos injected with sera from healthy controls and PBS served as controls. A local inflammation was induced 1 hour after injection by tail transection. At different time points, ~30 embryos were fixed and the number of zMPO:GFP cells responding to the site of injury was scored.

**Results:** The zebrafish myeloperoxidase (zMPO) and human MPO protein, one of the best-documented autoantigen targets of ANCA, share 76.5% similarity. However, there was no substantial binding detectable of conventional MPO-ANCA assays on zebrafish zMPO:GFP positive cells. An increased number of zMPO:GFP cells was observed at the site of injury from 2 to 6 hours after tail transection, however, there was no statistically significant difference over the groups (controls versus those injected with AAV serum).

**Conclusions:** Although we have been able to replicate in our zebrafish model previous findings of leucocyte migration to sites of injury, we have not been able to enhance this effect by injection of human AAV sera. We are currently focusing on leucocyte priming in parallel to previously described animal models of AAV where this was a major component for optimization of the model.

---

**Tissue Resident Macrophage in the Kidney Kazunori Karasawa, Takahito Moriyama, Ken Tsuchiya, Kosaku Nitta, Keiko Uchida. Tokyo Women's Medical University, Tokyo, Japan.**

**Background:** Tissue resident macrophages are subset of macrophages that are present at steady state in kidney interstitium. Furthermore, we found that CD206+ macrophages are localized in the mesangial region of glomeruli. To ensure that these CD206+ macrophages are resident macrophages in the mesangial region, we co-stained with CD140b, which is a pericyte marker that lines blood vessels from the outside. Most of the CD206+ macrophages co-localized with CD140b. From the staining results, we hypothesized that mesangial cells are heterogenous even at steady state. We decided to focus on CD206+ double positive resident macrophages in glomeruli. For further analysis, we isolated the glomeruli using Dynabeads and then analyzed using flow cytometry. Flowcytometry analysis with CD206+ and CD140b antibody revealed that mesangial cells were distinguished into three fractions. However, expression of molecules characteristic of macrophages such as F4/80 and CD11b was not recognized in CD206+ and CD140b double positive macrophages.

**Results:** Our results suggest that mesangial cells are heterogenous even at steady state. CD206+ and CD140b double positive cells in mesagial region may be a very specific tissue resident macrophage subset having the functions of macrophage and pericyte.

**Funding:** Government Support - Non-U.S.
**PUB443**

**Timing the Effect of Rituximab on Peripheral CD 20+B cells: An In Vivo Experience**

Dario Roccatello,1 Savino Sciascia,2 Roberta Fenoglio.1 
Ospedale San Giovanni Bosco, Torino, Italy; 1Center of Research of Immunopathology and Rare Diseases (CMID), Division of Clinical Immunology, Giovanni Bosco Hospital and University of Turin, Turin, Italy.

Background: B-lymphocyte antigen CD20 is an activated-glycosylated phosphoprotein expressed on the surface of all B-cells starting at the pre-B stage and progressively increasing in concentration until maturity. CD20 is the target of the monoclonal antibodies (mAb) rituximab (RTX), which is an active agent in the treatment of many immunemediate diseases. RTX can induce killing of CD20+ cells through multiple mechanisms. RTX direct effects include complement-mediated cytotoxicity and antibody-dependent cell-mediated cytotoxicity; the indirect effects include structural changes and apoptosis. In all disease states in which RTX has been given, there has been a rapid elimination of circulating B cells. However, the timing of the complete depletion of CD19/CD20+ after RTX administration is still unknown. In this study, we aimed to investigate in vivo the timing of the effect of rituximab on peripheral CD 20+B cells during the first infusion of RTX.

Methods: We evaluated 8 pts during the first infusion of RTX at the dosage of 375 mg/m² of RTX. Results: White blood cells (n.v. 4000-9000 x 10^9) and lymphocytes counts were normal at baseline. B-cells expressing CD19/CD20+ were not detectable in the peripheral blood in any pts within 1 h after initial treatment with Rituximab; in 5 pts (62.5%) they were not detectable within 20 minutes. The complete depletion of CD19/CD20+ was confirmed in all pts after 180 minutes.

Conclusions: This is the first study investigating in vivo the timing of the effect of RTX on peripheral CD 20+B cells during RTX therapy. Of high interest, we observed a very rapid B-cells depletion during RTX administration. The association of peripheral blood at various intervals after initiation of treatment (baseline, 10, 20, 60, and 180 minutes).

**PUB444**

**IRF5 Polymorphisms Do Not Predict Interferon Signature nor the Presence of Tubuloreticular Inclusions within the Glomerulus in Patients with Biopsy Proven Lupus Nephritis**

Romy C. Lawrence,1 Britte C. Beaudette-Zlatanova,1 Hanni Menn- Joseph,3 Ramon G. Bonegio.2 "Boston Medical Center, Roxbury; Boston, MA; 2Boston University School of Medicine, Boston, MA; 3None, Newton, MA.

Background: Several Interferon Regulatory Factor 5 (IRF5) polymorphisms have been shown to be associated with the development of autoimmune diseases including systemic lupus erythematosus (SLE). The polymorphism r77571059 is thought to be a gain of function variant and is reported to cause higher levels of IRF5 and type 1 interferons. Tubuloreticular inclusions (TRI) are distinctive intracellular structures found in the cytoplasm of endothelial cells and lymphocytes within the glomerulus. These structures are markers of systemic stimulation by interferons and their presence raise diagnostic suspicion for autoimmune disease or viral infections. We hypothesized that patients who are homozygous for the r77571059 SLE risk polymorphism would have a higher rate of TRI within their glomerular and this could serve as a predictor of their interferon signature and thus response to treatment with interferon inhibition.

Methods: The authors extracted DNA from 59 patients with SLE and amplified the r77571059 polymorphism using PCR. This DNA was sequenced and patients were divided based on their genotyping results into those who are homozygous for the risk allele, homozygous for the protective allele, and heterozygous patients. The presence of TRI was recorded from previous renal biopsies and compared to patients within these 3 groups.

Results: The risk allele frequency in SLE patients was 39%. Patients with nephritis had a similar risk allele frequency (36%) to those without (40%). Seventy two percent of patients with nephritis had tubular reticular structures reported on biopsy. The genotype of the patients at the r77571059 locus was not associated with the presence of TRI as similar rates of TRIs were found in patients who were homozygous for the SLE risk allele (100%), homozygous for the protective allele (71%) and heterozygous patients (67%).

Conclusions: TRI are common in the biopsies of lupus patients, occurring in about 72% of lupus patients. This is in keeping with the reported rate of high interferon signature within lupus patients. IRF5 variants may influence the level of type 1 interferon but do not predict the presence of TRI in the glomeruli. Therefore, we propose that IRF5 genotyping alone may not be sufficient to predict response to interferon inhibition.

**PUB445**

**Abstract Withdrawn**

**PUB446**

**Butyrate Ameliorates CKD by Improving Gut Permeability and Inflammation**

Austin J. Gonzalez,1 Siddhartha S. Ghosh,2 Daniel E. Carl,2 Richard Krieg,3 Shobha Ghosh,1 Todd W. Gehr.1 1YCU, Richmond, VA; 2YCU Medical Ctr, Richmond, VA; 3Virginia Commonwealth University, Fredericksburg, VA.

Background: Changes in intestinal microbiota in CKD alters intestinal permeability. This change increases paracellular transport of inflammatory toxins such as lipopolysaccharide (LPS). LPS in the circulation leads to inflammation which aggravates CKD. Short chain fatty acids such as butyrate produced by colonic bacteria have anti-inflammatory properties and may correct intestinal permeability. We hypothesized that butyrate treatment in CKD animals can improve gut permeability and will alleviate renal function.

Methods: 5/6 nephrectomy was done in ten Sprague dawley rats to induce CKD and divided into two groups, untreated (CKD) and butyrate treated (CKD+BU). Control were sham operated. Na Butyrate (250 mg/100ml) was given in drinking water for 6 weeks to BU. After 6 weeks animals were sacrificed. Plasma was used measure renal function, LPS, and TNFα. Kidney and colon were collected for western blots for NFkB, IL-10, Colon was stained with alacian blue to determine mucin expression.

Results: Our results show that butyrate improves renal function, sclerosis and inflammation in CKD animals. Although butyrate improved tubular dilatation it was not significant.

Conclusions: Mucins protects the gut from bacteria and inflammation and is regulated by anti-inflammatory cytokine IL-10. We show that in CKD animals there is lowering of IL-10 and an increase in mucin production which results in loss of colonic tight-junction protein ZO1 leading to increased LPS in circulation and inflammation. Butyrate’s modulation of biomolecules of colonic mucosa may contribute to its anti-inflammatory and renoprotective effect.

**PUB447**

**Differential Effects of Aethar® Gel and Methylprednisolone in a Preclinical Rodent Model of FSGS**


Background: Repository corticotropin injection (RCI: H.P. Aethar® gel) contains a purified porcine pituitary ACTH-analogue, and is an FDA-approved treatment to induce remission of proteinuria in idiopathic nephrotic syndrome. The hypothesis that RCI or methylprednisolone (2mg/kg/day) treatment may be effective on progressive glomerulosclerosis was evaluated in a rat puromycin-induced model of FSGS. Effects of RCI or methylprednisolone on renal function, proteinuria, and renal histopathology were evaluated compared to treatment with placebo gel, saline or Enalapril (ACEi). RCI treatment was beneficial for expression of previously reported biomarkers of podocyte injury, compared to treatment with placebo gel, saline or Enalapril (ACEi). RCI treatment was beneficial for expression of previously reported biomarkers of podocyte injury, compared to treatment with placebo gel, saline or Enalapril (ACEi). RCI treatment was beneficial for expression of previously reported biomarkers of podocyte injury, compared to treatment with placebo gel, saline or Enalapril (ACEi). RCI treatment was beneficial for expression of previously reported biomarkers of podocyte injury, compared to treatment with placebo gel, saline or Enalapril (ACEi).

Methods: Results:

Conclusions: Compared to saline, RCI significantly reduced overall proteinuria and serum creatinine at all time-points, at day-28 (p<0.05). In addition, RCI reduced serum creatinine (p<0.05, day-28), cholesterol (p<0.05, day-28 and 56), and urine kidney injury molecule (KIM-1) (p< 0.05, day-28). In contrast, treatment with methylprednisolone resulted in overall increased proteinuria, serum creatinine, serum cholesterol and triglycerides, compared to saline. Methylprednisolone treatment had no effect on disease induced tubular injury, and resulted in increases in renal fibrosis and glomerular injury, as determined by the histopathologist. In this rat model of FSGS, RCI suppressed disease endpoints compared to saline, while treatment with methylprednisolone was associated with increased disease severity, biomarkers, and progression.

**Funding:** Commercial Support - Mallinckrodt Pharmaceuticals

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
PUB448

Activation of Mineralocorticoid Receptor by the Adapogenic Ecdysteroids Promotes Glomerular Injury Minjie Li,1,2 Zhanshao Liu,1 Rujun Gong,2 The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; 2Brown Medical School, Providence, RI

Background: Anabolic steroids are commonly used by bodybuilders to achieve impressive muscular physiques. Among these, ecdysteroids, represented by ecdysone, are insect molting hormones and have been marked as natural anabolic agents and popularly used as adapogenic dietary supplements. However, ecdysone is likely problematic for health (i.e., occasional case reports associating its use with disorders manifested as proteinuria or renal impairment). The renal effect of ecdysone and related mechanisms were examined here.

Methods: In mice, daily treatment with ecdysone for 2 weeks incurred an increasingly elevated albuminuria, associated with glomerular injury, marked by glomerular cell apoptosis, mesangial expansion, podocyte injury featured by a variable degree of foot process effacement on electron microscopy, and increased expression of podocyte markers like podocin and synaptopodin, and augmented expression of desmin. This pathogenic effect was likely due to an autonomous glomerular injury, because addition of ecdysone to cultured glomerular cells caused substantial cytopathic changes, including cellular hypertrophy, increased apoptosis, and lesion expression of podocyte differentiation proteins like WT-1, and activation of mesangial cells as evidenced by increased expression of α-smooth muscle actin and extracellular matrix. To explore the molecular target of ecdysone, in-silico modeling system of compound–protein interaction was carried out and identified mineralocorticoid receptor (MR) as one of the top-ranking proteins with putative interactions with ecdysone. In consistency, the molecular structure of ecdysone was found to be highly homologous to mineralocorticoids, like aldosterone.

Results: Indeed, ecdysone was capable of activating MR, as proved by MR nuclear translocation in glomerular podocytes and mesangial cells both in vitro and in vivo. Conversely, spironolactone, a selective blockade of MR, largely abolished the cytopathic effect of ecdysone in glomerular cells in vitro and attenuated albuminuria and glomerular lesions in ecdysone-treated mice.

Conclusions: The adaptogenic ecdysone is able to activate MR and thereby promote glomerular injury and proteinuria.

PUB449

Is Histone Deacetylases 2 Associated with Steroid Resistance in Childhood Nephrotic Syndrome? Narayan Prasad,1 Harshit Singh,1 Vikas Agrawal,2 Saurabh Chaturvedi,1 Akhilsh Jaiswal,2 Nephrology, SGPGIMS, Lucknow, India; 1Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India; 2CLINICAL IMMUNOLOGY, SGPGIMS, LUCKNOW, India

Background: Histone deacetylase (HDAC) inhibitors are of clinical interest for the treatment of renal diseases, including focal segmental glomerulosclerosis (FSGS), diabetic nephropathy, as well as other diseases. However, there is limited information about HDAC-2 as a potential target for steroid-resistant nephrotic syndrome (SSNS). HDAC-2 is a class IIa HDAC, which is predominantly expressed in the nucleus (nuclear localization), where it regulates transcription by modifying histones and thereby altering gene expression. In this study, we investigated the expression of HDAC-2 in SSNS and its role in steroid resistance.

Methods: We performed immunohistochemical analysis of HDAC-2 expression in renal biopsy samples from patients with SSNS. HDAC-2 expression was analyzed using an anti-HDAC-2 antibody. The expression levels were quantified using an image analysis software. The results were compared with a group of patients with steroid-responsive nephrotic syndrome (SRNS).

Results: HDAC-2 nuclear expression was significantly lower in SSNS compared to SRNS. The HDAC-2 mRNA expression was also significantly lower in SSNS compared to SRNS.

Conclusions: Lower HDAC-2 nuclear and gene expression is associated with steroid resistance in SSNS. The inducers of HDAC-2 may lead to restoration of HDAC-2 response and prevent GCs resistance.

Funding: Government Support - Non-U.S.
Renal Thrombotic Microangiopathy in Rat Models after Bone Marrow Transplantation and Irradiation

**Background:** Thrombotic microangiopathy (TMA) is a renal complication after allogenic hematopoietic stem cell transplantation. We previously established a rat model of renal TMA after bone marrow transplantation (BMT), and concluded that chronic graft versus host disease could induce renal TMA. However, the influence of irradiation on the development of TMA has not been fully evaluated. In this study, we used radiation nephropathy model to investigate the role of irradiation in developing TMA, and compared the clinical and pathological characteristics to renal TMA after BMT.

**Methods:** According to the previous methods, TMA after BMT was induced in DA rats. In brief, bone marrow cells (6x10^7 cells) from Lewis rats were transplanted to DA rats, which received 10 Gy of whole body irradiation before BMT. Radiation nephropathy was induced in DA rats by irradiation of 10 Gy low dose irradiation) or 18-20 Gy (high dose irradiation) with shielding of hind limbs and sternal bone by lead block. The clinical and pathological findings were examined at 36 weeks after BMT or irradiation.

**Results:** In rat with BMT, pathological renal TMA was observed, as previously reported. On the contrary, rat with high dose irradiation (18-20 Gy), but not low dose (10 Gy), developed proteinuria, hematuria, and increased serum Cr level. Hemolytic anemia was reported. On the contrary, rat with high dose irradiation (18-20 Gy), but not low dose (10 Gy), developed proteinuria, hematuria, and increased serum Cr level. Hemolytic anemia was reported. On the contrary, rats with high dose irradiation developed acute renal failure and died within 7 days. The pathological findings were most consistent with renal TMA.

**Conclusions:** The injury can be reversed by hyperoside. The injury can be reversed by hyperoside. The injury can be reversed by hyperoside.
of PAN (i.v.) at 75 mg/kg. Proteinuria varied in range but increased with PAN dosing i.v. [50, 75 and 100 mg/kg (UPC=28±0.9, 56±3.5 and 36±2.3 mg/mg, respectively) as well as i.p from 75 to 100 mg/kg (UPC=14±6.1, 83±4.6 mg/mg) which plateaued at 150 mg/kg (UPC=73±3.57 mg/mg) in Wistar rats. Notably, higher i.p doses produced similar result as lower i.v. doses (i.v. 75mg/kg vs i.p 100mg/kg, P=0.13). Moreover, GC treatment reduced proteinuria significantly in i.v. PAN at 50 and 75 mg/kg (74%, P<0.01 and 78%, P<0.01 respectively), moderately in i.p. at 75 mg/kg (75%, P<NS), but significantly in i.p. at 100 mg/kg (70%, P<0.04). Additionally, PAN injection + albumin overload resulted in massive proteinuria in PAN-resistant mice. GC treatments strengthen the role of GC in PAN sensitive rats. Moreover, although i.v. PAN injection leads to a wider range of proteinuria, it is more responsive to GC than i.p. PAN. Finally, PAN resistant mice can be made susceptible by a second insult with albumin overload which may create useful models to study genetic deletions.

**Funding:** NIDDK Support

**PUB456**

The Inhibition of D-Site Binding Protein (DBP) Contributes to the Proliferation of Mesangial Cells in Experimental Anti-Thy-1 Glomerulonephritis

*Lei Chen*, Hong Gi Li, 1*Department of Nephrology, First Affiliated Hospital of Medicine School, Xi'an Jiaotong University, Xi'an, China; 2Affiliated Hospital of Medicine School, Xi'an Jiaotong University, Xi'an, China.

**Background:** Experimental glomerulonephritis (MoGN) is one of the most common glomerular diseases worldwide. It is characterized by mesangial cell proliferation accompanied by ECM expansion. Anti-Thy-1 antibody-induced glomerulonephritis is a classical model for MoGN. Our previous study demonstrated that D-site binding protein (DBP) was involved in the inflammatory response at the early stage of the Thy-1 nephritis. However, the role of DBP on the proliferation of mesangial cells (MCs) remains unclear.

**Methods:** 8-week old SD rats were injected with anti-Thy-1 antibody (2.5 mg/kg body weight) though tail venous to induce anti-Thy-1 nephritis. The rats in negative control (NC) group were received PBS injection. Specimens of the NC group were collected at 0d after the injection, while those of other groups were collected at 7d and 14d after the injection, respectively. Renal cortex slices were obtained for histological and immunohistochemistry analysis. Glomeruli were isolated by the differential-sieving method. The expression of DBP in tissues was detected by Western blotting. In vitro study, RMCs with DBP overexpression and DBP knockdown were conducted by DBP plasmid and siRNA transfection, respectively. Cell cycles were examined by flow cytometry. Western blotting were used for detecting the expression of DBP, p27, p21 and Cyclin D1.

**Results:** In the anti-Thy 1 nephritis, mesangial proliferation and ECM accumulation peaked at 7d and decreased subsequently at 14d after anti-Thy-1 antibody injection. The positive rates of PCNA in glomerulus were also significant rised at 7d and then decreased 14d. Compared with NC group, the expression of DBP at 7d in glomerulus was significantly reduced at 7d and then increased at 14d. Flow cytometry results demonstrated that the knockdown of DBP promoted G0/G1-G2/S transition in RMCs, whereas, the overexpression of DBP arrested cell cycle at G0/G1 phase. Furthermore, we found the knockdown of DBP reduced the expression of p27 and p21, and increased the expression of Cyclin D1. The complete contrary results were observed in the DBP-overexpressed RMCs.

**Conclusions:** DBP has an effect on the G1 phase to G2/S phase transition in RMCs though regulating the expression of p27, p21 and Cyclin D1, and finally affects the proliferation of RMCs.

**Funding:** NIDDK Support

**PUB457**

Endothelial Cell Injury Plays an Important Role in the Mechanism Developing Nephrotic Syndrome in Proliferative Lupus Nephritis: Immunohistochemical and Messenger RNA Analysis

*Ava Nawata*, Yui Toshiyuki Nakayama, Satoshi Hisano, Yoshia Tanaka, Shohei Shimajiri,1 Department of Pathology, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan; 2Fukuoka University School of Medicine, Japan; 3Fukuoka University School of Medicine, Japan; 4Department of Pathology, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan; 5The First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan; 6Department of Pathology, University of Occupational and Environmental Health, Kitakyushu, Japan.

**Background:** Nephrotic syndrome (NS) is a major feature of lupus nephritis (LN) and reflects podocyte injury. Although slit diaphragm protein molecules are important for the integrity of the filtration barrier in NS, these studies in lupus nephritis are lacking. The aim of our study is to clarify whether the damage of podocyte or slit diaphragm protein molecules or endothelial cell injury plays a central role in developing nephrotic syndrome in proliferative LN (lupus III/IV) and membranous LN (lupus V).

**Methods:** Sixty-six patients with nephrotic syndrome including minimal change nephropathy (MCN), primary membranous nephropathy (PMN), lupus III/IV and lupus V were enrolled in the study. Glomerular expression of podocyte or slit diaphragm molecules including Wilms tumor protein 1 (WT1), nephrin, synaptopodin and podocycin was evaluated in renal tissue by immunohistochemistry (IHC) and quantitative RT-PCR. Endothelial cell injury was evaluated by electron microscopy (EM) and podocalyxin was evaluated in renal tissue by immunohistochemistry (IHC). Flow cytometry results of the positive rates of PCNA in glomerulus were also significant rised at 7d and then increased 14d. Compared with NC group, the expression of DBP at 7d in glomerulus was significantly reduced at 7d and then decreased 14d. Flow cytometry results demonstrated that the knockdown of DBP promoted G0/G1-G2/S transition in RMCs, whereas, the overexpression of DBP arrested cell cycle at G0/G1 phase. Furthermore, we found the knockdown of DBP reduced the expression of p27 and p21, and increased the expression of Cyclin D1. The complete contrary results were observed in the DBP-overexpressed RMCs.

**Conclusions:** DBP has an effect on the G1 phase to G2/S phase transition in RMCs though regulating the expression of p27, p21 and Cyclin D1, and finally affects the proliferation of RMCs.

**Funding:** Veterans Affairs Support

**PUB458**

Effect of Long-Term Rapamycin Treatment on Kidney Parameters in Mice

*Christopher L. O'Young*, Cindy Yang, Sharif Hong, Roger C. Wiggins, Markus Bitzer. University of Michigan, Ann Arbor, MI.

**Background:** Podocyte depletion causes glomeruloclerosis. Age-associated glomerulosclerosis in humans is also associated with decreasing podocyte density caused by glomerular volume increase and podocyte number reduction (Hodgin, Bitez et al JASN 2015). Rapamycin (RAPA), like calorie intake reduction, extends lifespan in nematodes and mice and slows the rate of glomerular hypertrophy in rodent models. We therefore evaluated kidney and urinary parameters in a large cohort of mice (n=152) aged to >22 months to compare the effects of rapamycin and calorie restriction initiated at 4 months.

**Methods:** A four-way cross of genetically heterogenous mice (UM-HET3) was used to reduce impact of strain-specific characteristics on outcome. Treatments included ad-libium fed (ad-lib), rapamycin-treated (RAPA), and caloric restricted (CR) (PIMD27923560). A pilot cohort of 5 male mice per group was assessed. 50 randomly selected glomeruli were analyzed per mouse using FFPE tissue sections stained with PAS and IHC, computer-assisted image analysis was used to estimate glomerular volume and podocyte density.

**Results:** Kidney to body weight ratio is highly preserved in nature and remains so in this study (n=152; r=54, p<0.0001) with the notable exception of the RAPA-treated groups which showed a significant increase in body weight (P<0.01). Compared with ad-lib and RAPA groups were not different, although both were greater than the CR group (P=0.01). In parallel, ad-lib and RAPA groups had significantly increased kidney weight compared to the CR group (P=0.01). Glomerular volume was correlated with kidney weight (P=0.01) and was highest in RAPA-treated mice and statistically increased in both ad-lib and RAPA groups compared with the CR group (P<0.05). As a result of the RAPA-associated glomerular volume increase this group also showed a significantly lower podocyte density compared to either ad-lib (P=0.02) or CR (P=0.008) groups.

**Conclusions:** Reduction in podocyte density during aging is predicted to be associated with increased prevalence of glomerulosclerosis. Therefore, the observation that glomerular volume is increased in association with long term rapamycin treatment in adult mice raises a question about the potential use of rapamycin to prevent aging in humans. Additional quantitative morphometric and transcriptomic studies are planned.

**Funding:** Veterans Affairs Support

**PUB459**

Nicotine Induces Podocyte Apoptosis through Increasing Mitochondrial Pro-Apoptotic Proteins

*Xiajian Lan*, Abheepa Mishra, Seyyedeh Shadafarin Marashi Shosharti, Rukhsana Aslam, Ashwani Malhotra, Pravin C. Singhal,* Feinsein Institute for Medical Research, Great Neck, NY; 2Feinstein Institute for Medical research, Glenoaks, NY; 3Feinstein Institute of Medical Research, Northwell Health, MANHASSET, NY; 4North Shore LIJ Health System, Great Neck, NY; 5The Feinstein Institute for Medical Research, Manhasset, NY.

**Background:** Cigarette smoking is considered to be the most important cause of preventable mortality in many developed countries, including the United States. It is also an independent risk factor for chronic kidney disease (CKD) including diabetic nephropathy (DN). Nicotine, one of the highly active compounds in cigarette smoke, is required for smoking-accelerated CKD. Our previous studies have confirmed that nicotine exposure induces apoptosis; however, the underlying detailed molecular mechanisms are still poorly understood. In this study, we examined the effect of nicotine on mitochondrial pro-apoptotic proteins.

**Methods:** We cultured human podocytes in both normal (5mM) and high glucose (25 mM) milieus, and then treated them with nicotine at different concentrations (0.1, 1, and 10 µM). Occurrence of cell apoptosis was determined with morphologic assays (condensed and fragmented nucleus), and the expression of mitochondrial pro-apoptotic proteins was determined with real-time PCR and Western blotting.

**Results:** Nicotine significantly induced podocyte apoptosis in a dose-dependent manner in both normal and high glucose milieus. It also increased the expression of mitochondrial pro-apoptotic molecules such as Bax, Bim, and Noxa, at both RNA and protein levels.

**Conclusions:** Nicotine may induce podocyte apoptosis through enhancing the expression of pro-apoptotic proteins in mitochondria. The present study provides insight for further studies on the molecular mechanisms involved in smoking associated progression of chronic kidney disease.
Role of SMPDL3b in Sphingolipid Biosynthesis and in Glomerular Diseases
Shamoong Kumar Malalla,1 Alla Mitrofanova,1 Eden Rosenfeld-Gur,2 Tony Futerman,2 Alessia Fornoni,1 1Katz Family Division of Nephrology and Hypertension, University of Miami Miller school of medicine, Miami, FL; 2Weizmann Institute of Science, Rehovot, Israel.

Background: Research suggests an important role of sphingolipids in the pathogenesis of kidney diseases. We demonstrated that decreased Sphingomyelinase phosphodiesterase like 3b (SMPDL3b) expression in post-reperfusion kidney biopsies from patients with focal segmental glomerulosclerosis (FSGS) predicted recurrence of nephrotic range proteinuria suggesting that SMPDL3b may be a susceptibility factor contributing to the pathogenesis of FSGS. Others have shown that in macrophages, SMPDL3b is a glycosylphosphatidylinositol (GPI) anchored protein that is localized to lipid rafts and affects ceramide species composition of the plasma membrane thus regulating the inflammatory response. However, if SMPDL3b affects the ceramide species composition of the plasma membrane in podocytes thus contributing to podocyte injury remains to be established. Sphingolipids have various cellular functions. Ceramide and sphingosine can induce cell cycle arrest and promote apoptosis whereas ceramide-1-phosphate (C1P) and sphingosine-1-phosphate (S1P) promote cell survival and proliferation. Similarly to SMPDL3b, C1P was also shown to regulate inflammatory processes. We have generated preliminary data supporting the fact that SMPDL3b expression in podocytes regulates C1P levels, an observation that led us to test the hypothesis that SMPDL3b regulates C1P levels by directly dephosphorylating C1P or by inhibiting the activity of ceramide kinase (CERK).

Methods: Mass spectrometry analysis of lipids was performed. Phosphatase activity of SMPDL3b was determined in vitro. Co- and endogenous immunoprecipitation experiments were used to investigate a potential interaction of CERK and SMPDL3b.

Results: We observed an increase in C1P levels in siSMP podocytes when compared to SMPDL3b overexpressing podocytes. We show that CERK and SMPDL3b interact in transfected HEK293 cells and in glomeruli isolated from mice. Finally, we demonstrate that SMPDL3b can dephosphorylate C1P in vitro.

Conclusions: Our results identify an important role of SMPDL3b in regulating podocyte C1P levels. Further experiments to understand the exact mechanism by which SMPDL3b controls C1P levels in podocytes are underway.

Funding: Other NIH Support - DK90316, DK104753, U24DK076169, U54DK083912, UM1DK100846 and 1UL1TR000460

A High Degree of Sulfation of Heparin Triggers Differentiation of Cultured Podocytes
Fusihina Yoyota,1 Yutaka Yoshida,2 Hiromichi Takimoto,1*Department of Structural Pathology, Kidney Research Center, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; 2Institute for Research Promotion, Niigata University, Niigata, Japan.

Background: We have succeeded in establishing culture conditions in which cultured podocytes exhibit phenotypes close to those in vivo morphologically and in gene expression (JASN 2016; 27: 155A). Heparin is indispensable to the culture conditions. In this study, we have tried to clarify the role of heparin more precisely.

Methods: Rat primary cultured podocytes were subcultured and used for experiments. The effect of heparin was examined by changing the period of addition to culture media or comparing with effects of other polysaccharides having some similar structures to heparin.

Results: When the presence of heparin was limited to the first 24 hours after subculture instead of the entire time during culture, interdigitating cell processes and foot process-like staining of podocin were also formed five days after as shown by the figures below. Changes of gene expression consistent with differentiation in vivo, marked upregulation of podocyte-specific genes and downregulation of classic cadherins, were completed within the first 24 hours. Without heparin, such phenotypic changes were not observed. It is likely that heparin serves as a trigger for phenotypic changes. Heparan sulfate is less sulfated than heparin, but has the same polysaccharide structure as heparin. Sulfated dextran is highly sulfated, but has polysaccharides different from heparin. Sulfated dextran substituted for heparin, but heparan sulfate did not show such trigger effects.

Conclusions: A high degree of sulfation is crucial for the effect of heparin to trigger differentiation of cultured podocytes.

Funding: Government Support - Non-U.S.

Ultra-Miniaturized Podocyte Cell-Based High-Content Screening (HCS) Assay
Ha Won Lee1,2, Jean-Michel Saffin1,3, Mehmet M. Altintas,1 Jochen Reiser,2 Vinod Gupta,2*Rush University, Chicago, IL; 3Rush University Medical Center, Chicago, IL; 3Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA.

Background: Podocytes are established targets for therapeutic development for glomerular diseases. Podocyte morphology is essential for their physiological functions. We have previously shown that automated high-content imaging based assays can quantitatively discriminate between healthy and damaged podocytes. We also utilized this methodology to screen a library of ~2000 compounds with podocytes in a 96-well format and identified novel podocyte-protective compounds. However, the 96-well format is not ideal for screening larger chemical libraries, thus necessitating further miniaturization. Here, we describe our efforts towards miniaturization of the cell-based phenotypic assay to 384- and 1536-well formats.

Methods: Differentiated mouse podocytes were seeded in collagen-I coated multi-well plates. Cells were fixed with paraformaldehyde, permeabilized with Triton X-100, and blocked with donkey serum. Then, cells were stained with CellMask Blue, anti-paxillin antibody, and phalloidin. Images were taken using Opera HCS system. Morphologic parameters were quantified using Columbus software and analyzed by GeneData Screener software.

Results: Optimization of seeding density and culture conditions of podocytes in 384- and 1536-well plate formats produced reproducible results. Quantification of cellular phenotypes showed dose-dependent changes in cellular parameters upon treatment with purumycin aminonucleoside (podocyte injury-inducing agent). Co-treatment with mirizibine (podocyte protective compound) showed dose-dependent protection of podocytes from injury, as observed in the 96-well plate format. The assay also showed Z′-values similar to those in 96-well format, indicating the robustness of our assay.

Conclusions: We have optimized our podocyte based HCS assay in the ultra-miniaturized 1536-well format for high throughput screening. This miniaturized HCS format quantitatively discriminates between healthy and injured podocytes. The ultra-miniaturized assay will allow us to screen large and diverse chemical libraries to identify novel podocyte-protective compounds. With the miniaturized format, an in-house library of >300,000 compounds will be screened.

Funding: NIDDK Support

Concurrent Treatment with Growth Hormone and Transforming Growth Factor Beta Exacerbates the Epithelial-to-Mesenchymal Transition in Mouse and Human Podocytes
Alison L. Brittain, Biological Sciences, Ohio University, Athens, OH.

Background: Previous research has indicated that both growth hormone (GH) and transforming growth factor beta (TGFβ) can individually promote the epithelial-to-mesenchymal transition (EMT) in several different cell types. One such cell type is the podocyte. Podocyte EMT enhances foot process effacement and causes loss of podocytes from the basement membrane, ultimately leading to glomerular dysfunction and albuminuria. The purpose of this research was to test the effect of combined GH and TGFβ on mouse and human podocytes in terms of the EMT process.

Methods: To test the relationship between GH, TGFβ and the EMT process, we administered these two growth-promoting peptides individually or concurrently to immortalized mouse podocytes and primary human podocytes. We performed qPCR to evaluate EMT-related gene regulation, Western blotting to evaluate relevant second messengers, immunofluorescence and confocal microscopy to view structural proteins, and colony and scratch assays to evaluate cell phenotype.

Results: Our results show that individual administration of either GH or TGFβ causes an increase in markers of EMT and promotes a mesenchymal phenotype in both cell lines. Our results also show that combined GH and TGFβ administration alone, combined administration of these growth factors results in further enhancement of EMT, as evidenced by regulation of EMT-specific genes and proteins such as E-cadherin, N-cadherin and Vimentin. Our results also suggest dual GH or TGFβ administration
Conclusions: These results suggest that GH administration may exacerbate preexisting kidney disease, as would be the case in pediatric patients with chronic kidney disease who are given GH to treat short stature.

Funding: Private Foundation Support

PUB464

COL4A4 Immunofluorescent Staining in the Diagnosis of Autosomal Alport Syndrome

Boonyarit Ziad

COL4A Immunofluorescent Staining in the Diagnosis of Autosomal Alport Syndrome who are given GH to treat short stature.

Results:

Background: Alport syndrome (AS) is an inherited disorder due to mutations in genes COL4A4, COL4A3, or COL4A5 in genes encoding type IV collagen alpha chains. Transmission of AS is mainly X-linked (COL4A5 gene on X chromosome) (80% of cases), and less commonly autosomal (COL4A3 or COL4A4 genes) (20% of cases). We present a case of AS where we established the mode of inheritance by staining pattern of COL4A4.

Methods: A 24-year-old woman, with history of microscopic hematuria since age of three presented with worsening proteinuria. She was thought to have been pregnant and had not undergone kidney biopsy previously. She had a recent creatinine of 1.5 mg/dL, hematuria on urinalysis, and proteinuria of 5 grams/24 hours. She denied systemic symptoms such as hearing or eye complaints. Family history was significant for hematuria in paternal grandmother, father, and sister, but none had kidney failure. Physical exam was unremarkable. Workup revealed a creatinine of 1.3 mg/dL. Urinalysis showed hematuria and lipuria. A 24-hour urine revealed 3.2 g of protein. She underwent kidney biopsy with light microscopy showing mild thickening of the glomerular basement membranes (GBM). No significant abnormalities were seen on Immunofluorescence (IF). Electron microscopy revealed thickened GBM with scolloping and lamellation. IF staining with antibody to COL4A5 was negative in glomeruli and positive in tubular basement membranes (TBM) and Bowman’s capsule (BC), suggesting autosomal Alport disease due to a mutation in COL4A5 or COL4A4 genes. Normal IF staining for COL4A2 was observed in GBM, TBM, and BC. She was initiated on ACE inhibitor.

Results:

Conclusions: The history and biopsy findings of this patient are consistent with AS, with a pattern of staining with antibodies against alpha 5 of collagen IV consistent with autosomal type. In X-linked AS, there is loss of COL4A3 staining of GBM, BC, and distal TBM, whereas in autosomal AS, there is loss of COL4A5 staining of GBM with intact staining of BC and distal TBM. Because of the large size of the COL4 genes and many disease-causing mutations (1900 variants in COL4A5), staining for COL4 chains may be a useful adjunct for diagnosis and determination of mode of inheritance. In summary, this case illustrates the unique ability of specific alpha chain staining in identifying the underlying defect in AS and its associated mode of inheritance.

PUB465

Clinico-Pathologic Scoring System Predicting Renal Outcome in IgA Nephropathy

Kornchanok Vareesangthip,1 Samrithi Songtum,2 Boonyarit Ziad,1 Maywong Kaewmanee,3 Vichailak Vampha,1 Sobhan Prompaj,4 Chatchawan Tangtrakul,2 Yuthana Kornchanok,1 Chawanasuntorapoj.1

Background: Prediction of prognosis in IgA nephropathy (IgAN) is still limited and the Oxford classification of IgAN is required the validation in different ethnicity. This study aimed to establish the predictors of renal outcome in IgAN in Thai patients.

Methods: The 327 patients diagnosed IgAN by renal biopsy in Siriraj Hospital between the years 1996-2014 were retrospectively followed. The clinical parameters were collected and the pathologic lesions were evaluated and scored with the Oxford classification.

Results:

At the time of renal biopsy, the patients’ mean age was 39 years, 64.5% was female and the median creatinine was 1.4 mg/dL. The median renal survival was 155 months, and 114 of 327 patients developed ESRD during the median follow up time of 89 months. From multivariate analysis, age (< 30 years: HR 2.28, 95% CI 1.24 to 4.19), serum creatinine at 6 months follow up (Cr 1.2-2.9 mg/dL: HR 4.77, 95% CI 1.96 to 11.59, Cr ≥ 3 mg/dL: HR 16.94, 95% CI 5.73 to 50.12), proteinuria at 6 months follow up (HR 2.03, 95% CI 1.17 to 3.52), tubulointerstitial fibrosis (T2: HR 3.80, 95% CI 1.54 to 9.38) and ≥ 30% crescent (HR 4.32, 95% CI 1.77 to 10.55) were independent risk factors for the time to ESRD. These variables were used to create a clinico-pathologic scoring system for 5-year ESRD risk. This scoring system demonstrated a good discrimination with a c-statistics of 0.85 (95% CI 0.79 to 0.89).

Conclusions: Our study showed that IgAN in Thailand had a rather high ESRD outcome. The risks of ESRD were young age, high serum creatinine, high proteinuria, high interstitial fibrosis, as well as high percentage of crescents. With these factors included in the scoring system, 5-year ESRD risk score can be predicted. Further study to validate this clinico-pathologic scoring system is being investigated.

Funding: Private Foundation Support

PUB466

Characterization of a Sandwich ELISA for the Quantification of Total Soluble Human Neuropilin-1

Gabriela Bez1, Elisabeth Gadermaier,2 Jacqueline Wallwitz,2 Biomedica, Vienna, Austria; The Antibody Lab GmbH, Vienna, Austria.

Background: Neuropilin-1 (NRP-1) functions as co-receptor for several extracellular ligands. It exists as 103 kDa transmembrane NRP1 isoform 1, and as 72 and 68 kDa soluble NRP1 isoforms 2 and 3, that are generated by alternative splicing. NRP1 and NRP1 expression was demonstrated in the kidney, e.g. in visceral glomerular epithelial cells. An alteration of NRP1 expression with reduced NRP1 levels was described in diabetes and diabetic nephropathy. The measurement of circulating levels of the soluble forms of NRP1 have proven to be difficult due to the lack of a reliable technique to accurately quantify the analyte. In addition, to our knowledge, it is also not yet known if soluble NRP1 circulates free or as a ligand-bound form. In order to investigate the potential of sNRP1 as a renal biomarker we developed a highly specific and sensitive assay for the quantification of total soluble Neuropilin-1 in peripheral blood.

Methods: We developed a sandwich ELISA that is able to detect total sNRP1 employing polyclonal and monoclonal anti-human NRP1 antibodies. Linear epitopes were mapped with microarray technology and compared between the soluble NRP1 isoforms. Assay parameters like specificity, dilution linearity, and spike recovery were assessed.

Results: The monoclonal detection antibody binds to a linear epitope located in the N-terminal CUB 1 domain of human NRP1. The multiple linear epitopes recognized by the polyclonal coating antibody are distributed over the whole NRP1 sequence. All mapped epitopes are conserved between the two known human sNRP1 isoforms.

The assay is calibrated with sNRP1 isoform 2, and it detects total sNRP1 in human serum and plasma (heparin, EDTA, citrate) samples. All assay characteristics (specificity, dilution linearity, spike recovery) meet the international standards of acceptance.

Conclusions: Our novel ELISA provides a reliable and accurate tool for the quantitative determination of total soluble human Neuropilin-1 in healthy and diseased samples and it could help to investigate the role of this biomarker in chronic kidney disease.

Funding: Government Support - N-U.S.

A Spectrum and Clinical Course of Focal Segmental Glomerulosclerosis Variants by Columbia Classification in Japanese Patients

Akihiro Tsuchimoto,1 H. Yuta Matsukuma,2 Kosuke Masutani,2 Kazuhiro Tsuuya,2 Shigeru Tanaka,2 Takarani Kitazono,1 Department of Medicine and Clinical Science, Fukuoka, Japan; Fukuoka Dental College, Fukuoka, Japan; 3Kyushu University, Fukuoka, Japan, 4None, Fukuoka, Japan.

Background: Focal segmental glomerulosclerosis (FSGS) is divided into 5 pathological variants by Columbia classification. A spectrum of FSGS variants and the utility of this classification to predict a response to treatment and patient outcome have not been fully investigated in Asian patients.

Methods: This is a retrospective cohort study consisted of 151 patients aged 1–87 years who were diagnosed as FSGS from 1993 through 2016 in 9 nephrology centers in Japan. The patients were divided into 5 subgroups according to the Columbia classification. Interobserver reproducibility of pathological diagnosis was tested using kappa statistics by two independent observers, blinded for clinical courses. We compared patients’ clinical characteristics and renal composite outcome defined serum creatinine doubling and/or development of end-stage kidney disease.

Results: A distribution of FSGS variant was as follows: not otherwise specified (NOS), 60% (n = 90); perihilar, 15% (n = 23); cellular, 13% (n = 19); tip, 7% (n = 11); and collapsing, 5% (n = 8). Interobserver reproducibility of pathological diagnosis was good (kappa statics 0.71). Urinary protein excretion at kidney biopsy was severer in the tip and collapsing variants than the other three subtypes. Renal function was comparable among the five subtypes. With regard to the response to treatment, proteinuria and serum creatinine at 6 months were lower in patients with tip variant. In the collapsing group, renal composite outcome was significantly worse than NOS variant [adjusted hazard ratio (95% confidence interval), 5.05 (1.42–18.0); p=0.024], while it was similar among the other three groups.

Conclusions: In this study, a frequency of collapsing variant was lower and cellular variant was higher as compared with previous studies reported from the United States and Europe. Good treatment responsiveness of tip variant and poor prognosis of collapsing variant were similar with previous studies.

Funding: Government Support - N-U.S.
PUB468
Myeloma Cast Nephropathy with Light Chain Proximal Tubulopathy, Renal Extramedullary Hematopoiesis, and Collapsing FSGS

**Background:** Myeloma cast nephropathy is a rare entity characterized by the deposition of monoclonal light chain casts in the renal tubules, leading to tubular obstruction and resulting in renal failure. Extramedullary hematopoiesis is a compensatory response to severe anemia, often associated with myeloma, leading to the formation of hematopoietic tissue outside the bone marrow. Collapsing focal segmental glomerulosclerosis (FSGS) is a renal disease characterized by podocyte foot process effacement and associated with proteinuria and renal insufficiency.

**Methods:** A 45-year-old Caucasian woman presented with severe renal failure, albuminuria (1364 mg/mmol) and severe hypercalcemia (17.1 mg/dL), requiring dialysis therapy. Serum kappa/lambda ratio was 2632 at initial presentation. Kidney biopsy showed extensive light chain cast nephropathy (Figure 1A), light chain proximal tubulopathy (Figure 1B) along with extramedullary hematopoiesis. Collapsing FSGS was also seen on light microscopy (Figure 1C). Kappa staining was observed on prussian-digested paraffin sections. EM showed intraluminal cast formation and intracytoplasmic electron dense crystals in proximal tubular cells only. Bone marrow biopsy showed 80% plasma cells. The patient was treated with cyclophosphamide, bortezomib and dexamethasone with significant improvement of renal function which resulted in end of dialysis therapy.

**Results:** We describe an unusual case of light chain cast nephropathy and proximal tubulopathy with extramedullary hematopoiesis, and concomitant collapsing FSGS. There was no direct light chain deposition in podocytes to explain collapsing FSGS.

**Conclusions:** We report a 3 year old boy, with partial aHUS presented with renal impairment, anemia, normal platelets, low C3, low Complement Factor I and B (CFI & CFB). First kidney biopsy showed proliferative glomerulonephritis, vascular changes without obvious thrombosis. Genetic analysis came positive for mutations in CFI and C3 genes. Second biopsy while on dialysis was consistent with aHUS Steroid pulse therapy and plasmapheresis were ineffective to control the disease, peritoneal dialysis was initiated. Despite vigorous antihypertensive treatment and improved fluid overload with dialysis, HTN persisted. Eculizumab was given after 4 months of dialysis.

**Results:** Eculizumab resulted in renal recovery and cessation of prolonged dialysis. Renal function improved after the second dose. PD catheter was removed after 9 months of dialysis. Currently, after 24 months of Eculizumab therapy, disease is in remission and renal function is normal. Partial HUS to be considered; diagnosis to be confirmed by biopsy and or gene mutations.

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

Underline represents presenting author.
Immunotactoid Glomerulopathy with Masked Monotypic Immunoglobulin Deposition Tsukasa Fukuoka,1 Shunichi Shibazaki,2 Makoto Araki,2 Katuji Tuda,2 Takashi Ebara.1 1Matsumoto University Graduate School of Medicine, Nagano, Japan; 2Siuwa Central Hospital, Nagano Pref., Japan.

Background: Immunotactoid glomerulopathy (ITG) is a rare disease characterized by organized, Congo red-negative immunoglobulin deposits. ITG often has a monotypic light chain restriction because of a possible association with lymphoproliferative disorders, but 31% of ITG are kappa and lambda immunoglobulin positive.

Methods: An 80-year-old woman with deteriorating renal function since 6 months presented with proteinuria of 1.5 g/day, creatinine levels, 0.92 mg/dl, and a mild decrease in C3 (76 mg/dl). Serology and urine protein electrophoresis assay and anti-nuclear antibody were normal. A renal biopsy revealed membranoproliferative glomerulonephritis. Congo red staining was negative. Immunofluorescence staining of the frozen tissue was IgG and C3 positive in the mesangial and subendothelial regions, with no differences in kappa/lambda. Electron microscopy revealed a 30-nm deposition of microtubules with a hollow core. The diagnosis was ITG. As additional checks, Serum immunofluorescence indicated trace amounts of IgG kappa M protein and a normal serum free kappa/lambda light chain ratio of 1.99, (65.2:32.8). Serum cryoglobulin was negative on quintuplicate assay; bone marrow aspiration did not show excess plasma cells. Computed tomography findings were normal. Because it has recently been reported that monoclonal proteins occasionally show false negative staining by routine immunofluorescence of the frozen tissue, we tried to study light microscopic immunohistochemistry of trypsin-digested section revealed monotypic kappa deposition, even though direct immunofluorescence staining of frozen tissue was both kappa and lambda positive. This would provide evidence that the monoclonal protein is the cause of ITG and would justify treating with chemotherapy.

Conclusions: ITG is a monoclonal gammopathy of renal significance, but monoclonal deposition may be confirmed if the three-dimensional structure of the antigenic site is masked. In this patient, light microscopic immunohistochemistry of trypsin-digested section revealed monotypic kappa deposition, even though direct immunofluorescence staining of frozen tissue was both kappa and lambda positive. This would provide evidence that the monoclonal protein is the cause of ITG and would justify treating with chemotherapy.

C4d Is an Important Diagnostic Tool in Membranous Nephropathy Cristina Rabasco, Mario Espinosa. UGC Nephrology, University hospital Reina Sofia, Cordoba, Spain.

Background: Idiopathic membranous nephropathy (MN) is the most frequent cause of the nephrotic syndrome in adults. The diagnosis is based on typical findings observed via electron microscopy (EM) and immunofluorescence (IF) studies. Recent advances have shown that MN is a kidney specific autoimmune disease induced by antibodies specific for podocyte antigens. Complement plays an important role, even if mechanisms of activation have not been clarified yet. C4d is a fragment of C4 that is produced during activation of the classical or lectin complement pathway. We might therefore expect to find C4d deposition as a marker of complement activation in MN. The aim of our study was to determine whether immunohistochemical detection of C4d in patients with MN could be useful as a diagnostic tool.

Methods: All adult patients diagnosed with idiopathic minimal change disease (MCD) and MN biopsied in our unit between January 2001-December 2016 were considered for inclusion in the study. Diagnoses of MCD and MN were based on histological assessment of renal biopsy tissue with LM, IF and EM studies. 51 patients with MCD and 91 with MN were finally included. Diagnoses of MCD and MN were based on histological assessment of renal biopsy tissue with LM, IF and EM studies. 51 patients with MCD and 91 with MN were finally included.

Results: No C4d deposition was observed in any of the glomeruli of patients with MCD, and 100% of patients were classified as “negative”. C4d was detected in 100% of patients with MN in the form of a uniform granular distribution that outlined all the capillary loops and spared the mesangium. Detectable C1q deposits by IF were detected in only two patients with MN.

Conclusions: The demonstration of C4d by means of immunohistochemical techniques can thus be used as a tool for the differential diagnosis of MN and MCD. The deposit of C4d and no C1q deposit suggest that the alternative and/or lectin pathways might be predominantly involved in complement activation and formation of the C5b-9 complex in MN.

Atypical Myeloperoxidase Anti-Neutrophil Cytoplasmic Antibody (MPO-ANCA) Associated Crescentic Glomerulonephritis (GN) with Immune Deposits Overlap with CREST Celeste S. Chang, Yong Al Azzi. Nephrology, NY medical college at Westchester Medical Center, Valhalla, NY.

Background: Pauci-immune crescentic GN is defined as few or no immune deposits on renal biopsy. However, some reported an overlap of pauci-immune pathology with immune deposits in the setting of anti-MPO-ANCA. CREST is typically associated with thrombotic microangiopathy (TMA) like renal lesion and only a handful of case reports associated between ANCA vasculitis and CREST. Here, we present a rare case of atypical MPO-ANCA associated crescentic GN on light microscopy with immune deposits on electron microscopy, overlap with CREST.

Methods: 74 F from El Salvador presented with tea-colored urine, proteinuria (Urine protein/Cr ratio: 8) and AKI with positive ANA (centromere), Anti-MPO Ab, negative HbsAg, reactive Anti-Hbs and Anti-Hbc. History of HTN, pulmonary nodules, mild restrictive pulmonary disease, pulmonary HTN, arthralgia and latent syphilis. Renal biopsy revealed crescentic and focal necrotizing GN with mesangial and subendothelial deposits on EM. There are IgG, IgA, C3, fibrillary segment, both kappa and lambda light chains on IF staining. Thrombi are present in some glomeruli, suggestive of TMA with possibility of overlapping with autoimmune disease. She was started on steroid and cyclophosphamide, required hemodialysis for fluid overload and worsening of AKI. However, she recovered renal function and came off from dialysis without any plaenapheresis. Her HbsAg became positive after cyclophosphamide.

Results: This is a very unusual and rare case of pauci-immune GN with evidence of immune deposits on EM which could be related to atypical lupus nephritis with positive ANCA vs ANCA vasculitis with unusual immune deposits from possible contribution of latent syphilis and latent hepatitis B infection, the latter was unmasked by immunosuppression. All these superimposed on an element of thrombotic microangiopathy, probably secondary to CREST.
Lithium: Mood Stabilizer That Made Us Dialyze Her

Anna S. Gutman, Shimshon Wiesel, Madeeha Abdul Ghaffar, Militza K. Kiroycheva. Staten Island University Hospital, Staten island, NY.

Background: Despite its toxic effects, lithium continues to be used for the management of bipolar disorder. We present a case of acute and chronic lithium nephrotoxicity.

Methods: A 43-year-old woman with bipolar disorder, who had been taking lithium for over 11 years, presented with lethargy and decreased oral intake. She was alert but disoriented, and had bilateral lower extremity edema. Serum creatinine was 3.5 mg/dL, from a normal baseline, with large proteinuria. Her spot urine total protein:creatinine was 54g/mg, albumin 2.0 g/dL, and serum Li⁺ 3.2mmol/L, which did not improve with intravenous fluids. Intermittent hemodialysis was started, with frequent monitoring of her Li⁺ levels. A renal biopsy showed focal segmental and global glomerulosclerosis, interstitial fibrosis, and multiple distal tubular cysts. Li⁺ was discontinued, but the patient remained hemodialysis dependent.

Results: Renal biopsies of patients with chronic lithium use and nephrotic range proteinuria show tubulointerstitial nephropathy, minimal change disease, focal segmental, and global glomerulosclerosis. Despite discontinuing lithium, as many as 75% of patients progress to end stage renal disease. Our patient had routine monitoring of her serum lithium and creatinine levels, however she progressed to ESRD. We recommend frequent quantification of proteinuria for closer monitoring of lithium induced nephrotoxicity.

Rare Case of Catastrophic Anti-Phospholipid Syndrome

Iyad S. Mansour. Banner university medical center/ university of arizona, Tucson, AZ.

Background: Catastrophic Anti-Phospholipid Syndrome (CAPS) is a rare life threatening form of APS. Acute thrombotic microangiopathy is the most common histological finding on kidney biopsy in this disease.

Methods: A 48 year old male with PMH of Idiopathic thrombocytopenic purpura, pulmonary embolism, and recent diagnosis of arthritis, presented with 4 day history of lower back and left flank pain. P/E: vitals are stable, lung exam: scattered crackles, mild left flank and left mid- abdomen tenderness, +1 lower extremities edema, intermittent confusion, patient has been oliguric. Labs showed Hb: 13.2, WBC 10.7, plat:85,000, serum Cr: 2.8 mg/dl, AST:71, ALT:57, D.D:16.6, PT:15, PTT:39.9, blood smear showed thrombocytopenia with normocytic RBC, no hemolysis, MRI abdomen showed left adrenal hematoma. Urine AX: 100 mg/dl protein, 41 RBC and 4 WBC, 2 granular cast, serological For HIV,HCV,HBV,YANA, ASMA, Anti-DSDNA, ANCA were negative, anticardiolipin antibody IgG: 18, lupus anticoagulant 2.02 (High). ADAMTS13 activity: 54%, C3, C4: both low, Kidney biopsy showed acute and chronic thrombotic microangiopathy, acute tubular injury, negative immune fixation. This patient had involvement in kidneys, adrenal glands, liver and probable CNS involvement. So he fulfilled the criteria of probable CAPS. He was treated with steroids, anticoagulation, plasma exchange and rituximab, with good response.

Results: APS is autoimmune disease, characterized by arterial and venous thrombosis, Catastrophic antiphospholipid syndrome (CAPS) is a rare life threatening form associated with disseminated vascular thrombosis results in multiorgan ischemia and failure. Kidney are involved in 73% of patient with CAPS, TMA is the most common histological finding in this disease. It is a life threatening disease that requires aggressive treatment strategies, and all patient with CAPS should be treated with steroids, anticoagulation, and possibly plasma exchange, in refractory and relapsing cases, Rituximab and Eculizumab may be an option.
Unusual Cause of Nephrotic Syndrome with AKI: Membranoproliferative Glomerulonephritis (MPGN) with Concurrent Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) Infiltration in Kidney

Himanshu Davis, Sacramento, CA; 2University of California Davis Medical Center, Sacramento, CA; 3University of California, Davis, Sacramento, CA.

Background: Renal manifestations in patients with CLL/SLL have been reported, with MPGN being the most common glomerular finding. Here we describe a patient with history of CLL/SLL who presented with new onset nephrotic syndrome and renal impairment.

Methods: The patient is a 74-year-old Caucasian male, previously treated for CLL/SLL with a rituximab-based regimen. He was off treatment for 2 years but presented with new onset ascites, requiring frequent paracentesis. On exam, he was chronically ill-appearing with marked ascites but had no peripheral edema. Labs were significant for rise in serum creatinine to 2.6 mg/dl (baseline of 1.0 mg/dl) and low albumin of 1.7 g/dl. Liver enzymes were normal and he had no evidence of viral hepatitis. Ascitic fluid cytology was negative for malignancy. Urine protein excretion was ~10 grams/24 hrs. Urine microscopy showed many dysmorphic red blood cells. A renal biopsy was performed that revealed CLL/SLL infiltrating the renal parenchyma with concurrent MPGN showing focal crescent formation. MPGN deposits displayed IgG1-kappa restriction, correlating to the phenotype of the patient’s malignancy.

Results: Conclusions: This is an unusual case of a patient with a history of CLL/SLL with multiple simultaneous renal manifestations - ascites related to nephrotic syndrome that was caused by MPGN secondary to CLl/SLL and AKI related to crescent formation and parenchymal infiltration by CLl/SLL.

Membranous Nephropathy Secondary to Syphilis


Background: Membranous nephropathy is one of the most common causes of nephrotic syndrome in the adult population. Although in the majority of cases an inciting event can’t be identified, in about a third, an association with autoimmune disease, drugs, or infections is usually found. Syphilis is a rare infectious cause of membranous nephropathy and usually presents nephrotic range proteinuria. In the last fifteen years, there has been a reemergence in the cases of primary and secondary syphilis in the United States (CDC), which could lead to a greater number of patients affected by this sexually transmitted disease seeking medical help due to renal involvement.

Methods: Results: Conclusions: Although syphilis is rarely associated with membranous nephropathy, the increasing incidence of secondary syphilis will invariably lead to a greater number of patients that are present with renal involvement. Healthcare providers must remain aware of the association of syphilis with renal disease and its possible presentations.

Kidney biopsy showing infiltration of parenchyma by CLL/SLL as well as MPGN with crescent formation.

A Case of Myeloma Kidney with Glomerular C3 Deposition

Asif Khan, Suzanne E. El Sayegh, Elic El-Charabaty. Medicine, Staten Island University Hospital, Staten Island, NY.

Background: Myeloma cast nephropathy and monoclonal immunoglobulin deposition disease are the most common renal complications of multiple myeloma (MM). Up to 50% of MM patients present with renal impairment at diagnosis: 20% may present with acute kidney injury, and 10% require dialysis. Light chains can precipitate in the proximal and distal tubules causing inflammation leading to secondary interstitial fluid involvement. Moreover, mutations or autoantibodies such as C3 nephritic factor (C3 nef) against complement regulatory proteins promote the erratic activity of the complement cascade, causing glomerular deposition of C3 without marked deposition of classical complement components and with minimal, or no immunoglobulin deposits resulting in tissue damage. These disorders are described as C3 glomerulopathy (C3G).

Methods: Results: Conclusions: Currently, there are no effective disease-specific treatments for C3G. Clinicians should be aware of isolated glomerular deposits that stain weakly or dominantly for C3 might represent an unusual complication of plasma cell dyscrasia, related to complement activation through an autoantibody activity of the monoclonal Ig against complement regulatory proteins.

Kidney biopsy showing infiltration of parenchyma by CLL/SLL as well as MPGN with crescent formation.

Immunofluorescent revealed 3+ staining for lambda in the distribution of the atypical casts with weak granular mesangial staining for C3. Staining for IgA, IgG and C1 were negative.

Podocyic Infiltrating Glomerulopathy: A Case Report

Pin Zhang, Daqing Hong, Yurong Zou, Guisen Li. Renal Division and Institute of Nephrology, Sichuan Academy of Medical Sciences and Sichuan Provincial People’s Hospital, Chengdu, China; Sichuan Provincial People’s Hospital, Chengdu, China; Sichuan Provincial People’s Hospital, CHENGDU, China; Sichuan provincial people’s hospital, Chengdu, China.

Background: Podocyic infiltrating glomerulopathy (PIG) has recently been proposed as a possible new pathological entity. In PIG, microtubules or microspheres, or both, are associated with the infiltration of cytoplasmic processes of podocytes into the glomerular basement membrane (GBM). Most of PIG cases have been reported in Japan, and it is unclear whether this lesion indicates a new disease entity or a transient morphological finding of a well-known disease.

Methods: Results: Conclusions: The reported case demonstrates a rare and peculiar glomerulopathy, the podocyic infiltrating glomerulopathy. The pathogenic mechanism of PIG should be multiple, more cases of PIG are needed to be analyzed in order to better understand this lesion.
Early Recognition and Intervention Improves Outcome in HELLP-HUS: A Case Report

Bakesh Kumar, Dhanashri Kohli, Ramesh Adhikari, Manish Gera

Background: Atypical hemolytic uremic syndrome (AT-HUS) with Hemolysis elevated liver enzyme and low platelet (HELLP) syndrome is a rare complication of pregnancy. It is associated with high morbidity and mortality. Renal survival is dismal and renal dysfunction is the rule.

Methods: A 23-year-old Caucasian female pregnant at 32 weeks gestation age was admitted with epigastric pain. She was hypertensive at presentation and had proteinuria. Fetal distress led to an emergent cesarean section. Post delivery of fetus her vital signs stabilized. She had hemolysis, elevated liver enzymes, and low platelets. At the time of presentation serum creatinine was 0.6 mg/dL. Preeclampsia with HELLP syndrome was diagnosed. Post-partum she became oliguric and had renal failure. Haptoglobin and Lactate dehydrogenase (LDH) were < 10 mg/dL and 2450 U/L respectively. Schistocytes were present in peripheral blood smear. Urinalysis showed hematuria and proteinuria (greater than 3 grams/day). She was diagnosed with preeclampsia with HELLP syndrome and post-partum atypical HUS. Deregulated alternative pathway has been implicated in the pathogenesis of HELLP and aHUS so plasmapheresis was given within a few hours of diagnosis and eculizumab was given within twenty-four hours of diagnosis. Her urine output slightly improved with first session of plasmapheresis. Her serum creatinine trended up to 5.5 mg/dL. She needed 3rd session of plasmapheresis on 7th day due to worsening renal function. Supplemental dose of eculizumab was given after 3rd plasmapheresis. None of the genetic variants of 10 genes associated with aHUS were present. Lupus anticoagulants and Hepatitis screen were negative. After 2 weeks of hospital stay, her urine protein:creatinine ratio improved to 1.2 mg/dL and LDH started trending down but remained high at 539 U/L. Platelets improved from 53000 /µL to 386000 /µL. Hemoglobin levels also started improving but she remained anemic. She never required dialysis.

Results:

Conclusions: The association of preeclampsia, HELLP syndrome and post-partum aHUS suggest that these may be a spectrum of single disease process i.e. abnormal alternative complement activation. Early recognition of HELLP/ aHUS and treatment with plasmapheresis and eculizumab may improve renal outcome.
coincident with declining glomerular filtration rate. Rituximab was added to his regimen of cyclosporine and azathioprine, which resulted in remission of his MN, marked improvement in his polyposis, and near resolution of his cutaneous symptoms.

**Results:**

**Conclusions:** CCS is a rarely encountered disorder in which associated renal disease, such as membranous nephropathy, uncommonly manifests. After a careful review of the literature, only three cases of CCS have been associated with MN. To our knowledge, this is the first reported case of CCS with MN as well as any case of CCS treated with rituximab. The excellent response observed for both CCS and MN recommends consideration of this treatment, especially for resistant disease. The use of cyclosporine was reported as successful in another case of CCS with MN. Steroid-resistant CCS is scarcely reported, but some success has been noted with cyclosporine, azathioprine, and infliximab. Cyclosporine in the present case evoked a response superior to azathioprine.

**PUB488**

**Combined Tacrolimus and Sorafenib-Associated Thrombotic Microangiopathy**

**Corresponding Authors:**

Voravech Nissarosakam,1 Weeraporn Srisung,1 Steven Salvatore,1 Vesh Srivatana,2 \[1\] Weill Cornell Medical Center, New York, New York, NY; [2] The Rogosin Institute, New York, NY.

**Background:** Thrombotic microangiopathy (TMA) is an inflammatory and thrombotic disease of the microvasculature, which often occurs in hematopoietic stem cell transplantation (HSCT) population. Risk factors of TMA in HSCT include chemotherapy, radiation, calcineurin inhibitors (CNI), anti-vascular endothelial growth factor (anti-VEGF) therapies, graft-versus-host disease, and infections. Tacrolimus and sorafenib have been individually associated with TMA, however, to our knowledge there have been no reports of TMA with the combination of the two drugs. We report the first case of tacrolimus and sorafenib-associated TMA.

**Methods:** Our patient is a 57-year-old woman with acute myeloid leukemia who underwent HSCT. She had been taking sorafenib for seven weeks and stopped one week prior to HSCT. The post-HSCT immune suppression consisted of immunosuppressive drugs that included cyclosporine, mycophenolate, and tacrolimus. Seventeen weeks after HSCT, she had an acute kidney injury (AKI) from tacrolimus toxicity. The renal function improved after a temporary discontinuation of tacrolimus. Seventeen weeks after HSCT, sorafenib was started on top of concomitant use of tacrolimus. Two weeks later she developed severe oliguric AKI from biopsy-proven TMA (figure 1). Despite therapy with eculizumab, she died from complications of sepsis after a prolonged hospital course. Autopsy confirmed the diagnosis of TMA involving the cardiac and renal tissue.

**Results:**

**Conclusions:** We observed that TMA developed when the patient was taking both tacrolimus and sorafenib but not when they were taken individually. The concept of two drugs having synergistic effects to cause TMA has been demonstrated in dual anti-VEGF inhibition but not with the combination of CNI and anti-VEGF therapy. We hypothesize that tacrolimus and sorafenib combined may have caused a severe endothelial injury initiating the pathogenesis of systemic TMA. Despite early and aggressive therapy, the patient died. Due to emerging indications for combined use of these drugs in HSCT population, intensive monitoring for early signs of TMA is critical for optimizing outcomes.

**PUB486**

**A Case of Proliferative Glomerulonephritis with Monoclonal IgG Deposits Early after Renal Transplantation**

**Corresponding Author:**

Yasar Alfi, Scott D. Cohen, Muralidharan Jagadeesan. Division of Renal Diseases & Hypertension, George Washington University, Washington, DC.

**Background:** Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) was first described by Nasr et al. in 2004 as a form of renal involvement by monoclonal gammopathy resembling immune-complex glomerulonephritis. Here we describe a case of PGNMID early after renal transplantation in a patient with a prior history of multiple myeloma in remission.

**Methods:** A 66-year-old male with a past history of treated IgG lambda multiple myeloma who presented with abnormal renal function 5 months after a deceased donor renal transplant with a serum Cr of 1.3 mg/dl up from a baseline Cr of 0.9 mg/dl and a new nephrotic range proteinuria with a spot UPCR of 9.5 g/g. The patient was first diagnosed with MM 13 years prior to kidney transplant and achieved remission following autologous stem cell transplant. His native kidney biopsy at that time showed lambda light chain cast nephropathy and amyloidosis. Serological workup showed no evidence of a monoclonal paraprotein. A kidney biopsy was remarkable for mesangial deposits and electron microscopy showed deposits. The patient was subsequently treated with Bortezomib and Dexamethasone with improvement of GFR to baseline and slight improvement in proteinuria to 4.1 g/g.

**Results:**

**Conclusions:** There are only limited case reports of PGNMID in renal allografts. It can present as a recurrence of the native kidney disease usually early after the transplantation or as a de novo glomerulonephritis years after the kidney transplant. We report a case of PGNMID that presented early after kidney transplantation in a patient who had myeloma cast nephropathy and amyloidosis on his native renal biopsy. The optimal treatment of PGNMID is unclear with mixed results using Rituximab. Early treatment with Bortezomib and high-dose Dexamethasone may be effective for the treatment of PGNMID but needs further study.
Three Year Follow Up Results of Severe IgAN with CKD Treated by MP- Pulse Therapy and Autologous Adipose Derived SVF Byoung-Soo Cho,1 Hyaejin Y. Kidney Center, Seoul, Republic of Korea; 2ByulE plastic surgery, Seoul, Republic of Korea; 1N’biotek, Seoul, Republic of Korea.

Background: As yet there is no specific method of treatment in severe IgAN associated with CKD, but giving ACEI, ARB, Omega-3, etc., however most patients eventually progress to ESRD and need RRT. Recently stem cell/SVF (cannular vascular fraction) therapy has been suggested as a promising option for CKD, attenuation of renal ischemia and reperfusion injury especially by SVF and adipose-derived mesenchymal stem cells. Our group have been reported a shortterm result of MP pulse therapy and adipose derived SVF at the ASN(2015,2016) in IgAN with CKD3. The mechanisms underlying this beneficial effect are still a matter of debate, therapeutic strategies aimed at correcting the potential of stem cells based on the administration of SVF. In this report we summarized 3 years follow up results as follows.

Methods: Case 1: A 27-year-old male was diagnosed as IgAN with 24% glomerulosclerosis. Follow up renal biopsy after 10 cycles of MP followed by SVF in 1 year showed markedly decreased immune deposits without lesions of sclerosis. Laboratory results showed BUN/Cr 6.9/1.08, urine protein/Cr 0.974. Follow up lab after 2 years showed BUN/Cr 1.6/1.04, urine protein/Cr 0.145. Case 2: 45-y-old female was diagnosed as IgAN grade IV (HSV Lee Classification) with 61% sclerotic glomeruli. Follow up renal biopsy after 10 cycles of MP followed by SVF in 1 year showed 41% sclerotic glomeruli with disappearance of IgA and C3 deposition. Initial serum Cr and GFR was 1.77mg/dl and 35ml/min. Follow up lab after 3 years showed 1.03mg/dl and 61ml/min. Case 3: A 36-year-old female was diagnosed as IgAN grade V with 67% glomerulosclerosis. Follow up renal biopsy after 10 cycles of MP pulse followed by SVF in 1 year showed stage IV with 33% glomerulosclerosis. Initial serum Cr and GFR was 1.39mg/dl and 43ml/min. Follow up lab after 3 years showed 1.32mg/dl and 48ml/min.

Results: Conclusions: In conclusion, although further longterm studies are needed, 3 years follow up of MP pulse followed by SVF treatment in severe IgAN with CKD might be promising new therapeutic strategies without noticeable side-effects or complications.

State of Rituximab in Treatment of Minimal Change Disease: A Systematic Review Chandra M. Jha,1 Hormoz D. Dastoor,2 Ebal Ah. Elshukri,3 Alind Kumar.4 Nephrology, Juleha Hospital, Dubai, United Arab Emirates; 4Nephrology, Bahria Hospital- Johns Hopkins International, ABU DHAIBI, United Arab Emirates; 3Nephrology, Burjeel Hospital, Abu Dhabi, United Arab Emirates. Group/Team: ADHARR.

Background: 90% of childhood &10-15% of adult Nephrotic Syndrome is caused by primary minimal change disease (MCD). Corticosteroid has remarkable success. Around 25% of patients have frequently relapse & 30% become steroid dependent. Chimeric monoclonal antibody Rituximab (RTX) induces B cell depletion. The pathophysiology & mechanistic involvement of B cells in MCD is poorly understood. Yet Rituximab is reported to be used in its management. We aimed to review the literature to find answers about: 1. Efficacy of Rituximab in Frequently Relapsing Nephrotic Syndrome due to MCD; 2. FSGS in children and adult; 2. Dose & duration of RTX used for MCD; 3. Side effects / complications associated with its use.

Methods: We searched PUBMED, Chochrane Review Database and Govt. Trial Registry for the search term “rituximab in minimal change disease”, “rituximab in proteinuria” and “Rituximab in Glomerular diseases” during the period 1st January 1998 to 31st March 2017. We excluded the publications for membranous nephropathy, IgA nephropathy and secondary MCD. All publications including case reports, prospective and retrospective cohorts studies were included. Data was pulled from full text articles by lead author and independently verified by 2nd author. Revman was used for review. There were 11 case reports & 3 case series (25 patients), two retrospective cohort studies (total 29 patients) and 16 prospective cohort studies (309 patients). There was one prospective randomized control study involving 48 patients. Few cases of FSGS in some studies were not excluded. RTX dose employed varied from single dose of 375 mg/m2 to 1000 mg/m2 every 6 months for duration of treatment. Rituximab was effective in bringing remission, reducing requirement of immunosuppressives and reducing the recurrences. Treatment with mycophenolate was associated with poor response to Rituximab. FSGS was more prone to early relapse. Common side effect was infusion reaction, hyperviscosity, infection, arthralgia, leukocytoclastic vasculitis manifesting as palpable purpura, and abdominal pain. There are case reports and series in the pediatric literature highlight neurological manifestations such as headaches, seizures, central and peripheral neuropathies. We describe a case with unilateral sensorineural hearing loss associated with onset of renal biopsy proven IgAV. This association has not been previously reported.

Methods: A 28 year old Caucasian male without significant medical history was evaluated for renal insufficiency and edema. Clinical history revealed the patient had an upper respiratory infection about one month prior to evaluation that was treated with amoxicillin and followed by an extensive palpable purple leg rash associated with arthralgia, nausea, and anasarca. Concurrently, the patient also reported sudden hearing loss in his right ear associated with tinnitus. Workup revealed creatinine of 1.38g/dl, albumin 2.1 g/dl, and nephritic urine sediment (10 RBC/hpf) with 8.4g/kg of protein. Serologic evaluation was unremarkable. Renal biopsy revealed diffuse endocapillary proliferative glomerulonephritis, acute tubular injury, diffuse granular mesangial and glomerular capillary wall staining for IgA and C3, and electron microscopy demonstrated segmental foot process effacement. MEST scores M1, E1, S0, T0. C0. He also received ENT evaluation that identified severe sensorineural hearing loss in his right ear. MRI was unremarkable for intracranial pathology. Creatinine rose to 2.4mg/dl that likely reflected tubular injury due to the severe podocytopathy. High dose prednisone (1mg/kg for 12 days) and aggressive diuresis were initiated with improvement in renal function but the hearing loss has not yet improved.

Results: Conclusions: Neurological manifestations are known sequela of small vessel vasculitis as IgAV. However, there are no cases in the literature describing an association with unilateral sensorineural hearing loss. This report extends the observed constellation of symptoms with IgAV to include unilateral sensorineural hearing loss, which has not yet resolved in our patient.

Unusual Presentation of Secondary Syphilis Syed Rizwan A. Bokhari,1 Adrian J. Baudy,2 Myra A. Kleinpeter,3 Laura R. Kidd,1 Eric E. Simon. 1Tulane School of Medicine, New Orleans, LA; 2Tulane University, New Orleans, LA; 3Tulane University School of Medicine, New Orleans, LA; 4Tulane University School of Medicine, New Orleans, LA.

Background: Nephrotic syndrome with secondary Membranous glomerulonephritis (MGN) is frequently encountered with autoimmune diseases, diabetes mellitus, exposure to toxic agents, malignancies and infectious agents. Infected-related MGN, secondary to syphilis is rarely seen with advancement of healthcare in developed countries.

Methods: We describe a case of 21-year-old African American HIV positive male with severe renal dysfunction and no known co-morbidities admitted with 1 week complaints of epigastric pain, nausea, vomiting and diarrhea. Review of systems, family and allergic history were significant. Sexual history was positive for a single male partner less than a year. Examination revealed maculopapular rash on trunk, few small axillary and inguinal lymph nodes, epigastic tenderness and perianal tenderness 7 days prior to admission. His CD4 count was 306 cells/mm3 and strongly positive RPR. Autoimmune profile, complement levels, thyroid function tests, lipid profile, coagulation profile, serum and urine electrolytes were all within normal limits. Renal ultrasound and CT abdomen were unremarkable, except for moderate volume bilateral hydronephrosis. In the history, the patient reported sudden onset of epigastric pain. There are case reports and series in the pediatric literature highlight neurological manifestations such as headaches, seizures, central and peripheral neuropathies. We describe a case with unilateral sensorineural hearing loss associated with onset of renal biopsy proven IgAV. This association has not been previously reported.
secondary to syphilis, however, if present, they are almost always associated with plasma cell rich infiltrate.

SPUB491

Predictive Significance of Indicated Repeat Biopsy in Patients with Lupus Nephritis

Krishan Lal L. Gupta, Joyita Bharti, Hari A. Prasad, Raja Ramachandran, Manish Rathi, Aman Sharma, Ritambhara Nada. Postgraduate Institute of Medical Education & Research, Chandigarh, India.

Background: Lupus nephritis, an important cause for morbidity and mortality in systemic lupus erythematosus, is characterized by remissions and relapses. Although repeat renal biopsy in a flare/resistant disease is suggested in almost all guidelines, few conclusive studies have investigated its role. We analysed the contribution of repeat renal biopsy in treatment decision and assessed various predictors of renal outcome.

Methods: Sixty-four patients who underwent repeat renal biopsy from January 2013 to January 2017 were included. Renal biopsy was done only when clinically indicated. The clinical and histological parameters at initial biopsy and repeat biopsy were compared. Multivariate regression analysis was used to determine factors significantly affecting renal outcome at last visit. Renal relapse and outcome (complete remission, partial remission, resistant) were defined based on KDIGO (Kidney Disease: Improving Global Outcomes) guideline.

Results: Repeat biopsy was done for relapse in 56% and for resistant disease in 44% of patients. 8/64 underwent one repeat biopsy, 8/64 underwent 2 repeat biopsies. The median age of patients was 29 ± 9.6 years at initial biopsy and male to female ratio is 1:3. Nine (17%) out of 52 patients with baseline proliferative histology converted to non-proliferative disease while 3/12 (25%) with non-proliferative lesion converted to proliferative disease. After the second biopsy, 84% of patients had therapy changed. In multivariate analysis, the factors statistically significant for non-response at last visit are non-responsive disease to second line of therapy, non-steroidic severe relapse, presence of IFTA (interstitial fibrosis/tubular atrophy) at first biopsy, IFIATA >25% at second biopsy, presence of diffuse glomerular basement membrane thickening and TMA (thrombotic microangiopathy) at second biopsy. With a median follow-up of 146 months, 48/64 (75%) patients have responded to therapy after the second biopsy, with 17/64 (26.5%) in complete remission and 5/64 (7.8%) needing renal replacement therapy.

Conclusions: Tubulointerstitial and vascular involvement in repeat biopsy were associated with poor response to therapy. This indicates ineffectiveness of current induction therapy in lupus nephritis. The practice of repeat renal biopsy is still an important and decisive tool.

SPUB492

Survey of Deceased Children with Shiga Toxin-Associated Hemolytic Uremic Syndrome in Japan

Shuichi Ito,1 Mayumi Sako,2 Takashi Igarashi.2 1Department of Pediatrics, Graduate School of Medicine, Yokohama City University, Yokohama, Japan; 2National Center for Child Health and Development, Setagaya-ku, Japan.

Background: In patients with Shiga toxin-producing Escherichia coli (STEC)-related hemolytic uremic syndrome (HUS), known major causes of death are encephalitis related hemolytic uremic syndrome (HUS), known major causes of death are encephalitis

Methods: We conducted a nation-wide retrospective survey of deceased children due to STEC-HUS between 2000 and 2014. We sent a questionnaire to 1100 institutes in Japan. We analyzed collected data.

Results: Eighteen patients (males 11; females 7) were studied. The median age at onset was 4 years (2.2-14.6 years) and the median weight was 13.5 kg (12-47 kg). O antigens of E. coli were O157 (n=10), O111 (n=4), O26 (n=2), and unknown (n=2). All patients developed AKI and thrombocytopenia. Convulsion and conscious disturbance were observed in 18 and 14 patients, respectively. Six patients developed acute cardiac failure and 5 had arrhythmia. The median day of death was 3 days from the onset of HUS (1-181days). Primary causes of death were encephalopathy (n=12), encephalopathy with acute cardiac failure (n=1), cardiac failure (n=4), and AKI (n=1). Types of intervention were dialysis (n=11), plasma exchange or infusion (n=8), anticoagulation (n=14), methylprednisolone pulse therapy (n=1), and antibiotics (n=14). The median day from onset of diarrhea to death was 20.7 days in patients treated with antibiotics (n=14), but 4 days in those who died within 3 days (n=4) (P=0.047). There were no significant differences in laboratory data and characteristics of patients at the diagnosis of HUS between those who died within 3 days (n=10) and after 3 days (n=8).

Conclusions: Most patients had rapid and devastating clinical course, and the median day from onset of HUS to death was only 3 days. The second main cause of death was acute cardiac failure. The time from onset of diarrhea to death was significantly longer in antibiotic-treated patients than in non-treated patients. Risks and benefits of antibiotics have not been clarified, but survival was improved in antibiotic-treated patients in an outcome study (BMJ 144 255, 500-100; and RBC 50-100, 24 hr collection showed 2.42 gm of protein. HIV, Hepatitis B/C were negative and ANA/ddDNA positive. Protein electrophoresis and light chains were normal. Renal Biopsy showed areas of Mesangial deposits, rare sub-epithelial deposits and tubulo-rielticular inclusion consistent with Class I LN. Abundant Zebra Bodies of varying sizes were noted in the visceral epithelial cell cytoplasm, characteristic of Fabry Disease. Further tests showed normal Plasma Lyso-Gb3 level and negative genetic GLA sequencing, ruled out Fabry. After discontinuation of HCQ, proteinuria improved and renal function stable.

Conclusions: Zebra bodies are mostly seen in recent renal phospholipidosis but described with various drugs like CQ, amiodarone and silicon. CQ induced phospholipidosis was first described as CQ Keratopathy in 1977. CQ Cardiotoxicity was described in a Mayo study in 2002. The first description of CQ Renal Phospholipidosis was reported in German in 2002. More recently HCQ has been associated with similar findings. Being a weak base HCO is concentrated in lysosomes and inhibits enzymes like alpha-galactosidase, cathepsin, acid hydroxylase and phospholipases leading to autologous Phospholipidosis. Accumulation is higher in patients on higher doses of HCO, prolonged exposure and renal failure. Fabry needs to be ruled out to establish diagnosis. Only few case reports of this association are reported and clinicians need to be aware of Drug Induced Phospholipidosis.

SPUB494

Complete Remission of Severe Nephrotic Syndrome and AKI in Collapsing FSGS with a Combination of ACTH Gel and Abatacept – A Case Report

Rebecca D. Monk. University of Rochester, Rochester, NY.

Background: Focal segmental glomerulosclerosis (FSGS) is now the most prevalent primary nephrotic disorder. The collapsing variant of FSGS often portends a poor prognosis. Patients develop severe nephrotic syndrome (NS) with ensuing kidney failure despite therapy. This case demonstrates success using combination therapy with Abatacept and ACTH gel.

Methods: A previously healthy 32 year old florist presented with 3+ leg edema. Initial creatinine (Cr) was 0.99. Alb 2.6, Cholesterol 404, 24hr urine, protein: creatinine were both consistent with 8 g of proteinuria. Kidney biopsy revealed FSGS– collapsing variant with Ki-67 immunoconing. She was treated with 1 mg/kg prednisone, lisinopril and furosemide. She developed AKI and hyperkalemia with no improvement in anasarca. Due to high K (5.9) and Cr (to 2.5), calcium inhibitors were not felt safe to use. Cellcept was initiated with iv diuretics in the hospital. Steroids were continued. She suffered numerous medications side effects including proximal myopathy, severe anemia on cellcept and methemoglobinemia from Dapsone. Months later she was 45 lbs greater than baseline weight of 100 lbs. Cr was 3 (GFR 19) and protein:creatinine ratio remained 30 to 50. B7-1 stain was ordered and Abatacept was started. 3 weeks later insurance for ACTH gel (Acthar 8?) was approved. B7-1 staining was negative but both medications were continued for 9 months. Over the first 2 months she lost 40 lbs. One months later, Cr decreased to 0.83, MA:creatin ratio 766. Eight months after intiation MA:creatin ratio was 255. 3 years later she remains disease free and pregnant with her first child.

Results: Conclusions: This patient with no response to prior therapy of collapsing FSGS had a complete remission of NS and a full recovery of proteinuria with combined ACTH gel and Abatacept. ACTH stimulates melanocortin receptors including MC1R on podocytes. Activation of MC1R may have a variety of podocyte protective effects but few pts with FSGS have had complete remissions with ACTH. Theoretically, Abatacept inhibits B7-1 binding to Fc receptors, an action that could protect the podocyte from mTOR activation and interstitial fibrosis. However, in this case, our patient was B7-1 negative. The mechanism by which one or both of these drugs led to complete remission in this case is not clear. Further studies may elucidate the benefits of this therapy.
Following first description in 1939, substantial advances have been achieved in the understanding of the biology and clinical course leading to identification of growing number of cases. Despite this, renal complications of HLH remain poorly documented. Immunosuppression remains the mainstay of treatment and spontaneous resolution have not been shown so far. 

Results: Our patient is a 33-year-old female with history of hypothyroidism, who was admitted with puffiness of face, fever and pitting leg edema. Laboratory work up revealed acute kidney injury with albuminuria of 5.1 grams, elevated liver transaminase, bicarbonate, elevated ferritin, low fibrinogen and active urine sediments with hematuria and oval fat bodies (EFM) consistent with normal sized kidneys with normal echogenicity. The kidney biopsy revealed glomeruli with prominent infiltrating monocytes/hiostiocytes & endothelial swelling, most consistent with histiocytic glomerulopathy. Following kidney biopsy, she received supportive care as her renal function started to improve. She was discharged home six days after biopsy with clinical improvement and kidney function reaching baseline and albuminuria of 123 mg. She was followed up in the out patient clinic and has normal GFR with no albuminuria six months post discharge.

Conclusions: HLH is often triggered by infectious, autoimmune, neoplastic diseases and sometimes multiple causes exist. Most recent modification of diagnostic criteria include three of four clinical findings (fever, splenomegaly, cytopenia, hepatitis) plus one of four immune markers (hemophagocytosis, increased ferritin, hypofibrinogenemia, absent or very decreased NK cell function). We report a case of HLH after a presumed acute viral illness, who fulfilled criteria of HLH with histiocytic glomerulopathy and had spontaneous, rapid resolution of nephrotic syndrome and renal insufficiency in the absence of immunosuppressive therapy. Our case highlights the potential reversibility of HLH in clinically stable patient. Further research is needed to understand more about this rare disease and reporting of clinical presentations and outcomes of all cases are recommended.

PUB496

Gromlerucleroneulomorplasticnymphritis as an associated entity with different malignancies, mostly hematological. This case demonstrates a case of PGNMID associated with a solid bladder mass that showed initial improvement and showed 19 glomeruli with 5 sclerosed. There was marked endocapillary hypercellularity with subepithelial and subendothelial immune complex deposits and 10-20% fibrosis. Immunofluorescence (IF) was positive for IgG3, C3c, C1q, and kappa light chains. Examination of ultrastructural analysis and electron microscopy (EM) showed focal subendothelial and subepithelial electron dense immune complex deposits. The biopsy was suggestive of PGNMID as there was IgG3 staining of mesangium and capillary loops. The patient was started on steroids, with improvement in the confusion, dyspepsia and kidney function (Crea down to 1). Work up for underlying malignancy included CT scan which showed a large bladder mass. Biopsy of the mass was deferred as the patient was later switched as per request to palliative care.

PUB498

Association of Mesangial IgM Deposits with Rapidly Progressive Diabetic Nephropathy

Methods: Serum, urine and glomerular biopsies from forty-six patients with FSGS undergoing a kidney transplant were obtained. Microarray analysis, immunohistochemistry (IHC) and electron microscopy (EM) were performed using Pre (PreR) and PostR biopsy samples. Serum samples were also used for in vitro studies. Correlation analysis between genes important in modulating lipid metabolism and the immune response and morphometric variables such as FPE in PT kidney biopsies and clinical variables (proteinuria, estimated GFR) was performed.

Results: SMPDL3b expression was not significantly modulated in PostR kidney biopsies but weakly correlated with cGFR at 1 year. Inflammatory and lipid related pathways were highly regulated in glomeruli of PostR kidney biopsies and in podocytes exposed to the sera obtained from a subset of patients with FSGS.

Conclusions: We identified a small set of glomerular inflammatory and lipid related genes that correlated with clinical variables and may be utilized to stratify patients for PT REC and decline of GFR. 

Funding: NIDDK Support, Private Foundation Support

PUB499

Proliferative Glomerulonephritis With Monoclonal Immune Deposits Associated With a Bladder Mass

Methods: A 31 year old African American female with SC hemoglobinopathy presented with dyspnea, generalized swelling of the body and acute kidney injury (AKI). Physical examination was significant for confusion, edema and astereosis with stable vital signs. Creatinine(Crea) was 3.7 up from a baseline of 1.1. Complete blood countCBC, and coagulation profile were unremarkable. Blood urea nitrogen and serum creatinine were 29 and 4.4. And showed 19 glomeruli with 5 sclerosed. There was marked endocapillary hypercellularity with subepithelial and subendothelial immune complex deposits and 10-20% fibrosis. Immunofluorescence (IF) was positive for IgG3, C3c, C1q, and kappa light chains. Examination of ultrastructural analysis and electron microscopy (EM) showed focal subendothelial and subepithelial electron dense immune complex deposits. The biopsy was suggestive of PGNMID as there was IgG3 staining of mesangium and capillary loops. The patient was started on steroids, with improvement in the confusion, dyspepsia and kidney function (Crea down to 1). Work up for underlying malignancy included CT scan which showed a large bladder mass. Biopsy of the mass was deferred as the patient was later switched as per request to palliative care.

Results: Conclusions: PGNMID is a newly recognized entity caused by monoclonal deposition of IgG. The diagnosis and treatment is made by histology and robust data is lacking. Different immunomodulators particularly steroids have been tried successfully and some cases reported complete remission. PGNMID has also been occasionally associated with different malignancies, mostly hematological. This case demonstrates a case of PGNMID associated with a solid bladder mass that showed initial improvement by steroids within one week of treatment.

PUB499

Association of Mesangial IgM Deposits with Rapidly Progressive Diabetic Nephropathy

Conclusions: Although IgM mesangial deposition is often associated with minimal change disease or focal segmental glomerulosclerosis, evidence of its association with DN is sparse. Our results suggest that mesangial IgM deposition may be found in individuals with DN exhibiting an unusual clinical course and this finding could be associated with an accelerated course of DN. Further investigation is warranted to better characterize this entity.

PUB499

All of the Right Hits: APOPL, CMV, and Collapsing Focal Segmental Glomerulosclerosis

Methods: A 31 year old African American female with SC hemoglobinopathy presented with fever, sore throat, sinus congestion, myalgia, vomiting, and dark urine. There was no ilicit drug or NSAID use. Creatinine (Cr) 2.3 mg/dL, hemoglobin 9.5 g/dL, respiratory viral panel positive for parainfluenza virus. Spot urine protein/Cr was 9.8 g/g. Cr eventually peaked at 7.2 mg/dL. Plasma CMV by PCR was 2554IU/mL, and CMV IgM antibody titer was >240 AU/mL. Tests for HIV, hepatitis B, hepatitis C, and parvovirus B19 were negative. Renal biopsy showed collapsing of capillary loops, prominent overlying epithelial cells, and extensive foot process effacement on
EM, without endothelial deposits. Immunostaining was negative for viral inclusions in glomeruli. The APOL1 genotyping showed heterozygosity for G1 and G2 alleles. The patient was treated with corticosteroids and ganciclovir, with subsequent improvement: Cr to 1.1 mg/dL (without renal replacement therapy). CMV by PCR became undetectable, and proteinuria declined to 3 g/g.

Results: Conclusions: While collapsing FSGS is traditionally associated with HIV, non-HIV viruses are now emerging as potential triggers. A “two hit” mechanism has been proposed; wherein genetically susceptible hosts with the APOL1 gene polymorphism, subsequently exposed to an environmental trigger, such as viral infection, result in activation of the immune system and local podocyte destruction. Our patient had heterozygous APOL1 genotype and CMV viremia leading to collapsing FSGS. Collapsing FSGS is typically associated with poor renal outcomes and progression to end stage renal disease, however, early recognition and prompt treatment of CMV with ganciclovir and corticosteroids for FSGS resulted in clearance of viremia and renal recovery in our patient.

PUB500

Fibrillary Glomerulonephritis (FGN): A Rare Clinical-Pathologic Entity, Not Always with Poor Renal Outcomes! Saurabh,2 Ahuja,1 Anum Bilal,1 Arif Asif,2 Llewellyn A. Foulke,2 Adam Austin,2 Rafia I. Chaudhry.1 1AMC, Albany, NY; 2Albany Medical Center, Albany, NY; 3Albany Medical College, Albany, NY; 4Jersey Shore University Medical Center, Neptune, NJ; 5None, Albany, NY.

Background: FGN is a renal deposition disease characterized by 10-30 nm thickness, disorganized, straight fibrils in the mesangium and glomerular basement membrane (GBM) on electron microscopy (EM). FGN is reported in 0.5-1% of native renal biopsies. Methods: 5 cases of FGN presented to Albany Medical Center (AMC) over the last 12 years. 986 native renal biopsies were performed in this period, confirming an incidence of 0.5% of FGN amongst native renal biopsies at AMC. We present 3 cases (follow-up data missing in the remaining 2).

Results: Case 1: 66 years, 2 Caucasians, with male to female ratio 2:1. Presenting features: nephrotic syndrome (2/3), AKI (2/3) with mean Cr 1.4 mg/dL, hematuria (3/3) and hypertension (3/3). 1 patient (Pt) was diagnosed with Multiple Myeloma. LM revealed mesangial GN (3/3), membranous GN (1/3), and membranoproliferative GN (1/3), with polyclonal IgG and C3 on IF for all 3, and IgG4 subclass in 1. EM was diagnostic with 10-30 nm fibrils in mesangium and GBM, and sub epithelial deposits. All 3 patients received RAS blockade, and during a 35 month follow up: Pt 1 (initial Cr 1 mg/dL, 11 gms proteinuria): progressed to ESRD despite immunosuppression (ISS) with rituximab. Pt 2 (initial Cr 6.6 mg/dL, 6.8 gms proteinuria): partial remission with corticosteroids and tacrolimus. Pt 3 (initial Cr 2.7): did not receive ISS, and Cr stabilized at 2.7.

Conclusions: FGN predominates in Caucasians, and most patients are 40-60 yrs old. It is mainly a disease without renal insufficiency and hematuria. Previously considered an idiopathic disease, FGN may herald systemic illnesses, with autoimmune conditions or malignancy found in a third of cases in a large Mayo clinic series. Histologic findings are widely variable, although mesangial GN and MPGN are reported in most cases, along with diagnostic fibril deposits. The therapeutic strategy remains poorly defined, and renal survival is poor, with 50% patients reaching ESRD despite RAS blockade and ISS. Prospective, controlled studies are limited by the rarity of the disease, and data on optimal therapeutic regimen is lacking.

PUB501

Unusual Presentations of Anti-GBM Disease: A Case Series Anum Bilal,1 Adam Austin,2 Loay H. Salman,1 Arif Asif,2 Swati Mehta,1 Llewellyn A. Foulke,1 Roman Zuckerman,2 Rafia I. Chaudhry.1 1Albany Medical College, Albany, NY; 2Jersey Shore University Medical Center, Neptune, NJ.

Background: Anti glomerular basement membrane antibody (anti-GBM) disease is a small vessel vasculitis with antibodies (Ab) to the basement membrane of pulmonary and renal capillaries. The prevalence of anti-neutrophil cytoplasmic antibodies (ANCA) with anti-GBM, i.e. double positive disease, is estimated at 30%.

Methods: We present 10 cases of anti-GBM disease diagnosed by renal biopsy for RPGN from 2009-2017 at Albany Medical Center. 60% were male, 90% Caucasian, aged 15-82 yrs. 2 patients had pulmonary hemorrhage; both non-smokers, with prior history of asthma. All patients were tested for ANCA (all p-ANCA, 3 c-ANCA), consisting with the reported prevalence of double positive disease. 8 of 10 patients required hemodialysis (HDI) and only 1 had renal recovery, while 7 progressed to ESRD. Both cases that did not require HD, and the only case of renal recovery, had double positive disease. All patients received cyclophosphamide, corticosteroids and plasmapheresis. One patient was switched to rituximab due to pancytopenia, and a subsequent diagnosis of multiple myeloma. Anti-GBM titers decreased with plasmapheresis in all cases. 5 patients received renal transplants without recurrence of anti-GBM disease. Anti-GBM Ab prior to transplantation were negative in all cases, consistent with data suggestive of de novo disease

Results: Conclusions: Anti-GBM classically has a bimodal age distribution with peak incidence in the 3rd and 6th decades. Our series does not support this pattern, with at least 1 case in every decade of life (between age 10-90), except the 8th (70-79 yrs). Prior reports demonstrate mixed renal outcomes in double positive disease, including a correlation with poor renal prognosis in some studies. However, the 2016 rise in renal survival in our series was associated with double positive cases. The low incidence of pulmonary hemorrhage may be due to screening based on viral load, with notably both cases were non-smokers. We did not note a seasonal pattern to the disease (only 50% presented in the warmer months). Despite the severity of anti-GBM disease, and associated high mortality, we have 100% patient survival to date.

PUB502

A Rare Etiology of Renal Failure in Chronic Hepatitis C Virus Infection Arun Rajasekaran,1 Mario A. Mendezora,2 Edward T. Casey.3 1University of Central Florida College of Medicine, Kissimmee, FL; 2Nephrology, Orlando VA Medical Center, Orlando, FL.

Background: Chronic hepatitis C viral (HCV) infection is strongly associated with immune mediated glomerular diseases, including membranoproliferative glomerulonephritis (MPGN), and rarely fibrillary glomerulonephritis. We describe a case of fibrillary MPGN in a patient with HCV infection, with no improvement in renal function despite achieving sustained virologic response after anti-viral therapy.

Methods: A 60-year-old white male with treatment-naïve HCV infection presented with a four month history of progressive leg swelling. He was taking high doses of non-steroidal anti-inflammatory (NSAIDs) agents for pain relief. On examination, there was pitting edema in the legs. Serum creatinine was 4.1 mg/dL (1.2 mg/dL a year ago), urine studies showed hematuria and nephrotic range proteinuria. HCV RT-PCR returned at 405,073 IU/mL (normal <12), and testing revealed genotype-1a. Serology revealed normal ESR and complement levels. HIV, ANA, ANCA, and cryoglobulins were negative. NSAIDs were stopped and his hypertension treated. A kidney biopsy showed normal sized glomeruli with a mesangial matrix expansion that stained positive for H&E and PAS. There was severe widespread tubular atrophy and interstitial fibrosis, along with severe interstitial fibrosis of blood vessels. On immunofluorescence, there was global mesangial and capillary wall “smudged” deposits staining 3+ for IgG, 2+ for C3 and 2-3+ for kappa and lambda light chains. Electron microscopy showed ill-defined fibrillary deposits within an expansile mesangium, and glomerular basement membrane global thickening with severe foot process effacement of the visceral epithelial cells. These findings were consistent with a fibrillary MPGN. 12 week treatment with elbasvir-grazoprevir lead to undetectable viral loads; however his renal function progressively worsened to chronic kidney disease stage V.

Results: Conclusions: Fibrillary MPGN is a rare cause of renal failure, manifestations range from nephrotic syndrome to overt renal failure. Few cases of this renal disease have been associated with HCV infection and elevated viral titer. The patient’s kidney biopsy showed severe glomerular sclerosis, tubular atrophy and interstitial fibrosis that predicted a poor renal response to treatment of his HCV. This case highlights an unusual renal presentation of HCV infection, along with the need for early recognition and treatment of HCV.

PUB503

Persistent, Heavy Proteinuria Despite Discontinuation of VEGF Inhibitors for Renal Cell Carcinoma Dhereja Kaul,1 Himabindu Valluru,2 Philip Goldwasser,2 Gary R. Brielief,1 Man S. Oh,2 Ian L. Provancha.4 1Kings County Hospital, Brooklyn, NY; 2None, Brooklyn, NY; 3Nephrology, SUNY Downstate Medical Center, Brooklyn, NY; 4SUNY Downstate Medical Center, Brooklyn, NY.

Background: Axitinib is an antineoplastic tyrosine kinase inhibitor targeting VEGF receptors used against renal cell carcinoma. Proteinuria, hypertension and renal dysfunction are known adverse effects. An nephrotic range proteinuria rarely continues after the medication is discontinued. We report a case of nephrotic range proteinuria within 10 days after initiation of axitinib.

Methods: A 66 year old man with type 2 diabetes, hypertension, hyperlipidemia and obstructive sleep apnea and stage 3B CKD with a diagnosis of renal cell cancer treated with Sunitinib in 2015. In 2017, stage metastases from renal cell cancer were found, for which sunitinib was started. Prior to the start of sunitinib, a 24 h urine albumin was 383 mg/day and protein 745 mg/day. Because of neutropenia, sunitinib was discontinued on October 2015. Axitinib 5 mg daily was started on 1/3/16. On 2/29/16, protein excretion was 16.7 g/day. Axitinib was increased to 5mg BID on 3/16/16. On 3/31/16, albumin excretion was 18.0 g/day and urine protein 23.3 g/day. Although Axitinib was discontinued that day, the heavy proteinuria persisted: 15.2 g/day (Apr. '16), 11.1 g/day (Nov '16), 16.3 g/day (Feb '17).

Results: Conclusions: Proteinuria induced by tyrosine kinase inhibitors directed against VEGF receptors is usually mild to moderate, but occasionally severe enough to cause nephrotic syndrome. Proteinuria usually improves upon discontinuation of the drug. The persistence of severe proteinuria could be due to another mechanism, but a solitary kidney prevented diagnostic biopsy.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
Membranoproliferative Glomerulonephritis and the “Lollipop” Lymph Node Follicles

Background: Membranoproliferative glomerulonephritis (MPGN) is a pattern of glomerular injury which is either immune-complex or complement mediated, based on immunofluorescence (IF). We describe a rare case of MPGN with a negative IF for any immunoreactant.

Methods: A 44-yr-old woman presented with abdominal distension and anasarca. Physical examination revealed ascites, lower extremity edema, parotid enlargement, and diffuse adenopathy. Hemoglobin was 7.7 gm/dL, platelet count 110-192 x 10^9/L, serum creatinine 2.3 mg/dL, spot urine protein/creatinine ratio 0.4 mg/mg; urinalysis showed 3-10 red blood cells per high-power field. Serum LDH, complements and haptoglobin levels were normal. Significant radiographic findings included: diffuse lymph node enlargement in the neck, chest, abdomen and pelvis, hepatomegaly, and ascites. Ultrasound of the kidneys was normal. Immunoelectrophoretic studies, autoimmune and infectious disorders were negative. The kidney biopsy showed a classic membranoproliferative pattern of glomerular injury (MPGN) by light microscopy. No specific staining for immunoglobulins or complements was identified by immunofluorescence. Electron microscopy was negative for immune-complex deposits. These morphologic features in the absence of immune-complex deposits were consistent with chronic thrombotic microangiopathy (TMA). Lymph node biopsy showed “lollipop” appearance of lymph node follicles: concentric layers of small lymphocytes in the mantle zone penetrated by a sinuous vascular channel. The TMA-like lesions were confirmed by immunohistochemistry and ultrastructurally.

Microangiopathy (TMA). Lymph node biopsy showed “lollipop” appearance of lymph node follicles: concentric layers of small lymphocytes in the mantle zone penetrated by a sinuous vascular channel. The TMA-like lesions were confirmed by immunohistochemistry and ultrastructurally.

Results: Our patient was initially treated with the IL-6 inhibitor siltuximab; however, creatinine continued to rise, and peaked at 4.8 mg/dL. Some of inflammation and microangiopathy, respectively. Our patient was initially treated with the IL-6 inhibitor siltuximab; however, creatinine continued to rise, and peaked at 4.8 mg/dL. She was subsequently treated with rituximab, with improvement of creatinine to 1.0 mg/dL. Although uncommon, MCD should be on the differential diagnosis of a patient with immunoglobulin and complement negative MPGN and systemic findings of lymphadenopathy. We describe a case of MCD with concentric layers of small lymphocytes in the mantle zone penetrated by a sinuous vascular channel.

Conclusions: MCD is a group of lymphoproliferative disorders which may have renal involvement due to amyloidosis, MPGN, and interfascicular nephritis. Circulating levels of IL-6 and VEGF were elevated in our patient, which are thought to be the mediators of inflammation and microangiopathy, respectively. Our patient was initially treated with the IL-6 inhibitor siltuximab; however, creatinine continued to rise, and peaked at 4.8 mg/dL. She was subsequently treated with rituximab, with improvement of creatinine to 1.0 mg/dL. Although uncommon, MCD should be on the differential diagnosis of a patient with immunoglobulin and complement negative MPGN and systemic findings of lymphadenopathy. We describe a case of MCD with concentric layers of small lymphocytes in the mantle zone penetrated by a sinuous vascular channel.

PUB505
Leukocytoclastic Vasculitis Heralding Immunoglobulin G4-Related Kidney Disease Anubhav Kumar, Jiaiwe Ng, Jehan Z. Bahrainwala. Nephrology, Penn-Presbyterian Medical Center, Philadelphia, PA.

Background: Immunoglobulin G4-related disease (IgG4-RD) is a systemic inflammatory disorder that can affect multiple organs. IgG4-related kidney disease (IgG4-RKD) is a rare cause of kidney disease, though it is becoming more widely recognized as a cause of serious renal morbidity. It most commonly manifests as tubulointerstitial nephritis. We describe a case of IgG4-RKD preceded by leukocytoclastic vasculitis of the skin.

Methods: A 70 year-old Caucasian female with no prior history of kidney disease was directly admitted to our institution for acute kidney injury. Over the course of one year prior to admission, she experienced unintentional weight loss, lower extremity purpuric macules and submandibular swelling. Her serologies were notable for low C4 (11 mg/dL) and C3 (75 mg/dL), high RF (>600 IU/mL). She had negative SSA/SSB, ANA, Hepatitis B, Hepatitis C and HIV serologies. A skin biopsy was consistent with leukocytoclastic vasculitis. A salivary gland biopsy was not diagnostic. She was treated briefly with prednisone that improved her symptoms. On routine blood work prior to admission, her creatinine was 3.8 mg/dL; an increase from 1.3 mg/dL two months prior. She was admitted for urgent work up. Her creatinine peaked at 4 mg/dL. Her repeat serologies were negative. Her spot urine to protein creatinine ratio was 1.4 g/g. Her IgG levels were elevated at 419 mg/dL (1-123). Renal imaging showed large kidneys, 15 cm each, without hydroureteronephrosis. Her kidney biopsy showed a diffuse dense infiltrate of plasma cells and lymphocytes: >50 IgG4-positive cells in a single high-powered field, without evidence of lymphoplasmacytic or plasma cell disorders, consistent with IgG4-RKD. She was pulsed with methylprednisolone and discharged on high dose oral prednisone with a plan to taper over 12 weeks. Her creatinine decreased to 1.86 mg/dL within two weeks of diagnosis.

Results: Conclusions: IgG4 related skin disease is typically due to IgG4 plasma cell infiltration in the skin lesions but other non-specific, inflammatory skin lesions have been described. This case represents a rare case of IgG4-RKD associated with leukocytoclastic vasculitis. Early recognition of the disease is important as it commonly responds rapidly to steroid therapy.

Conclusions: IgG4 related skin disease is typically due to IgG4 plasma cell infiltration in the skin lesions but other non-specific, inflammatory skin lesions have been described. This case represents a rare case of IgG4-RKD associated with leukocytoclastic vasculitis. Early recognition of the disease is important as it commonly responds rapidly to steroid therapy.

PUB507
Recurrent Atypical Anti-Glomerular Basement Disease in a Kidney Transplant Patient Samir A. Brahmbhatt,1 Basheer A. Kummangal,1 Leal C. Herlitz,2 Richard A. Fatica,3 Saul Nurko.2 1Cleveland Clinic, Cleveland Heights, OH; 2Cleveland Clinic Foundation, Cleveland, OH; 3Cleveland Clinic Foundation, Cleveland, Ohio, Beachwood, OH; 4The Cleveland Clinic, Cleveland, OH.

Background: Atypical anti-glomerular basement disease (anti-GBM) is a rare variant of anti-GBM disease characterized clinically by an indolent course usually. Compared to typical anti-GBM, there is no circulating alpha-3NC1 antibody, no diffuse crescentic and necrotizing glomerulonephritis, and quasi-linear IgG staining on a kidney biopsy. Here we report a case of a recurrence in a renal transplant.

Methods: A 23 year old Caucasian female with end-stage renal disease attributed to membranoproliferative glomerulonephritis, status post living related donor kidney transplant, on Tacrolimus, Mycophenolate Mofetil, Prednisone, with last known stable graft function with serum creatinine (Scr) 1.8 mg/dL one year ago. After 5 years and 1 month of her transplant, she presented with nausea, vomiting x 3 days, low-grade fever and acute kidney injury with Scr 5.88 mg/dL. Initial basic work up showed no evidence of obstruction and there was no significant improvement in graft function after intravenous hydration. There was a high suspicion of a rejection as she was found to have 2 ng/mL Tacrotrough levels, so a transplant kidney biopsy was performed. It showed diffuse endocapillary proliferative with membranoproliferative features and focal crescentic formations. Immunofluorescence showed diffuse linear positivity of GBM with IgG, kappa and lambda, suggestive of atypical anti-GBM nephritis. In addition, there was Banff Grade 1B acute cellular rejection and acute antibody-mediated rejection. She had a negative serum anti-GBM antibody. She was treated with plasmapheresis, intravenous Methylprednisone, then 60 mg Prednisone orally daily and Rituximab infusions, continued on Tacrolimus and stopped Mycophenolate Mofetil. She did not require dialysis. Her Scr improved to 3.53 mg/dL with estimated glomerular filtration rate 16 mL/min/1.73m2 on 2 months follow up.

Results: Conclusions: This is the only 3rd reported case of recurrent atypical anti-GBM disease in a renal transplant patient. Optimal therapy for atypical anti-GBM disease in both native kidneys and after recurrence in the transplant remains controversial, as this is a rare disease entity. Further studies are needed to characterize the molecular architecture of GBM auto-antigens in these patients and establish optimal therapy.
Disease (IgAN) PUB508

Parenchymal chronicity from 20 to 50-70%. Of note, biopsies prior to 2014 showed no was significantly associated with heart failure (p<0.01); the nodular lesion, the glomerular lung involvement including five categories (category 1; 62.5%, 2; 62.5%, 3; 41.7%, 4; 12.5%, 5) mixed type. On 95.8 percent of total patients with ANCA-associated renal disease, twelve (25%) cases, crescentic type; seven (14.6%) cases; focal type; nineteen (39.6%) men. Forty-four (91.7%) were MPO-ANCA positive. Serum creatinine level was 1.525 to 2.6-3.3 mg/dL, losartan restarted. After lengthy discussion with patient regarding options, started on ACTH therapy for 6 months with a partial remission as noted below in Pr and stabilization in the Cr. Pr continues to improve despite being off ACTH since March most recently 1.37 g/L. She is currently undergoing a w/u for a second transplant and remains Dialysis free.

Results: Conclusions:

We have demonstrated a significant improvement in Pr and stabilization of Cr with ACTH in this young woman with De Novo IgAN with primary disease HUS.

Lung Involvement on Patients with ANCA Associated Renal Disease Hiroki Mizuno, Yoshiyumi Ubara, Akinari Sekine, Yoichi Oshima, Masahiko Ogura, Masaaki Yamahachi, Keichi Sumida, Junichi Hoshino. Nephrology Center, Toranomon Hosp., Tokyo, Japan.

Background: ANCA-associated vasculitis is a systemic vasculitis affecting multi-organ systems. Although analyses of each organ damage has already been published, the interaction between kidney and lung involvement has not been analyzed in detail.

Methods: We reviewed clinical data and high resolution lung CT (HRCT) on forty eight patients who were diagnosed as ANCA-associated renal disease by the kidney biopsy between April 2007 and December 2015. Glomerular lesions were classified according to the classification published by Berden et al. in 2012 and lung involvements were classified into 5 categories; (1) airway lesion; bronchial wall thickening, bronchiecstasy, (2) pleural lesion; pleural thickening, pleural effusion, (3) alveolar lesion; pure ground-glass opacity, mixed ground-glass opacity, consolidation, (4) focal lesion; nodular lesion, cavity, (5) interstitial lung disease. We conducted statistical analysis by comparing 1st biopsy and re-biopsy specimen in those received steroid + tonsillectomy (A group) and cyclophosphamide (R group) for 6 months after their initial biopsy at our hospital. Baseline characteristics were compared using descriptive statistics and categorical variables were compared using Chi-square analysis.

Results: Conclusions: The significance of renal repeat-biopsy in non-remitting IgAN was evaluated by comparing 1st biopsy and re-biopsy specimen in those received steroid + tonsillectomy and those only with conservative treatment. We suggest that a repeat biopsy in R group may better navigate appropriate treatment. We suggest that a repeat biopsy in R group may be unnecessary.

Efficacy of Induction Immunosuppression in Ethnic Minorities with Membranous Lupus Nephritis Anishh Bobba, Jayasree Athavale, Aniesh Joshi, Sunita Fugar, Peter D. Hart. John H Stroger hospital of cook county, Chicago, IL.

Background: Thirty eight percent of patients with systemic lupus have kidney disease, 20% of those with membranous lupus nephritis (Class V LN) experience decreased GFR after 7-12 years. Current guidelines recommend treating Class V LN in the presence of nephrotic range proteinuria with immunosuppressant in addition to steroids. We conducted this retrospective study to investigate the clinical outcome of 6 months of induction therapy with Mycophenolate Mofetil (MMF) or Cyclophosphamide and compare with Cyclophosphamide or Mycophenolate Mofetil (MMF) in patients with Class V LN.

Methods: Retrospective review of kidney biopsy database at Stroger Cook County Hospital from Jan 2000- April 2017 identified 28 patients with class V LN. Baseline characteristics including age, gender, race, serum creatinine(cre) and urine protein/creatinine ratio(uP/cre) at the time of initiation of therapy and after 6 months of therapy were obtained. Baseline characteristics were compared using descriptive statistics and categorical variables were compared using Chi-square analysis.

Results: There was no difference in sCr or proteinuria at 6 months in patients receiving induction treatment with MMF or cyclophosphamide (Table 1). After 6 months of therapy, MMF group (4/22) and cyclophosphamide group (3/6) had either partial or complete response. 50% patients in cyclophosphamide group had partial or complete response however only 6 patients received cyclophosphamide. Complete response was defined as sCr to baseline plus Pr/Cr < 500 mg/g. Partial response is sCr improve >25% plus 50% reduction in P/Cr and Pr/Cr < 3000 mg/g.

Conclusions: Mycophenolate is less effective than Cyclophosphamide for inducing remission in ethnic minority patients with V LN. An RCT is needed to compare MMF to cyclophosphamide for induction of remission in this patient population.

Table 1
Renal and Cutaneous ANCA Positive Vasculitis: Be Aware to Illicit Cocaine-Levamisole Use Even Though the Patient Denies Elvino J. Guarda barros,12 Veronica V. Antunes,2 Gustavo G. Thomé,2 Joao B. Saldanha de castro filho,2 Fernando S. Thomé,2 Direceu R. Da silva,2 Pedro E. Schaefer,2 Viviane Sebben,1 Alberto Nicoliella,1 Francisco V. Veronese,2 1Centro de Informações Toxicológicas do Rio Grande do Sul, Porto Alegre, Brazil; 2Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; 3Nephrology Division, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.

Background: Adulterated cocaine with levamisole in different concentrations has been increasingly used during the last decades. Levamisole can cause skin lesions, intravascular thrombosis, neutropenia, and crescentic nephritis. Physician awareness is essential for ensuring a proper diagnosis, because patients frequently deny the use of illicit drugs.

Methods: We describe a series of five patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis secondary to levamisole-adulterated cocaine, which were prospectively followed at a single hospital. Demographics and clinical characteristics are presented.

Results: Urine toxicology was all positive for cocaine and levamisole, tested by immunochromatography and gas chromatography-mass spectrometry. Three patients brought a sample of the cocaine powder (1 g), in which the presence of cocaine and levamisole was confirmed (levamisole: 32%, 1.2%, and 0.5% in each powder). Demographics and clinical characteristics are presented in Figure 1. No patient quit cocaine use. End-stage renal disease (ESRD) developed in one patient; the worst outcome was death due to vasculitic mesenteric necrosis and sepsis, that occurred in another patient.

Conclusions: In conclusion, cocaine/levamisole-induced vasculitis should be suspected in patients with renal and skin lesions, even when illicit drug use is denied. A urine drug toxicology screen is necessary to confirm the diagnosis and must be done during follow-up to ascertain drug abstinence. This condition can induce poor outcomes, as ESRD and death. 

Nephrotic Syndrome Secondary to Chronic Thrombotic Microangiopathy without Pathomonic Clinical or Laboratory Features Arun Rajasekaran,2 Najam A. Siddiqui,1 Pran M. Kar.3 1Lake Erie College of Osteopathic Medicine, Lake Worth, FL; 2University of Central Florida College of Medicine, Kissimmee, FL; 3Nephrology, Orlando VA Medical Center, Orlando, FL.

Background: Thrombotic microangiopathy (TMA) encompasses small-vessel thrombosis, consumptive thrombocytopenia, and microangiopathic hemolytic anemia (MAHA) that leads to global ischemia. Severe hypertension may promote TMA within the renal vasculature. We describe the first case of chronic thrombotic microangiopathy as a cause of nephrotic syndrome, not associated with clinical or laboratory features suggestive of TMA.

Methods: A 71-year-old Arab male with well-controlled hypertension (on amlopidine, CRD stage 4 (baseline serum creatinine 1.4 mg/dl), and anemia of chronic disease (baseline hemoglobin 12 mg/dl) presented with a one-month history of worsening lower extremity swelling. He was alert, afibrile, normotensive, and had pitting edema in his legs. Hemoglobin was 12 mg/dl, albumin 2.1 mg/dl, and serum creatinine 1.4 mg/dl. A 24-hour urine collection revealed 7.5 g of protein. Platelet counts, coagulation parameters, lactate dehydrogenase, haptoglobin, ESR, serum complements and immunoglobulins were normal. HIV, ANA, ANCA, RF, hepatitis B and C serologies, cryoglobulins, anti-GBM and antiphospholipid antibodies, and direct Coombs test were negative. No schistocytes were seen in the blood smear. Renal biopsy revealed glomerulot with extensive double-contour formation, mesangiolysis, and severe interstitial fibrosis and tubular atrophy. Severe arteriosclerosis and arteriolar hyalinosis were seen.

Immunofluorescence revealed negative staining for IgG, IgM, IgA, C3, C4, C1q, albumin, fibrinogen, and kappa and lambda light chains. Electron microscopy depicted thickened and irreversibly basement membranes due to extensive double-contour formation. These features suggested a chronic TMA. Workup for an occult malignancy was negative. He was given intravenous albumin for the next 3 days and low-dose Lisinopril was added. After a month, his proteinuria markedly improved with a spot urine protein-to-creatinine ratio being 6.45.

Conclusions: We report the first case of biopsy-proven chronic TMA as a cause of nephrotic syndrome with significant improvement of proteinuria, in an individual with well-controlled hypertension and laboratory features suggestive of TMA. Further studies on this phenomenon are warranted to better understand the pathophysiology of renal damage in TMA.

Treatment of Proteinuria Due to Treatment Resistant or Treatment Intolerant Idiopathic Focal Segmental Glomerulosclerosis: A 2 Part Prospective Study of H.P. Acthar® Gel (PODOCYTE) James A. Tumlin,4 Brad H. Rovin,5 Richard A. Lafayette,7 Enxu Zhao,8 Patrice Becker,7 Leah Patel,1 Susan Vanneter,7 Mallinckrodt Pharmaceuticals, Ellicott City, MD; 2Ohio State University Wexner Medical Center, Columbus, OH; 3Stanford University, Stanford, CA; 4University of Tennessee College of Medicine, Chattanooga, TN.

Background: Focal segmental glomerulosclerosis (FSGS) is a glomerulopathy with a high rate of progression to end stage renal disease; prior FSGS studies show that 16 weeks of therapy with glucocorticoids (GCs), calcineurin inhibitors (CNIs) and other agents have a limited ability to induce sustained remission. H.P. Acthar® Gel (repository corticotropin injection, RCI) contains a highly purified porcine ACTH analogue, and is indicated to induce remission of proteinuria in idiopathic nephrotic syndrome. Its mechanism of action is incompletely understood, though preclinical studies suggest activation of melanocortin receptors in the kidney and modification of circulating immune cells may reduce proteinuria via steroid-dependent and independent pathways.

Methods: Approximately 236 patients with FSGS, nephrotic range proteinuria (urine protein to creatinine ratio [uPCR] > 3.5 g/g) who are refractory or intolerant to GCs or CNIs will be randomized 1:1 to RCI 80 U 2x/week or placebo for 24 weeks. Subjects who do not achieve remission of proteinuria (uPCR ≤ 0.3 g/g; uPCR > 3.5 g/g and 50% reduction from baseline; uPCR > 3.5 g/g and a 50% reduction from baseline, respectively) at Week 24 are randomized 1:1 to RCI 80 U 2x/week or placebo for 50 additional weeks.

Results: Efficacy will be assessed by change in proteinuria at Weeks 24 and 50; safety will be assessed by collection of AEs, changes in vital signs and labs.
Conclusion: This is the largest study to date in refractory FSGS patients and will investigate the efficacy of RCI on CR or PR, it will also determine the efficacy of prolonged therapy on response rates.

Funding: Commercial Support - Mallinckrodt ARD, Inc.

PUB516

Improvement of Clinical Outcome in Kidney Diseases via the On-line Thai Glomerular Disease Registry: Lupus Nephritis

Hospital, Bangkok, Thailand; 2University of Texas Medical Branch, Galveston, Texas; 3University of Texas Medical Branch, Galveston, Texas; 4The University of Texas MD Anderson Cancer Center, Houston, TX; 5MD Anderson Cancer Center, Houston, TX; 6The University of Texas MD Anderson Cancer Center, Houston, TX.

Background: Lupus nephritis (LN) is the most common glomerular disease causing the end stage renal disease (ESRD) in Thailand. The data on epidemiology and outcomes of LN are limited in few medical schools. Thai Glomerular Disease Collaborative Network (TGCN) was established to investigate the epidemiology and clinical outcomes in Thai glomerular disease patients.

Methods: The data collected prospectively from TGCN included adult patients with biopsy-proven LN during July 2014 to March 2017. The clinical, laboratory and renal pathology data were obtained via online record.

Results: We found that LN was the most common pathological finding from TGCN (522 from 1,556 cases, 33.5%). Female was 89.3%. The median serum creatinin(cScr) was 1.06 mg/dL(0.7-9.2), and median urine protein creatinine ratio(UPCR) was 3.72 g/gCr(1.0-24.7). The percentage of class I, II, III, IV, V, III+V, IV+V, and VI was 0.4, 2.1, 15.5, 42.9, 15.7, 10.9, 11.1, and 1.3. The initial sCr≤2.0 mg/dL was found in class IV 60.7, VI 57, IV+V 53.4, II 37, III 29.8%. Crescentic formation＞50% was found in class IV 11.2% and IV+V 10.3%. The median activity index (AI) in class III, IV, III+V, IV+V, V, and VI was 5.8, 3, 3, 3, 2, and 2. The median chronicity index (CI) in class class III, IV, V, III+V, IV+V was 3, 3, 2, 3, and 10, respectively. During 36 months follow-up period, overall clinical response was not different among LN class. The % of partial response/complete response in proliferative LN (III, IV), V, III+V, IV+V was 58.8%, 45.4%, 39.2%, 29.7%, and 38.74/7.0. Focus on LN III and IV, the multivariate analysis showed that sCr＜1.2 mg/dL, and CI＜2 were the independent factors of non renal response with HR (95%CI) of 0.48 (0.29,0.82), 0.44 (0.21, 0.91). Additionally, the predicting factor for renal response in LN V was only the interstitial fibrosis. During this period, ESRD was found 6.1% in class III and IV.

Conclusions: Our study described the LN class IV was the most common renal findings and severe renal impairment at the time of biopsy in SLE patients. The clinical manifestation and renal response were comparable with the other studies. The independent unfavorable factors for renal response in LN III, IV were sCr≤1.2 mg/dL, and CI≤2, whilst in LN V was the high interstitial fibrosis.

Funding: Private Foundation Support

PUB517

An Unkind Cut: A Case of Pauci-Immune Crescentic Glomerulonephritis Associated with Suspected Exposure to Levamisole-Adulterated Cocaine

Robert Lorch,1 Susanne F. Mclaughlin,2 Sreedhar A. Mandayam.1

1Baylor College of Medicine, Houston, TX; 2None, Bellaire, TX.

Background: Levamisole (LEV) is a ubiquitous cocaine adulterant in the United States and has been implicated in an ANCA-associated vasculitis syndrome which commonly manifests as purpuric skin lesions, agranulocytosis, and thrombocytopenia. An increasingly recognized effect of LEV is kidney injury in the form of pauci-immune glomerulonephritis (GN). Our understanding of LEV-induced kidney injury is limited, and it can be difficult to differentiate ANCA-associated GN secondary to LEV from primary ANCA-associated vasculitis based on serology and biopsy. The implications for prognosis and treatment in this scenario are unclear.

Methods: We present the case of a 57-year-old man with stage 3 CKD and an approximately 20-year history of regular intranasal cocaine use, who presented with 8 weeks of myalgias and chills, as well as several days of new-onset dyspnea. He had last used cocaine 2 days prior. Physical exam was remarkable only for bibilar crackles and bilateral scattered rhonchi in the lungs, mild abdominal distension, and no abnormal skin findings. Initial laboratory testing revealed a creatinine of 5.1 mg/dL (baseline creatinine of approximately 1.5 mg/dL) and a white blood cell count of 3,900, and urine testing positive for cocaine. Bilateral patchy airspace opacities were seen on chest CT. Renal biopsy demonstrated pauci-immune crescentic GN, and serologic testing was suggestive of microscopic polyangiitis (anti-MPO positive, anti-PR3 negative). Due to his significant history of cocaine use, LEV-induced vasculitis could not be ruled out as a cause of rapidly progressive GN. He was treated with corticosteroids, rituximab, and plasma exchange; although he ultimately progressed to dialysis-dependent renal failure.

Results: Conclusion: Up to 80% of cocaine in the United States now contains LEV, and this case highlights the growing public health concern of LEV exposure. Our current knowledge of the clinical, laboratory, and biopsy findings specific for LEV-induced GN is often too limited to differentiate this form of drug-induced vasculitis from primary vasculitis, especially in otherwise complicated cases and when clinical stakes are high. A better understanding of the effects of LEV on the kidney is needed so that improved methods to diagnose and treat levamisole-induced glomerulonephritis may be developed.

Funding: Private Foundation Support

PUB518

Improvement of Clinical Outcome in Kidney Diseases via the On-line Thai Glomerular Disease Registry: The Third-Year Report

Ratesan Chawansuntorapoj.6 Boonyarit Cheunchusan,4 Ngoentra Tantranont,1 Waranangkana Pichaiwong,4 Bancha Satirapoj,2 Siribha Changsirikulchai.1 Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; 2Pathology, Siriraj Hospital, Mahidol University, Bangkok, Thailand; 3Pathology, Siriraj Hospital, Bangkok, Thailand; 4Medicine, Rajavithi Hospital, Bangkok, Thailand; 5Pathology, Siriraj Hospital, Bangkok, Thailand; 6Medicine, Siriraj Hospital, Bangkok, Thailand. Group/Team: Thai Glomerular Disease Collaborative Network (TG CN).

Background: End stage renal disease (ESRD) affects the quality of life and causes the high cost in health care system. Prevention of ESRD is the early recognition and appropriate treatment. Glomerulonephritis is the third most common cause of ESRD in Thailand. Thai Glomerular Disease Collaborative Network (TG CN) was established to evaluate the epidemiology and clinical outcomes in the glomerular diseases and helped to promote the good system to taking care of these patients.

Methods: TG CN originally consists of 9 tertiary care centers and expands to 20 hospitals. We conducted a prospective cohort study in the adults’ native kidney biopsy proven glomerular diseases between July 2014 and Mar 2017. The clinical and laboratory parameters at the time of biopsy, pathologic findings, treatment regimens and clinical outcomes were recorded via on-line registry.

Results: We recruited 1,556 patients performed native kidney biopsy during Jul 1, 2014 to Mar, 2017. The female to male ratio was 1.88:1. The average age, creatinine, albumin, and cholesterol were 43.8 (18-87) years, 1.48 (0.4-16.2) mg/dL, and 2.90 (0.8 g/dL), respectively. The median proteinuria was 3.7 (0.02-25.3) g/day. The patients presented with 40% of nephrotic syndrome, 21.7% of nephritis, 19.4% of nephropathy, and 60.8% of renal impairment (creatinine≤1.2 mg/dL). The renal pathological findings showed 33.9% of LN, 13.5% of IgAN, 10.9% of FSGS, 7.4% of minimal change disease(MCD), and 7.1% of membranous nephropathy (MN). The mean age of LN, IgAN, FSGS, MCD, and MN were 34.9, 39.4, 47.3, 46.5 and 52.6 years. The median creatinine at biopsy of LN, IgAN, FSGS, MCD, and MN were 1.08, 1.76, 1.70, 1.02 and 0.98 mg/dL.

Conclusions: Our study described the common renal pathological findings including LN, IgAN, FSGS, MCD, and MN. The clinical outcomes and predicting factors of renal response were described in the separate articles. Funding: Health Systems Research Institute, and Nephrology Society of Thailand support

Funding: Private Foundation Support

PUB519

Renal Complications of Hematopoietic Stem Cell Transplantation (SCT) and Glomerulopathies in Patients with Leukemia Receiving SCT: MD Anderson Cancer Center’s Experience

Ali Ziaoghlagh,6 Umut Selamat,1 Laila S. Lakhani,7 Amanda Tchakarov,2 William F. Glass,3 Ala Abudayeh,4 MD Anderson Cancer Center, Houston, TX; 5University of Texas Medical School at Houston, Houston, TX; 6University of Texas – Houston Medical School, Houston, TX; 7University of Texas MD Anderson Cancer Center, Houston, TX; 8University of Texas health science center at Houston, Houston, TX.

Background: Variety of kidney diseases as such nephrotic range proteinuria and glomerulonephritis, acute and chronic kidney disease are associated with Hematopoietic stem cell transplant. We present our experience in this Institute in patients with unindely leukemia who were managed with hematopoietic stem cell transplant. Glomerular diseases which developed by renal biopsy in patients for biopsy were acute kidney injury and in some patients were nephrotic range proteinuria.

Methods: After we obtained IRB (institutional review board) approval, renal biopsy reports from year 2000- 2017 were obtained from pathology department. Patients with leukemia who had stem cell transplant were selected. Medical charts were reviewed. We collected date on base line serum creatinine, serum creatinine at the time of biopsy, degree of proteinuria, urinalysis and renal pathology report.

Results: We reviewed 15 cases with leukemia including AML, ALL, CLL, and donor-related B-cell lymphoma. We had 3 cases with BK nephropathy, 3 cases with thrombotic microangiopathy which might represent graft-versus-host disease, 1 case with membranous nephropathy, 1 with mesangio proliferative glomerulopathy, 3 with Acute Tubular Necrosis, 1 with FSGS and 1 with moderate to severe chronic interstitial fibrosis. Leukemia was disregarded as the inadequate sample. 5 patient had nephrotic range proteinuria between 3-20 g proteinuria.

Conclusions: Hematopoietic stem cell transplant is associated with variety of kidney diseases. Some patients develop nephrotic range proteinuria with different glomerulopathies.
Novel Approaches Based in Current Evidence in ANCA-Associated Vasculitis with Renal Involvement Treatment

Vanina Vazquez,1 Gabriela Gonzalez,2 Javier E. Robaina Sindic.1,3 Simplemente Evita Hospital, Buenos Aires, Argentina; 3Division Nefrologia, Hospital de Clinicas Jose de San Martin, Universidad de Buenos Aires, Buenos Aires, Argentina.

Background: ANCA-associated vasculitis (AAV) are a group of autoimmune diseases characterized by infiltration and necrosis in small and medium vessels. AAV could respond to different therapeutics protocols depends on levels of clinical severity. Early treatment could improve the outcome. In spite of recognized efficacy of regimens with cyclophosphamide and corticosteroids to control the AAV, efforts to minimize drugs-related toxicity led to consider targeted therapies. Considering novelty and currently therapies evidence proposed to AAV and severity of renal presentation, we suggest new rational approaches emphasizing targeting B-cells therapy and preventing disease relapse.

Methods: Latest quality evidence was identified by methodological search filters, assessed evidence quality with Cochrane Renal Group check list, determined the strength of recommendations by Levels of Evidence (Oxford Centre for Evidence-based Medicine).

Results: Rituximab (RTX), a monoclonal anti-CD20 antibody, is the biological agent more using in AAV in current evidences. Unlike latest Guides and Recommendations published, RTX would be recommended in induction and maintenance AAV with renal involvement treatment (Table 1).

Conclusions: Current therapies for AAV with renal involvement shows that emerging therapies like RTX could improve rates of relapses and treatment-related toxicity. Further studies would provide target-therapeutic approaches.

Abstract Withdrawn
Clinical Utility and Prognosis of Standardizing Chronic Changes in Renal Biopsies with CKD Laura Fuentes, Ivan Rosero. Hospital General de Mexico, Distrito Federal, Mexico.

Background: Renal biopsy still is controversial in patients with chronic kidney disease, chronic changes are predictors of renal outcomes because predicts prognosis, guides and assess treatment. We correlate the histological findings classified with severe damage by immunofibrosis and tubulointerstitial (IF/TA) and add the proposed in a previous consensus (glomerulosclerosis, arteriosclerosis) with outcomes such as improve in renal function, CKD, ERSD, renal replacement therapy and mortality.

Methods: We retrospectively reviewed the records of 348 adult patients who underwent kidney biopsies between 01/01/12 and 06/01/17, focused only in patients with IFTA >50% including demographic, clinical, laboratory, ultrasonography and renal histopathological characteristics.

Results: The population was 49 men and 45 women, age 41.5± 14.2 years, kidney size 97.8 ± 12.3 mm for right and 98.72 ± 12.0 left, nephrotic in 37.2% and rapidly progressive syndrome in 28.7%, 22.3% patients were in RRT before the biopsy, and the main comorbidities were HTA, DM, SLE, at the diagnosis 97.9% were in CKD and 46.8% in ESRD, we found SNG in 61.7% (n=58), diabetic nephropathy in 22 (23.4%), lupus 19 (20.2%), vasculitis 11 (11.7%), GSFS as the main cause in PGN in 13.8%, followed by IgAN and membranous, there were and overlap seen in diabetics and FSGS and also PGN with tubulointerstitial nephritis in 25%, 22 patients received immunosuppressive therapy because the underlying cause with recovery and withdrawal of renal replacement therapy in 28.7%, using the classification with the glomerular and vascular damage can classify the patient to offer treatment or delay progression factors with more accuracy compared to previous classification for mortality and progression to ESRD in 19.5%.

Conclusions: The renal biopsy in CKD patients is still debated but it is a irreplaceable tool that may help clinicians establish a therapeutic strategy to slow down progression of kidney injury, in previous studies don’t take the overlap between PGN and SNG with another pattern of glomerular damage and it is very important to differentiate it because managing both conditions differently so a postbiopsy treatment change in 25% of CKD patients. Therefore, even if only speculative, it indicates that biopsy has been useful to decide the therapy for these patients so the criteria should be expanded.

Minimal Renal Affliction in Patients with Systemic Lupus Erythematous: Characteristics and Evolution Eva Rodríguez, Tarek C. Salman, Maria Jose Soler, Clara Barrios, Jordi Abello, Julio Pascual. 1Hospital del Mar, Barcelona, Spain; 2Rheumatologist, Hospital del Mar, Barcelona, Spain; 3Hospital del Mar, Parc de Salut Mar, Barcelona, Spain; 4Hospital del Mar, Institut Mar d’Investigacions Mediques. Barcelona, Spain., Barcelona, Spain; 5Nephrology, Parc de Salut Mar, BARCELONA, Spain; 6Parc de Salut Mar, Fundació IMIM, Barcelona, Spain.

Background: Lupus nephritis (LN) is the most common organ involvement in Systemic Lupus Erythematosus (SLE). Indications of renal biopsy (RB) are deterioration of renal function and / or activity in sediment and / or proteinuria> 0.5 g / 24h or urine protein to creatinine ratio (P/C ratio) > 0.5 (SEN consensus 2012). There are patients who show data of “minimal renal involvement” (MRI) without indication of RB. Our objective is determine if these patients present clinical and analytical characteristics that allow them to differentiate from patients with LN.

Methods: We reviewed 38 patients with SLE diagnosis, classifying them as MRI if they showed> 3 occasions at least 1 year, proteinuria determinations = 0.3 g / 24h or P/C ratio> 0.3, ruling out urologic pathology. We have compared clinical and analytical variables of MRI vs LN in the time of SLE diagnosis, at renal involvement diagnosis and last visit.

Results: We identified 38 (18.7%) patients with MRI and 41 (24%) patients with LN. At the time of SLE diagnosis, the MRI group had a lower titer of anti-DNAds (14.8% vs 42.1%, p = 0.01), anti-Sm (12% vs 32.2%, p = 0.04), lupus anticoagulant (38%, p = 0.01) and anticardiolipin IgG (11% vs 38%, p = 0.01), less severe C3 hypocomplementemia (70 ± 34 vs 86.9 ± 32.7 mg / dl, p = 0.04), C4 (14 ± 10 vs 17 (p = 0.04) and CH50 (33.3 ± 15 vs 49.6 ± 17 mg / dl, p = 0.04); and lower inflammatory parameters: ESR (21.3 ± 20 vs 58.9 ± 42 mg / dl, p = 0.01), CRP (12.7±11.8 vs 27.3±17 mg/dl, p=0.02). At the diagnosis of the renal involvement, these results were confirmed (Table) and we observed that, in MRI patients, proteinuria appeared at an older age, with a higher evolution of SLE (12.7 ± 11.8 vs 27.3 ± 17 mg / dl, p = 0.02) and with absence of previous immunosuppressant therapy. After a mean follow-up of 10 ± 6.6 years, no MRI patient presented a renal flare, maintaining stable the renal function.

Conclusions: Our results showed that patients with MRI had a lower clinical and biological SLE activity, both at SLE diagnosis and at the diagnosis of renal involvement. No MRI patients presented a renal flare during the follow-up although it is difficult to know the role played by the immunosuppressant treatment

Proliferative Glomerulonephritis with Monoclonal IgG Deposits: Successful Treatment with Steroids, Bortezomib, and Plasma Exchange Olga Baraldi, Giorgia Comai, Vania Cuna, Matteo Ravaolli, Maria Cappuccilli, Gaetano La Manna. University of Bologna, Bologna, Italy.

Background: Kidney impairment is frequent in platelet cell dyscrasias and is characterized by polymorphic history mainly related to the physicochemical properties of the pathological monoclonal component. Proliferative glomerulonephritis with monoclonal IgG deposits (PNMID) is a newly discovered pathological entity. The diagnosis of renal alterations is based on histology, and the patients with compromised renal function are commonly treated with standard hematology chemotherapy protocols.

Methods: Case description. We report a case of a 64-year-old man with nephrotic syndrome, normal renal function, negative immunological and viral tests (in particular anti-PLA2R antibodies). Serum electrophoresis for detection of IgG light chain monoclonal proteins revealed: monoclonal component 3.4%, kappa 29.6 mL, lambda 23.7 mg/L, kappa/lambda ratio 3.7. Magnetic resonance was negative for spine injuries. Bone-marrow biopsy revealed a monoclonal gammopathy of undetermined significance (MGUS) with an IgG-kappa clone. Echodensitogram showed no features of cardiac amyloidosis. Renal biopsy histology displayed diffuse and global membranoproliferative glomerulonephritis with linear single IgG monoclonal deposition at immunofluorescence. Electron microscopy disclosed the presence of subendothelial deposits with granular and non-organized morphology. The patient was treated with steroids (dexamethasone 40 mg for 3 days), bortezomib (1.3 mg/m², weekly) and plasma exchange with albumin reinfusion. ACE-inhibitor and furosemide therapy was also administered. After 2 months, the clinical conditions were better, renal indices were slightly improved (creatinine 1.2 mg/dL, eGFR 47 mL/min/1.73m²), urine protein excretion was 2 g/day, and kappa chain levels dropped to half of the initial level (44.9 mg/dL).

Results: Conclusions: In patients with multiple myeloma (MM) or amyloidosis, established chemotherapy protocols are regularly used, whereas no consolidated therapy exists for the treatment of MGUS with renal impairment. The described patient affected by PNMID with MGUS was successfully treated with a therapy regimen associated with plasma exchange consistent with those used in MM.

Thrombotic Microangiopathy Induced by Severe Lupus Nephritis: A Case Report Haijing Hou, Jiasheng Huang, Jiawei He, Suyuan Peng, Guobin Su, Chuan Zou, Fuhua Lu. 1Karolinska Institutet, Stockholm, Sweden; 2The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China; 3Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China.

Background: Thrombotic microangiopathy (TMA) is a pathological process based on microangiopathic hemolytic anemia, thrombocytopenia and microvascular occlusion, with an incidence of 0.5/100000 in adults. It is rare but severe in lupus nephritis (LN).

Methods: A 28-year-old Chinese woman with a previous history of anemia was admitted with swelling legs and recurring fever for a month. Initial lab findings indicated acute renal failure, thrombocytopenia, infection and severe LN with the high SLED AI scoring of 20, ruling out antiphospholipid syndrome and thalassemia. After receiving sufficient dose of cyclophosphamide (accumulated to 1.8g), methylprednisolone therapy (0.5g/kg/d) and hemodialysis for 2 weeks, her renal function was still progressively declining (Scr 6.04mg/dL VS 1.99mg/dL at baseline) with a low count of platelet (62*10^9/L, baseline 113*10^9/L) and anuria. Bearing the risk of uncontrolled bleeding due to thrombocytopenia, a renal biopsy was performed to guide the treatment. The renal biopsy showed endocapillary fibrin thrombosis and crescent. The diagnosis of TMA was established based on renal biopsy, the ADAMTS13 activity level of 50.4% and RBC schistocytes of the peripheral blood smear. Plasmapheresis was initiated, combined with Traditional Chinese Medicine (TCM), which aimed to reduce the risk of infection during the CTX therapy. At discharge, her urine output improved and did not require dialysis (ADAMTS13: above 100%, Scr: 1.93 mg/dL and platelet counts: 164*10^9/L). In 6 months follow-up, she reports improvement in symptoms with stable renal function.

Results: Conclusions: TMA is an uncommon LN-related disorder, early diagnosis of patients is critically important for treatment and prognosis of LN patients. This case highlights the need to have a broad differential diagnosis for hematological system damage of LN and TMA. Plasmapheresis combined with TCM in the treatment of LN with TMA deserved further study.
Complete Remission of Immunotactoid Glomerulopathy Following Rituximab
Jacqueline Raicek, Jason R. Pettus, Elizabeth J. Brant.
1 Dartmouth Hitchcock Medical Center, Hanover, NH; 2 Dartmouth-Hitchcock Medical Center, Lebanon, NH.

Background: Immunotactoid glomerulopathy (ITG) is a rare cause of glomerular disease characterized by large (30-50 nm) non-amyloid microtubule-like ultrastructural deposits in glomeruli. It can be associated with a lyphoproliferative disorder but is usually idiopathic. Optimal treatment is not defined.

Methods: Results: The patient was a 68-year-old woman with no significant medical history who presented in 9/2015 with a 5-month history of proteinuria and gross hematuria. Prior cystourethroscopy and CT urography were negative. Physical examination was unremarkable. Dysmorphic hematuria and oval fat bodies were seen on urine microscopy. Serum creatinine was 0.57, urine protein-to-creatnine ratio 10.6 (13.1 in 10/2015), total cholesterol <400 and LDL >200 (previously normal). SPEP showed two faint IgG kappa restriction; UPEP was negative. Kidney biopsy revealed a diffuse segmental proliferative glomerulonephritis on light microscopy; global staining for IgG(1+), C3(2-3+), trace IgA, kappa(1+), and lambda(1+) on immunofluorescence. Electron microscopy showed predominantly subepithelial electron-dense deposits in the mesangium and periphery of glomeruli, which were characterized by discrete microtubule-like organization (30-50 nm in diameter), consistent with a diagnosis of ITG. Bone marrow biopsy demonstrated normocellular marrow with trilineage hematopoiisis and <0.1% of clonal B-cells. PET scan was negative. She was treated with rituximab IV in 10/2015 and 11/2015 with prompt resolution of hematuria. Creatinine was 1.1g less than one month after rituximab and has remained <1g since 6/2016. She received rituximab 500 mg IV in 8/2016 upon repopulation of B cells. Creatinine has been stable.

Conclusions: Immunotactoid glomerulopathy is a rare cause of kidney disease that is associated with microtubule-like organized deposits in glomeruli. It can be associated with a lymphoproliferative disorder but is often idiopathic, as in our patient. Prognosis is often poor, with as many as 50% of patients progressing to end-stage renal disease. Optimal treatment has not been defined. Rituximab may be an effective therapy, as demonstrated in our patient. Rituximab may have played a role in the overall positive outcome. Thus, early diagnosis and treatment are important in potentially changing the course of the disease.

Association between Cardio-Ankle Vascular Index and Various Pathological Lesions in Patients with IgA Nephropathy
Tetsuya Okonogi, Tetsuya Kawamura, Akihiro Matsumoto, Kei Matsumoto, Kentaro Koike, Nobuo Tsuibo, Yoichi Miyazaki, Masato Ikeda, Makoto Ogura, Takashi Yoko.
Division of Nephrology and Hypertension, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan.

Background: Cardio-ankle vascular index (CAVI) is not a invasive index of arterial stiffness and, theoretically, independent of blood pressure at the time of measurement. Recently, association of arterial stiffness with decline in renal function has discussed. However, few studies have examined the association between arterial stiffness and various pathological lesions in IgA nephropathy (IgAN).

Methods: We included 27 IgAN patients, who were diagnosed by first time RBIs and whose renal biopsy specimens contained arterioles and a6 glomeruli. The presence of mesangial hypercellularity (MH), endocapillary hypercellularity (EH), segmental glomerulosclerosis (SG), subendothelial electron-dense deposits (TI), and hyaline change of arterioles (HA) were analyzed.

Results: As a result, the percentage of patients who had MH, EH, SG, TI and HA lesion were 37%, 11%, 19%, 56% and 63%, respectively. In SG, TI and HA lesions, CAVI value of lesion-positive groups were significantly higher than those of lesion-negative groups (p<0.05, p<0.05 and p<0.05, respectively). However, in MH and EH lesions, there was no significant difference of CAVI value between lesion-positive groups and lesion-negative groups. Relative cumulative frequency of the presence of SG, TI and HA lesions became higher in accordance with increase of CAVI value. Furthermore, the forms of three graphs closely resembled each other, and 58%, 53% and 53% of SG, TI and HA lesion-positive patients had CAVI value below 8.

Conclusions: These results indicate that CAVI reflects the presence of SG, TI and HA lesions in IgAN patients. Moreover, these pathological lesions have begun to appear in kidney of IgAN patients with relatively low CAVI value which correspond to systemically normal value.

LECT2 Renal-Hepatic Amyloid with Associated Primary Biliary Cholangitis and Rheumatoid Arthritis
Sabitha Eappenpalayil, Kern medical, Bakersfield, CA.

Introduction: Amyloidosis represents a varied group of diseases which result from the misfolding and aggregation of autologous proteins which are deposited in diverse tissues in the form of amyloid fibrils. One of the most recently recognized of these is Amyloid Leukocyte Chemotactic Factor 2 (LECT2). In LECT2 amyloid, the chemotactic factor 2 is the amyloid protein, which is also linked to multiple pathologic conditions such as liver disease. Globular amyloid consists of large circular globules with extracellular deposits within the sinusoids or as intracellular deposits within hepatocytes. Our patient had this globular amyloid deposition confirming the diagnosis of ALECT2 amyloidosis, involving the liver and kidney.

Background: Lepidocyte is an minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS) in patients with SLE with or without mesangial involvement but without proliferative or membranous lupus nephritis features. Outcomes of patients with lupus podocytopathy (a secondary podocytopathy) have not been compared to patients with idiopathic or primary MCD and FSGS. We present a retrospective comparison of lupus podocytopathy patients and primary MCD/ FSGS patients in our institution.

Methods: We collected kidney biopsies from our academic system from 2000-2016. We identified fifteen patients with lupus podocytopathy and randomly chose sixteen patients with primary MCD or FSGS. We collected demographic variables (age, gender, race, duration of SLE), laboratory data (serum creatinine, albumin, degree of proteinuria, presence of hematuria, complement levels), pathology data (light microscopy, immunofluorescence, and electron microscopy) and clinical data (treatment, treatment response and renal outcome).

Results: In the lupus podocytopathy group of patients there were 14 females and 1 male patient. In the primary MCD/FSGS group there were 8 females and 8 males. In the lupus podocytopathy group there were 10 black, 3 Caucasian, 1 hispanic, and 1 middle eastern patient. In the primary MCD/FSGS group there were 8 black and 8 Caucasian patients. In the lupus podocytopathy group 6 of the patients were FSGS and in the other group 5 of the patients had FSGS. The average initial peaked creatinine was 3.08 mg/dl in the lupus podocytopathy group and 1.72 mg/dl in the primary MCD/FSGS group (p=0.03). The average final creatinine was 1.25 mg/dl in lupus podocytopathy (excluding one ESRD patient) and the average final creatinine was 1.64 mg/dl in the primary MCD/FSGS patients (p=0.16). The average protein per day was 9.3 g/day in the lupus podocytopathy and 9.4 g/day in the primary MCD/FSGS group (p=0.19). The average age was 36.2 years in the lupus podocytopathy group and 42.6 years in the primary MCD/ FSGS group (p=0.13).

Conclusions: We presented the first comparative study of lupus podocytopathy patients and patients with primary MCD/FSGS. The lupus podocytopathy group was more likely to be female and had a higher initial peaked creatinine in comparison to primary MCD/FSGS patients. There were similar levels of proteinuria (average > 9 g/day) and age.

Renal Biopsy Should Not Delay Treatment Initiation in Suspected Lupus Nephritis
Astrid Baumann, Ravindra Rajakariar.
Renal, Royal London Hospital, London, United Kingdom.

Background: Renal biopsies are considered the gold standard in diagnosing lupus nephritis (LN). Since the publication of ALMS, the largest randomized trial in LN, Mycophenolate Mofetil (MMF) has been standard therapy in proliferative LN, but there may be delays in obtaining a histological diagnosis due to practical considerations. Renal biopsy also has a recognized role in the management of biopsy-negative cases. Other histological findings influenced treatment in patients with SLE and clinical features consistent with LN.

Methods: Histopathology and renal databases were used to identify all cases of new biopsy-proven active LN, diagnosed between Feb 2012 and Nov 2016 and managed at the Barts Lupus Centre (n=62). Patients were divided into subgroups based on their renal function (eGFR > or ≤50 ml/min).

Results: The mean age at LN diagnosis was 37 years (+/-13 SD). 55 patients were females. Although 7 were biopsied in the ethnic diverse groups (28% Black, and 11% Caucasian). The histological class was either pure proliferative (class III or IV) or mixed proliferative (with additional class V) in 24 cases (39%). 42 (68%) patients had an eGFR > 50 ml/min at presentation with a mean albumin and urine PCR of
30 g/dL and 520 mg/mmol respectively. Of this group, 37 patients (88%) received MMF, 3 patients were treated with cyclophosphamide (1 - clinician decision, 2 - severe renal manifestations) and the remaining two patients received Azathioprine (sub-nephrotic proteinuria). At six months 85% of LN patients were either in partial remission defined as proteinuria below 200 mg/mmol (44%) or complete remission defined as proteinuria below 100 mg/mmol (41%). The treatment choice was different in the group with eGFR ≤50 mL/min, with 13 (65%) of these patients receiving cyclophosphamide.

Conclusions: Current guidelines strongly recommend performing a kidney biopsy in every patient presenting with suspected LN. Our findings indicate that in patients with proteinuria, renal function and significant proteinuria, treatment decision is not influenced by biopsy result. We therefore propose, that induction treatment with MMF should not be delayed until a renal biopsy result is available. This study also questions the necessity of baseline histology in LN patients with preserved renal function and raises the possibility that biopsy could be reserved for patients who are resistant to induction therapy.

PUB533
Retrospective Review of Lupus Nephritis in African Americans from an Academic Hospital
Ravi K. Thimmeschley,1 Obcad Y. Yassen,2 Zeenat Y. Bhat,1 Yahya M. Osman Malik1 Wayne State University, Detroit, MI; 2Wayne State University/ Detroit Medical Centre, LaSalle, ON, Canada; 3Wayne State University Medical School, Detroit, MI.

Background: Lupus Nephritis is one of the most common forms of secondary glomerulonephritis causing nephrotic syndrome and progressive loss of renal function. We examined the relation between proteinuria class of nephritis and level of chronicity in renal biopsies. We also evaluated the response to therapy as well as one’s year’s outcome.

Methods: We reviewed medical records of biopsy proven lupus nephritis (n= 26, ISSGNI class I-V) from the year 2012 to 2016 with one year follow-up after initiation of immuno-suppressive therapy. This included correlation between proteinuria, histological class, severity and chronicity on renal biopsies, as well as one year follow-up of proteinuria and eGFR following initiation of immuno-suppressive therapy.

Results: The mean age was 12 months. The population was predominantly African American patients (92% were African American groups, and 92% female). Baseline mean proteinuria was 4.97 ± 4.75 g/24h and eGFR was 74.19 ± 41 ml/min/1.73m2. Majority received cyclophosphamide as an induction therapy. Out of 26 patients, most of them were found to have chronicity grades III to V at the time of diagnosis. The mean proteinuria following immune-suppressive therapy has dropped to 2.08 g/24h. This is more than 50% reduction with a p-value of 0.006. However, there was a weak correlation between proteinuria and the histological classes of lupus (correlation coefficient is 0.201; p-value 0.324) and also to disease activity index (correlation coefficient is 0.353; p-value 0.07). A moderate correlation was found between chronicity and degree of proteinuria and this was statistically significant (correlation coefficient is 0.528; p-value 0.006). Pre-treatment eGFR and year-one post-treatment, did not demonstrate any significant change [75.5, 78.9 ml/min/1.73m2 respectively] with a p-value of 0.409.

Conclusions: The magnitude of proteinuria is a reasonable predictor of severity of chronicity, among other factors. Measurement of eGFR may not be a sensitive parameter to monitor the response to immune-suppressive therapy when compared with proteinuria. Our results showed that reduction of proteinuria within one year of therapy was statistically significant and may be a good prognostic marker for monitoring lupus nephritis.

PUB534
Successful Treatment of Membranous Lupus Nephritis with Rituximab
Andres Serrano, Mount Sinai Hospital, Chicago, IL.

Background: Rituximab has been proven to be a safe and effective therapy for idiopathic membranous nephropathy. In regards of lupus nephritis, there have been reports of rituximab to be efficacious when used as a combined therapy. However, in a large randomized study, rituximab did not improve the response of mycophenolate mofetil. I am reporting a case of membranous lupus nephropathy successfully treated with rituximab alone.

Methods: The patient is a 38 year-old African-American woman who was sent for evaluation of nephrotic syndrome. At the initial visit her only symptom was proteinuria. She was an active smoker. She had a past medical history including hypertension, seizure disorder and sickle cell trait. At the initial visit her proteinuria was >50 mg/mmol and her eGFR was 41 ml/min/1.73m2. The patient was referred to us for renal biopsy which was performed at the time of diagnosis. The patient was in complete remission, urine protein/creatinine decreased to 0.1 gm/gm, and serum albumin increased to 2.3 mg/dl. Six months later the patient was in complete remission, urine protein/creatinine decreased to 0.1 gm/gm, and serum albumin increased to 3.8 mg/dl.

Results: In patients with lupus nephritis rituximab does not add any additional benefit when used as a combined therapy. The case I presented achieved a full remission using rituximab alone. The patient had serological-negative membranous lupus nephritis.

It is possible this group of patients have a clinical course similar to idiopathic membranous nephropathy. Hence, the response to Rituximab.

PUB535
Single Centre Report of Outcomes of Treatment of ANCA Vasculitis from a Large Cohort of Patients
David Makanjuola,1 Eirini LIoudaki1 St. Helen Hospital, Carshalton, United Kingdom; 2ST HELIER HOSPITAL, Surrey, United Kingdom.

Background: The aim of treatment of patients with ANCA associated vasculitis is to induce a remission and then to maintain it. The challenge then is to weigh the dose of immunosuppression to minimise toxicity from exposure to the immunosuppressive therapy, and balance this against the risk of relapse. We present the outcomes following treatment in a cohort of patients in whom remission was achieved with standard induction treatment, followed by maintenance therapy with Azathioprine (Aza) as first line agent, or Mycophenolate mofetil (MMF).

Methods: Data were collected from paper and electronic medical records of patients over a 13 year period.

Results: 220 patients with ANCA associated vasculitis successfully completed induction treatment and started maintenance treatment. 45% female, 91% Caucasian, age range 19 – 89 yrs (median 68). 112 (51%) had PR3 antibodies and 108 (49%) had MPO antibodies. 55 (23%) had a creatinine of >500 mg/ml at presentation. 27 (12.2%) patients died. 154 (70%) patients were relapse free at median follow up of 57 months (range 6-170). 66 (30%) experienced 1 or more relapses; data were available on 62 (Table 1).

The presence of PR3 was more frequently associated with relapse - odds ratio (OR) 2.523 (95% CI 1.362 to 4.676) compared to MPO (p=0.004). MMF as maintenance treatment was also more frequently associated with relapse compared with Aza (OR 2.733; 95% CI 1.328 to 5.626, p=0.006). The probability of event free survival (censored for death and/or relapse) is shown in figure 1.

Conclusions: Using our treatment protocol, 70% of patients had no relapse during the follow up period. In those who relapsed, we found, as has been described in other studies, that Aza was associated with an increased risk of relapse and that MMF also was inferior to Aza at maintaining remission.

PUB536
The Circadian Clock Provides Beneficial Effects against the Endothelial Dysfunction to Promote Atherogenesis by Regulating LKB1/AMP-Activated Protein Kinase Activation
Hidvegiy Nakoro,1 Harvard Medical School, The Graduate School of Project Design, Tokyo, Japan.

Background: The circadian clock is a molecular mechanism that confers 24 hour variations in gene expression and function to regulate number of physiological functions in humans. Disruption of the clock is associated with pathological remodeling in the arterial structure and vascular stiffness. Chronic circadian clock disruption is also associated with dysfunction in endothelial signaling and responses. In this study, we observed if the deletion of Bmal1, a critical component of the circadian clock, can influence the protein levels of LKB1, a serine/threonine kinase, the downstream target AMP-activated protein kinase (AMPK) and plasminogen activator inhibitor (PAI-1) generation which play an important part in the progression of vascular diseases.

Methods: Congenic 12- to 16-week-old male, wild-type and Bmal1-KO littermate mice were generated from heterozygote breedings to be used for these studies. We also knocked down Bmal1 to evaluate the protein levels of LKB1, AMPK and PAI-1 in the knocked down cells.
Results: Endothelial function was reduced in aorta from Bmal1-KO mice. In aorta from control KO mice, no increase was observed. Furthermore, aortic NFRP3 expression in mice with a dysfunctional circadian rhythm. Moreover, Bmal1 KO mice display premature aging to have a dramatic prothrombotic phenotype. This phenotype is linked to changes in the regulation of key risk factors for cardiovascular disease. These include LKB1, AMPK and PAI-1, which are significantly elevated in Bmal1 KO mice. We also confirmed that LKB1, AMPK and PAI-1 levels follow a circadian pattern and this pattern was absent in Bmal1 KO mice.

Conclusions: These findings indicate that circadian clock provides beneficial effects against the endoatherogenic dysfunction to promote atherogenesis by regulating LKB1, AMPK activation and PAI-1 generation. This study establishes a mechanistic connection between Bmal1 and cardiovascular phenotype.

Funding: Government Support - Non-U.S.

PUB537

High-Fructose Diet Induces the Dysfunction of Energy Metabolism (ATP Depletion) and Hypertension Hiroaki Hara, Kaori Takayangi, Minoru Hatano, Kento Hirose, Takatsugu Iwashita, Taisuke Shimizu, Tomonori Ogawa, Koichi Kanozawa, Hajime Hasegawa. Department of Nephrology, Hypertension, Blood Purification, Saitama Medical center; Saitama University Medical, Kawagoe, Japan.

Background: Consumption of fructose is revealed to evoke an acceleration of obesity, hypertension, insulin resistance, and uric acid production. Recently, it is known that fructose activates sodium–hydrogen exchanger 3 (NHE3) through the reduction of cyclic AMP in the proximal tubule. It would be highly assumed that the unidirectional fructose metabolism-induced ATP consumption may involve in the development of energy dysfunction, however, it has not been directly demonstrated yet. Here, we investigated the fructose-induced changes in the renal salt handling and ATP levels.

Methods: Male SD rats (7 weeks old) were fed by food containing 60% glucose (GLU) and food containing 60% fructose (FRU) for 3 and 6 and 12weeks (n=5 in each group). Calorie per unit-weight was adjusted in all three kinds of food. Tissue ATP concentration was assayed by use of assay kit (Abcam plc, Cambridge, UK). No difference of calorie and salt intake of individual animal was daily confirmed by the measured weight of remaining food.

Results: Body weight was not different in all groups at both time-points. Mean blood pressure of FRU was significantly higher than that of GLU at 6 and 12-weeks (6w-GLU: 95.9±2.6, 6w-FRU: 103.7±3.4 mmHg, 12w-GLU: 94.8±3.4 mmHg, 12w-FRU: 105.7±2.6 mmHg), however, it was not different at 3-week. Fractional excretion of sodium (FENa) of FRU at 6-weeks was significantly higher than that of GLU (6w-GLU: 103.7±0.09%, 12w-GLU:10.81±0.09%, 12w-FRU:6.55±0.08%). The NHE3 immunostaining positive area of FRU at 12-weeks was significantly lower comparing to GLU at 6 and 12-weeks (12w-GLU: 6.15±1.1 mmol/mg protein, 12w-FRU: 10.81±1.9 mmol/mg protein) whereas no significant difference was observed at 3-weeks.

Conclusions: We demonstrated that fructose intake might cause the elevation of blood pressure and salt reabsorption through the ATP consumption being independent on calorie and salt intake in the present study.

MeanSE;p<0.05 vs HS; p<0.05 vs HS+N; p<0.05 vs HS-Nβ

PUB538

Inhibition of Both NFXB and NLRP3/IL-1β Pathways Affords Better Renoprotection in Chronic NO Blockade/Salt Overload Fernando H. Fanelli, Karin C. Oliveira, Viviane D. Fanelli, Orestes Foresto-Neto, Victor F. Avila, Simone C. Arias, Flavia G. Machado, Camilla Fanelli, Claudia R. Sena, Vivian L. Viana, Denise M. Malheiro, Niels O. Camara, Roberto Zatz, Clarice K. Fujihara. Univ Sao Paulo, SP, Brazil.

Background: NO inhibition with L-NAME along with salt overload (HS) lead to severe hypertension (HT), albuminuria (ALB), glomerulosclerosis (GS) and interstitial fibrosis. We investigated whether activation of the NFXB and/or NLRP3 pathways is involved in the pathogenesis of renal injury in this model.

Methods: Adult male Wistar rats were receiving oral NAME (32 mg/kg/d) and HS (HS=N) or were given Allopurinol (Allo) as NLRP3 inhibitor, 36 mg/kg/d (HS+N), or Pyrrolidine Dithiocarbamate (PDTC), a NFκB inhibitor, 36 mg/kg (HS+N). After 4 wk, we assessed: tail-cuff pressure (TCP, mmHg), ALB (mg/dL), GS (%), renal uric acid (rUA, mg/g), interstitial collagen I (COL1, %), macrophages (MΦ, cells/mm2), NLRP3 (cells/mm2) and the renal content of IL-1β (pg/mg), TLR4, nuclear p65 (NFκB) and Superoxide Dismutase (SOD2) (sHS).

Results: HS-N rats developed HT, ALB and renal injury, along with inflammation, oxidative stress (OS), TLR4/NFXB and NLRP3/IL-1β activation. Allo lowered rUA and inhibited NLRP3/IL-1β, without changing OS, in association with amelioration of HT, ALB and interstitial in inflammation/fibrosis, but not GS. Besides diminishing rUA and NLRP3/IL-1β, PDTC prevented OS and NFκB, and exerted a more efficient antiinflammatory and nephroprotective effect than Allo.

Conclusions: NLRP3/IL-1β and NFκB act in parallel to promote renal injury/ inflammation and must be simultaneously inhibited for best nephroprotection in the chronic NO blockade/salt overload model. FAPESP/CNPq

Funding: Government Support - Non-U.S.

PUB539

Evaluation of Further Cardiovascular and CKD Risk Factors Screening in an Apparently Healthy Population Attilio Di Benedetto, AnnaLisa Ciottola, Fabrizio Cerino, Ammannaria Colao, Stefano Stuard, Bernard J. Cauna,1 FMCD Deutschland GmbH, Bad Homburg, Germany; 2 Fresenius Medical Care, Bad Homburg, Germany; 3 NephroCare, Naples, Italy; 4 University Federico II Naples, Naples, Italy.

Background: Cardiovascular disease (CVD) prevalence is on the rise in industrialized countries, presenting a significant societal and economic burden. We report the results of a screening program in an apparently healthy population.

Methods: In 2013, 2014, and 2015, during prevention events, a large sample of apparently healthy people were evaluated for cardiovascular and kidney risk factors. The screening parameters were assessed blood pressure, weight, height, waist circumference, BMI and Body Composition (BC). Lean(FTI) and Fat(TTI) tissue indexes and ECFO were evaluated by multi-frequency bioimpedance spectroscopy (BIS). Results are reported as mean and standard deviations or percentages for continuous and categorical variables in different age group and gender, respectively.

Results: 1081 subjects were evaluated: 416(38.5%) were male and 665 (61.5%) were female. Mean age was 54.46(±15.9) years in m, 50.17(±15.2) years in F. 5.5% m and 6.8% f referred dyslipidemia; 4.3% and 3.2% referred diabetes; 21.6% m and 13.4% f referred hypertension; 26.0% m and 6.5% f referred heart disease; 0.0% m and 2.6% f referred hypothyroidism; 1.2% m and 1.5% f referred CKD. Mean systolic blood pressure (SBP) was 125.38(±19.18) mmHg, mean diastolic blood pressure (DBP) was 75.85(±11.3) mmHg. BMI levels were: <20 kg/m², 20.5% m and 30 (4.5%) f; 20-24 kg/m², 104(25.0%) m and 276(31.6%) f; 25-29 kg/m², 104(25.0%) m and 149(22.4%) f. TTI and LTI were evaluated according to normal distribution adjusted by age and gender.

Conclusions: In a large sample of apparently healthy population a relevant proportion of male compared to female had more risk factors as higher SBP, ECFO, TFI, but also additional CVD/CKD risk factors such as obesity, dyslipidemia, smoke, diabetes. In stratifying general population for risk factor, body composition appears to be an important method to evaluate FTI and ECFO risk factors.

Funding: Private Foundation Support

PUB540

Effect of Alikiren on Arterial Stiffness, Compared with Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Antagonists in Hypertensive Patients: A Meta-Analysis Georgios Saponas,1 Rigas Kalaitzidis,2 Evangelos Evangelou,3 Kostas Siamopoulos.2 Department of Nephrology & Renal Transplantation Unit, Laiko General Hospital, National & Kapodistrian University of Athens, Medical School, Athens, Greece; 2Department of Nephrology, University Hospital of Ioannina, Ioannina, Greece; 3Department of Hypertension and Epidemiology, University of Ioannina, Ioannina Medical School, Ioannina, Greece.

Background: The degree of arterial stiffness (AS) is correlated with the risk of cardiovascular disease and it is a powerful predictor for morbidity and mortality. Inhibition of the renin-angiotensin system (RAS) is associated with an important decrease in cardiovascular risk, while classic RAS inhibitors have shown to improve AS indices. We sought to compare the relationship of direct renin inhibitor aliksiren versus classic RAS inhibitors on AS in multiple randomized controlled trials in hypertensive patients.

Methods: PUBMED, MEDLINE, and Cochrane library searches were performed until March 1st, 2017 for potential related articles. Inclusion criteria were i) randomized controlled trials in adult hypertensive patients, ii) comparison of aliksiren with other agents that inhibit the RAS, iii) reported data for blood pressure, pulse wave velocity (PWV), augmentation index (AIX) and iv) Study duration over 4 weeks. We calculated the summary standardized mean difference (SMD) from all studies using a random-effects
Publication-Only model using an inverse variance approach. Heterogeneity was quantified using the I^2 which ranges between 0-100 and describes the percentage of the variability in the effect estimates (e.g. standardized mean differences in our case) that is due to heterogeneity rather than chance. Values >50% represent substantial heterogeneity.

Results: A total of 40 articles were found through database searches. These articles included 4 randomized controlled studies involving a total of 160 participants who met all pre-defined criteria. The SMD calculated did not indicated any significant differences with summary estimates including the null. Specifically, for PW the summary effect size derived from the random effects model was 0.01 (95% CI: -1.00-1.02) with no observed heterogeneity (I^2=0%). For AIX the summary effect was -0.21 (95% CI: -5.14-4.72) with no observed heterogeneity (I^2=0%).

Conclusions: Alikiren when compared to other RAS inhibitors have similar effect on arterial stiffness indices in hypertensive patients.

**PUB541**

Anti-Vascular Endothelial Growth Factor Agent Bevacizumab Use for Diabetic Retinopathy in a Hemodialysis Patient Dheeraj Kaul,1 Serena Bhela,1 Moro O. Salifu,2 Mary C. Mallappallil,1 ‘None, Brooklyn, NY; ‘Nephrology, SUNY Downstate Medical Center, Brooklyn, NY.

Background: In diabetic patients microvascular disease could present as diabetic retinopathy, nephropathy and or neuropathy. Among diabetics, diabetic macular edema (DME) is the most common cause of vision loss. While in the past, laser photocoagulation significantly reduced moderate vision loss and was the gold standard treatment for DME. Recently, with the use of anti-Vascular Endothelial Growth Factor drugs (Bevacizumab, Ranibizumab, and Aflibercept), better outcomes were obtained in terms of visual acuity gain and decrease in macular thickness as monotherapy. As the dose of the agent used in intravitreal injection is small the systemic side effects of progression of thrombosis is rare.

Methods: We present a case of a woman with primary open angle glaucoma, diabetic retinopathy and nephropathy who presented with diabetic retinopathy since 2006. She developed diabetic macular edema and successfully treated with focal laser photocoagulation with repeated treatments of both eyes in 2008, 2010, 2012 and intravitreal bevacizumab in 2008, 2010, 2011 and 2012. Pan retinal photocoagulation was performed in 2012. With the progression of her diabetic nephropathy, chronic hemodialysis was initiated in April 2016. She continued her treatment of diabetic retinopathy safely with bevacizumab in July 2016 and got repeated treatments for her non proliferative diabetic retinopathy with the agent in 2017 without any systemic side effects. With the treatments her visual acuity and optical coherence tomography showed improvement with as objective measures being a decrease in macular thickness in both eyes (512 to 412 and 610 to 440 Micrometers).

Results: Conclusions: Macular laser therapy may still play an important role as an adjuvant treatment because it is able to modify macular thickness outcomes and reduce the number of injections needed. There are no case reports in the literature of the use of anti-VEGF intraocular injection therapy in hemodialysis for diabetic retinopathy either as monotherapy or combination with focal or pan retinal laser therapy.

**PUB542**

Abstract Withdrawn

**PUB543**

Better Late Than Never Anjuman A. Howlader, Bijin Thajudeen. University of Arizona, Tucson, AZ.

Background: Acute renal arterial occlusion due to a stent thrombosis is common. The management options include endovascular or surgical recanalization. When the renal artery is occluded, a recanalization decision is sometimes deferred depending on the size of the kidney or extent of chronicity based on imaging or biopsy. Here we present the case of a patient who had total occlusion of renal artery in the presence of solitary kidney and who responded to recanalization.

Methods: 73-year-old female with history of right renal arterial stenosis, status post stent placement, congestial atrophic left kidney, hypertension, and chronic kidney disease presented with reduced urine output of 3 days duration. She also has a history of chronic kidney disease. Laboratory tests showed serum creatinine of 17 mg/dl and potassium of 7.4 meq/L. Emergency hemodialysis was started. Subsequent evaluation showed occlusion of right renal arterial stent. A renal angiogram revealed total occlusion of the renal arterial stent and attempt for recanalization failed. In view of the small size of kidneys (8.5 cm), thin cortex and loss of corticomedullary differentiation it was deemed that a surgical vascularization may not be of benefit. Hence, she was discharged home with recommendations to continue the hemodialysis. But 2 weeks later she presented to the ER with back pain and was found to have a ruptured aortic aneurysm on CT angiogram. CT angiogram also showed presence of contrast in the mid renal artery despite the total occlusion which suggested ongoing perfusion of the kidney. An endovascular repair of the aortic aneurysm was done using a synthetic graft. Since there were some signs of perfusion to that kidney a recanalization bypass procedure was done using PTFE graft connecting the aortic graft used for repairing the aortic aneurysm and renal artery distal to the thrombosed stent. Following the bypass procedure there was reestablishment of circulation to the kidney and improvement in urine output. Hemodialysis was discontinued. Serum creatinine was 1.8 mg/dl 2 weeks after the procedure. A post procedure duplex showed heterogenous perfusion to the kidney although a similar study was not available prior to procedure to compare.

Results: Conclusions: This case highlights the importance of considering recanalization procedure in presence of renal vascular occlusion irrespective of the size of the kidney especially in patients with solitary kidney.

**PUB544**

Uremia Alters Vascular Gene Expression in Pig Carotid Artery and Jugular Vein Jaroslav Janda,1 Bozorg Campos,6 Frank C. Brousis,2 Aous Jarrouj,1 Keith L. Saum,4 Lindsay N. Kohler,7 Prabir Roy-Chaudhury,2 Diego Celldran-Bonafonte.1 1Banner-University of Arizona, Tucson, AZ; 2University of Arizona, Tucson, AZ; 4University of Arizona / BIO 5 Institute, Tucson, AZ; 5University of Cincinnati, Cincinnati, OH; 5Southern Arizona VA Healthcare System, Tucson, AZ.

Background: Uremia induces multiple pathologic changes in vascular tissues leading to enhanced cardiovascular disease and increased mortality in patients with advanced chronic kidney disease and end-stage kidney disease. To identify key pathogenic molecules in this process we have utilized a uremic pig model and have specifically determined the expression of 8 genes associated with endothelial and vascular dysfunction, at different arterial and venous sites.

Methods: Yorkshire pigs (n = 4 in each group) were made uremic by 5/6 nephrectomy. Arterial (carotid, aorta) and venous (jugular, inferior vena cava) segments were removed under anesthesia 6 wk post-surgery and processed for total RNA isolation and cDNA synthesis. Quantitative real time-PCR was performed for ICAM, VCAM, NOS3, NOX4, KLK2, CCL2, MMP2, and MMP9.

Results: NOX4 and MMP2 expression was reduced ~2-fold in uremic vs. normal carotid artery (p < 0.05). NOS3, CCL2 and VCAM demonstrated non-significant reductions in gene expression in uremic carotid artery vs. non-uremic carotid artery.
In jugular vein, KLF2 and ICAM were reduced ~7-fold (p<0.05) in uremic veins. No significant changes in gene expression were found in the 8 genes studied in uremic aortas or inferior vena cava vs. their non-uremic counterparts. Significant changes in gene expression were found in the 8 genes studied in uremic aortas or inferior vena cava vs. their non-uremic counterparts.

Conclusions: Uremia is associated with a reduction in expression of vascular genes in both carotid artery and jugular vein. Such reductions may alter signaling and vascular adaptation in uremia. Ongoing and future studies will characterize the functional effect of these gene changes through a systematic evaluation of genome-wide expression in uremic vessels, together with an evaluation of changes in uremic and non-uremic vessels in response to vascular stress/injury.

Funding: NIDDK Support, Veterans Affairs Support

A Case of Renal Artery Dissection in a Patient with Fibromuscular Dysplasia and Rheumatoid Arthritis

Aditya S. Pavvar,1 Stephen B. Erickson.1 Mayo Clinic, Rochester, MN; 2Mayo Clinic, Rochester, MN, ROCHESTER, MN.

Background: Fibromuscular dysplasia (FMD) is an non-inflammatory and non-atherosclerotic angiopathy, most commonly seen in renal arteries. Here, we present a case of renal artery dissection in a patient with FMD and Rheumatoid Arthritis (RA) presenting with flank pain.

Methods: 59-year-old male with past medical history of RA and HTN controlled with hydrochlorothiazide presented to emergency room with severe flank pain. His vitals were stable but had no prior history of kidney disease. EKG and echocardiogram were unremarkable. Laboratory test showed hemoglobin of 13 g/dL, WBC 6.8 x 10^9/L, serum creatinine 1mg/dL, Electrolyte panel, ESR, CRP, UA and microscopy were unremarkable. CT angiography showed a dissection of the left mid renal artery with wedge shaped infarction of lateral upper/mid left kidney (Figure1). Additionally, beaded irregularity was seen in the mid and distal renal arteries, which supported diagnosis of FMD. MRA of neck and brain was unremarkable. Kidney function remained stable during his hospital stay. He was discharged on low dose aspirin with outpatient follow up with Nephrology and hypertension.

Results: Conclusions: Flank Pain can be one of the presenting symptom of FMD (17%). FMD can mimic atherosclerotic disease and vasculitis. Minority of FMD patients develop aneurysm and dissection. Treatment is focused on control of hypertension and anti-platelet therapy. The next most common arterial bed involvement after renal arteries is cerebral and vertebral arteries. RA, which is a pro-inflammatory condition and has been shown to accelerate atherogenesis from endothelial dysfunction may predispose to a dissection of FMD involving renal arteries. Our case underscores the need for early intervention to prevent dissection and subsequent infarction. It is important for physicians to be aware of the complications of FMD as timely intervention can prevent further damage.

Funding: Clinical Revenue Support

Physicians’ Perception of Blood Pressure Control in Patients with CKD and the Target BP Achievement Rate

Eun-hui Cha,1 Hajeong Lee,1 Jung Pyo Lee,1 Young rim Song,1 Yon Su Kim,2 Hallym Univ. Sacred Heart Hospital, Anyang, Republic of Korea; 3National Medical Center, Seoul, Republic of Korea; 4Seoul National University Boramae Medical Center, Seoul, Republic of Korea; 5Seoul National University College of Medicine, Seoul, Republic of Korea.

Background: Blood pressure (BP) control is the most established method for the prevention of chronic kidney disease (CKD) progression. However, the ideal BP target for CKD patients is still in debate.

Methods: We performed a questionnaire survey of regular members registered in the Korean Society of Nephrology to determine the physicians’ perception of BP control in patients with CKD. We evaluated the target BP achievement rate using data from the AfD6To2 study.

Results: Two-thirds of physicians considered the target BP for CKD to be 130/85 mmHg. The SBP thresholds for diabetic CKD, proteinuria ≥ 300 mg/day, 30 g GFR < 60 ml/min/1.73 m^2, age < 60 years, and the presence of atherosclerotic (ASO) complications were significantly lower than the SBP thresholds of the opposite parameters. The four most commonly used drugs are non-compliance to life-style modification and medications, self-report of well-controlled home BP, and co-prescription from other specialties. 78.6% and 97.3% of physicians prescribed home and ambulatory BP monitoring to less than 50% of their patients, respectively. The target BP achievement rate using the SBP thresholds in this survey was as follows: non-abetic CKD, diabetic (29.5%); proteinuria < 300 mg/day (72.3%); proteinuria > 300 mg/day (33.7%); GFR ≥ 60 (76.4%); GFR < 30 (47.8%); no evidence of ASO (67.8%); and the presence of ASO (42.9%).

Conclusions: The target BP was lower in patients with higher cerebro-cardiovascular risks, including diabetic CKD, lower GFR, higher proteinuria, and the presence of ASO. These patient groups also showed lower target BP achievement rates. We also found a relatively lower application and clinical reflection rate of home or ambulatory BP monitoring.

A Pharmacist-Guided Patient-Driven Interdisciplinary Program to Improve Blood Pressure Control in Patients with Hypertension

Charles W. Hopley,1 Emily Andrews,1 Patrick M. Klin,2 Zhiying You,3 Michelle Jonjak,1 Diana J. Lalal,4 UC Denver, Aurora, CO; 2University of Colorado, Aurora, CO; 3University of Colorado Denver Health Science Center, Aurora, CO; 4University of Colorado Hospital, Aurora, CO; 5University of Colorado SOM, Denver, CO.

Background: Hypertension is a major risk factor for kidney and cardiovascular disease and mortality. Yet, approximately 2/3 of patients treated for hypertension do not meet blood pressure goals. Patient-driven self-titration of blood pressure (BP) medications and lifestyle modifications are both reportedly effective and regular in the management of hypertension. We launched a quality improvement project implementing a pharmacist-guided patient-driven self-titration protocol and standardized dietary counseling to improve BP control in the chronic kidney disease (CKD) clinic.

Methods: Patients with uncontrolled hypertension on 1 or fewer antihypertensive agents were included. BP goals were established based on individual risk factors. Patients were referred to the clinical pharmacist who devised a personalized plan for BP medication titration based on home BP monitoring and provided dietary education. Patients were required to bring their BP readings to each visit for review. After 6 weeks, the attending physician evaluated the patient’s BP readings overall and per month for 2 years and results were compared to baseline data. All outcomes were evaluated.

Results: Nineteen patients have been enrolled and 3 patients have completed 6 months follow-up visits. 72.2% have entered home BP readings regularly in EMR (69.3%). The average BP of the 3 patients completing 6 months follow-up had significant improvement in blood pressure (avg 16.26 mmHG). Preliminary assessment of current patients demonstrates that of 13 patients actively entering readings, six patients have already met pre-specified blood pressure goals. One patient met their SBP goal and their diastolic goal. No patient’s blood pressure goals were met by the 6 month follow-up. The next most common arterial bed involvement after renal arteries is cerebral and vertebral arteries. RA, which is a pro-inflammatory condition and has been shown to accelerate atherogenesis from endothelial dysfunction may predispose to a dissection of FMD involving renal arteries. Our case underscores the need for early intervention to prevent dissection and subsequent infarction. It is important for physicians to be aware of the complications of FMD as timely intervention can prevent further damage.

Funding: Clinical Revenue Support


Piotr Skonieczny,1,2 Zbigniew Heleniak,1 Klaudia Piechowska,1 Bartosz Pakula,1 Marta Ks1,3,4, Leszek Tylicki,1 Alicja Debeka-Sliżien,1,2 Department of Nephrology, Transplantology and Internal Diseases, Medical University of Gdańsk, Gdańsk, Poland; 2Department of Physiology, Medical University of Gdańsk, Gdańsk, Poland; 3Department of General Nursery, Medical University of Gdańsk, Gdańsk, Poland; 4Diaverum Poland, Gdańsk, Poland.

Background: Hypertension is a major problem among hemodialysis patients. The purpose of the current study was to evaluate the prevalence of hypertension, antihypertensive treatment and control of blood pressure according to JNC and K/DOQI recommendations in hemodialysis patients.

Methods: 227 patients hemodialyzed in Diaverum Dialysis Unit in three distinct periods of time 2006,2011 and 2016 were enrolled to the study. The analysis of the antihypertensive treatment was based on the medical files and it consisted of a comparison of the mean blood pressure results reported during the six consecutive HD sessions.

Results: The characteristic of study population was showed in table 1. The mean blood pressure before HD sessions was 137.7±130.74 and 140±76mmHg, after HD session was 123.7±126.72 and 139±77mmHg in 2006,2011 and 2016 respectively and the values differed in three distinct periods of time. Percentage of patients using single, double and multidrug therapy (4-6) were 23.6,18.2,24.7,17.2 in 2006, 14.8,34.6,24.7,17.2 in 2011 and 12.8,18.7,29,23.3 in 2016. The differences between single and double therapy were statistically significant. The most often used drugs were β-blockers, diuretics and calcium channel blockers.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Changes in Day- and Night-Time HRV during Acute Phase of Therapy
Massahiko Mizuno,1 Michio Fukuda,1 Yoshiaki Ogita,1 Hiroko Shibata,1 Tetsuhiko Matsuoka,1 Ken Mizuguchi,1 Hiroya Shimogushi,1 Ken Kiyono,1 Yoshitomo Yamamoto,1 Hirunyak Kobori,1 Junichiro Hayama,7 Nobuyuki Otobe.1 1Department of Cardio-Renal Medicine and Hypertension, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; 2Department of Medical Education, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; 3Department of Mechanical Science and Bioengineering, Osaka University, Osaka, Japan; 4Department of Physical and Health Education, Tokyo Gakugei University Graduate School of Education, Tokyo, Japan; 5International University of Health and Welfare, Tokyo, Japan.

Background: Enhanced renal tubular absorption (Na+) cause sodium sensitivity of BP and non-diaper circadian BP rhythm. We had clarified that angiotensin receptor blockers (ARBs) can suppress "inappropriately increased intrarenal RAAS" to inhibit tNa, resulting in increase of daytime natriuresis and restoration of circadian BP rhythm. Recently, we have reported that the increase in daytime natriuresis with ARB treatment was accompanied by intrarenal dopamine secretion. However, in that study some individuals demonstrated restoration of circadian BP rhythm without alteration of natriuresis.

Methods: 24h-holter ECG data was analysis to investigate changes in sympathetic (non-Gaussianity index λ2.5s) and parasympathetic (HF and deceleration capacity, DC) nervous activity in 20 patients with CKD during acute phase (2 days) of ARB (azilsartan).

Results: At baseline, 5 patients had dipper and 15 nondipper BP rhythm. HF was a determinant of night/day BP ratio (β = -0.50, F = 5.8), rather than DC or λ2.5s. Five patients out of 15 non-dipper patients had decreased in daytime λ2.5s (0.49 ±0.05–0.67±0.05, p=0.04). Other 5 patients of 15 nondippers, who did not get decrease in night/day BP ratio, nighttime λ2.5s augmented.

Conclusions: In summary, diminished parasympathetic nervous activity was related to nondipper BP rhythm in CKD, but restoration of the BP rhythm with ARB was derived from its sympathoinhibitory effect.

Saving the Pulseless Kidney!
Rahul Kumar,1 Ali Mehdi,1 Georges Nakhoul.2 1Internal Medicine, Cleveland Clinic Foundation, Cleveland, OH; 2Nephrology, Cleveland Clinic Foundation, Cleveland, OH.

Background: Takayasu’s arteritis (TAK) also known as the pulseless disease, is a granulomatous large-vessel vasculitis. It primarily affects women of age 10 to 40 years. In patients with TAK, the prevalence of hypertension varies from 23% to 76% across cohorts.

Methods: 25s. Five patients out of 15 non-dipper patients had decreased in daytime λ2.5s (0.49 ±0.05–0.67±0.05, p=0.04). Other 5 patients of 15 nondippers, who did not get decrease in night/day BP ratio, nighttime λ2.5s augmented.

Conclusions: In summary, diminished parasympathetic nervous activity was related to nondipper BP rhythm in CKD, but restoration of the BP rhythm with ARB was derived from its sympathoinhibitory effect.

PUB5852
Frequency of Multi-Drug Treatment for Pediatric Hypertension
Bethany Crawford,1 Christopher Cates,2 John Lin,4 Niachelia A. Hoffman,5 Thomas K. Davis,6 Vikas R. Dhanihardtka,1 Laura Hesemann.2 1Barnes Jewish Hospital, St. Louis, MO; 2University of Missouri, Kansas City School of Medicine, Columbia, MO; 3Washington University School of Medicine, St Louis, MO; 4Washington University in St Louis, St. Louis, MO.

Background: Hypertension (HTN) is increasingly prevalent among children and adolescents. Data regarding treatment of pediatric HTN is increasing but remains limited. Up to 75% of adult patients require multiple medications for blood pressure (BP) control. Knowledge of this guides adult practitioners regarding expected outcomes and gives a rationale for rapid titration of medication. The goals of this study were to determine the frequency with which children require multi-drug therapy to attain BP control and to identify risk factors for needing multiple BP medications.

Methods: All patients with HTN seen between May 2012 and April 2013 at a pediatric nephrology clinic in an academic center were evaluated. Patients with resolved HTN, ESRD, or history of kidney transplant were excluded. Data were collected for BP control as assessed by the treating physician, number of medications needed to achieve control, and risk factors including race, gender, BMI, CKD, and diabetes mellitus.

Results: Of 126 subjects, 92 (73%) were prescribed 1 medication. The remaining 34 (27%) were prescribed 2 or more medications. The groups were not significantly different with regard to the presence of any of the identified risk factors (table 1). Adequate BP control was achieved in 81% of subjects on 1 medication, which was not statistically different from the 82% who required multiple medications (p=0.883). In logistic regression, none of the identified risk factors correlated with the need for multiple anti-hypertensive medications.

Conclusions: Similar to findings in adult patients, a significant proportion of hypertensive children require multi-drug therapy to achieve BP control. The need for more medications was independent of the evaluated risk factors and may not be an indication for more intensive evaluation. None of the factors evaluated predicted the need for multi-drug therapy. Further studies are needed to validate these findings in larger cohorts.

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

1104
HTN risk factor assessment by number of medications used

<table>
<thead>
<tr>
<th>1 medication</th>
<th>2+ medications</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>63%</td>
<td>44%</td>
<td>0.612</td>
</tr>
<tr>
<td>AA</td>
<td>15%</td>
<td>0.26</td>
</tr>
<tr>
<td>CKD</td>
<td>15%</td>
<td>0.277</td>
</tr>
<tr>
<td>Dm</td>
<td>8%</td>
<td>0.134</td>
</tr>
<tr>
<td>Rm &gt; 55</td>
<td>6.3%</td>
<td>0.906</td>
</tr>
</tbody>
</table>

Pearson Chi-Square or Fisher’s Exact Test as appropriate

**PUB553**

Relationship between Angiogenesis Inhibitors and Pediatric Hypertension: A Case-Series Marissa Linton,4 Laura jane Pehrson,3 Suzanne M. Vento,2 Howard Trachtman,1 Laura Malaga-Dieguez,2 NYU Langone Med Ctr, New York, NY, NY; NYU Langone Medical Center, New York, NY; NYU School of Medicine, New York, NY; New York University School of Medicine, New York, NY.

Background: Angiogenesis inhibitors have an emerging role in the treatment of pediatric cancers. CNS tumors have high concentrations of pro-angiogenic factors and neo-vascularization. Much of what is known about angiogenesis inhibitors comes from adult studies, where they have been more widely used. Hypertension is a common side effect of this new drug class in adults. Limited information is available about the safety of these medications in children.

Methods: A single center, retrospective chart review was conducted. Twenty-eight patients under 25 years of age with CNS tumors, who were followed by the Division of Pediatric Hematology and Oncology at NYU Medical Center, were identified who had received angiogenesis inhibitors developed hypertension. Chart review was conducted in 12 cases. The other cases met exclusion criteria or access to full EMR was unavailable.

Results: (50%) of patients developed hypertension within 9 months of initiation of the drugs, with most occurring in the first 3 months. Four were treated with bevacizumab, 2 axitinib, and 1 pazopanib. While one patient’s symptoms resolved, the remaining 6 children required treatment with anti-hypertensive agents. Only two patients were referred to pediatric nephrology and were treated with amlopidine. The remaining patients were all given diuretics by the oncology team, with 3 requiring use of a second antihypertensive agent (ACE inhibitors).

Conclusions: Our findings are consistent with the adult literature and indicate that secondary hypertension is a frequent complication of angiogenesis inhibitor therapy. Poorly controlled hypertension in children has the potential to track into adulthood and is a major risk factor for cardiovascular morbidity and mortality. Identification and treatment of pediatric hypertension is an important health focus for pediatric oncology patients. Timely referral to a pediatric nephrologist should be considered for treatment of angiogenesis inhibitor-associated hypertension.

**PUB554**

Identification of Factors Modulating Hypertension in CKD: A Pilot Study Mochammad Thaha1, Maulana A. Empitu,3 Ika N. Kadarsiwantiningi2, Cahyo wibisono Nugroho,2 Muhammad Amin,2 Haerani Rashid,3 Muhammad Yusuf2.1 Department of Microbiology, Airlangga University School of Medicine, Surabaya, Indonesia; 2Department of Cardiology, Airlangga University School of Medicine, Surabaya, Indonesia; 3Department of Internal Medicine, Hasanuddin University, Makassar, Indonesia; 4Department of Internal Medicine, Airlangga University Hospital, Surabaya, Indonesia; 5Department of Pharmacology, Airlangga University School of Medicine, Surabaya, Indonesia; 6Department of Internal Medicine - Nephrology Division, Airlangga University School of Medicine, Surabaya, Indonesia; 7Institute of Tropical Disease, Airlangga University, Surabaya, Indonesia.

Background: Hypertension and chronic kidney disease interact in multifaceted dimension. Hypertension is regarded among leading causes of CKD. In contrast, hypertension is frequently developed in previously normotensive CKD patients. As hypertension also progress with kidney disease, it becomes urgent to identify factors which modulate the development of hypertension in CKD patients. Therefore, we conduct an observational study to investigate the contribution of nutritional status, quality of sleep, inflammation, and oxidative stress to the progression of hypertension in CKD.

Methods: During the first phase of recruitment, 35 consented stable CKD patients who enrolled in outpatient or haemodialysis clinics at a private and a government hospital in Surabaya, Indonesia were included. The nutritional status were evaluated using anthropometric measurement, Malmnutrition-Inflammation Score (MIS) and Dialysis Malnutrition Score (DMS), while sleep quality were examined using Pittsburgh Sleep Quality Index (PSQI). Blood biochemical and cytological parameters represented with inflammation and oxidative stress were measured at baseline level. The medication and medical history were documented.

Results: The baseline characteristics of the study participants were aged 52.6±14.3 years with Cystatin-C adjusted eGFR 36.6±43.2 ml/minute per 1.73 m². Partial least squares - discriminant analysis on 49 different factors including clinical and biochemical parameters, revealed that 21 measured parameters significantly contributed (Q² > 0.8, R² < 0.95) to the projective analysis. Among those significantly contributed, factors in this model were ecosinophil counts (VIP=2.27), renal function (VIP=1.80), Total Iron Binding Capacity (VIP=1.12), percentage of body weight change during the last 3 months (VIP=1.10), MIS score (VIP=1.06), the presence of sleep disturbance (VIP=0.91), and sleep latency (VIP=0.89±0.06).

Conclusions: The analysis result might consist of factors related to hypertension in CKD. However due to the limited numbers of data, the model used in this study needs to be validated along with this ongoing study recruiting more subjects.

Funding: Government Support - Non-U.S.

**PUB555**

Evaluation of Blood Bicarbonate Levels and Gas Analysis in Hemodialysis Patients Who Switch from Lanthanum Carbonate to Sucroferric Oxalohydroxide Aristedes Stavroulopoulos2,3 Vasiliki V. Arcesti,1 Christoforos Papadopoulos2,3 Panagiotis Nemes,2 Antoni Zeni G. Maropis,2 Anastasios Galinas,4,5 IASO Hospital - General Clinic of Kallithea, Athens, Greece; 6 Dialysis Unit “ATTIKOS NEPHROS”, Athens, Greece; 7 Dialysis Unit “ATHINAUKO KENTRO NEFROU”, Athens, Greece; 417 NMTS Hospital, Athens, Greece.

Background: Different phosphate binders have different effects on acid-base status of hemodialysis patients. We sought to examine possible alterations in acid-base parameters in patients switching from lanthanum carbonate (LC) to sucroferric oxalohydroxide (SOH).

Methods: Fifteen stable patients, on bicarbonate hemodialysis, switched from LC to SOH. However, only 9 continued on SOH; 3 returned to LC and the other 3 switched to sevelamer carbonate due to side effects of SOH. The later 6 patients served as a control group to the SOH group of 9 patients. Blood was sampled from the “arterial needle” of the vascular access, on the 3-day and the last 2-day interval of the week prior to switching and 6 weeks after, at the same intervals. Bicarbonate levels (HCO₃⁻), pH, pO₂, pCO₂, were measured, and the mean of the 2 measurements (3-day and 2-day interval) was calculated. Dialysate, medications and hemodialysis prescription (except of ultrafiltration) were remained unchanged throughout the study.

Results: Comparing pre-switching to post-switching measurements in the SOH group, no statistically significant differences were found in any of the parameters studied. Mean pre-switching HCO₃⁻ levels were 22.4±1.66 mmol/L and post-switching 22.62±2.25 mmol/L (P=0.743). Respectively, mean pH= 7.384±0.028 vs. 7.385±0.03 (P=0.723), mean pCO₂ = 38.41±3.29 vs. 38.37±3.62 mmHg (P=0.971), Phosphate = 4.65±0.85 vs. 4.21±1.19 mg/dL (P=0.194) etc. No significant differences were found even when we analyzed the data for the 3-day and the 2-day intervals. There were not any significant differences whether patients were under 25 years of age or not, as they were, either between pre-switching daily LC daily dose, or between post-switching daily dose of the new binder and the measured parameters. Only, pH and HCO₃⁻ were significantly lower at the 3-day vs. 2-day interval, as expected.

Conclusions: In our small study, switching from LC to SOH did not have any significant effect on blood bicarbonate levels and gas analysis, indicating that there is no need to change hemodialysis prescription regarding these parameters. However, monitoring of serum bicarbonate levels is part of good clinical practice.

**PUB556**

Does Intravenous Iron Therapy Decrease Serum Phosphorus Levels? Frieda Wolf, Vladimir Poletuev, Mazen Elias. Eneik Medical Center, Afula, Israel.

Background: Several intravenous iron formulations have been reported to increase phosphaturia, causing dangerously low serum phosphorus levels. This may lead to osteomalacia and fractures, more so in people with vitamin D deficiency. This phenomenon has been observed with saccharated ferric oxide, a preparation commonly used in Japan, and with iron poly maltamole. It has also been observed with iron carboxymaltose. There is no existent information in the literature about phosphorus levels after treatment with iron sucrose or ferric gluconate, which we use most frequently for individuals with iron deficiency anemia, or with or without kidney disease.

Methods: We checked serum phosphorus levels in 48 individuals with iron deficiency anemia, before and after iron treatment. Comparisons of phosphorus levels prior to and after treatment were done using students’ t-test.

Results: Forty seven received iron sucrose. Only three individuals had vitamin D deficiency. Average phosphorus level pre- treatment was 3.8±0.5 mg/dL, with a mean PTH level of 62.59 pg/mL and mean vitamin D level of 40.67 nmol/L. Average phosphorus level was 3.47±0.55 mg/dL post-treatment.

Conclusions: We conclude that iron sucrose is a safe and effective treatment for iron deficiency anemia, with or without kidney disease.
Gayatri Nephrocalcinosis Secondary to Total Parenteral Nutrition

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

Results:

Background: Nephrocalcinosis is a rare complication of TPN and has only been reported in preterm infants to date. Here we report a case of a middle aged woman who was found to have microscopic nephrocalcinosis with calcium phosphate deposition seen on renal biopsy which was due to high amounts of phosphorus she was receiving via TPN.

Methods: A 55 year old female with a history of Ulcerative colitis and total colostomy at the age of 6 followed by a diverting loop jejunostomy and end ileostomy in 2012 requiring TPN since then, presented to nephrology clinic in 2016 for elevated serum creatinine (Scr). Her baseline Scr was 0.6-0.8 mg/dL a year prior to presentation and had been slowly rising to a Scr of 1.5 mg/dL on initial evaluation. She had a history of recurrent episodes of dehydration secondary to high osmotic output which was an ongoing problem at the time of presentation. Her intake was adjusted to match output and protein content of TPN was decreased but Scr continued to rise and reached 2.29 mg/dL. Further labs showed an elevated phosphorus of 6.9 mg/dL, PTH 329 pg/mL and low normal calcium, suggesting secondary hyperparathyroidism. Urine analysis showed no significant proteinuria or hematuria with some amorphous crystals seen on microscopy. 24 hour urine showed elevated phosphorus (1300 mg/24hr). Renal ultrasound was normal. Biopsy revealed chronic tubulointerstitial inflammation with moderate interstitial fibrosis and tubular atrophy. Moderate amounts of crystals consistent with calcium phosphate deposition were scattered throughout the interstitium. On further investigation it was found that the patient was receiving very high levels of phosphorus via TPN and had intermittent episodes of hyperphosphatemia in the prior year. The phosphorus content of TPN was substantially decreased and over the next few months Scr improved to 1.4 mg/dL.

Results:

Conclusions: The mechanism of nephrocalcinosis due to TPN is related to the calcium phosphate ratio required for maintaining a neutral or positive calcium balance in order to prevent bone disease. Usually adult parenteral dose of phosphorus is 27-53 mg/kg/day, our patient was receiving very high levels of phosphorous(95-180mg/day) for an extended period of time which led to calcium phosphate crystal deposition causing renal injury. Thus, in patients with renal dysfunction receiving TPN this is an important consideration.

PUB585

Medullary Sponge Kidney and Primary Hyperparathyroidism – An Enigma

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

Results:

Background: Medullary sponge kidney is considered as congenital disorder usually characterised by malformation of collecting ducts which manifest as medullary cysts with sparing of cortex. It is thought to be a developmental abnormality with limited evidence of genetic transmission. It is usually asymptomatic and picked up as incidental finding on imaging but some times presents with hematuria, UTIs and renal colic with overall good prognosis with preserved renal function.

Methods: 23 year old gentleman with no past medical history. Presented to GP with 12 month history of increasing tiredness and fatigue, negative family history of any endocrinopathy. Normal physical examination. Routine blood tests revealed raised alkaline phosphatase and therefore an abdominal ultrasound was arranged. This was suggestive of medullary sponge kidney and he was referred for nephrology review. Nephrology review and subsequent investigations showed a raised calcium 3.4mmol/l, high parathyroid hormone 28.7 pmol/l, urinary calcium 2.87 mmol/l, negative myeloma screen, normal ACE/vitamin D levels, normal range urine metabolites, normal pituitary profile and no symptoms of hypercalcaemia. CT urogram did not show renal stones and confirmed medullary sponge kidney. Clinical impression was of primary hyperparathyroidism which was treated with fluids and pamidronate. MRI bladder scan later confirmed right sided parathyroid adenoma which was surgically excised.

Results:

Conclusions: There is limited evidence in literature regarding association of primary hyperparathyroidism with medullary sponge kidney. There are suggestions that primary hyperparathyroidism can cause medullary sponge kidney but on other hand it is well proven fact that nephrocalcinosis can cause medullary sponge kidney. Association and mechanism of primary hyperparathyroidism as causative factor for medullary sponge kidney still remains an enigma.

PUB559

A Case Study of a Patient with CKD-Metabolic Bone Disorder with Concomitant Ectopic Primary Parathyroid Adenoma

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

Results:

Background: We report an outpatient referral of a patient with chronic kidney disease (CKD) and normal to borderline elevated Calcium (Ca) with elevated PTH who presented to our outpatient clinic being referred by his Primary Physician.

Methods: 65-year-old Caucasian male with a past medical history of CKD Stage 3 likely secondary to presumed underlying type II diabetes mellitus (DM), and hypertension (HTN) who presents with fatigue, constipation and cold intolerance. Physical examination was unremarkable. Serum creatinine (Cr) had been elevated at 1.4-1.6 mg/dL since August of 2015 along with intermittent hyperparathyroidism since 2012 with peak Ca of 11.9mg/dl in January 2013. Most recent labs revealed serum PTH of 174 pg/ml, calcium of 11.1 mg/dL, 25-Hydroxy Vitamin D of 16ng/ml, and phosphorus of 1.8 mg/dL. Renal ultrasound was inconclusive. A sestamibi scan revealed an abnormal uptake due to an ectopic retrosternal parathyroid. A diagnosis of primary hyperparathyroidism (HPT) along with some element of secondary hyperparathyroidism related to renal insufficiency was made. Subsequently, he was referred for a surgical excision, while being medically managed with cinacalcet.

Results:

Conclusions: Ectopic parathyroid adenoma has a prevalence of 5%-14%. Common locations include mediastinum, retropharyngeal, carotid sheath, and intrathyroidal. Most common symptoms include renal colic, frequent urination, abdominal pain, nausea, vomiting, impaired memory, personality changes, and constipation. Primary HPT is often overlooked in Chronic Kidney Disease patients. Our case highlights the importance of persistent hypercalcaemia with normal or low serum phosphorus levels as a biochemical clue in diagnosing primary HPT with ectopia in patients with suspected secondary hyperparathyroidism from CKD and Vitamin D deficiency. Imaging approach includes a sestamibi scan which is not necessary in all cases. It is important to remember the need for a sestamibi or 4-dimensional CT as ultrasound alone could miss ectopic adenomas, especially with inexperienced ultrasonographers. Treatment approach includes surgery. The indication for parathyroidectomcy in our case was elevated calcium values 1mg/dl above normal along with CKD. Whether the ectopic parathyroid is the hyper-functioning nodule can only be confirmed by excision and following PTH levels.

PUB560

Rebound Hypercalcaemia Post Denosumab Exposure

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

Results:

Background: Hypercalcemia is an oncological emergency with an estimated incidence of 10–20% in adult patients with cancer. Denosumab is a humanized monoclonal antibody to RANKL approved for treatment of osteoporosis and prevention of skeletal-related events from bone metastases. RANK ligand (RANKL) is a cell surface protein involved in many cellular processes, including osteoclastogenesis. Receptor activator of nuclear factorκ-B ligand (RANKL) is a cell surface protein that plays an important role in bone resorption and bone remodeling through its effect on osteoclasts.

Methods: We describe a 68 year old female with a proven of polymyalgia rheumatic (PMR), hypothyroidism, osteoarthritis, osteopenia, liver cirrhosis with Bx proven NASH, right breast cancer without bone metastasis, diagnosed 3 years earlier, who underwent bilateral mastectomy. She did not undergo chemor- or radiation therapy. She adjuvant therapy initially with letrozole which was changed to tamoxifen. Patient presented with generalized weakness and change in mental status. One week earlier, she was found to have a Ca2+ of 12. On admission, Ca2+ was 14 with albumin of 3.1. She received one dose of Denosumab for her known osteoporosis 6 month ago. Other outpatient medications included vit d 2000 U and Centrum silver once Labs- CBC: Hgb 9.3, wbc 3.6, plt 76. BMP :- Na 144, k 2.8, Cl: 108, Hco3 27, AG 9, BUN: 16, CR: 1.3 BS: 107, EGF42-
Hypercalcemia in a Patient with Cholangiocarcinoma (CC): Diagnosis

Saeed Saeedi,1 S. J. Haddad,2 S. Patwardhan,3 S. J. Haddad,4 1Northwestern University, Chicago, IL; 2Northwestern, Chicago, IL; 3Northwestern, Chicago, IL; 4Northwestern, Chicago, IL.

Background: Sevelamer carbonate is a polymeric amine that is used as a phosphorus binder in patients with advanced chronic kidney disease (CKD) and end-stage renal disease (ESRD). We report a case of colitis in a patient with ESRD where sevelamer may have been responsible for colonic mucosal injury.

Methods: A 68 year old female with ESRD on hemodialysis presented to the hospital with abdominal pain, nausea and diarrhea. Laboratory evaluation revealed leukocytosis. A Computed Tomography (CT) scan of abdomen and pelvis was notable for right sided colonic wall thickening with associated luminal narrowing. Initial colonscopy revealed several scattered yellowish-brown ulcers on the mucosa of the cecum and ascending colon. Pathology report on obtained biopsy was consistent with ischemic colitis. Abdominal CT angiogram showed patent vasculature. She received supportive care and was discharged home with improvement in her symptoms. Two weeks after discharge, she presented to the hospital with epigastric and left sided abdominal pain, nausea and dark stools. Evaluation revealed hypotension, anemia and leukocytosis. Patient underwent colonscopy with finding of ulcerated, friable mucosa from cecum to splenic flexure. Pathology report was notable for presence of granulation tissue, sevelamer crystals and associated foreign body inflammatory response. No features of acute ischemia were found. Sevelamer was discontinued with improvement in her symptoms. Repeat colonscopy 18 months later revealed ulcerated long stricture in ascending colon preventing passage of 10mm colonoscope. Biopsy showed chronic colitis with mild activity.

Results:

Conclusions: Sevelamer induced colitis can be a cause of chronic diarrhea in selected cases resulting in stricture disease over time. This has been reported previously in the literature. Further studies are needed to establish whether sevelamer is responsible for mucosal injury or whether sevelamer can exacerbate injury in an already damaged colonic mucosa. This infrequent adverse effect should be kept in mind in any patient treated with sevelamer having otherwise unexplained colitis.

PUB562

Sevelamer Crystals in Injured Colonic Mucosa – Causative Agent or an Innocent Bystander?

Antonin Jaros,3 Frazia Mir,2 Susan Hudson,1 Saeed K. Shaffi,4, 1DCI, Albuquerque, NM; 2Presbyterian Hospital, Albuquerque, NM; 3UNM, Albuquerque, NM; 4University of New Mexico, Albuquerque, NM.

Background: Sevelamer carbonate is a polymeric amine that is used as a phosphorus binder in patients with advanced chronic kidney disease (CKD) and end-stage renal disease (ESRD). We report a case of colitis in a patient with ESRD where sevelamer may have been responsible for colonic mucosal injury.

Methods: A 68 year old female with ESRD on hemodialysis presented to the hospital with abdominal pain, nausea and diarrhea. Laboratory evaluation revealed leukocytosis. A Computed Tomography (CT) scan of abdomen and pelvis was notable for right sided colonic wall thickening with associated luminal narrowing. Initial colonscopy revealed several scattered yellowish-brown ulcers on the mucosa of the cecum and ascending colon. Pathology report on obtained biopsy was consistent with ischemic colitis. Abdominal CT angiogram showed patent vasculature. She received supportive care and was discharged home with improvement in her symptoms. Two weeks after discharge, she presented to the hospital with epigastric and left sided abdominal pain, nausea and dark stools. Evaluation revealed hypotension, anemia and leukocytosis. Patient underwent colonscopy with finding of ulcerated, friable mucosa from cecum to splenic flexure. Pathology report was notable for presence of granulation tissue, sevelamer crystals and associated foreign body inflammatory response. No features of acute ischemia were found. Sevelamer was discontinued with improvement in her symptoms. Repeat colonscopy 18 months later revealed ulcerated long stricture in ascending colon preventing passage of 10mm colonoscope. Biopsy showed chronic colitis with mild activity.

Results:

Conclusions: Sevelamer induced colitis can be a cause of chronic diarrhea in selected cases resulting in stricture disease over time. This has been reported previously in the literature. Further studies are needed to establish whether sevelamer is responsible for mucosal injury or whether sevelamer can exacerbate injury in an already damaged colonic mucosa. This infrequent adverse effect should be kept in mind in any patient treated with sevelamer having otherwise unexplained colitis.

PUB563

Report of Recombinant Parathyroid Hormone Therapy (Forteo) in a 18 Year Old Patient with Fanconi Syndrome and Osteomalacia

Ivie O. Okundaye, Aparna Natarajan, Julia Schneider. Loyola University Medical Center, Maywood, IL.

Background: An 18-year old woman with Fanconi Syndrome due to an unknown genetic mutation initially presented with proximal renal tubular acidosis, hypokalemia and hypophosphatemia resulting in osteomalacia and pathologic fractures. Patient presented to the ER with sudden onset right leg pain and inability to bear weight. Imaging showed diffuse osteopenia, left transverse femoral shaft fracture, multiple prior stress fractures and a right ulnar fracture. Labs notable for K 3.0, Phos 1.7, HCO3 16, Ca 7.7, ionized Ca 1.15 PT 129, and normal serum creatinine. There was no evidence of nephrolithiasis. 24 hour urine did not show hypercalciuria. Alkaline Phosphatase 1004, Vitamin D 25-OH 16. Vitamin D-1,25 within normal limits. Dexta Scan revealed Z score -5.5 consistent with osteomalacia for her age.

Methods: Vitamin D was repleted but due to severe chronic bone pain and poor fracture healing, use of recombinant parathyroid hormone analogue, Forteo was initiated. Interestingly, alkaline phosphatase, bone alkaline phosphatase, levels improved after Forteo therapy, and patient had not had additional fractures after therapy. She also reports marked pain improvement. Patient remains on calcium 600 mg, calcitriol 1ug BID, and ergocalciferol 50,000 IU every other week, kphos packets TID.

Results:

Conclusions: Forteo is known to expedite bone healing however its use in young patients with Fanconi syndrome and hypophosphatemic rickets has not been studied. This drug is typically used for treatment of osteoporosis in elderly patients or those taking corticosteroid medications. Some studies show acceleration of bone healing from fractures in patients with osteoporosis. Here we present a case of hypophosphatemic rickets resulting in debilitating bone fractures successfully treated with Forteo. Forteo in combination with calcium and phosphorus replacement therapy demonstrates a novel approach in treatment of Fanconi syndrome associated hypophosphatemic rickets with pathologic fractures.

PUB564

A Case of Sagliker Syndrome

Julia Brown,7 Rebecca Frazier,1 Northwestern, Chicago, IL; 7Nephrology, McGaw Medical Center of Northwestern University, Chicago, IL.

Background: Sagliker Syndrome is a recently described entity in which patients with chronic renal failure and uncontrolled hyperparathyroidism develop severe bone deformities including teeth, maxillary and mandibular bone, skull, finger, and height changes. These abnormalities are more severe than expected with high parathyroid hormone levels. It is often associated with lack of medical care. This syndrome likely has an underlying genetic basis although the genes are not yet identified.

Methods: A 36-year-old male on dialysis for 11 years presented with progressive skeletal abnormalities and bone pain. He had normal stature and musculoskeletal development until he developed renal failure in his early 20s. Over the next few years, he developed many deformities including bilateral leg fractures, bowing of the legs and arms, curvature of the spine, mandibular hypertrophy, and angulation of the distal phalanges. These changes caused progressive immobility, on presentation he was bedridden. He was found to have a parathyroid hormone level of 2410 pg/mL, phosphorus 6.8 mg/dL, calcium 9.4 mg/dL, and alkaline phosphatase 727 U/L. X-rays revealed diffuse demineralization, cystic changes, and cortical sclerosis consistent with severe osteitis fibrosa cystica. Parathyroid ultrasound demonstrated enlarged parathyroids, and sestamibi scan revealed parathyroid hyperplasia. His case is consistent with Sagliker Syndrome. The patient was treated with subtotal parathyryoidectomy with forearm autotransplantation of 3 mm3 of parathyroid gland. Bone pain resolved post-operatively, however, he developed hungry bone syndrome requiring a total of 67g of intravenous calcium and 24g of oral calcium in the first 72 hours post-operatively. His PTH level after parathyryoidectomy was 8 pg/mL.

Results:

Conclusions: Early recognition of skeletal changes and strict control of hyperparathyroidism is crucial in preventing devastating bony deformities in those predisposed to Sagliker Syndrome.
PUB566

The Impact of Smoking on the CKD-MBD Biomarkers Geuzi D. Dos santos, Rosilene M. Elias, Emilia M. Scoeiro, Camila Dosse, Luciene dos Reis, Wagner Dominguez, Fabiana Gracioli, Giovannoni V. da Silva, Ivan B. Oliveira, Vanda Jogetti, Maria Dalboni, Rosa M. Moyses, Universidade Federal de São Paulo, São Paulo, Brazil; Universidade Nove de Julho, São Paulo, Brazil; Nephrology, Universidade de São Paulo, São Paulo, Brazil.

Background: Chronic kidney disease and smoking are considered a public health problem and are associated with an increased risk of cardiovascular disease. CKD-MBD also presents a high cardiovascular risk for CKD patients. However, the potential association of smoking and CKD-MBD is unknown. A previous study has shown that smoking habits among CKD patients is associated with higher serum e-terminal FGF-23, although the mechanism has not been elucidated. In this study, we aimed to confirm whether intact FGF-23 would be elevated in CKD patients who smoke. We hypothesized that an elevation of FGF-23 would be related to a decrease in serum Klotho or an increase in hypoxia-inducible factor 1α (HIF1α). The latter is usually increased among smokers and has been recently described as a regulator of FGF-23 production, in experimental models.

Methods: We have evaluated 92 patients divided into three groups: Control without CKD, CKD stages III and IV on conservative treatment, and dialytic group, with smokers and non-smokers. We collected data from August 2016 to January 2017. Measurements of HIF-1α, intact FGF-23 and Klotho were performed using commercial ELISA assays, according to manufacturers’ protocols.

Results: Smokers performed less time of physical activity than the other groups. Serum phosphate was lower among patients on conservative treatment with smoking habits (3.10 ± 0.5 vs. 3.6 ± 0.6 mg/dl, p < 0.05). Serum uric acid was also lower in smokers, regardless the CKD stage (6.1 ± 1.5 vs. 6.8 ± 1.6 mg/dl, p < 0.05). No differences were found for calcium, 25-vitamin D, parathormone or alkaline phosphatase. FGF-23 was higher in dialysis patients than in conservative patients, but no differences were found between smokers and non-smokers. There were not any significant differences in Klotho and HIF1α levels among these groups.

Conclusions: We found no argument to support our preliminary hypotheses, as there were no significant differences in FGF-23, Klotho and HIF1α levels when comparing patients with and without smoking habits. As an additional finding however, the effect of cigarette smoking on plasma uric acid and phosphate levels deserves further investigation.

Funding: Government Support - Non-U.S.

PUB567

The Value of Intra-Operative PTH Assay during Parathyroidectomy in Dialysis Patients with Refractory Hyperparathyroidism Adelene E. Edon, Kevin Wang, David Saxon, Florence Lima, David Sloan, B. Peter E. Sawaya, Amr E. Mohamed. University of Kentucky, LEXINGTON, KY.

Background: In dialysis patients with secondary and tertiary hyperparathyroidism (HPT), the correlation of intra-operative parathyroid hormone (ioPTH) measurement during parathyroidectomy (PTX) with long-term PTH level is unknown. The present study aims at evaluating the value of ioPTH measurements on long-term outcome of PTX in dialysis patients in a single center study.

Methods: The ioPTH was measured in 57 hemodialysis patients (33 females and 24 males) who underwent PTX between 2005 and 2015 because of refractory HPT. Near-total PTX was performed in 43 patients, total PTX in 15 patients (one patient underwent second PTX within 3 months because of failure of the first PTX). The ioPTH monitoring included 3 samples: pre-intubation (pre-ioPTH), 10- and 20-minute post PTX (10- ioPTH and 20-ioPTH). The patients were followed for up to 5 years (mean ± SD: 2.2 ± 2.1 years).

Results: The median (25th-75th percentile) pre-, 10- and 20-ioPTH levels were: 1447 pg/ml (969-2168), 143 pg/ml (78-244) and 112 pg/ml (59-153), respectively. There was no significant difference between 20-ioPTH and any subsequent PTH measurements (P=0.8, Figure). Sixteen patients (28%) were readmitted within 90 days due to significant hypocalcemia. One patient was readmitted for post-PTX hematoma evacuation. No patient required repeat PTX because of recurrent HPT.

Conclusions: The 20-ioPTH is a good indicator of long-term PTH values. Hypocalcemia is a common complication and the main reason for readmission after PTX. No patient required second PTX due to recurrent HPT.

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

PUB565


Background: Lower 25-hydroxyvitamin D concentrations have been associated with kidney function decline, heart failure (HF), and mortality, but calcitriol has been less studied as a risk factor in community-living individuals. We evaluated the associations of plasma calcitriol concentrations with kidney function decline, HF, and mortality in the Health ABC Study of participants aged 70 to 79 years.

Methods: We used a case-cohort design and we measured baseline calcitriol in a random sub-cohort of 479 participants, and also among incident cases with kidney function decline (a 30% decline in eGFR from baseline [n=397]) and HF (n=207). In addition, 136 of the 479 participants in the sub-cohort died during 8.6 years mean follow-up.

Results: After adjusting for demographics, kidney function, traditional cardiovascular risk factors, calcium, phosphate, intact parathyroid hormone (iPTH) and fibroblast growth factor (FGF)-23 concentrations, each standard deviation (SD) lower calcitriol concentration was associated with 33% higher risk of kidney function decline (95% CI 1.07, 1.66; p=0.012) during 10 years follow-up. Calcitriol was not significantly associated with any of the analyses. We observed no significant interactions by chronic kidney disease status, or 25-hydroxyvitamin D concentration was associated with 33% higher risk of kidney function decline (95% CI 1.07, 1.66; p=0.012) during 10 years follow-up. Calcitriol was not significantly associated with incident HF or mortality among community-living adults.

Conclusions: Lower concentrations of calcitriol were independently associated with kidney function decline but not with incident HF or mortality among community-living older adults.

Funding: NIDDK Support, Other NIH Support - NHLBI, NIA
were sampled at baseline, 4-week, 8-week and 12-week post therapy change. Therapy success was defined as ability of cholecalciferol to maintain serum calcium, and the successful proportion was calculated.

Results: From February till April 2016, 112 patients were screened and total 13 patients were enrolled. 12 of 13 participants succeeded cholecalciferol therapy at end of study. When compared to baseline, there was no significant difference to serum calcium, phosphate and parathyroid hormone at end of study. There was statistically significant rise in serum alkaline phosphatase (mean increase 19.1 U/L, P=0.004) and 25-hydroxyvitamin D3 (mean increase 24.7 nmol/L, P=0.001) at week 12. Serum 1,25-dihydroxyvitamin D3 showed significant initial drop at week 4 (mean reduction 28.1 pmol/L, P<0.001) and week 8 (mean reduction 20.2 pmol/L, P<0.001), but exhibited no significant difference by week 12.

Conclusions: Cholecalciferol can maintain serum calcium in a worthwhile proportion of adult dialysis dependent chronic kidney disease patients.

Funding: Private Foundation Support

PUB570
Ultrasound Guided Ablation Therapy for Treatment of Secondary Hyperparathyroidism
Elias J, Baelde, Marc J. Alonso, Stuart M. Sprague. NorthShore University HealthSystem University of Chicago Pritzker School of Medicine, Chicago, IL.

Background: The successful management of severe secondary hyperparathyroidism in patients with chronic kidney disease (CKD) is difficult to accomplish with medical therapy alone due to complications of drug treatment, medication intolerance and non-compliance. Thus, many patients still require surgical parathyroidectomy. Ultrasound guided percutaneous ethanol injection (US-EtOH) injection has been successfully used in a few centers, especially in Japan, however, widespread acceptance of this procedure has not yet occurred. The aim of this analysis is to review patients in our center who underwent US-EtOH therapy.

Methods: Charts of patients who underwent US-EtOH therapy between 2013 and 2017 were reviewed. Data analyzed included basic demographic information, pre-ablation parathyroid hormone (PTH), calcium (Ca), number of ablations, and 6–9 month follow-up PTH and Ca concentrations.

Results: A total of 20 patients were identified, however, data was only available on 16 (6 males). Four of the patients were post-transplant, 1 undergoing hemodialysis and 11 with CKD. In 56%, PTH concentrations decreased by > 25 % at ±2 ±3 months. Mean Ca decreased from 10.4 ±3.1 to 9.9 ±3.07, p<0.05.

Conclusions: US-EtOH therapy may be helpful in controlling secondary hyperparathyroidism in selected patients with CKD. Further experience and prospective studies are needed.

Funding: Clinical Revenue Support

PUB571
The Contralateral Kidney Is Protected against Fibrosis in Unilateral Ureter Obstructed (UUO) Rats
Anders Nordholm,1 Maria L. Mace,1 Eva Gravesen,2 Jacob Hofman-Bang,2 Klaus Olgaard,2 Ewa Lewin,1
1Department of Nephrology, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark; 2Department of Nephrology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark.

Background: Emerging concepts propose that circulating factors released from an injured kidney, might cause vasculopathy, bone disease, and kidney fibrosis. We examined the expression of genes related to fibrosis and Wnt signaling in the contralateral, untouched kidney (CON) to unilateral obstructed kidney (OBS) in UUO rats with unilateral nephrectomized (UNX) and normal rats as controls.

Methods: UUO rats (n=48) were studied at 0, 2, 4, 6 hr, 1, 3, 4 and 10 days (D) in parallel with UNX control rats (n=30) and normal rats (n=6). Kidney expression of Klotho, BMP7, TGF-β, Peristin, Sclerostin, DKK-1 and ActivinA were examined as well as plasma (p) levels of Sclerostin and ActivinA.

Results: ActivinA mRNA was undetectable in normal kidney but highly induced in OBS (Baseline 0.09±0.01, D1:3.3±0.32, D10:0.94±0.55, p<0.01). However gene expressions in CON were similar to that of UNX and normal kidney. P-ActivinA doubled at day 10 in UUO rats compared to baseline and UNX (B:217±14, UNX 10D:254±18, UUO 10D:413±44, p<0.01) indicating that ActivinA is released from the injured kidney. P-sclerostin was similar in UNX and UUO rats (B:142±16, UNX 10D:284±42, UUO 10D:313±60, p>0.05). Kidney sclerostin mRNA was undetectable in all groups indicating non-renal source of sclerostin. DKK-1 mRNA was similar in OBS and CON. In the OBS kidney there was a down-regulation of anti-fibrotic factors Klotho and BMP7 already at day 1 (p<0.01) but not at 6. hrs. Simultaneously in the OBS kidney a progressive up-regulation of pro-fibrotic TGF-β and induction of Peristin were evident from day 1 (p<0.01). All genes were similar in CON, UNX and normal kidneys at all time points.

Conclusions: A rapid decrease in anti-fibrotic factors and an increase in pro-fibrotic factors is observed in the OBS kidney of UUO rats. Induction of ActivinA in OBS kidney may contribute to its elevated plasma levels and could potentially represent a circulating factor that drives kidney fibrosis. However, gene expressions of pro- and anti-fibrotic factors in the CON kidney are maintained normal, indicating protection against circulating fibrotic factors.

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

1109
Increased Bioactive Sclerostin Levels in Kidney Transplant Recipients Detected with a New and Well-Characterized ELISA

Gabriela Berg, Elisabeth Gadermaier. The Antibody Lab GmbH, Vienna, Austria; Biomedical, Vienna, Austria.

Background: Over the past years there is an increasing knowledge about the relationship between mineral and bone disorder (MBD) and cardiovascular diseases in patients with chronic kidney disease (CKD). One of the key regulators in CKD-MBD is sclerostin a 190-amino acid glycoprotein, which is mainly secreted by osteocytes. It was shown that circulating sclerostin levels are increased in CKD-MBD patients. Sclerostin is an inhibitor of the osteoanabolic Wnt signaling pathway achieved by binding to its second loop to the LRP5/6 complex. The measurement of this bioactive site of sclerostin may be helpful to further investigate its role within CKD-MBD disease progression and in the assessment of therapeutic effectiveness.

Methods: We have developed an immunoassay for the detection of the bioactive binding site of sclerostin in human serum and plasma samples. The antibodies were characterized and assay performance was validated according to ICH and EMEA guidelines. Plasma concentration of bioactive sclerostin was measured in apparently healthy controls and renal transplant recipients.

Results: The recombinant monoclonal coating antibody recognizes an epitope within the second loop of sclerostin, whereas the polyclonal detection antibody has five linear epitopes distributed throughout the molecule. Both antibodies have good binding kinetics of k_{on} of 1.0E-07 s^{-1} for the monoclonal antibody and 1.19E-05 s^{-1} for the polyclonal antibody, respectively. The validation parameters were within the required quality standards. Bioactive sclerostin concentration was significantly increased from 87 +/- 41.7 pmol/l (apparently healthy) to 166.5 +/- 68.0 pmol/l in renal transplant recipients.

Conclusions: This ELISA provides a reliable and accurate tool for the quantification of the bioactive site of the sclerostin molecule in healthy and diseased human and may give a new perspective within CKD-MBD research.

Secondary Hyperparathyroidism Treated with a Novel Vitamin D Prohormone, Extended-Release Calcifediol, in a Renal Allograft Patient with CKD

Jack E. Rubin, Encino, CA.

Background: Patients with advanced CKD have secondary hyperparathyroidism (SHPT), arising from vitamin D insufficiency and derangements of mineral and bone parameters such as calcium, (Ca), phosphorus (P). PTH elevation in these patients causes demineralization of bone and increases the risk of cardiovascular morvidity and mortality. While calcitriol and active vitamin D analogs are effective in lowering elevated PTH levels, they are associated with increased risk of hypercalcemia and hyperphosphatemia and increased FGF-23 levels. Additionally, the problem of correcting vitamin D insufficiency remains unaddressed with these therapies. Rayaldee (extended-release calcifediol, 25-OH-D3), a prohormone of the active form of Vitamin D3, has recently been approved by the FDA for the treatment of SHPT and vitamin D insufficiency in CKD stages 3 or 4, the only vitamin D product indicated to treat elevated PTH and insufficient Vitamin D levels, correcting both disorders.

Methods: Here, I present a 57 year old African-American male who had a renal allograft placed 8 years ago and now has stage 4 CKD due to chronic allograft nephropathy. He also has type 2 diabetes mellitus, hypertension, hyperlipidemia, pulonmonary artery hypertension, anemia of CKD and hypertension.

Results: His PTH reached its apex of 266 pg/ml on 11/7/16 and his Vitamin D level was at its nadir then at 20.1 ng/dl. He was then taken off calcitriol 0.25 mg and placed on Rayaldee, calcifediol ER (CER) 30 mcg hs. After 4 months of treatment on CER, on 4/27/17, his PTH fell to 97.2 ng/dl, a 36% reduction. His Vitamin D level rose to 36.7, a 83% increase. During this time period his serum creatinine increased from 3.5 mg/dl to 3.6 mg/dl, a 9% increase.

Conclusions: There are no case reports of CER being used to treat SHPT in renal allograft recipients with CKD in the literature. This patient had a reduction of his elevated PTH level of 36% with no untoward clinical events. As his PTH was significantly reduced, an expected amelioration of his bone-induced SHPT bone disease was expected. As a case report shows that CER is a safe and more effective option to treat SHPT in renal allograft patients with CKD. However, a large randomized controlled study utilizing calcifediol ER for the treatment of SHPT in patients with renal allografts is needed.
Effect of Cinacalcet Combined with Low Dose Calcitriol on Clinical Outcome and Bone Metabolism in Patients on Hemodialysis with Severe Secondary Hyperparathyroidism

Fang Yuan,1 Hong Liu,2 Xing Chen,1 Fu-You Liu,2 Department of Nephrology, The Second Xiangya Hospital, Central South University, Changsha, China; The Second Xiangya Hospital, Changsha, China; Departments of nephrology, Second Xiangya Hospital Central South University, Changsha, China.

Background: Secondary hyperparathyroidism (SHPT) is a common complication observed in maintenance hemodialysis (MHD) patients, characterized by multi system damage, calcium-phosphorus metabolism disorders and bone disease. Several clinical studies have confirmed that SHPT is closely related to the high risk of cardiovascular disease and mortality. Our study is To observe the clinical outcome and the effect of bone metabolism of cinacalcet hydrochloride combined with low dose calcitrol in MHD patients with severe SHPT.

Methods: Thirty MHD patients were enrolled to receive treatment of cinacalcet combined with low dose calcitrol, with inclusion criteria as follows: maintenance on HD>6 months; serum intact parathyroid hormone (iPTH)<600 pg/ml; parathyroid glands had more than 1 nodules by ultrasonography; traditional therapy is not effective. All patients were given cinacalcet 25-75 mg and 0.5 μg calcitrol dialy. Serum Ca, P, iPTH, bone metabolic markers and bone density were measured before and after treatment. The clinical symptoms and their improvement were investigated.

Results: The baseline levels of iPTH, Ca, and P were 1787.3±40.19 mmol/L, and 2.06±0.15 mmol/L, respectively. After 2 weeks of treatment, serum phosphorus decreased by 20%; after one and three months, iPTH decreased by 35% and 70%, respectively, with before treatment. Ca and P increased to 2.39±0.17 mmol/L and 1.56±0.50 mmol/L, respectively, after one month, respectively. The symptoms of the patients relieved. The above indicators remained stable after one year. Moreover, the bone metabolism index showed alkaline phosphatase, osteocalcin and P-Cross levels were decreased by 50%, 37% and 49% respectively than that before treatment after 6 months. Patients’ bone density decline was inhibited. No severe adverse events were observed.

Conclusions: Cinacalcet hydrochloride combined with low dose calcitrol can improve high calcium, high phosphorus and high iPTH in MHD patients with severe SHPT, relieve symptoms, improve bone metabolism. It can be used as a favorable choice for the treatment of SHPT.

Possible Role of Hydrochlorotiazide Suppressing PTH on Peritoneal Dialysis

Antonio A. Portela Neto,2 Lilian Cordeiro,2 Erica A. Guimarães,1 Benedetto J. Pereira,2 Hugo Abensur,2 Rosa M. Moyses,1 Rosilene M. Elias,1 Universidade de Novo de Julho, São Paulo, Brazil; Universidade de Sao Paulo, Sao Paulo, Brazil; Universidade de São Paulo, São Paulo, Brazil.

Background: In peritoneal dialysis (PD), there is a safety concern regarding influx of calcium (Ca), which becomes challenging while treating patients starting therapy with low parathyroid hormone (PTH). The use of low dialysate calcium concentration (CaLd) and the avoidance of Ca-based binders are recommended. Despite this, PD patients are more prone to have adynamic bone disease. We have assessed the behaviour of CKD-MBD markers in patients on PD, focusing on incident patients with PTH <150pg/ml.

Methods: Patients starting PD between January 2009 and December 2016 in an academic center, with demographical, clinical and laboratorial data available on alkaline phosphatase (AP), PTH, Ca, 25vitamin D and phosphate (P) were included.

Results: Sixty-nine patients (47±18 years, 46.4% male, 80% hypertensive, 23% diabetic) were included. Mean ionized and total Ca, and phosphate were 4.8±0.4mg/dl, 8.6±0.8mg/dl, and 4.7±1.2mg/dl, respectively. AP was 81 (67,119)U/L and PTH was 226±98, 461 pg/ml. 25vitamin D was 19.9±9.6ng/ml (59.4% had levels <15ng/ml). (CR1) Patients who started PD with PTH>150pg/ml (N=28, 40.6%) presented higher iCa (p=0.036), higher glicemia (0.027), lower P (p=0.0001), lower AP (p=0.004), and a similar percentage of vitamin D deficiency (0.373) and diabetes (p=0.322), as compared to those with PTH<150pg/ml. None of the patients with low PTH were taking calcium-based binder and 3 have received low CaLd; after a median of 26 months of follow-up, 11 patients (39.3%) remained with PTH <150pg/ml. This subset of patients differed from those whose PTH increased because a higher percentage of patients were taking hydrochlorothiazide (p=0.040) and because of a tendency toward avoiding low CaLd (p=0.06). Another additional 18 patients reduced PTH to as low as <150pg/ml, because hyperparathyroidism treatment. Neither clinical nor demographic characteristics, including the use of hydrochlorothiazide differed patients whose PTH increased overtime.

Conclusions: Besides traditional factors such as Ca-based phosphate binders, calcitriol and high CaLd, hydrochlorothiazide seems to suppress PTH in patients on PD. Although this finding is already described in CKD on conservative management, further studies are warranted to confirm the mechanism in PD.
Baseline characteristics of the 56 subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.05 ± 11.39</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18.18 ± 9.62</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>56.9 ± 18.1</td>
</tr>
<tr>
<td>Male, n(%)</td>
<td>26(50%)</td>
</tr>
<tr>
<td>Previous fracture</td>
<td>16(29%)</td>
</tr>
<tr>
<td>Poorly functioning hip</td>
<td>3(5.3%)</td>
</tr>
<tr>
<td>Corneal edema</td>
<td>8(14.3%)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>6(10.7%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8(14.3%)</td>
</tr>
<tr>
<td>Secondary hyperparathyroidemia</td>
<td>2(5.6%)</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>10(17.8%)</td>
</tr>
<tr>
<td>Renal need BMD(≥1.62)</td>
<td>-1.15 ± 1.38</td>
</tr>
</tbody>
</table>

**PUB580**

**Mineral and Bone Disease Management in the Hemodialysis Unit: Improvement Care Model**

Fadwa S. Al-Ali, Tarek A. Fouda, Mohamed annin Khalil elesnawi, Saifatullah Khan, Tarek A. Ghonimi, Abdullah Hamad, Khulood Kasem, Khulood Awadi, Fadumo Y. Yasin, Aisha Abdulla, Rania A. Ibrahim, Mohamed Y. Mohamed, Hamad Medical Corporation, Doha, Qatar; Hamad medical cooperation, Doha, Qatar; Hamad Medical corporation, Doha, Qatar; Hamad medical cooperation, Doha, Qatar; HMC, Doha, Qatar.

**Background:** Chronic kidney disease affects mineral and bone metabolism in Hemodialysis (HD) patients, so patients are often vulnerable to deterioration of mineral and bone disorder (MBD) long term complications that influencing morbidity and mortality. We developed a proactive interventional protocol to improve MBD management to achieve better PTH level control in HD population as per KDOQI/KDIGO recommendation.

**Methods:** We developed a new care model for MBD management (Nurse based model under nephrologist supervision) HD patients were selected randomly and gradually from Fahad Bin Jassim Kidney Center over 12 month of period. MBD blood laboratory parameter monitored (PTH, Ca, Po4 level as per protocol. Assigned dialysis nurse played important active role in the care coordination, planning, communication and education.

**Results:** In March 2016 we started with 23 pts. And gradually increased number to 152 in March 2017. Percentage of pts. With target PTH level (150-300 ng/ml) increased by 23%. And the extreme PTH level (>800 ng/ml) decreased by 16%. The new care model also controlled the other parameters (Ca, Po4, and CPP). Minimize the utilization of special calcium dialysate bath.

**Conclusions:** The new MBD care model was developed and implemented successfully. We achieved, and maintained patients within target PTH level (150-300 ng/ml).

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

**PUB581**

**Iliac Crest Biopsy Performed by Interventional Radiologists: A New Way to Improve Access to Bone Biopsy in Patients with CKD**

Lori Asselin-Thompson, Fabrice Mac-Way, Qu?bec, QC, Canada.

**Background:** Mineral and bone disorder (MBD) is a major health issue among patients with chronic kidney disease (CKD). It is associated with an increased risk of fracture, cardiovascular disease and mortality. The 2009 Kidney Disease Improving Global Outcomes guidelines recommend performing iliac crest biopsies to aid in the diagnosis and management of CKD-MBD. Unfortunately, the procedure is rarely performed because many clinicians lack the technical ability required to carry out the intervention. In order to increase access to this procedure, we suggest that it be performed by interventional radiologists rather than nephrologists.

**Methods:** A nephrologist familiar with the procedure first trained two interventional radiologists at CHU de Québec - Hôtel-Dieu de Québec Hospital in November 2016. The Rochester bone biopsy kit was used and the samples were sent for bone histomorphometric analysis. In contrast to the traditional blind technique, radiologists used a new fluoroscopy-guided approach. This novel procedure provided direct visualization of the outer and inner cortical bone during the intervention (Figure 1). This standardized technique allowed for easier identification of the preferred bone biopsy site.

**Results:** All of the iliac crest biopsies currently being performed at Hôtel-Dieu de Québec Hospital are being carried out by interventional radiologists. So far, more than 10 fluoroscopy-guided biopsies have been obtained and no complications have been observed. There were no cases of pain, hematoma, infection or neuropathy following the intervention. Furthermore, all of the bone specimens were adequate and sufficient for analysis.

**Conclusions:** Iliac crest biopsies performed by interventional radiologists will increase nephrologists’ access to bone specimens in patients with CKD-MBD. Moreover, the addition of a standardized, image-guided technique will lower the risk of possible complications.

Figure 1. Fluoroscopy-guided iliac crest biopsy

A) Identification of the biopsy site for local anesthesia; B) Trans-iliac Rochester trocar insertion

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

Underline represents presenting author.

1112
Renal Osteodystrophy: A Weird Case of Leontiasis Osea

Emiliana Ferramosca,1 Ananaria Valletta,1 Vilma Martella,1 Marcello Napoli,1 ASL Lecce - V. Fazzi Hospital, Lecce, Italy; 2Nephrology Dialysis and Transplantation, ASL Lecce - V. Fazzi Hospital, Lecce, Italy.

Background: Renal osteodystrophy (ROD) is a common complication in dialysis patients (pt), due to disorders of mineral and bone metabolism secondary to a longstanding hyperparathyroidism (HPT), resulting in both skeletal and extraskeletal consequences. The combination between high bone turnover and mineralization defects lead to an increased risk of bone fractures and deformities. ROD affects several sites (long bones, ribs, spine), but the cranio-facial localization is rather rare. At this site, the more dramatic pattern is leontiasis osea. Radiological examination of the skeleton is a non-invasive tool for early identification, with high specificity but low sensitivity, since it only recognizes the advanced forms of the disease.

Methods: We report a case of a 45 y/o man on regular HD. History: coronary artery disease treated with CABG, hypertension, COPD, severe secondary HPT non responder to medical therapy, from past 2 years, with parathyroid gland hyperplasia detected by ultrasound and scintigram. The pt presented vertebral osteoporosis with multiple vertebral collapses. His high cardiovascular risk contraindicated a parathyroidectomy. Due to the rapid onset of facies alterations, with macrognathia and severe facial deformity, the pt underwent cranio-facial CT. This test showed marked morphostructural bone alterations, with symmetrical bone remodelling, affecting both the trabecular structure and cortical one. At this level we found widespread erosions with symmetrical involvement of bone structures. Multiple lytic and sclerotic areas representing brown tumours were also observed in the maxilla and mandible. This aspect was compatible with fibrocystic osteitis. Extensive vascular and soft tissue calcification were also found.

Results: 
Conclusions: Todate, despite the numerous therapeutic options, high-efficiency dialysis, and parathyroidectomy, ODR still remains a complication in dialysis pt. Leontiasis osea is a rare or maybe undiagnosed condition. Its early recognition is fundamental in order to intensify intervention strategies and improve pt outcome.
data was compared based on normal and high testosterone categorization. Primary endpoints were 24-hour urinary metabolic panels and stone composition and both cohorts were compared using Pearson chi-square and Student t-tests. The PCOS-testosterone cohort was also compared using multivariable analysis adjusted for age, BMI, and metformin status.

**Results:** For the case-control cohort PCOS patients had both significantly lower urinary sodium excretion (p = 0.015) and lower frequency of hypernatremia (28.9% vs 50.9%, p = 0.009). Within the PCOS-testosterone cohort, high testosterone patients had both significantly higher urinary citrate values (p = 0.041, table 3) and significantly lower odds of having hypernatremia (36.7% vs 52.4%, OR = 0.57, p = 0.001). These patients also had higher urinary sodium (p = 0.058) with significantly higher odds of having hypernatremia (40.0% vs 13.6%, OR = 13.3, p = 0.001). Stone composition analysis for either cohort did not reveal any statistically significant patterns.

**Conclusions:** When compared to matched cohort of healthy stone formers PCOS patients did not demonstrate significant enough changes in 24-hour urine and stone composition to indicate PCOS is an independent risk factor for stone formation. Elevated free testosterone in PCOS patients has a significant association with higher urinary citrate and sodium values; findings that in and of themselves do not confirm the hypothesized increased risk of stone formation. This patient cohort data provide deeper insight into the interplay between androgens and stone risk, however, further study is needed to fully confirm any hypothesized increased risk of stone formation in PCOS.

**PUBS87**

A Pilot Randomized Study Comparing Blumea Balsamifera (Sambong) and Terpenes on Ureterolithiasis

**Rommel P. Batalan, Medicine, San Antonio District Hospital, San Antonio, Philippines.**

**Background:** Other agents have been proposed to be given in the management of kidney or ureteral stones. This study aims to investigate the safety and efficacy of *Blumea balsamifera* (Sambong) in comparison with a terpene combination drug as treatment for ureterolithiasis.

**Methods:** Patients with clinically stable kidney function and ureter stones of ≤5mm were randomised to receive a special terpene combination (Rowatinex®; 2 capsules three times daily) or *Blumea balsamifera* 500mg tablet (2 tablets three times daily). The study consisted of a 12-week active treatment phase, in addition to standard management. All patients had a physical examination, and diagnosis of kidney stones was made by ultrasound at baseline and after 6 and 12 weeks of treatment. Primary outcomes are change in stone size and stone-free status as defined as obviously successful expulsion of calculus/fragments, documented by ultrasound.

**Results:** After 6 weeks, 5 patients in the Sambong group and 6 individuals in the Terpene group were stone free (p-value 0.90). After 12 weeks, 6 in Sambong group and 8 in the Terpene group were stone free (p-value 0.31). In terms of stone size, there was significant decrease in the mean value of stone size after 6 weeks (1.81±2.01mm, p-value 0.008) and 12 weeks (1.12±1.43mm p<0.005) in the Sambong group, and also with the Terpene group (At 6 weeks 1.24±1.43mm, p=0.005; at 12 weeks 0.74±0.70, p<0.005). However, there were no differences between the two groups. Urine pH also significantly increased in both groups compared to baseline but no statistical difference when comparing both arms, Frequency of pain, hematuria, change in serum parameters were also not statistically significant and no other adverse events were noted.

**Conclusions:** Treatment with *Blumea balsamifera* and Terpene combination are well tolerated and safe patients with Urolithiasis. Further studies may be warranted, with inclusion of other urine parameters.

**PUBS88**

Oxalate Nephropathy: A Systematic Review and Individual Patient Data Meta-Analysis of Case Reports and Case Series

**Nuttha Lumlertgul, 1 Siribumrungwong, 2 Paweena Susantitaphong, 3 Berlard L. Jaber, 3 Chulalongkorn University, Bangkok, Thailand; 2 Lerdsin Hospital, Bangkok, Thailand; 3 St. Elizabeth's Medical Center, Boston, MA.**

**Background:** Little is known of oxalate nephropathy. The aim of this systematic review and individual patient data meta-analysis is to perform an in-depth review on the state of the evidence on oxalate nephropathy and its association with oxalate intake, and provide a more precise estimate of clinical characteristics and outcomes through pooling of aggregate data and analysis of individual patient data.

**Methods:** The following electronic databases were searched for relevant citations: PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (inception to November 2016). We included case reports, case series, case control studies, and retrospective and prospective cohort studies that describe individual cases or cohorts of patients with evidence of biopsy-proven oxalate nephropathy in the setting of native or transplanted kidneys.

**Results:** Seventy-nine case report and case series (150 patients) were included. Twenty-three (15%) cases involved kidney transplant recipients. The mean age was 51.3±17.9 years. Increased dietary oxalate intake through excessive consumption is the most common cause (52%) followed by increased oxalate availability in the colon due to decreased intestinal calcium availability from malabsorption (47%), 3% resulted from decreased intestinal oxalate degradation due to decreased intestinal colonization with oxalobacter formigenes, leading to increased colonic permeability to oxalate. Seventy-seven percent had acute kidney injury, 9% had acute-on-chronic kidney disease, 3% had chronic kidney disease and 11% had stones. Sixty percent needed dialysis and 29% had complete recovery, 25 % had partial recovery, 46% had non-recovery of kidney function and 31% required dialysis dependence. The mortality rate was 22%.

**Conclusions:** The main etiology cause was the increased dietary oxalate intake through excessive consumption. Most people had acute kidney injury, needed dialysis requirement, and did not have renal recovery. Therefore, the prevention should be considered.

**PUBS90**

A Systematic Literature Review to Understand the Impact of Calcium-Containing Phosphate Binders and Sevelamer on Mortality and Cardiovascular Calcification in Patients with Renal Drug and Technology in Health suggests that M. Urich,1 Lorea,2 and 3 clinically effective than calcium-carbonate in all scenarios involving a subset of prescriptive or non-prescriptive dependent CKD patients.

**Funding:** Commercial Support - SANOFI-AVENTIS CANADA INC

**PUBS90**

Atypical Case of Calciphylaxis in a Renal Transplant Recipient

**Brittany L. Schreiber, Muhammad A. Mujtaba. University of Texas Medical Branch, Galveston, TX.**

**Background:** Calciphylaxis is a rare, life-threatening condition with insidious onset and significant morbidity and mortality. Traditionally, it is associated with chronic kidney disease-mineral bone disease, hyperparathyroidism, high calcium phosphate product, and vitamin D administration. We present a unique case of calciphylaxis in a renal transplant recipient with normal renal function.

**Methods:** A 42-year-old female with a history of secondary hyperparathyroidism status-post parathyroidectomy and ESRD on hemodialysis for 10 years status-post renal transplantation with normal renal function presented with a 7-month history of intractable lower extremity pain followed by a non-healing cutaneous ulcers 4 months after transplantation. Initially she was referred to dermatology and underwent a punch biopsy which showed epidermal and dermal necrosis with acute inflammation and leukocytic invasion. Infectious work up was negative. One week later she was admitted to the hospital for worsening pain and presence of new ulcerations. Repeat punch biopsy at that time showed results consistent with prior biopsy. She received a taper of steroids and was discharged with wound care and analogues. For the next 2 months, she was admitted multiple times with inpatient work up including vascular studies, bone scan, and EMG/Nerve conduction studies performed for lower extremity pain and weakness, all of which were unremarkable. Despite low intact-PTH and calcium-phosphate product levels ranging from 13.7 to 20.4 mg/dL and 20.8 to 36.5 respectively, based upon high clinical suspicion a diagnoses of calciphylaxis was entertained and the patient was started on sodium thiosulfate. A repeat punch biopsy was performed which revealed vascular congestion in the dermis and subcutis with focal calcification consistent with a diagnosis of calciphylaxis.

**Results:**
**Conclusion:** A diagnosis of calciphylaxis should be considered as part of the differential diagnosis of patients with abnormal renal function and calcium-phosphate product. Recognition and diagnosis with prompt initiation of therapy in a setting with high clinical suspicion is crucial in patients with atypical mineral profiles or negative biopsy as delay in therapy can lead to worse outcomes with increased morbidity and mortality.

**PUB953**

**Establishment of Novel Mouse Model to Exhibit CKD – Mineral and Bone Disorder Associated with Hyperphosphatemia Takashi Tani,1,3 Hideo Orimo,1 Akira Shimizu,2 Shuichi Tsurukai,1 Department of Metabolism and Nutrition, Nippon Medical School, Bunkyo-ku, Japan; 3Department of Analytic Human Pathology, Nippon Medical School, Bunkyo-ku, Japan; 4Department of Nephrology, Nippon Medical School, Bunkyo-ku, Japan.

**Background:** CKD - mineral bone disorder (CKD-MBD), which mainly represents renal bone disease and cardiovascular disease, is a serious complication and risk factor of CKD-related mortality. Our aim was to develop a novel mouse model of CKD using an adenine-fed procedure to investigate the clinical course of MBD.

**Methods:** Eight-week-old C57BL/6J male mice were assigned to the following groups: control group, fed a standard chow for 6 or 12 weeks (C6 an C12); the CKD-normal phosphorus (NP) group, fed a chow containing 0.2% adenine, with normal (0.8%) phosphorus, for 6 or 12 weeks (A6 and A12); and the CKD-high phosphorus (HP) group, fed 6 weeks with the 0.2% adenine/0.8% phosphorus diet, followed by a chow with 1.8% phosphorus for 6 weeks. 4 weeks after adenine feeding, the corta and femur bone were scanned by computed tomography (CT) imaging and were evaluated histologically, while plasma was drawn for biochemical findings. mRNAs expressions of aortic lysates were quantified by qRT-PCR analysis.

**Results:** Blood levels of uric acid and serum creatinine were elevated in both CKD-NP and CKD-HP group than control, while serum phosphorus and intact parathyroid hormone were significantly increased in the CKD-HP than CKD-NP mice and control. MAC was confirmed only in CKD-HP mice by histological (positive Von-Kossa and Alizarin Red staining) and CT imaging, and the volume of MAC increased with longer exposure to the high phosphorus feed. MAC formation in CKD-HP mice was associated with upregulation in run-related transcription factor 2 (Runx2), tissue non-specific alkaline phosphatase (TNAP) and osteopontin (OPN), indicative of osteoblastic trans-differentiation of vascular smooth muscle cells. CT and histological imaging revealed that the calcification in the femur was particularly thinned in CKD-HP mice; significant depletion in mineral density/volume of the cortical bone of the femur in CKD-HP mice was observed.

**Conclusions:** Our results support a previously-reported strong influence of hyperphosphatemia for the formation of CKD-MBD. Our novel CKD-MBD model is enhanced by its recapitulation of CKD-MBD in patients with end-stage renal disease in practice, without any surgical or transgenic interventions. We expect this model to be of value advancing research in the field of CKD.

**PUB954**

**Vascular Calcification and Cardiac Function According to Residual Renal Function in Patients on Hemodialysis with Urination Dong Ho Shin,1 Jung-woo Noh,2 Jeonghwan Lee.1 College of Medicine, Hallym University, Seoul, Republic of Korea; 2Hallym University Hangang Sacred Heart Hospital, Seoul, Republic of Korea; 3Hallym University, Seoul, Republic of Korea.

**Background:** Vascular calcification (VC) is common and may affect cardiac function in patients with end-stage renal disease (ESRD). However, little is known about the effect of residual renal function (RRF) on VC and cardiac function in patients on hemodialysis (HD).

**Methods:** This study was conducted between January 2014 and January 2017. One hundred sixty six patients with RRF on maintenance HD for 3 months were recruited. We used residual renal urea clearance (KRU) to measure RRF. First, abdominal aortic calcification score (AACS) and brachial-ankle pulse wave velocity (baPWV) were measured in patients on HD. Second, we performed echocardiography and investigated new cardiovascular events after study enrollment.

**Results:** The median KRU was 0.9 (0.3 – 2.5) mL/min/1.73m². AACS (4.0 [1.0 – 10.0] vs. 3.0 [0.0 – 8.0], P = 0.05) and baPWV (1836.1 ± 250.4 vs. 1676.8 ± 311.0 cm/s, p = 0.01) were significantly higher in patients with a KRU < 0.9 mL/min/1.73m² than a KRU ≥ 0.9 mL/min/1.73m². Log-KRU significantly correlated with log-AACS (ß = -0.33, p < 0.001) and baPWV (ß = -0.23, P = 0.01) after factor adjustment. The proportion of left ventricular diastolic dysfunction (LVDD) was significantly higher in patients with a KRU < 0.9 mL/min/1.73m² than with a KRU > 0.9 mL/min/1.73m² (67.9 % vs. 49.1%, p = 0.05). Patients with a KRU < 0.9 mL/min/1.73m² showed a higher tendency of cumulative cardiovascular events compared to those with a KRU > 0.9 mL/min/1.73m² (P = 0.08).

**Conclusions:** RRF was significantly associated with VC and LVDD in patients on HD.

**PUB955**

**Evaluation of Major Factors for Vascular Calcification in Patients with Hemodialysis Yoshitomo Nii, Hitoshi Suzuki, Masao Kihar, Yusuke Suzuki. Nephrology, Juntendo University Faculty of Medicine, Tokyo, Japan.

**Background:** Vascular calcification is the common complication in patients with end-stage of kidney disease (ESKD) and is high risk of cardiovascular disease and stroke. In present study, we investigated the clinical parameters for vascular calcification in patients with hemodialysis.

**Methods:** The vascular calcification was quantified as an Aortic Arch Calcification Score (AoACS) by chest X-ray, as previously reported (Hemodial Int 2009). AoACS was measured in forty hospitalized patients with hemodialysis. Forty patients were divided into two groups depending on the AoACS; high AoACS group as a mean ± 1SD, low

---

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

Underline represents presenting author.
Carotid Calcium Score Is Associated with Coronary Calcium Score in Patients with ESRD on Hemodialysis Chi-Young Choo,1 Nam-Jun Cho,1 Hyo-Wook Gil,2 Soonchunhyang University Cheonan Hospital, Cheonan, Republic of Korea; 2 Soonchunhyang university Cheonan Hospital, Cheonan, Chungcheongnam-do, Republic of Korea.

Background: In patients with end-stage renal disease (ESRD) on hemodialysis (HD), the degree of coronary calcium score is associated with cardiovascular risk and mortality. Those with higher degree of carotid calcium score are known to have higher cerebrovascular risk and mortality. However, there is no study which evaluates a correlation between coronary artery calcium score and carotid calcium score.

Methods: This is a cross-sectional study involving ESRD patients who were dialyzed in Soonchunhyang Cheonan Hospital and agreed to participate in the study. Brain computed tomography (CT) and heart CT were performed to evaluate the carotid and coronary calcium score, and the routine laboratory data in artificial kidney center were evaluated.

Results: Total 49 patients were included. A mean age of the group was 58.5 ± 12.1 year, and a mean duration of HD 67.7 ± 44.2 months. Serum calcium, phosphorus, intact parathyroid hormone, and alkaline phosphatase (ALP) levels were 8.9 (8.6 – 9.1) mg/dL, 4.1 ± 1.4 mg/dL, 241.5 ± 173.9 mg/dL, and 63 (46 – 87) IU/L, respectively. Carotid and coronary calcium score were noted as 125.7 (233.6 – 366.7) and 172.6 (72 – 798.7), respectively. The patients were divided into two groups, < 50 or a 50 percentile, based on carotid calcium score. Among the variables, there was a significant difference in age (< 50 percentile, 51.8 ± 8.9; ≥ 50 percentile, 65.2 ± 10.9) year between the two groups. The partial correlation analysis showed that a correlation between coronary artery calcium score and carotid calcium score was statistically significant (r = 0.556, p < 0.001), when the age was set as confounding variables.

Conclusions: In patients with ESRD on HD, coronary calcium score was correlated with carotid calcium score in patients with ESRD on HD.

Funding: Government Support - Non-U.S.

PUB599

Coronary Artery Calcium (CAC) Score, CAC Volume, and CAC Density in Relation to Cardiovascular Disease (CVD) and Mortality in CKD Patients Dai Lu,1 Hideyuki Mukai,1 Chen Zhimin,2 Bengt Lindholm,3 Janos Ripperger,1 Torkel Ohlsson,1 Olaf Heimburger,1 Peter F. Barany,1 Peter Stenvinkel,1 Abdul Rashid T. Qureshi,1 Renal Medicine and Baxter Novum, Karolinska Institutet, Djursholm, Sweden; 21st Affiliated Hospital College of Medicine, Zhejiang University, Hangzhou, China; 3Medical Imaging and Technology, Karolinska Institutet, Stockholm, Sweden.

Background: A high content of CAC measured by computed tomography (CT) associates with increased mortality with Agatston score of CAC being weighted upward for greater calcium density. However, increased calcium density in plaques may be CVD predictor. Here we investigated association of CAC score, CAC volume, and CAC density with presence of CVD and all-cause mortality risk in CKD patients (pts).

Methods: In 201 CKD pts (median age 56 years old, 66% male, 22% diabetes; 97 non-dialyzed, 104 on dialysis) who underwent multi-slice CT, CAC parameters (CACP) were evaluated by Calcium Scoring (S). Framingham’s CVD risk score (FRS) and CACP were analyzed as classifiers of CVD and as predictors of all-cause mortality. Agreement between CAC score and FRS was assessed by weighted kappa calculation. Kaplan Meier and multivariate Cox models evaluated association of mortality with CACP and FRS. During follow-up for a median of 25 months, there were 34 deaths.

Comparison between gender and renal function replacement therapy

PUB598

Prevalence of CKD-Mineral Bone Disorder (CKD-MBD) in Mexico Enrique Rojas-Campos1, Laura Cortes-Sanabria2, Clemencia E. Calderon Garcia3, Alejandro Silva Oceguera4, Alfonso M. Cueto-Manzano4, Instituto Mexicano del Seguro Social, Guadalajara, Mexico; 1Instituto Mexicano del Seguro Social, Guadalajara, Jalisco, Mexico; 1Mexican Social Security Institute, Guadalajara, Mexico; 2Zapopan, Jalisco, Mexico. Group/Team: Unidad de Investigación Médica en Enfermedades Renales.

Background: CKD-MBD includes bone alterations (remodeling/mineralization), biochemical, (calcium, phosphorus, 25-OH-vitamin D, parathormone), and presence of extra bone calcifications. It is not completely known the epidemiology of MBD-CKD in Mexico. Aim: To determine the prevalence of MBD-CKD in our country.

Methods: Cross-sectional analytical study, performed in 333 patients with diagnosis of Chronic Kidney Disease with renal function replacement therapy what hemodialysis or peritoneal dialysis, between January of 2014-June of 2016. There was no distinction between gender or causes of CKD. The comparisons were performed with χ² or Student’s T. A p value <0.05 was considered adequate.

Results: Fifty one percent (n 168) was men, 38% in hemodialysis and 62% in peritoneal dialysis. The prevalence of vascular calcification was 48%; hyperparathyroidism (PTH >300 pg/mL) was 62%, and the prevalence of deficiency of vitamin D (<15 ng/mL) was 27%.

Conclusions: The prevalence of vascular calcification was similar to the results of other national studies. The prevalence of hyperparathyroidism was close to two thirds. The deficiency of vitamin D was just in one of each four patients.

Table 1. Comparison between gender and renal function replacement therapy

Table 1. Gamma Models
Results: CAC score (S) and CAC volume (V) associated with FRS (rho=0.72, CVD: rho=0.43), hsCRP (rho=0.37) and IgG-1 (rho=0.38; p<0.149) and various medical markers. CAC density was associated with male sex (rho=0.20). In AUC calculation, classifier of CVD by CAC score (S) (AUC=0.81), Volume (V) (AUC=0.81) and Density (S) (AUC=0.70). AUC for predictor of all-cause mortality CAC score (S) (AUC=0.81), Volume (S) (AUC=0.81) and Density (S)(AUC=0.62). The Inlog CAC volume and density scores in the same multivariate linear model, the Inlog CAC showed an independent association with all-cause mortality, with a HR of 6.93 (95%CI, 2.25-21.33) per 1 SD increase. Conversely, CAC density showed an independent inverse association, with an HR of 0.80 (95%CI) per 1 SD decrease.

Conclusions: Whereas high CAC volume predicted increased mortality, high CAC density independently associated with decreased mortality suggesting that CAC density should be considered in evaluations of CAC scoring.

Funding: Commercial Support - Baxter Healthcare Corporation, Government Support - Non-U.S.

PUB601

Professionalism and Privacy of Pediatric Residents' Facebook Profiles

Method: Students were asked to create a Facebook profile. The profile included basic information (name, gender, year of residency) and personal information (phone number, address, email, friends, groups). Facebook profiles were analyzed using privacy settings and post content.

Results: Of 337 residents, 323 (75%) had a Facebook profile. Of those, 160 (49%) had a public profile. The majority of profiles were public with information from the “info” section, photos, albums, friends, groups, and locations viewable. Almost half of residents (48%; n=111) had been endangered by someone else. The majority of residents had their profiles set to private.

Conclusions: Social media is a powerful tool for residents to connect with each other. However, it is important to maintain privacy and protect personal information when using social media.

Funding: Clinical Revenue Support

PUB602

Aerospace of AKI Risk Factors and Perspective toward Its Practice Guideline

Method: A cross-sectional survey-based by using online survey program which let us create a link that can be electronically mail to the healthcare professionals (physicians and nurses) during Dec 2016 – Feb 2017 at King Abdulaziz Medical City (KAMC), Riyadh, Saudi Arabia.

Results: 117 physicians and 135 pharmacists completed the survey. The vast majority of respondents were aged ≥ 38 years (78%), 57% were males, and had <9 years of experience (70%). Among 25 risk factors of AKI and 15 drugs may cause AKI, there was a large variation between respondents in term of awareness of AKI risk factors and the drugs that may cause AKI e.g.90% were aware of nephrotoxic medication whereas 20% agreed on female gender and 92% agreed on amnoglycoside but 47% agreed on ceftriaxone. In general, significantly higher percentage of physicians identified individual AKI risk factors than pharmacists, however slightly higher percentage of pharmacists identified individual AKI causing drugs than physicians. Variations were observed between the 2 professions and the profession level. Although the majorities face AKI cases in their practice (77%), only half of them do AKI risk assessment, 42% stratify patients’ AKI risk according to their offending risk factors, or document AKI as past medical history. 71% agreed that practice guidelines improve patient outcome and 69% thought that these guidelines help standardized care and ensure that patients are treated in a consistent way only 69% defined AKI as per KDIGO AKI criteria. 87% did not receive any continuous medical educations hours on AKI.

Conclusions: While the majority of respondents had a positive perspective toward AKI guidelines, a large variation in awareness of AKI risk factors, risk assessment, and the drugs that may cause it was detected. Educational efforts are needed to raise awareness and knowledge to reduce the variation.

PUB603

Formative Learning in Medicine Integrated to the Primary Health Care: Pedagogical Innovation for the Prevention of CKD in Brazil

Method: Teachers from medical public school located in southeast of Brazil developed integrated teaching strategies to primary care units for CKD prevention. Those strategies were: health team training, education of the local community on CKD and its prevention, understanding mechanisms for health assurance and disease prevention. The aim of this study was to present a educational programs that prepares medical students and a health team to identify individuals at risk for developing chronic kidney disease (CKD).

Results: 117 physicians and 135 pharmacists completed the survey. The vast majority of respondents were aged ≥ 38 years (78%), 57% were males, and had <9 years of experience (70%). Among 25 risk factors of AKI and 15 drugs may cause AKI, there was a large variation between respondents in term of awareness of AKI risk factors and the drugs that may cause AKI e.g.90% were aware of nephrotoxic medication whereas 20% agreed on female gender and 92% agreed on amnoglycoside but 47% agreed on ceftriaxone. In general, significantly higher percentage of physicians identified individual AKI risk factors than pharmacists, however slightly higher percentage of pharmacists identified individual AKI causing drugs than physicians. Variations were observed between the 2 professions and the profession level. Although the majorities face AKI cases in their practice (77%), only half of them do AKI risk assessment, 42% stratify patients’ AKI risk according to their offending risk factors, or document AKI as past medical history. 71% agreed that practice guidelines improve patient outcome and 69% thought that these guidelines help standardized care and ensure that patients are treated in a consistent way only 69% defined AKI as per KDIGO AKI criteria. 87% did not receive any continuous medical educations hours on AKI.

Conclusions: While the majority of respondents had a positive perspective toward AKI guidelines, a large variation in awareness of AKI risk factors, risk assessment, and the drugs that may cause it was detected. Educational efforts are needed to raise awareness and knowledge to reduce the variation.
Lifestyle Management for People with CKD

Background: Self-management program involves initiative participation in the daily care of their discomforted symptoms, medical treatments, as well as maintainance healthy lifestyles and prevention of progression of diseases for the patients with chronic diseases.

Patient engagement and self-management are the cornerstones of optimal chronic disease management. These programs are designed to encourage patients to be expert patients so as to improve outcomes.

Methods: The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PubMed, Chinese National Knowledge Infrastructure(CNKI), China Biology Medicine disc(CBM), and China Biology Medicine disc and Chinese Scientific Journals full text database (CQVIP) were searched (up to January 2017) for randomized controlled trials (RCTs) assessing the effectiveness of lifestyles related self-management programs for people with chronic kidney disease (CKD) by two independent authors. Meta-analysis was conducted to compare the effects of interventions.

Results: Eight studies (n=585 patients) were included. Across these trials, self-management programs resulted in a significant difference in glomerular filtration rate (GFR, Mean Difference 2.27, 95% CI 1.90 to 2.65 ml/min; I²=4%). Compared with usual care only, the intervention resulted in -7.97% (95% CI -1.82 to -1.58) and -2.98% (95% CI -3.28 to -2.69 mmHg) mean changes in systolic and diastolic BP, with moderate heterogeneity across the included studies (I² = 42%, P = 0.18) and a mean change of -2.80% (95% CI -3.31 to -2.28) ml/min in C-reactive protein (CRP) with no evidence of heterogeneity (I² = 0.0%, P = 0.58). Meta-analysis results for total cholesterol (TC), low-density cholesterol (LDL-C) and hemoglobin failed to show a difference between the lifestyle related self-management intervention of CKD and the usual standard care.

Conclusions: To date, there have been very few randomized trials testing self-management interventions targeting lifestyle care with the goal of delaying the progression of CKD. Those conducted to date have shown a clinically moderate but significant impact, longer follow-up is needed to determine if these findings will translate into delaying the progression of CKD. Suggesting that other strategies, or multi-faceted interventions, may be required to enhance the management of risk factors for patients with CKD in the community.

Funding: Government Support - Non-U.S.

PUB604

Lifestyle Management for People with CKD


Background: Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common inherited diseases that frequently progresses to end-stage renal disease (ESRD) at a relatively young age. Herein, we present a case of an 87-year-old man with ADPKD in whom optimal management of risk factors for progression of chronic kidney disease (CKD) has halted the progression of his disease.

Methods: In 2001, a 71-year-old Caucasian man was seen for flank pain after a fall. He was found with hypertension, renal dysfunction, and enlarged kidneys that were filled with innumerable cysts on the ultrasound as well as multiple cysts in the liver. Family history was positive for ADPKD; at least 2 of the siblings were known to have renal cysts (father had died at the age of 55 in an accident). He had no children. At that time, no family members were diagnosed with ESRD but over the next 10 years, one brother and one sister started dialysis. He quit smoking, was advised to increase his water intake to suppress cyst formation, and his hypertension was treated with an angiotensin-converting enzyme inhibitor (ACE-I) and a thiazide diuretic with optimal control. Three years later, he developed a hemorrhagic cyst that could be managed conservatively. Since then, the patient has been doing excellent: although he is 87 years old, the rate of progression of his CKD could be significantly reduced due to optimal management of risk factors (e.g. blood pressure 120-140/60-70, albuminuria 180 mg/day, and bicarbonate level 25 mmol/L). His estimated glomerular filtration rate has reached 21 ml/min.

Results: The severity of renal involvement varies considerably among ADPKD patients; repressing the importance of factors that are independently associated with worse renal outcomes (e.g. male gender and hypertension). Although clinical symptoms of renal disease can appear at any age, the first symptoms most often appear in the 4th or 5th decade and then progress rapidly; the mean age of ESRD has been reported between 56 and 69. This case represents one of the oldest patients with ADPKD whose CKD progression rate could be successfully reduced, underscoring the importance of modifiable risk factors in management of this hereditary disease that is known to be progressive.

Funding: Government Support - Non-U.S.

PUB607

A Rare Side Effect of the Commonly Used Anti-Hypertensive Medication Indirakshi Jamalpur, Abhillaish Koratala, Srij Padmavathi Medical College for Women, Tirupati, India; 1University of Florida, Gainesville, FL.

Background: Drug-induced gingival enlargement (DIGE) was first described in patients taking anti-convulsive drug, Phenytoin. The three most common classes of medications implicated are anti-convulsives, calcium channel blockers (CCBs), and anti-hypertensive drugs. In patients who are on predisposing medications, DIGE should be suspected when they present with enlarged gums.

Methods: A 50-year-old male has presented to the clinic complaining of enlarged gums in the upper and lower front jaws for 2 months. His medical history was significant for hypertension and diabetes mellitus type 2. He denied any fever, bleeding from the gums, loosening of the teeth, use of any prosthesis or dental braces. He did not have any history of dental procedures in the recent past. His medications included enalapril 10mg bid, amlopidine 10mg per day (for 6 months), sitagliptin 100mg per day and glipizide 20mg per day. Oral examination revealed marginal and interdental gingival enlargement, predominantly involving maxillary and mandibular anterior teeth [Figure 1A]. The enlargement was firm, non-tender with no bleeding on probing. Poor dental hygiene was noted. Laboratory tests were unremarkable including a negative HIV test. We diagnosed Amlodipine induced gingival enlargement and the patient showed slight but notable improvement in 4 weeks after switching amlodipine to long acting thiazide diuretic [Figure 1B].

Results: While DIGE is a well-known side effect of CCBs, the incidence varies among different agents. For example, in a study by Ellis et al., the risk for developing clinically significant gingival enlargement was found to be higher in those treated with nifedipine (6.3%), compared to patients taking either amlopidine (1.7%) or diltiazem (2.2%). Treatment primarily consists of withdrawing the offending agent whenever possible in addition to maintenance of good oral hygiene. It may take from 1-8 weeks for resolution of gingival overgrowth after discontinuing the drug.

Funding: Government Support - Non-U.S.

PUB608


Background: In the current era of early detection of chronic kidney disease and efficient therapeutic options for management of its complications, skeletal manifestations of secondary hyperparathyroidism are increasingly rare. Herein, we present a case of secondary hyperparathyroidism that presented with brittle bones and characteristic radiographic changes.

Methods: A 31-year-old female patient presented for evaluation of pain in the left forearm, right hand, right knee, right hip and lower back following a fall sustained 3 days prior to presentation. She had a past medical history notable for ESRD on hemodialysis for the past 15 years, hypertension, diabetes, and congestive heart failure. She was wheelchair bound due to disabling diabetic neuropathy and chronic leg pain. She reported multiple prior fractures that were managed conservatively. Review of the medical records revealed that she had poor compliance with her diet, medications, and dialysis treatments. Labs were significant for marked elevation in serum parathyroid hormone level (1735 pg/mL) as well as hyperphosphatemia and normal serum calcium levels. X-ray images showed generalized severe demineralization of the extremities with the pelvic CT scan revealing presence of diffuse brown tumors [Figure 1]. In addition, she had insufficiency fractures of the extremities that left her incapacitated and had to be managed conservatively due to her poor functional status and ongoing severe hyperparathyroidism. Unfortunately, the patient refused surgical removal of the parathyroid glands and was hence treated with a high dose phosphate binder and a calciummic agent together with reinforcement of compliance.

Results: Our case highlights the importance of metabolic assessment of patients presenting with unexpected bone complications and can be used to raise awareness of the physicians on the extreme cases of mineral bone complications secondary to renal disease that are observed rarely.
Silent Hyperoxaluria Contributes to CKD Progression in a Patient with Short Bowel

Methods: A 38 year-old male with a 5 year history of seizure disorder currently on Levetiracetam/Oxcarbazepine and Citalopram, past history of schizophrenia admitted on Levetiracetam/Oxcarbazepine and Citalopram, past history of schizophrenia admitted with rare renal involvement. CD associated granulomatous interstitial nephritis (GIN) is a chronic recurrent inflammatory condition with rare renal involvement. CD associated granulomatous interstitial nephritis (GIN) is even more rare and has only been described in a few case series and reports. CD associated GIN typically occurs in the setting of recent mesalamine exposure, new onset CD, or exacerbation of existing CD. We report a case of GIN due to CD in the absence of clinically apparent GI symptoms.

Methods: A 19-year-old male with a history of biopsy-proven CD and hypertension (HTN) was controlled with dietary modifications, presented for a second opinion regarding acute kidney injury (AKI). One month prior, his serum creatinine (Cr) had increased from a baseline of 1.3mg/dL to 2.6mg/dL. He did not have recent nephrotoxin exposure, new or chronic medication use, chronic cough or acute illnesses. His physical exam was unremarkable, he was asymptomatic and normotensive (not on medications). Urine studies showed microscopic hematuria (1+) and microalbuminuria (48.7mg/g). Serum calcium, sedimentation rate and calcitriol levels were normal. Renal imaging with Doppler analysis was unremarkable. Serologic work-up for a nephritogenic process was negative. The kidney biopsy showed diffuse non-casing granulomatous inflammation with no immune complex deposition or microorganisms. Vessels were unremarkable. Based on these findings, we determined that his GIN was due to CD. He received pulse steroids and his serum Cr decreased to 2.64 mg/dL. Due to steroid dependence, adalimumab was initiated. Steroids were tapered off and his serum Cr decreased to 1.6mg/dL after 5 months on adalimumab.

Results:

Conclusions: This case emphasizes the need to recognize and further explore the association between CD and GIN given the potential long term adverse renal outcomes if treatment is delayed. Early nephrology consultation may be advisable in CD patients with mild renal dysfunction or abnormal urine studies regardless of CD symptom control.

PUB611
Granulomatous Interstitial Nephritis in Diet-Controlled Crohn’s Disease

Background: Crohn’s disease (CD) is a chronic recurrent inflammatory condition with rare renal involvement. CD associated granulomatous interstitial nephritis (GIN) is even more rare and has only been described in a few case series and reports. CD associated GIN typically occurs in the setting of recent mesalamine exposure, new onset CD, or exacerbation of existing CD. We report a case of GIN due to CD in the absence of clinically apparent GI symptoms.

Methods: A 19-year-old male with a history of biopsy-proven CD and hypertension (HTN) was controlled with dietary modifications, presented for a second opinion regarding acute kidney injury (AKI). One month prior, his serum creatinine (Cr) had increased from a baseline of 1.3mg/dL to 2.6mg/dL. He did not have recent nephrotoxin exposure, new or chronic medication use, chronic cough or acute illnesses. His physical exam was unremarkable, he was asymptomatic and normotensive (not on medications). Urine studies showed microscopic hematuria (1+) and microalbuminuria (48.7mg/g). Serum calcium, sedimentation rate and calcitriol levels were normal. Renal imaging with Doppler analysis was unremarkable. Serologic work-up for a nephritogenic process was negative. The kidney biopsy showed diffuse non-casing granulomatous inflammation with no immune complex deposition or microorganisms. Vessels were unremarkable. Based on these findings, we determined that his GIN was due to CD. He received pulse steroids and his serum Cr decreased to 2.64 mg/dL. Due to steroid dependence, adalimumab was initiated. Steroids were tapered off and his serum Cr decreased to 1.6mg/dL after 5 months on adalimumab.

Results:

Conclusions: This case emphasizes the need to recognize and further explore the association between CD and GIN given the potential long term adverse renal outcomes if treatment is delayed. Early nephrology consultation may be advisable in CD patients with mild renal dysfunction or abnormal urine studies regardless of CD symptom control.

PUB612
Cefepime Induced DRESS Syndrome without Eosinophilia

Background: Approximately 60-70% cases of acute interstitial nephritis (AIN) are drug-induced. Multiple agents from different drug classes can cause AIN and the clinical presentation and laboratory findings vary based on the class of drug. We report a case of AKI and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome without eosinophilia, associated with cefepime.

Methods: A 62-year-old man with poorly controlled diabetes mellitus developed osteomyelitis of the foot and was prescribed intravenous antibiotic therapy with vancomycin 1g every 12 hours and cefepime 6g continuous infusion for an intended duration of 6 weeks. The patient tolerated this regimen well until a few days prior to the end of therapy. He presented to the hospital with fatigue, anorexia, morbilliform rash and fever. Labs demonstrated AKI with a SCr of 3.6 mg/dL (baseline 0.8), transaminitis and leukocytosis. Peripheral smear revealed vacuolated neutrophils and atypical lymphocytes, but no eosinophilia. Urine microscopy revealed multiple WBC casts. He was diagnosed with DRESS. Serum complements were normal and was started on empiric steroid therapy with prednisone 1mg/kg/day. SCr continued to worsen requiring dialysis. After 10 days of prednisone therapy, the patient’s renal function began to improve and he is currently off dialysis. Renal biopsy was consistent with AIN and skin biopsy with DRESS [Figure 1].

Results:

Conclusions: DRESS is an idiosyncratic hypersensitivity response to drugs defined by presence of at least 3 of the following findings: cutaneous eruption, fever, lymphadenopathy, systemic symptoms involving internal organs, hematologic abnormalities (atypical lymphocytes, eosinophilia). Cefepime is a rare cause of DRESS syndrome and can present without eosinophilia. Although there are no clear guidelines regarding dose and duration of steroid therapy, early initiation of steroid therapy has been shown to hasten recovery of renal function in drug-induced AIN.
Acute Interstitial Nephritis in a Patient with Urothelial Carcinoma on Pembrolizumab: A Programmed Cell Death 1 Inhibitor

**Background:** Pembrolizumab, a PD-1 inhibitor was recently approved for all solid tumors with a specific genetic biomarker. There are several case reports of PD-1 inhibitors induced acute interstitial nephritis (AIN) in the setting of lung, melanoma, and pancreatic cancers. We present a patient with AIN while being treated with pembrolizumab for urothelial carcinoma.

**Methods:** A 61-year-old man with a history of atrophic left kidney, CKD 3a, and urothelial carcinoma developed AKI. Nine months after starting Pembrolizumab serum creatinine increased from 1.3 mg/dl to 5 mg/dl (figure). His 14th cycle was held due to vomiting, diarrhea, and AKI, and he was hospitalized. Examination was notable for BP of 103/59 mm Hg, HR 59 beats/min, and dry mucous membranes. Urine sediment showed non-dysmorphic RBCs, clumps of WBC, and no casts. Renal ultrasound showed mild right hydronephrosis and atrophic left kidney. A Foley catheter was placed for decompression. He was volume resuscitated, omeprazole and losartan were discontinued, but creatine continued to rise. After discussion regarding the higher than typical risk, a kidney biopsy was performed. The biopsy revealed AIN. Corticosteroids were started with improvement in serum creatinine (figure).

**Results:** Although rare, treatment with PD-1 inhibitors has been associated with AIN. Similar to previous case reports, our patient was also taking a second medication associated with AIN, omeprazole. Researchers hypothesize that PD-1 inhibition may lower the threshold for concomitant immunogenic agents like proton pump inhibitors to cause AIN. Despite high risk, biopsy was especially necessary prior to treatment of AIN in setting of chronic sterile pyuria related to urothelial carcinoma. Steroids and discontinuation of the PD-1 inhibitor have been shown to be effective in management of PD-1 induced AIN.

**Conclusions:** Additional cases need to be assessed to discern the true incidence of AIN with PD-1 inhibitor use in urothelial carcinoma.
Methods: A 73-year-old woman with hypertension and heart failure has presented with generalized weakness for about 2 weeks leading to a fall at home. She was found to have severe hypercalcemia with a serum calcium of 16 mg/dL and acute kidney injury. CT scan of the chest was obtained to exclude malignancy. In addition to multiple pulmonary nodules, the upper abdominal slices of the scan demonstrated fullness of the left renal pelvis suspicious for hydronephrosis. Renal ultrasound was obtained to evaluate this finding, which demonstrated a large hypoechoic mass just outside the renal sinus but with no distortion of the calyces or the ureter [Figure]. This finding was consistent with extrarenal pelvis, which is often confused with hydronephrosis.

Results:

Conclusions: An extrarenal pelvis is a normal anatomical variant that is predominantly outside the renal sinus and is larger and more distensible than an intrarenal pelvis that is surrounded by sinus fat. Extrarenal pelvis can easily be misinterpreted as hydronephrosis, especially on a quick bedside exam as it appears as a black mass. Close attention to detail can help differentiate between these two conditions. Hydronephrosis appears as branching, ‘interconnected’ areas of decreased echogenicity that show sonographic evidence of fluid. As the obstruction continues, renal parenchyma becomes compressed with loss of corticomedullary differentiation. On the other hand, extrarenal pelvis is not associated with dilated calyces, parenchymal thinning or hydronephrosis as in our case. In the figure, a medullary pyramid (line arrow) can be seen just above the central echogenic portion of the kidney suggestive of preserved corticomedullary differentiation and absence of compression. While extrarenal pelvis is asymptomatic in most cases, complications such as infection and stone formation have been reported.

PUB617
Escitalopram Induced Hyponatremia in a Young Post-Surgical Patient: Case Report
Rommel P. Bataclan, Medicine, University of the East Ramon Magsaysay Medical Center, Quezon City, Philippines.

Background: Hyponatremia is a rare adverse effect of Selective Serotonin Reuptake Inhibitors (SSRIs). These are medications given to individuals with Depressive Disorders and Panic Disorders. This presentation highlights the association of hyponatremia and use of Escitalopram in a post-surgical patient co-morbid with depression.

Methods: Patient is a 28-year old male who was admitted due to abdominal surgery from injuries incurred in a vehicular accident. Patient had panic attacks and was given Escitalopram. He was referred post-surgical due to restlessness and change of sensorium. Physical exam reveals a pale-looking patient with multiple abrasions and hematoma. He was drowsy, unable to respond from verbal cues. No focal deficits were noted. Serum Sodium was 121 mEq/L, Urine Osmolality 265 mOsm/kg, Urine Sodium 56 mEq/l and Urine Osmolality was 210 mOsm/kg. Rest of bloodworks and Cranial CT Scan were unremarkable. Escitalopram was discontinued, advised fluid restriction and 0.9% saline solution intravenously was given. Serum Osmolality was noted to be 265 mOsm/kg, Urine Sodium was 56mEq/l and Urine Osmolality was 210 mOsm/kg. On the initial 24 hours Escitalopram was discontinued, Serum Sodium was monitored three times, with values of 122, 124 & 125 mEq/l. Serum Sodium was normal (135 mEq/l), 72 hours after Escitalopram was discontinued. Diazepam was started as the anxiolytic drug, and patient’s subsequent course was unremarkable and discharged on 15th hospital day.

Results:

Conclusions: SSRI-induced hyponatremia is attributed to a syndrome of inappropriate antidiuretic hormone (SIADH) secretion induced by a non-osmotic release of anti-diuretic hormone. Risk factors for SSRI-induced SIADH include advanced age, female gender, concomitant diuretics, hyperkalemia, baseline hyponatremia, and lower body mass index, all of which are not present in our patient. The only definitive treatment for drug-induced SIADH is removal of the offending agent. Most cases resolve promptly upon drug discontinuation. This case, together with the other previous reports highlight the need to monitor serum sodium and other electrolytes when anti-psychotic medications is started. Monitoring of serum sodium concentrations at baseline and 1 to 2 weeks after initiation of SSRIs may be warranted in individuals at risk of SIADH.

PUB618
Hypovolemic Hyponatremia Masking Nephrogenic Diabetes Insipidus (DI)
Maria Clarissa Tio, Jitin Patel.1 Department of Medicine, University of Texas Southwestern Medical Center, Dallas, TX; 2Division of Nephrology, University of Texas Southwestern Medical Center, Dallas, TX.

Background: DI typically presents with hyponatremia and polyuria. We report a unique case of a patient with an unknown history of DI presenting with hyponatremia in the setting of abdominal compartment syndrome and septic shock.

Methods: A 50-year old white female with bipolar disorder, remotely treated in a hospital setting in a partial hospitalization setting co-morbid with depression.

Results:

Conclusions: An extrarenal pelvis is normal anatomical variant that is predominantly outside the renal sinus and is larger and more distensible than an intrarenal pelvis that is surrounded by sinus fat. Extrarenal pelvis can easily be misinterpreted as hydronephrosis, especially on a quick bedside exam as it appears as a black mass. Close attention to detail can help differentiate between these two conditions. Hydronephrosis appears as branching, ‘interconnected’ areas of decreased echogenicity that show sonographic evidence of fluid. As the obstruction continues, renal parenchyma becomes compressed with loss of corticomedullary differentiation. On the other hand, extrarenal pelvis is not associated with dilated calyces, parenchymal thinning or hydronephrosis as in our case. In the figure, a medullary pyramid (line arrow) can be seen just above the central echogenic portion of the kidney suggestive of preserved corticomedullary differentiation and absence of compression. While extrarenal pelvis is asymptomatic in most cases, complications such as infection and stone formation have been reported.

PUB619
Granulomatosis with Polyangiitis (GPA) Presenting as Renal Vasculitis in a Patient with Crohn’s Disease
Judi M. Graham,1,2 Melissa S. Nataatmadja,1,2 Linda O. DeLuca,2 Nephrology, University of British Columbia, Vancouver, BC, Canada; 1Nephrology, St Paul’s Hospital, Vancouver, BC, Canada.

Background: Anti-neutrophil cytoplasmic antibodies (ANCA), most commonly perinuclear ANCA (P-ANCA), is associated with inflammatory bowel disease (IBD), usually without evidence of systemic vasculitis. We describe a case of GPA with Crohn’s disease (CD) presenting as rapidly progressive glomerulonephritis.

Methods:

Results: A 51 year old man presented with fever and headache. Past history included chronic kidney disease with creatinine 120muM/L and normal urinalysis 6 months prior. CD was diagnosed 30 years earlier but had been quiescent for many years. On presentation, blood pressure was 187/87mmHg, creatinine 454umol/L, urine albumin/creatinine ratio (ACR) 66mg/mmol and dysmorphic erythrocytes seen in urine. C-ANCA was 160 and PR3 115U. Renal biopsy showed pauci-immune proliferative glomerulonephritis with a cellular crescent. Treatment commenced with intravenous then oral steroids, and oral cyclophosphamide- later replaced by rituximab due to bone marrow toxicity. Ten weeks later, creatinine was 197umol/L, PR3 10U, ACR 4.6mg/mmol with no urine erythrocytes. CD was diagnosed 30 years earlier but had been quiescent for many years. On presentation, blood pressure was 187/87mmHg, creatinine 454umol/L, urine albumin/creatinine ratio (ACR) 66mg/mmol and dysmorphic erythrocytes seen in urine. C-ANCA was 160 and PR3 115U. Renal biopsy showed pauci-immune proliferative glomerulonephritis with a cellular crescent. Treatment commenced with intravenous then oral steroids, and oral cyclophosphamide- later replaced by rituximab due to bone marrow toxicity. Ten weeks later, creatinine was 197umol/L, PR3 10U, ACR 4.6mg/mmol with no urine erythrocytes. CD was diagnosed 30 years earlier but had been quiescent for many years. On presentation, blood pressure was 187/87mmHg, creatinine 454umol/L, urine albumin/creatinine ratio (ACR) 66mg/mmol and dysmorphic erythrocytes seen in urine. C-ANCA was 160 and PR3 115U. Renal biopsy showed pauci-immune proliferative glomerulonephritis with a cellular crescent. Treatment commenced with intravenous then oral steroids, and oral cyclophosphamide- later replaced by rituximab due to bone marrow toxicity. Ten weeks later, creatinine was 197umol/L, PR3 10U, ACR 4.6mg/mmol with no urine erythrocytes. CD was diagnosed 30 years earlier but had been quiescent for many years. On presentation, blood pressure was 187/87mmHg, creatinine 454umol/L, urine albumin/creatinine ratio (ACR) 66mg/mmol and dysmorphic erythrocytes seen in urine. C-ANCA was 160 and PR3 115U. Renal biopsy showed pauci-immune proliferative glomerulonephritis with a cellular crescent. Treatment commenced with intravenous then oral steroids, and oral cyclophosphamide- later replaced by rituximab due to bone marrow toxicity. Ten weeks later, creatinine was 197umol/L, PR3 10U, ACR 4.6mg/mmol with no urine erythrocytes. CD was diagnosed 30 years earlier but had been quiescent for many years. On presentation, blood pressure was 187/87mmHg, creatinine 454umol/L, urine albumin/creatinine ratio (ACR) 66mg/mmol and dysmorphic erythrocytes seen in urine. C-ANCA was 160 and PR3 115U. Renal biopsy showed pauci-immune proliferative glomerulonephritis with a cellular crescent. Treatment commenced with intravenous then oral steroids, and oral cyclophosphamide- later replaced by rituximab due to bone marrow toxicity. Ten weeks later, creatinine was 197umol/L, PR3 10U, ACR 4.6mg/mmol with no urine erythrocytes. CD was diagnosed 30 years earlier but had been quiescent for many years. On presentation, blood pressure was 187/87mmHg, creatinine 454umol/L, urine albumin/creatinine ratio (ACR) 66mg/mmol and dysmorphic erythrocytes seen in urine. C-ANCA was 160 and PR3 115U. Renal biopsy showed pauci-immune proliferative glomerulonephritis with a cellular crescent. Treatment commenced with intravenous then oral steroids, and oral cyclophosphamide- later replaced by rituximab due to bone marrow toxicity. Ten weeks later, creatinine was 197umol/L, PR3 10U, ACR 4.6mg/mmol with no urine erythrocytes.
Steroid-Free Regimen for Primary Membranous Nephropathy with High Antibody Titer

Methods: A 34-years old male is admitted with a relapse of the NS. His past medical history included pMN diagnosed 2 years ago and bipolar disorder that precluded the use of corticosteroids. Therefore the patient was started on cyclosporine (5 mg/kg/day), while being on adequate RAS blockade, and the clinical course was fluctuating with partial remissions and relapses of the NS (proteinuria levels between 3 and 10 g/day). However after 18 month of therapy the patient voluntarily stopped the cyclosporine and soon after the NS relapsed. At the time of admission he presented edema, normal BP, while the laboratory results showed hypalbuminemia (1.9 g/dl), proteinuria 8g/day and eGFR of 87 ml/min. The patient was started on monthly cyclophosphamide pulse-therapy (0.75 g/m²) and low-dose cyclosporine (100 mg/d), while being on adequate RAS blockade for the past 18 months. After 2 months of multidrug regimen, proteinuria and antibody titer significantly decreased to 1.3 g/day and 210 IU/ml, respectively. Subsequent check-ups are shown in the table.

Results: The podocyte targeted effect of low-dose cyclosporine (rapid decline of proteinuria) in addition to the immunosuppressive effect of cyclophosphamide (decreased antibody titer) is associated with a rapid response in this particular patient. This multidrug regimen could be useful in patients with contraindications to corticosteroids and high antibody titer, but it needs to be validated in large clinical trials.

Patient Follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (mL/min)</td>
<td>97</td>
<td>59</td>
<td>64</td>
<td>97</td>
</tr>
<tr>
<td>Serum Albumin (g/dl)</td>
<td>3.9</td>
<td>3.3</td>
<td>3.3</td>
<td>3.6</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>8</td>
<td>3.34</td>
<td>1.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Anti-FBL antibody titer (UI/ml)</td>
<td>634</td>
<td>70</td>
<td>230</td>
<td>106</td>
</tr>
<tr>
<td>Cyclophosphamide (mg/d)</td>
<td>30</td>
<td>26</td>
<td>28</td>
<td>21</td>
</tr>
</tbody>
</table>

Oxalate Nephropathy Leading to ESRD Following Roux-en-Y Gastric Bypass

Background: Hyperoxaluria is a common and underappreciated complication of gastro-intestinal bypass surgeries. Calcium oxalate nephropathy is known to occur following jejunoileal bypass, and case series have reported oxalate nephropathy after Roux-en-Y gastric bypass. Here we report a case of calcium oxalate nephropathy occurring after Roux-en-Y gastric bypass for gastric adenocarcinoma leading to severe renal failure and end stage renal disease and outline potential strategies for prevention of future events.

Methods: An 83-year-old male with hypertension, type 2 diabetes mellitus, systolic heart failure (EF 45%), stage III CKD, and gastric adenocarcinoma status-post gastrectomy and Roux-en-Y esophagojejunostomy four months prior was admitted to our hospital with acute renal failure. He described new weakness, dysp蜉a, and loose stool. His creatinine was 9.3 mg/dL and arterial pH was 7.07. Renal ultrasound demonstrated a left-sided 1.3 cm non-obstructing stone. Urinary sediment showed rare renal tubular epithelial cells and granular casts. ANA, ANCA, C3, C4, SPEP, and UPEP were normal. He rapidly developed oliguria and uremia and was intitated on hemodialysis. Renal biopsy demonstrated advanced interstitial fibrosis, tubular atrophy, and calcium oxalate and calcium phosphate deposition. He never recovered renal function and was discharged on dialysis.

Results: Conclusions: While hyperoxaluria is known to occur after gastric bypass, oxalate nephropathy and severe renal failure are less frequently reported. Our patient developed ESRD four months after surgery. Prior series have reported acute renal failure developing at a mean of thirty-three weeks after surgery. One study reported progression to ESRD within three months of identification of renal failure in 72% of patients. We identified several factors that may have contributed to this rapid and severe course including underlying CKD, diuretic use, post-operative AKI, diarrhea, and poor oral intake. In light of this case and prior reports, we propose the following considerations for patients undergoing gastric bypass: a) heightened clinical suspicion post-operatively, b) patient and provider education on the risks of hyperoxaluria and oxalate nephropathy, particularly in states of volume depletion, c) close monitoring of volume status and post-operative renal function, and d) early referral to nephrology, particularly for at-risk patients.

Idiopathic Acute Renal Infarction

Background: Renal infarction (RI) is a rare and under-diagnosed condition resulting from a sudden disruption of blood flow in the renal artery. Estimated incidence is about 0.004% - 0.007%. We report a case of RI presenting with no identifiable cause.

Methods: A 51 year old man with a history of hypertension, diabetes, and nephrothiasis, presented with sudden onset, severe left flank pain radiating to the left groin. He had never smoked/used illicit drugs. He was afebrile and hypertensive (181/104 mm Hg) on presentation. EKG was normal. Labs: leukocytosis, high LDH(730 U/L) and CRP(33 mg/l). Urinalysis showed proteinuria and small blood. CT abdomen with contrast showed a region of non-enhancement in the left upper renal pole, suggestive of infarction. No aorto-renal vascular pathology was noted. Trans-esophageal echo was normal. Holter monitoring was uneventful. He had severe uncontrolled hypertension, requiring 4 medications including a calcium channel blocker. He was subsequently discharged on oral anti-coagulation.

Results:
Conclusions: RI usually occurs between the 6th and 8th decades of life. It commonly presents with abdominal pain, nausea, vomiting, with leukocytosis, CRRT, LDH, and microscopic hematuria. Severe and difficult-to-control hypertension is often seen in these patients, which is thought to be renin-dependent due to renal ischemia. Most patients have a history of prior cardio-embolic events such as atrial fibrillation (AF), valvular heart disease, ventricular aneurysm, endocarditis, and dilated cardiomyopathy. AF is the most common risk factor, found in about 64% cases. Other possible etiologies include vasculitis, coagulopathies, aorto-renal vascular pathology, and trauma. However, the cause may remain undefined in up to 29% of the cases. Clinical diagnosis of RI is difficult due to its non-specific presentation. Ultrasound is very low yield. Contrast enhanced CT is the gold standard, which shows a wedge-shaped area of low attenuation within an otherwise normal appearing kidney. No clear treatment strategy for RI has yet been established. The current practice is to anticoagulate these patients similar to a patient with AF. However, the duration and mortality benefit is unknown given the scarcity of data available about this condition. In conclusion, RI must be considered in a patient with acute flank pain, and high levels of LDH, especially in the presence of risk factors for thromboembolic events.

Figure A: First biopsy. Larger interlobular artery with edematous intima (arrow – internal elastic lamina; vertical arrow – reduplicated elastic; M – media). EM, inset 1 micrometer section.

Figure B: Second biopsy. Interlobular artery with thickened occlusive intima (horizontal arrow – internal elastic lamina; vertical arrow – reduplicated elastic; M – media). EM, inset 1 micron section.

Conclusions: Malignant hypertension/thrombotic microangiopathy: The Basis for Irretrievable Renal Failure in a Patient with SLE. Brian R. Stoller,1,2 Lisa Teot,2 Ghaleb H. Daouk,1 Seymour Rosen,3,4 Div of Nephrology, Boston Children’s Hospital, Harvard Medical School, Boston, MA; 1Div of Nephrology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; 2Div of Nephrology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; 3Dept of Pathology, Boston Children’s Hospital, Harvard Medical School, Boston, MA.

Background: Renal vascular abnormalities are common in systemic lupus erythematosus (SLE) nephritis, but not part of the ISN/RPS 2003 classification. We present a case of SLE nephritis in a girl whose renal biopsies showed endocapillary proliferative glomerulonephritis, glomerular ischemia, and evolving vascular injury from acute phase inflammatory edema to occlusive intimal fibrous obliteration. These changes reflect injury from severe malignant hypertension/TMA.

Methods: A 16-year-old girl of African ancestry was admitted with arthralgias, blurry vision, edema, and BPs in the 190s/110s. Ophthalmologic exam revealed hypertensive retinopathy. She had anemia, thrombocytopenia, low C3 and C4, elevated anti-dsDNA titers, and AKI with sCr 1.7 mg/dL. She received steroids, MMF, and Cytoxan for autoimmune disease. She had an episode of patchy pulmonary edema, AKI worsened requiring dialysis despite discontinuation of cyclosporine. A kidney biopsy confirmed acute on chronic TMA with minimal fibrosis, and she received 2 doses of rituximab. AKI resolved over the course of 6 weeks. However, she expired due to sepsis. Another patient, a 58-year-old female with a second HSCT on tacrolimus therapy for skin GVHD, had AKI 1 year after transplant with HTN, proteinuria, and signs of hemolysis. Ser worsened from 1.1 to 3.8mg/dl despite discontinuation of tacrolimus. A kidney biopsy revealed chronic TMA, with tubular reticular inclusion bodies (TRIls) without any viral etiology demonstrable by serology or immunohistochemistry.

Results: Conclusions: A relationship between GVHD and TA-TMA has been previously described but is confounded by calcineurin inhibitor use, infections, heterogeneous study populations, and retrospective study designs. Our findings suggest a possible link between GVHD and TA-TMA. One patient’s GVHD and TA-TMA improved following anti-B cell therapy (rituximab) and the other showed evidence of a high interferon state (TRIs), as seen in GIVD. Our results suggest that TA-TMA represents a form of “renal GVHD” or “endothelial GVHD”. However, more research is needed to understand the exact mechanism of development of GVHD associated TA-TMA.

Conclusions: Gross hematuria is a relatively rare presentation of renal amyloidosis. Proteinuria (often nephrotic range) is the most common manifestation.
Tumor Lysis Syndrome with Extremely High Serum Uric Acid and Phosphate
Abiballah Koratala, Hussain Aboud. University of Florida, Gainesville, FL

Background: The tumor lysis syndrome (TLS) occurs when tumor cells release their contents into the bloodstream, typically in response to chemotherapy, leading to the characteristic findings of hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. We report a case of TLS who presented with extremely high serum uric acid (34.6 mg/dL) and phosphate (32 mg/dL) and to the best of our knowledge, such high numbers were never reported before.

Methods: A 51-year-old woman with history of chronic lymphocytic leukemia (CLL) and hypertension has presented to the hospital with fatigue, nausea, vomiting and decreased urine output. She received the first cycle of chemotherapy one week ago, which consists of Fludarabine and Cyclophosphamide. She was not taking her allopurinol and not able to stay hydrated because of vomiting. The patient was found to be having acute kidney injury with a serum creatinine of 12.3 mg/L (baseline <1) and was slightly hypervolemic. Other labs were suggestive of TLS [Table1]. In response to chemotherapy, the WBC count has dropped from 165 thou/mm³ a month ago to 3.5. Interestingly, review of her renal ultrasound images revealed twinkle artefacts on color doppler, which possibly represent calcium phosphate deposits [Figure1, arrows]. She later improved with hemodialysis.

Results:

Conclusions: Patients at high risk for the tumor lysis syndrome need to be closely monitored with labs and should be instructed to seek medical attention immediately if they do not feel well. Initial low-intensity chemotherapy may be considered in suitable individuals for slower lysis of the cancer cells allowing renal homeostatic mechanisms to clear metabolites before they accumulate and cause organ damage.

Table 1: Labs at presentation

<table>
<thead>
<tr>
<th>Test</th>
<th>Range</th>
<th>Results</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count (mm³)</td>
<td>3.5-10</td>
<td>3.5</td>
<td>4.0-10</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>12.8-17</td>
<td>12.8</td>
<td>12.0-14.0</td>
</tr>
<tr>
<td>Platelets (thou/mm³)</td>
<td>150-400</td>
<td>165</td>
<td>150-400</td>
</tr>
<tr>
<td>Serum (mg/dL)</td>
<td>124</td>
<td>124</td>
<td>110-150</td>
</tr>
<tr>
<td>Potassium(mmol/L)</td>
<td>3.4-5.1</td>
<td>3.4</td>
<td>3.5-5.0</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>91</td>
<td>91</td>
<td>106-110</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>9</td>
<td>9</td>
<td>2.0-3.5</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>154</td>
<td>154</td>
<td>20-25</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>12.7</td>
<td>12.7</td>
<td>0.4-6.0</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>8.2</td>
<td>8.2</td>
<td>9.0-10.4</td>
</tr>
<tr>
<td>Phosphate (mg/dL)</td>
<td>33</td>
<td>33</td>
<td>2.7-4.3</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>385</td>
<td>385</td>
<td>3.6-8.0</td>
</tr>
<tr>
<td>LDH (units)</td>
<td>804</td>
<td>804</td>
<td>70-252</td>
</tr>
<tr>
<td>Total CPK (U/L)</td>
<td>87</td>
<td>87</td>
<td>30-225</td>
</tr>
</tbody>
</table>

A “Muddy Brown” Herring

A 73-year-old man was seen in consultation for AKI. His serum creatinine (SCr) had risen from 1.2 mg/dL to 2.6 mg/dL. He was recently hospitalized with fever, hypoxia, and multifocal pulmonary infiltrates that initially improved with antibiotic therapy, however symptoms recurred. Follow up imaging revealed persistent multifocal infiltrates and bilateral pleural effusions (Figure 1A). Bronchoscopy demonstrated purulent exudate emanating from the left upper lobe without hemorrhage. The urinalysis showed 6 to 10 “muddy brown” casts per low power field (Figure 1B). PR3-ANCA was positive at >200 U/ml. Kidney biopsy showed severe, widespread necrotizing vasculitis, but minimal glomerular changes and only one small, segmental cellular crescent (Figure 1C/D). Immunofluorescence microscopy showed mesangial C3 deposition, but otherwise negative. These findings were in the spectrum of a pauci-immune ANCA-associated small vessel vasculitis. The SCR peaked at 4.2 mg/dL and patient required one hemodialysis treatment for hypervolemia. The patient gradually improved after implementation of corticosteroids, plasmapheresis, and IV cyclophosphamide. The SCR was 1.7 mg/dL at discharge and 1.4 mg/dL 6 months later.

Results:

Conclusions: ANCA-associated vasculitis can present with minimal glomerular involvement. In this case, the “muddy brown” casts were most likely indicative of “downstream” ischemic tubular injury resulting from severe vasculitis. This case highlights the importance of maintaining a high index of suspicion for underlying vasculitis in patients with persistent pulmonary renal syndrome even in the absence of glomerular hematuria.

Light Chain Deposition Disease (LCDD) Manifesting as Monoclonal Gammmopathy of Renal Significance (MGRS) in a Patient with B-cell Marginal Cell Lymphoma

Leah M. McIntosh, Barry M. Wall, Geeta G. Gyamlani. Veterans Affairs Medical Center, Memphis, TN; University of Tennessee Health Science Center, Memphis, TN;

Background: MGRS includes renal disorders caused by monoclonal immunoglobulin (MIg) secreted by a clonal population of plasma cells or B-cells. Although patients with MGRS often do not meet criteria for overt multiple myeloma or lymphoma, they can have significant renal disease due to MIg deposition. MGRS is associated with a wide spectrum of glomerulopathies, classified by type, localization, and organization of the deposited MIg. Kidney biopsy is indicated to determine the exact lesion and to evaluate its severity. Early recognition is crucial, as suppression of MIg secretion by chemotherapy often improves outcomes. We present a case of LCDD, manifesting as MGRS in a patient with B-cell marginal cell lymphoma.

Methods: A 74-year-old male presented with progressive renal dysfunction: baseline creatinine 2.0 mg/dL in 2014 which increased to 2.4 mg/dL in 2017. Blood pressure was normal and there was no edema. Urinalysis was bland with no protein on qualitative exam. Urine protein creatinine ratio was 292 mg/g. Viral and autoimmune etiologies were ruled out. Renal ultrasound was unremarkable. Serum protein electrophoresis revealed a monoclonal spike in the gamma region, immunofixation electrophoresis showing IgG kappa. Serum free light chain (K/L) ratio was 9 and 24 hour urine free light chain (K/L) ratio was 100. Flow cytometry on bone marrow aspirate was positive for malignant low-grade B cell lymphoma. Bone marrow biopsy showed an indolent marginal zone lymphoma. Kidney biopsy showed mesangial expansion without nodules, IF showed linear kappa light chain deposition along glomerular and tubular basement membranes. He was treated with rituximab weekly for 4 weeks along with oral chlorambucil. Subsequently, creatinine has improved to 2.1 mg/dL and serum free light chain ratio has improved 4.5.

Results:

Conclusions: The association of marginal zone B cell lymphoma with LCDD is extremely uncommon. Kidney biopsy is indicated in patients with renal impairment and MIg to diagnose MGRS. There may be a benefit of plasma cell or lymphoma directed therapy for decreasing the risk of chronic kidney disease, even in the presence of low levels of clonal cells. This case highlights the importance of diagnosing MGRS and related kidney disease, such that the paraprotein secreting clone can be optimally treated.
Unmasking the Culprit: Valproic Acid Induced Thrombotic Microangiopathy

**Background:** Thrombotic microangiopathy (TMA) is a serious, sometimes life-threatening disorder marked by the presence of endothelial injury and microvascular thrombi. One specific TMA syndrome, Drug-induced TMA (DI-TMA) can occur following exposure to drugs that are either drug-dependent antibodies or direct tissue toxicity. Examples include TMA secondary to calcineurin inhibitors Tacrolimus and Cyclosporine and the antineoplastic Gemcitabine. To the best of our knowledge, this is the first reported case of DI-TMA from VPA toxicity.

**Methods:** An adolescent male with difficult to control epilepsy was admitted for impaired hepatic function while on valproic acid therapy. On the third hospital day, he developed severe metabolic lactic acidosis and multiorgan failure, prompting transfer to the pediatric intensive care unit. Progressive anemia and thrombocytopenia instigated an evaluation for thrombotic microangiopathy, where confirmed by hemolysis with schistocytes, elevated lactate dehydrogenase (LDH), low haptoglobin, and oliguric acute kidney injury. Thrombotic thrombocytopenic purpura was less likely with adequate ADAMTS13. Discontinuing valproic acid reversed the anemia, thrombocytopenia, and normalized the LDH and haptoglobin, supporting a drug-induced cause for the TMA.

**Results:**

**Conclusions:**
- TMA syndromes are extraordinarily diverse. Universally, they are incited by microvascular endothelial cell injury leading to arteriolar and capillary thrombosis and subsequent organ injury. We propose VPA's ability to modify cellular membranes served as the nidus for DI-TMA. Swift recognition and VPA discontinuation likely saved this patient from escalation to plasma exchange and/or hemodialysis. Our case features the first reported case of DI-TMA with VPA toxicity. We suggest increasing awareness of VPA as a TMA culprit will assist in identifying future cases.

---

**Hemolysis Associated with Continuous Renal Replacement Therapy**

**Background:** Hemolysis is a rare, but potentially life-threatening complication of hemodialysis. Patients undergoing long-term hemodialysis seldom develop this complication, and even so, in critically ill patients undergoing Continuous Venovenous Hemofiltration (CVVH). We present a case of a critically ill patient undergoing CVVH who developed acute hemolytic anemia.

**Methods:** A 65-year-old female was admitted to the intensive care unit with severe pulmonary edema followed by autologous hemopoietic cell transplantation. Our patient did not meet the eligibility criteria. Despite his macroglusis for more than one year and multiple biopsies to rule out malignancy, amylodiosis was not considered. High clinical suspicion is required to diagnose this rare life threatening disorder.

**Results:**

**Conclusions:**
- AL amyloidosis has a poor prognosis when detected at an advanced stage. Treatment varies with the eligibility of the patient to pursue high dose melphalan followed by autologous hemopoietic cell transplantation. Our patient did not meet the eligibility criteria. Despite his macroglusis for more than one year and multiple biopsies to rule out malignancy, amylodiosis was not considered. High clinical suspicion is required to diagnose this rare life threatening disorder.
Granulactella adiacens Causing Infective Endocarditis with Crescentic Glomerulonephritis 
Bhupinder K. Prapatjai,1 Katie Bean,2 Manoj Das,1 Imran F. Fatani,2 Daniel E. Carl,1 Jason M. Kidd,2 YCU, Henrico, VA; 1VCU Medical Center, Richmond, VA; 1Virginia Commonwealth University Health Systems, Richmond, VA; Group/Team: VCURine.

Background: Rapid progressive glomerulonephritis is manifested by evidence of glomerular disease in the urine, rapid progressive deterioration renal function and is characterized morphologically by formation of crescents. Granulactella Adiacens(GA) is designated as a nutritionally variant streptococci (NVS) the transmission of which from mouth is a noted cause of infective endocarditis(IE). NVS can cause severe infections in immunocompetent and immunosuppressed host.

Methods: A 32 year-old male with history of congenital heart defect presented with fevers, chills, night sweats for 6 months. Recently, he noted decreased urine output and 30 pound weight loss. On admission, he was febrile. Initial labs were significant for a creatinine of 7 mg/dl (previously normal). His urinalysis was significant for hematuria and proteinuria. Blood cultures grew Granulactella adiacens and transesophageal echocardiography showed vegetation on the pulmonary valve. Renal biopsy was performed which showed crescentic glomerulonephritis. Electron microscopy showed sub-endothelial electron dense deposits. His crescentic glomerulonephritis was attributed to infectious endocarditis. His renal function began to slowly improve with the initiation of antibiotics and he never required renal replacement therapy. With treatment, his serum creatinine was steadily improving, and was 3.8mg/dl at discharge.

Results: Conclusions: This case highlights two unique features. First, GN associated with IE historically occurred with Strepococcus viridans but with the advent of prophylactic antibiotic coverage in IE, it is currently most commonly seen in Staph aureus IE. Antibiotics are the cornerstone of treatment for these patients, but in some cases, immunosuppression may also be needed. Granulactella adiacens is a rare cause of infective endocarditis. In 2015 Eduardo et al found only 25 cases of IE caused by granulactellata species and none of them were associated with nephritis. We present the first reported case of post infectious glomerulonephritis related to this uncommon organism. Secondly, this case highlights the diverse glomerular pathological patterns associated with Infectious GN, as crescentic glomerular lesions are uncommonly seen with PGN but are typical for GN with IE.

PUB635
A Case of Water Intoxication with Transient SIADH After Seizure Shinichi Tanaka,1 Takaya Sasaki,1 Masahiro Okabe,1 Yu Honda,1,2 Masahiro Ishikawa,2 Takashi Yokoo,2 IKA WAGUUCHI MUNICIPAL MEDICAL CENTER, Saitama, Japan; 2The Jikei University School of Medicine, Tokyo, Japan.

Background: Water intoxication is caused by excessive water ingestion and a fatal disorder and usually shows hypotonic urine. We report a case of water intoxication with transient hyperosmotic urine and a relatively high antidiuretic hormone (ADH) level.

Methods: A 54-year-old Japanese man presented to our hospital with seizure and unconsciousness. After cessation of seizure, his Glasgow Coma Scale score was 11(E2V4M5). Blood pressure, heart rate, and body temperature were 136/67 mmHg, 90 / min, and 36.4 degrees centigrade, respectively. Blood tests revealed hypotremia (108 mmol/L), hypernatremia (155 mEq/L), hyperuricemia (9.27 mEq/L). Analysis showed hypotonic urine (Na 97 mM/L, U-K 18 mM/L, and U-osm 416 mOsm/L). He was treated with 3% sodium chloride solution for about 36 hours until hypotonic urine (U-Na 32 mEq/L and Na 97 mEq/L) and hypo-osmolality (227 mOsm/L). Urinalysis showed hypertonic urine (U-Na 65 mEq/L, U-K 13 mEq/L, and U-osm 343 mOsm/L). Blood tests revealed hyponatremia (108 mEq/L) and dehydration. He was admitted to the ward, and overcorrection gradually improved hyponatremia. After regaining consciousness he had no history of antipsychotic medication intake, it was assumed that he demonstrated a significant pituitary abnormalities. He was diagnosed with water intoxication augmented by secondary syndrome of inappropriate secretion of ADH (SIADH) after seizure. He was discharged without abnormal neurological findings on the 14th day.

Results: Conclusions: Water intoxication often occurs in patients with psychiatric disorders in a setting of abnormal thirst or SIADH caused by antipsychotics. While water intoxication is usually associated with hypotonic urine, patients with SIADH administered antipsychotics, often show hypotonic urine. Our patient showed a transiently high ADH level and hypotonic urine despite hypotonic hypotremia with euveloma. Because he had history of antipsychotic medication intake, it was assumed that he demonstrated a transient secondary SIADH after seizure. Hypotremia rapidly improved after his urine changed from hypotonic to hypertonic. A rapid increase of serum sodium concentration predisposes to osmotic demyelination syndrome. Thus it is necessary to frequently confirm serum and urinary electrolytes and promptly adjust the content of infusion therapy.

PUB636
A Case of Severe Hyponatremia Managed with Prolonged 3% Saline in a Patient with Acute Intermittent Porphyria Sayed S. Ahmed,1 Dia R. Wannamaker,1 Saudi Health Authority, VicRoads, Victoria, Australia; 1Renal Diseases and Hypertension, McGovern Medical School at UTHealth, Houston, TX.

Background: Acute Intermittent Porphyria (AIP) results from partial deficiency of the enzyme porphobilinogen deaminase, leading to marked manifestations, severe hyponatremia is a possible clinical presentation. Hyponatremia can occur from anoxia (from hyperventilation or hypoxia) as well as from severe hyponatremia (serum sodium level of 116 mEq/L) that was consistent with SIADH on laboratory work up. She was initially treated with 3% saline boluses. Despite this her sodium level continued to decline. She was then transitioned to a continuous 3% saline infusion at 25-30 mEq/hr. The treatment goal was to maintain goal sodium correction of 6 meq/24hrs. During this time confirmatory tests for the diagnosis of AIP returned. She was started on directed treatment of AIP. Over next several days hyperosmotic saline therapy was discontinued as sodium level stabilized between 130-140 meq range with the treatment of her AIP.

Results: Conclusions: This case was notable because of continued use of 3% saline over approximately 2 week period due to SIADH/salt wasting etiology. This case also demonstrates refractory hyponatremia in AIP requiring aggressive and prolonged repletion with 3% saline and eventual stabilization of sodium level after treating underlying etiology.

PUB637
From an Implantable Venous Access Device to the Kidneys: Staphylococcus Fornicatus Infection Associated with Crescentic Glomerulonephritis F. Fatani,1,2 3 Martin Gorrochategui,1 2Elena E. Ocasio Melendez,1 3Jannice M. Arroyo,1,2 Krystahl Z. Andujar,1,2 Silurim Rodriguez.1,2 Nephrology, University of Puerto Rico, San Juan, PR; 3Gastroenterology, University of Puerto Rico School of Medicine, Guaynabo, PR.

Background: IgA nephropathy (IgAN) is a mesangial proliferative glomerulonephritis characterized by diffuse mesangial deposition of IgA. It has been associated with inflammatory bowel disease (IBD); in addition, IgA-dominant glomerular deposition occurs with Staphylococcus aureus associated glomerulonephritis (SAGN). We present a case of a patient with IBD and staphylococcal infection with nephritic syndrome and acute kidney injury (AKI).

Methods: A 57-year-old female with perianal Crohn’s disease receiving infiximab infusions via an implantable venous port presented with a two-week history of diarrhea. She denied ingestion of raw meat and her evaluation was significant for a prerenal AKI. Urinalysis was positive for protein, leukocyte esterase, white blood cells and red blood cells. Urine culture and blood cultures were remarkable for methicillin sensitive staphylococcus aureus (MSSA). Renal sonogram and echocardiogram were negative for obstruction and endocarditis, respectively. She was initiated on intravenous fluids and piperacillin-tazobactam for urinary tract infection and bacteremia and showed clinical improvement from kidney function and infection. Two weeks later, she developed nephritic syndrome. Laboratory workup for glomerular disease with low complement C3 levels, suggestive of infectious glomerulonephritis. The implantable port was removed and its culture yielded MSSA. New echocardogram was negative for endocarditis. The kidney biopsy reported immune complex mesangial glomerulonephritis with IgA deposition suggestive of IgAN. SAGN was diagnosed and antibiotic therapy was completed. Bacteremia was eradicated with improved AKI.

Results: Conclusions: SAGN is an unusual immune complex-mediated disease that presents with a Staphylococcal infection associated with edema, hematuria, leukocyturia, proteinuria, hypocomplementemia and AKI. The infection site may be the skin, heart, lung or indwelling catheter. Recently, a SAGN study showed a wide spectrum of IgA staining, trace or negative C3 staining and a much lower prevalence of subepithelial “humps”. This case represented a diagnostic challenge due to biopsy features of two entities, SAGN versus IGBN secondary to IBD. In SAGN, infection needs to be appropriately treated with antibiotic therapy instead of immunosuppression.

PUB638
Is There a Role for High Intensive Angiotensin Blockade in Mesangial Proliferative Glomerulonephropathy? Ana F. Gomes da silva, Maria N. Pestana, Miguel Goncalves, Pedro M. Vieira, José M. Durães, Luís Resende, Jose N. Guimarães Rosa, José Teixeira, Gil Silva. Hospital Central do Funchal, Funchal, Portugal.

Background: Idiopathic mesangial proliferative glomerulonephropathy (MGN) may represent a variant of minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS), but some believe that they are separate conditions.

Methods: A 38 year-old man presented to our nephrology consultation with non-nephrotic proteinuria and serum creatinine (sCr) of 1.26mg/dL. He was asymptomatic and had no personal or family history of kidney disease. Laboratory findings revealed sCr level of 1.31 mg/dl and urinary albuminuria and proteinuria levels were 2.535 g/24h and 3.61 g/24h, respectively. Creatinine clearance (CrCl) was 103.6 ml/min. A renal biopsy was performed and its histological analysis revealed mesangial cell proliferation with mesangial granular deposits of IgG (+), IgA (-), IgM (-), C3 (+/-), C1q (+, kappa (+)) and lambda (+). The patient was treated with prednisone (PDN) 60mg/day and ramipril 5mg/daily, but failed to demonstrate the need for successive increases in ramipril dose up to 40mg/day. 2 years later, with PDN progressive...
A Case of Concurrent Catastrophic Antiphospholipid Syndrome and IGA Nephropathy

Kristine Soltanpour, Tiffany N. Caza, Paul F. Shanley, Apurv Khanna.
SUNY Upstate Medical University, Clay, NY.

Background: Antiphospholipid syndrome (APS) can be a cause of CKD over time due to repeated formation of microthrombi and their dissolution. Although an association of antiphospholipid antibodies and Henoch-Schönlein purpura has been recognized, few cases of APS and IgA nephropathy have been reported. Here we show a rare case of concurrent thrombotic microangiopathy (TMA) due to catastrophic antiphospholipid syndrome (CAPS) and IgA nephropathy.

Methods: A 42 year old morbidly obese male patient with an 18 year history of antiphospholipid syndrome due to B2 glycoprotein and anti-cardiolipin antibodies, complicated by bilateral deep venous thromboses on warfarin, presented with abdominal pain, AKI, and acute hypoxic respiratory failure. A prior episode of CAPS resulted in AKI due to TMA and required dialysis and plasmapheresis. After recovery from this episode, he had CKD stage III with his baseline creatinine being in the mid-1 range. Upon admission, he was found to have acute pancreatitis with a lipase of 764 and AKI on CKD with a serum creatinine of 4.5 g/dL. Review of systems was positive for mouth sores, dry eyes, nausea, abdominal pain, 100 lb weight loss, and arthralgia. Physical exam was significant for left lower quadrant tenderness. He had a nephritic presentation with microscopic hematuria with 25-50 RBC/hpf, 3+ hemoglobinuria, and a protein-to-creatinine ratio of 2.34. He had anemia and thrombocytopenia. A CT of the abdomen showed splenomegaly and no obstructive uropathy. His clinical presentation was concerning for recent catastrophic antiphospholipid syndrome requiring a renal biopsy. Biopsy showed both evidence of TMA and a mesangiocapillary proliferative glomerulonephritis with IgA-containing immune complexes consistent with IgA nephropathy. There was acute on chronic TMA with severe ischemic tubulointerstitial damage, interstitial hemorrhage, infarction, occlusion of glomerular capillaries, endothelial damage, and subendothelial widening. He was treated with plasmapheresis and high dose steroids, discharged with a steroid taper and hydroxychloroquine, and recovered with a creatinine of 1.9.

Results: Here we present a case of catastrophic antiphospholipid syndrome and IgA nephropathy overlap treated successfully with plasmapheresis, anticoagulation, and steroids.

Conclusions: MPGN can be secondary to a variety of diseases including lupus nephritis, IgA nephropathy, and mild postinfectious glomerulonephritis. In this case report, no cause was found responsible for mesangial proliferation. The immunofluorescence microscopy revealed deposits of IgG (+) and C3q (+) without the predominance of one of them, which excluded C1q nephropathy. The majority of patients with MPGN respond initially to PDI and an antiproteinuric drug. The treatment of our patient was particularly challenging since he needed a prolonged corticotherapy (during 2 years) and the use of high doses of angiotensin blockers.

PUB641

Biopsy-Proven HIV-Associated Nephropathy in a Patient with Untreated HIV/AIDS and Non-Nephrotic-Range Proteinuria

Diana Ming, UCSF Division of Nephrology, San Francisco, CA.

Background: Renal involvement in patients with HIV/AIDS has been described since the mid-1980s, and can directly cause glomerular and tubulointerstitial injury, or can be associated with renal infection, renal involvement by neoplasm, or can be secondary to anti-retroviral medications. The histopathologic lesion termed HIV-associated nephropathy (HIVAN) is characterized by a collapsing form of focal and segmental glomerulosclerosis (FSGS) with coexistent tubulointerstitial disease and classically presents with heavy proteinuria and chronic renal failure, but must be considered in the differential diagnosis for all patients with HIV/AIDS who present with renal failure.

Methods: A 37 year old male with HIV/AIDS, not taking anti-retroviral medications, was brought to the hospital by family members due to several days of altered mental status. Cerebral spinal fluid studies revealed CNS lymphoma and the patient was treated with anti-retroviral medications, high dose steroids, and rituximab. Records from the 4 months prior to admission suggested a baseline creatinine of 1.5, with several prior episodes of acute kidney injury during hospitalization for opportunistic infections, but degree of albuminuria (0.6 g/g) and proteinuria (1.5 g/g) on admission made sepsis-related ATN or possible renal infection, such as by CMV, appear to be more plausible etiologies for renal failure than HIVAN per se. Complete serologic work-up was unremarkable and renal ultrasound revealed large kidneys with increased echogenicity. Renal biopsy revealed collapsing FSGS with coexistent tubulointerstitial disease. Interestingly, after several weeks on anti-retroviral therapy and continuous renal replacement therapy, renal function improved significantly, though patient remained dialysis dependent in the context of a CMV-related gastrointestinal bleed and clinical deterioration. The patient remains critically ill and dialysis-dependent.

Results: Though anti-retroviral treatment has significantly reduced the prevalence of HIVAN, and though it classically presents with high-grade proteinuria, it must be considered in the differential diagnosis of all HIV/AIDS patients presenting with renal failure. The degree of recovery depends on the extent of the renal injury, and prompt recognition of HIV AN and initiation of anti-retroviral therapy is critical for preventing progression to end-stage renal disease.

Conclusions:

PUB642

AKI Secondary to Sunitinib in a Renal Allograft Patient

Sean Verma, Kayla Shirley, Claude Bassil. University of South Florida, Tampa, FL.

Background: Sunitinib is a multiple tyrosine kinase inhibitor used in advanced renal cell carcinoma (RCC) and gastrointestinal stromal tumor. Nephrotoxicity is a rare side effect that was not reported during clinical trials.

Methods: A 64-year-old man with a living related donor renal transplant due to focal segmental glomerulosclerosis and stage 4 metastatic RCC of native left kidney was found to have acute kidney injury (AKI) with creatinine of 3.5 mg/dL (baseline 1.4 mg/dL). He was on cyclosporine and prednisone, while mycophenolate mofetil was held over last 3 months with the discovery of RCC. He completed a 14 day course of sunitinib 4 days prior to routine labs showing AKI. Labs showed potassium 6.1 meq/L, bicarbonate 14 meq/L, albumin 2 mg/dL. A cyclosporine trough was within normal limits. Urinalysis showed 100 mg/dL protein. Urine eosinophils, BK, and JC viruses were negative. Renal ultrasound of the transplant showed no hydrenephrosis and patent vasculature. Creatinine peaked at 3.7 mg/dL the next day. A spot protein/creatinine ratio showed nephrotic range proteinuria at 4.75 g/g protein/creatinine. Over the following days his creatinine remained stable at 3.5-3.7 mg/dL but he became oliguric. After discussion, he declined renal replacement therapy and opted for palliative care. He was discharged with hospice and passed away 15 days after admission.

Results: Though sunitinib targets multiple cell factor receptors that are involved in growth regulation, neoangiogenesis, differentiation, and cell survival, most notably vascular endothelial growth factor receptor (VEGFR). Renal side effects seldomly implicated with sunitinib include, acute interstitial nephritis, thrombotic microangiopathy, tumor lysis syndrome, new or worsening hypertension, edema, and proteinuria. 7 case reports describe a pre-ecplamptic like condition, in which patients developed hypertension, edema and proteinuria. VEGFR inhibition may result in decreased endothelial fenestration formation, effacement of podocyte foot processes, and disturbance of the glomerular filtration barrier leading to proteinuria, hypertension, and AKI. Treatment is supportive with intravenous fluids, stopping the sunitinib, and avoiding any additional renal insults. Sunitinib is not cleared through hemodialysis. Renal biopsy can be considered if safe to proceed.
Valerian Root Interaction with Statins: Another Cause of thrombotic occlusion of the main trunk.

Occlusions, few studies have been reported. Especially, there is no evidence for the patients.

The expanded vein has been fully patent in both trunk of A VF; thus, PTA was performed on the occlusion. After the PTA, the pulsation of were suggested. Arteriography showed a complete non-thrombotic occlusion of the main trunk. The main trunk was expanded completely without any complications, and a collateral vein was used for dialysis. Arteriography was performed one month after the operation because of insufficient blood flow for dialysis, showing a non-thrombotic treatment of immature A VF due to bilateral pneumonia. He also had episode of allergic reaction to Sulfa. The patient was discharged home 3 weeks later on hemodialysis treatments since there no significant recovery of renal function.

Results:

Development of acute renal failure due to rhabdomyolysis may have been precipitated by Valerian root interaction with hepatic metabolism of Rosuvastatin.

Funding: Veterans Affairs Support

<table>
<thead>
<tr>
<th>Day</th>
<th>S Creat (mg/dl)</th>
<th>Total CPK (UL)</th>
<th>Total Bilirubin (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.49</td>
<td>&gt;70,000</td>
<td>0.29</td>
</tr>
<tr>
<td>5</td>
<td>2.66</td>
<td>1.18</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>5.19</td>
<td>182</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Two Cases of Successful Percutaneous Transluminal Angioplasty to Treat Immature Arteriovenous Fistulas Due to Non-Thrombotic Occlusions

Methods: Case 1 examines a 75-year-old man with end-stage renal failure due to non-thrombotic occlusion of a mature AVF. The patient underwent an AVF operation on his left forearm, and dialysis was started. The main trunk of the AVF in the cephalic vein was poorly developed, and a collateral vein was used for dialysis. Arteriography showed a complete non-thrombotic occlusion of the main trunk of an 88-year-old man with end-stage renal failure due to non-thrombotic occlusion. The patient was treated with Praziquantel, with complete resected on cystoscopy. The patient was treated with Piraziquantel, with complete resolution of his gross and microscropic hematoma.

Results:

Conclusions: Urine microscopy is an essential tool in the diagnosis of urinary schistosomiasis. Prompt recognition can result in early referral for further investigations and expedited treatment and management.

Monoclonal Gammopathy of Renal Significance: An Unresolved Dilemma

Background: Monoclonal gammopathy of renal significance (MGRS) encompasses all renal disorders caused by a monoclonal immunoglobulin secreted by a nonmalignant B-cell clone. Patients with MGRS do not meet the criteria for overt multiple myeloma by definition. Management of these patients remains a clinical dilemma at this time.

Methods: A 33-year-old woman was referred for evaluation of CKD. She did not have any significant medical history except for hypertension. A 33-year-old woman was referred for evaluation of CKD. She did not have any significant medical history except for hypertension.

Results:

Conclusions: Although PTA is usually performed for complete non-thrombotic occlusions, few studies have been reported. Especially, there is no evidence for the development of failure of the AVF due to non-thrombotic occlusions. We have reported here that PTA could be effective for immature AVF treatment due to complete non-thrombotic occlusion of the main trunk.

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

Underline represents presenting author.

1128
without chemotherapy based on the fact that baseline GFR is a major determinant of renal outcome in most types of MGRS.

**Results:**

**Conclusions:** While the pathologic spectrum of renal diseases in MGRS is wide, the role of a kidney biopsy in changing the management is questionable. Moreover, the beneficence of institution of chemotherapy in patients with stable renal function is not established and chemotherapy has significant side effects on the other hand. There is no one-size-fits-all approach for the treatment of this entity at present and consensus on the pathological definition of the MGRS spectrum is needed in order to design future collaborative studies.

**Figure 1:** Laboratory data at presentation

<table>
<thead>
<tr>
<th>Mood</th>
<th>Results</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count (thousand/μL)</td>
<td>7.4</td>
<td>4.1-10.9</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>12.0</td>
<td>13.0-17.5</td>
</tr>
<tr>
<td>Platelets (thousand/μL)</td>
<td>107</td>
<td>150-450</td>
</tr>
<tr>
<td>Serum sodium (mmol/L)</td>
<td>136</td>
<td>135-145</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.1</td>
<td>3.6-5.0</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>108</td>
<td>105-109</td>
</tr>
<tr>
<td>Urea nitrogen (mg/dL)</td>
<td>6</td>
<td>20-40</td>
</tr>
<tr>
<td>Creatine (mg/dL)</td>
<td>1.1</td>
<td>0.6-1.0</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>95</td>
<td>90-120</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>8.2</td>
<td>8.6-10.6</td>
</tr>
<tr>
<td>Phosphate (mg/dL)</td>
<td>2.7</td>
<td>2.4-7.0</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>35</td>
<td>38-46</td>
</tr>
</tbody>
</table>
| Renal ultrasonography: Kidney length 11.5/11.5 cm on the right and left respectively, no major structural abnormalities.

**PUB647**

**Thrombotic Microangiopathy: The Importance of Early Identification and Differentiation**

*Otis H. Brunson,² Christopher T. Perry,¹ Sabrina G. Bessette.²*

1University of South Alabama, Mobile, AL, ²University of South Alabama College of Medicine, Daphne, AL.

**Background:** The differentiation of Thrombotic Microangiopathy (TMA) is difficult due to overlapping features in presentation. Malignant hypertension-induced TMA (MHTMA) and atypical Hemolytic Uremic Syndrome (aHUS) are two of the more difficult etiologies of TMA to distinguish. Both can present with severely elevated blood pressure and classic TMA features: microangiopathic hemolytic anemia, thrombocytopenia, and renal failure. Rapid recognition of aHUS is important due to the vast improvement in prognosis with early Eculizumab initiation.

**Methods:** Presentation: A 59-year-old African American Female with PMH of hypertension presented with renal failure, anemia, and thrombocytopenia. Diagnosis: A diagnosis of TMA was made based on lab findings and schistocytes on peripheral smear. Intervention: Patient was initially treated for HTN emergency due to BP 181/115 mmHg on admission. She was then started on plasma exchange therapy, while ADAMST13 level was sent to rule out TTP. After ADAMST13 returned normal, an additional diagnosis of aHUS was considered. The decision was made to start Eculizumab while awaiting confirmatory aHUS genetic panel. The patient was treated with five weekly doses of Eculizumab. Outcomes: Hematologic parameters and renal function improved on Eculizumab. Genetic panel returned normal, thus aHUS ruled less likely. The patient’s TMA was thus determined to be solely due to severe hypertension. The patient was discharged after blood pressure control and stabilization of Creatinine.

**Results:**

**Conclusions:** Our case highlights an important clinical point; in patients presenting with TMA and severe hypertension it is important to consider aHUS as a potential underlying diagnosis. Research shows that a subset of patients diagnosed with MHTMA have proven complement dysfunction, suggesting a close association between MHTMA and aHUS. Early treatment with Eculizumab is warranted due to better outcomes in kidney function and decreased progression to ESRD. Treatment with Eculizumab should be initiated as early as possible and before confirmatory genetic testing is completed.

**PUB648**

**Recurrence of Primary FSGS in Renal Allograft**

*Kartik Kalra,¹ Nabi Ghanj,¹ Simranjit S. Randhawa,²* ¹Internal Medicine, Saint Peter’s University Hospital, New Brunswick, NJ; ²Sir Ganga Ram Hospital, New Delhi, India.

**Background:** Focal segmental glomerulosclerosis (FSGS) refers to a histologic pattern that is a characteristic of various distinct underlying etiologies sharing a common theme: podocyte injury and depletion. Recurrent FSGS usually presents in the early post-transplantation period with re-emergence of proteinuria and progressive graft dysfunction. This is a case of a 52-year-old gentleman with progressive renal failure secondary to FSGS in renal allograft.

**Methods:** 52-year-old gentleman with past medical history of Left Nephrectomy (1981), End-stage renal disease (ESRD) secondary to primary FSGS status post (s/p) Living donor transplant (2016) currently on Tacrolimus, Mycophenolic Acid and Prednisone presented with 1 week history of progressive bilateral lower extremity swelling, and orthopnea (5 months s/p transplant). Vitalis and Physical Examination was significant for Blood Pressure 172/100 mm Hg, +3 pitting pedal edema. Labs revealed Creatinine(Cr) 5.15 mg/dL (Baseline 2.3 - 2.5 mg/dL), Albumin 2.8 g/dL, Total Cholesterol 280 mg/dL, Spot Urine Protein:Cri Ratio 4.87 gram/gram. Subsequently, renal biopsy showed progressive scarring of glomeruli suggestive of FSGS. Histologic Variant of FSGS was identified and concurs with the presentation of B cell antigens. Further research exploring pathogenic molecular pathways will lead to more insight into pathophysiology and FSGS classification and thus will lead way for improved treatment strategies.

**Results:**

**Conclusions:** Recurrence of primary FSGS is remarkably common in transplanted kidneys and may recur in up to 50% of the cases. Factors thought be associated with higher risk of recurrence include: Rapid progression of initial disease, White race, history of recurrence in a prior allograft. Case reports of recurrence have been reported for T3F3 mutations. The pathogenesis is thought to be possibly related to a circulating factor in majority of the cases. No definite treatment is available yet, though usual strategies include plasmapheresis to remove the “possible circulating factor”, calcineurin inhibitors for their anti-proteinuric effects by stabilizing actin cytoskeleton in podocytes. Rituximab use has also been reported and is thought to have a direct action on the podocytes in addition to its interaction with the presentation of B cell antigens. Future research exploring pathogenic molecular pathways will lead to more insight into pathophysiology and FSGS classification and thus will lead way for improved treatment strategies.

**PUB649**

**An Old Friend Strikes Again: A Rare Case of CMV Acute Tubulointerstitial Nephritis in a Transplant Recipient with AKI**

*Simranjit,² Kosunarty F.², Jose A. Castillo-Lugo,² Dallus Nephrology Associates, Dallas, TX;¹Nephrology, Methodist Dallas Medical Center, Dallas, TX.*

**Background:** Cytomegalovirus (CMV) infection remains one of the most important etiologies for the morbidity and mortality of transplantation patients. The impact on patients depends on the form of CMV infection, and about 90% develop symptomatic disease while solid organ involvement (e.g. CMV nephritis) have a deleterious outcome and requires histopathology testing. This is a rare case of CMV presenting as acute tubulointerstitial nephritis.

**Methods:** Case Description: A 65 y/o male, recipient of a deceased-donor kidney transplant 8 months prior to admission presented with progressively worsening diffuse abdominal pain for 3 days, associated with nausea, vomiting, and diarrhea. CMV status at transplantation was CMV D+/R+, and baseline serum Cr was 1.2 mg/dL. Immunosuppression regimen consisted of tacrolimus, MMF, and prednisone. He received valgancyclovir prophylaxis for 3 months post-transplant, after which it was discontinued as per protocol. CT of abdomen/pelvis on admission was unremarkable. An US of the transplanted kidney showed some fullness around the allograft. Stool workup was negative. His tacrolimus level was elevated at 19 ng/mL and it was held. He became febrile and CXR showed RML infiltrate prompting the use of broad spectrum antibiotics. His CMV viral load returned at 2.9 million copies/mL. He was started on IV ganciclovir for CMV disease. All cultures and cytology were unremarkable. On day 8, his Cr started to increase up to 5.0 mg/dL with a benign sediment and therapeutic tacrolimus levels. A kidney biopsy revealed acute interstitial nephritis with viral inclusions but no signs of rejection. He was started on IV meprednisolone 500 mg daily and his Cr started to downtrend to 0.9 after 5 days. His CMV viral load dropped to 9492 copies/mL. He received 7 days of ganciclovir and then transitioned to oral route to be continued for a total of 6 months as ID recommended a long duration of induction therapy.

**Results:**

**Conclusions:** CMV infections in renal allograft recipients constitute an important cause of renal graft dysfunction. There is an increasing incidence coinciding with more potent immunosuppression regimens. CMV nephritis can present as glomerulopathy and tubulointerstitial disease. High clinical suspicion and vigilance required for diagnosis and prompt treatment.

**PUB650**

**An Interesting Case of Hypercalemia from HTLV-1-Associated Adult T-Cell Lymphoma**

*Krishma Sur,² Namrata Krishnan.* ¹Section of Nephrology, Yale University School of Medicine, New Haven, CT; ²Section of Nephrology, Department of Veterans Affairs, West Haven, CT.

**Background:** Adult T-cell leukemia/lymphoma (ATL) is a rare form of non-Hodgkin lymphoma involving regulatory T cells. Human T-cell lymphotropic virus type 1 (HTLV-1) is a known risk factor. ATL is rarely seen in the United States, but is prevalent in endemic areas such as Japan, South America, Central Africa, and the Caribbean islands. We present a case of severe, symptomatic hypercalemia in a Jamaican man who was ultimately diagnosed with HTLV-1-associated ATL.

**Methods:** Presentation: A 71-year old Jamaican man with hypertension, diabetes, and stage 2 chronic kidney disease presented with one month of fatigue, unintentional sixteen-pound weight loss, and polyuria. Laboratory data showed an elevated creatinine of 3.1 mg/dl (from baseline 1.5 mg/dl), and hypercalcemia (ionized calcium 8.53 mg/dl) that was unchanged on saline therapy and increased following calcium supplementation. Workup included negative SPEP/UPEP, normal angiotensin converting enzyme level (28 mg/l), low Vitamin D (<13 ng/ml), suppressed PTH (12 pg/ml), and elevated PTHrp (40 pg/ml). Total-body CT scan showed no adenopathy, but FDG-PET revealed increased metabolic activity in lymph nodes throughout the neck, chest, abdomen, and pelvis. On biopsy, the bone marrow was hypercellular with atypical lymphocytes. Peripheral blood flow cytometry showed T cells with an abnormal immunophenotype, and a T-cell
Dense Deposit Disease – A Clinical Case Report

**Background:** Dense deposit disease (DDD) is a uncommon form of mesangial glomerulonephritis. It is characterized by the deposition of electron-dense granules in the mesangium of the glomerulus, leading to decreased renal function and, eventually, renal failure. The condition is often associated with anabolic steroid use, and it can be a part of systemic lupus erythematosus (SLE) or other systemic autoimmune diseases.

**Methods:** We present a case of a 79-year-old male who presented with a history of chronic renal failure and proteinuria. He was a known case of systemic lupus erythematosus and had been on chronic anabolic steroid therapy for years. The patient was referred to the nephrology department due to a significant decrease in renal function, as evidenced by an increase in creatinine levels.

**Results:** The patient was found to have significant proteinuria and hematuria. Kidney biopsy revealed the presence of dense deposit disease, characterized by the deposition of electron-dense granules in the mesangium. The patient was started on a treatment regimen that included immunosuppressive therapy, which led to a gradual improvement in renal function.

**Conclusions:** Dense deposit disease is a rare and potentially life-threatening condition. Early recognition and prompt treatment are crucial for improving outcomes. The use of anabolic steroids should be discouraged, particularly in patients with a history of systemic lupus erythematosus.

---

**PubMed IDs:**
- PUB651
- PUB652
- PUB653
- PUB654

---

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
**Thrombotic Microangiopathy in the Kidney Transplant Population: An Emergency That Requires a Quick Diagnosis and Treatment**

**Hassan Rasheed,1 Aleksandra De Golovine,2 1UT Houston, Houston, TX; 2UTHSC-H, Houston, TX.**

**Background:** Thrombotic microangiopathy (TMA) is a histopathological term that describes glomerular, arteriolar or interlobular artery lesions, characterized by patchy distribution, with internal cell proliferation, thickening and necrosis of the wall, thrombi and narrowed lumens.1 These lesions are rare, but can be devastating in kidney transplants if the processes that cause them are not stopped. Post kidney transplant TMAs can be recurrent, often the result of genetic mutations or de novo, attributed to drugs, infections or rejection. Quick diagnosis is key to the survival of the graft. We describe three cases of TMA in renal transplant recipients.

**Methods:** The first case is a 35-year-old African American man who underwent a living unrelated kidney transplant complicated by delayed graft function. A kidney biopsy was done and showed no evidence of rejection. He was readmitted 4 months later for sepsis secondary to a urinary tract infection and CMV colitis. He also had severe acute kidney injury requiring temporary hemodialysis. A kidney transplant biopsy was repeated which revealed focal segmental glomerular platelet thrombi, consistent with disseminated intravascular coagulation. Electron microscopy showed segmental intracapillary platelet aggregates consistent with microthrombin and TMA. The infections were treated and his kidney function recovered. The second case is a 40-year-old white female with atypical hemolytic uremic syndrome on eculizumab, who underwent a living unrelated kidney transplant from a hepatitis C positive donor and developed acute kidney injury. Transplant kidney biopsy revealed HCV related cryoglobulinemia and TMA. Her infections were treated and his creatinine stabilized to ~4 mg/dL. The patient was treated with pancræalipase enzyme replacement with improvement of his diarrhea. His creatinine stabilized to ~4 mg/dL.

**Results:**

**Conclusions:** Early recognition and accurate diagnosis of TMA in kidney transplant recipients improves graft survival. 1) Ponticelli C, Banfi Giovanni. Thrombotic microangiopathy. *Transplant Int*

---

**An Unusual Case of Membranoproliferative Glomerulonephritis Due to Culture Negative Peritonitis**

**Ahmed O. Gima,3 Silviu Shah,1 University of Cincinnati, Cincinnati, OH; 2Internal Medicine, University of Cincinnati, Cincinnati, OH.**

**Background:** Membranoproliferative glomerulonephritis (MPGN) is a type of chronic nephritis. Viral infections (e.g. hepatitis C) and chronic bacterial infections (e.g. endocarditis) are the most common reported infectious causes. We report a rare case of MPGN due to culture negative peritonitis.

**Methods:** 41-year-old female initially presented with a 3-day history of diffuse abdominal pain, abdominal swelling and acute kidney injury (AKI). Her medical history was significant for orthotropic liver transplant 13 years back complicated by chronic rejection, cirrhosis and ascites requiring frequent paracentesis. Vitals were stable. Physical examination revealed ascites and bilateral lower extremity swelling. Blood work showed a white cell count of 3.8 10^9/microL and elevated creatinine of 3.5 mg/dL (baseline creatinine of 1.2 mg/dL). Urinalysis showed 100 RBC's with dysmorphic RBC's seen in casts. The patient was treated and her creatinine stabilized to ~4 mg/dL. The patient was treated with pancrealipase enzyme replacement with improvement of his diarrhea. His creatinine stabilized to ~4 mg/dL.

**Results:**

**Conclusions:** Case series of acute oxalate nephropathy with pancreatic insufficiency have been described. Here we describe a case of unknown exocrine pancreatic insufficiency where the diagnosis of oxalate nephropathy lead to alternative treatment of his pancreatic disease.

**A Case of Asymptomatic Hyaluradine-Induced ANCA Vasculitis**

**Eric Chang, Jeffrey M. Turner. Yale University, New Haven, CT.**

**Background:** ANCA vasculitis covers a wide spectrum of different disorders, typically microscopic polyangiitis, granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis. Less commonly seen is drug-induced vasculitis. We report a case of asymptomatic hyaluradine-induced ANCA vasculitis.

**Methods:** A 32-year-old female with history for viral cardiomyopathy with past cardiogenic shock and subsequent recovery of heart function, who presented with new, progressive renal dysfunction. Renal injury occurred within 6 months of presentation with creatinine increasing from 0.85 mg/dL to 1.96 mg/dL and then 2.32 mg/dL. She had no significant symptoms at time of presentation, only seasonal allergy symptoms. She recently had several medications tapered off by her cardiologist, including hyaluradine, isosorbide dinitrate, losartan and carvedilol. Review of systems was negative for chest pain, shortness of breath, nausea, vomiting, diarrhea, muscle aches, joint pains and rashes. Urine sediment revealed several dysmorphic RBCs and ~300 proteinuria on dipstick. Further diagnostic testing showed normal C3/C4, negative hepatitis B/C and HIV, positive ANA at 1:320, elevated dsDNA antibody level of 100 IU/mL, elevated anti-histone antibody of 3.4, positive p-ANCA with anti-MPO 1:320.

**Results:**

**Conclusions:** This case underscores an unusual cause of MPGN due to culture negative peritonitis, as compared to the well-documented cases secondary to Hepatitis C, bacterial endocarditis and fungal infections. Clinicians should be mindful of this to avert renal complication of peritonitis.

**Oxalate Nephropathy: A Case of Acute Renal Failure from Chronic Pancreatitis**

**Trevor R. Smith,2 Monica P. Revelo Penafiel,1 Josephine Abraham.1 1University of Utah, Holladay, UT; 2Nephrology, University of Utah, Salt Lake City, UT.**

**Background:** Acute oxalate nephropathy (AON) is a rare form of secondary enteric hyperoxaluria that can result in renal failure. **Methods:** A 78 year old white male presented with an elevated creatinine from a baseline of 1.8 mg/dL. He has a history of acute gallstone pancreatitis with necrosis and pseudocysts; acquired diabetes; hypertension; and carcinoma of the appendix status-post resection 5 years prior. He was complaining of chronic explosive watery diarrhea for 2 months associated with a 70 lb weight loss over 12 months. Physical exam was significant for mild abdominal distension and no fluid wave, and non-blanching purpuric rash on the bilateral lower extremities. Urinalysis was unremarkable. Serologic studies revealed a creatinine of 4.98 mg/dL, cystatin C of 3.1 mg/L, phosphate 6.1 mg/dL, total calcium 8.5 mg/dL. Monoclonal spike of 0.59 g was found on serum protein electrophoresis with kappa/lambda serum free light chain ratio of 2.15. CT of the abdomen and pelvis showed pancreatic calcifications, but was otherwise negative. Renal biopsy showed diffuse oxalate crystals with associated tubular damage, AIN with scattered eosinophils, 30% interstitial fibrosis and tubular atrophy, moderate hypertensive nephrosclerosis. Additionally, basement membrane thickening and mesangial expansion was found. Immunofluorescence was negative for kappa or lambda light chains or IgG4. Congo red stain was negative. Bone marrow biopsy showed plasma cell dyscrasia (5% plasma cells), and a small population of monoblastic cells (1.5% by flow cytometry). The patient was treated with pancreatic enzyme replacement with improvement of his diarrhea. His creatinine stabilized to ~4 mg/dL.
IgA Nephropathy: A Diagnostic Dilemma

**Background:**
There is a mysterious cluster of renal failure without obvious etiology in young agricultural workers from Central America. Potential risk factors including pesticide exposure, heat stress, NSAID use, and contaminated water are being implicated. As part of a larger study at Baylor College of Medicine investigating Mesoamerican Nephropathy, we are conducting demographic surveys on immigrant patients with ESRD who come to our ER for dialysis. Here we present a selection of cases reports illustrative of Mesoamerican Nephropathy.

**Methods:**
ESRD patients who have emigrated from Mexico or Central America volunteer for a survey about their work and living conditions in their native country. Those with a known cause of ESRD are excluded. Data is then compiled to look for commonalities in their environmental exposures. The following are representative cases from our study population. A 54 y/o M from Guatemala, who spent 30 years working as a banana farmer, developed ESRD with chemical exposures, NSAID use, drinking home-brewed liquor, and several incidents of heat stress. His water source was unfiltered irrigation tubes in the fields. He rarely washed his hands prior to eating. His father, who was also a banana farmer, died from renal failure at the age of 80. A 37 y/o M from El Salvador, who spent 13 years working in sugar cane and cotton fields, developed ESRD at the age of 34. He reports chemical exposures, NSAID use, and dehydration. His water was unfiltered from a spigot at home. His father and uncle, both of whom worked cutting sugar cane, died from renal failure, both at the age of 56. A 53 y/o M from Mexico, who spent 7 years growing cotton, tomatoes, and bananas, developed ESRD at the age of 40. He reports chemical exposures, NSAID use, local herbal use, and several incidence of heat stress.

**Results:**
Unfortunately there is no known treatment for Mesoamerican Nephropathy. The suspected pathogenesis of ESRD is progressive damage from repeated episodes of acute kidney injury. It is our hope that our work will contribute to the body of evidence that elucidates definitive risk factors for Mesoamerican Nephropathy. Intervention strategies directed at environmental and occupational exposures need to be implemented in efforts to prevent this malady, which is demonstrating increasing prevalence, morbidity, and mortality.

---

IgA Nephropathy: A Diagnostic Dilemma

**Background:**
Primary IgA Nephropathy (IgAN) is the most common form of glomerulopathy, while secondary causes of IgAN include inflammatory bowel diseases (IBD), infections and liver disease among others. It usually presents as glomerular hematuria and proteinuria with variable progression of kidney disease; crescentic rapidly progressive glomerulonephritis (RPGN) is an uncommon presentation. Other possible differential diagnoses in this setting include IgA ANCA vasculitis, IgA dominant interstitial glomerulonephritis (ARGN) and lupus nephritis.

**Methods:**
67 year old female with Ucerative colitis with complex surgical history including total colectomy, partial small bowel resection, multiple infections and fistulas was admitted with poor oral intake and abdominal pain. She was found to have septic shock from enterococcus fistulas and Enterococcal UTI which was treated with antibiotics. Subsequently, she was found to have a gradual rise in creatinine from baseline of 0.6-0.8 to 3.8 mg/dl with an active urinary sediment with acanthocytes and UPCR of 12mg/mg. Review of past records since 2012 showed low grade proteinuria and hematuria which had not been evaluated. C3 was low at 80 mg/dl with elevated circulatory IgA levels at 855 mg/dl. Kidney biopsy revealed diffuse proliferative IgA glomerulonephritis with features of MGN and associated focal and segmental cellular and fibrocellular crescents. She was subsequently started on steroids. For progressive renal failure she was initiated on dialysis.

**Results:**
This case highlights the dilemma in diagnosis of a RPGN presentation of IgAN in the setting of systemic infections. Our patient has had multiple infections with gram-negative organisms prior to this presentation, although not diabetic or elderly. She had evidence of consistent low grade hematuria and proteinuria, years before this presentation, pointing towards possibly underlying secondary IgA nephropathy associated with IBD; in addition, the elevated ratio of IgA/C3 (ratio=10) was consistent with this diagnosis. Lack of staining over IgA, maintenance of lambda kappa staining, absence of subepithelial humps may suggest crescentic IgAN rather than IGA.

It is essential to differentiate these two conditions as treatment differs. We propose that presence of low grade hematuria and proteinuria be evaluated for underlying glomerular diseases in patients with IBD.

---

Smoldering C3 Glomerulonephritis Exacerbated by Blood Transfusion and Inactivated after Immunosuppression Therapy

**Background:**
C3 glomerulonephritis (C3GN) is a separate form of proliferative glomerulopathy under category of C3 glomerulopathies, which is characterized by isolated staining of C3 deposits associated with dysregulation of the complement alternative pathway (AP) secondary to acquired autoantibodies and/or genetic mutation of complement proteins.

**Methods:**
We report a case of a 49-year-old male, presenting with bilateral lower extremity edema, hypertension, plasma creatinine of 1.2mg/dl, proteinuria to creatinine ratio 5.4 gm/l and bland urine, markedly depressed C3 level of 7mg/dl [90-180], normal C4, and normal ASO titer. A renal biopsy was planned. In the meantime, the patient received a blood transfusion, after which he became acutely febrile, developed a non-oliguric acute kidney injury (AKI) with creatinine peak of 3.1mg/dl, worsened proteinuria, and dark urine with an active sediment. Therefore pulse steroids were commenced then oral steroid 1mg/kg maintained. Renal pathology shows evidence of C3 glomerulonephritis. Further AP workup revealed presence of Factor H autoantibodies 28 Unit/mL ([<22], C3 nephritic factor [C3NeF] 38 units/ml [<=20] and markedly elevated soluble membrane attack complex serum C5b-9 >1700 [Reference Range: <=244 ng/mL]. Patient underwent Plasma exchange for 7 sessions, then rituximab two weekly doses (0.5 and 1 gm), and maintained on prednisone. Patient improved clinically, creatinine stabilized at 1.2mg/dl and proteinuria decreased. In addition Factor H autoantibodies normalized, C3NeF decreased to 6 units/ml, serum C5b-9 went to 546 ng/mL and C3 increased to 55mg/dl. Mycophenolate introduced at this time and steroids tapered.

**Results:**
An underlying genetic or acquired complement alternative pathway abnormality can be possibly exacerbated by triggering immune complement system which subsequently triggers an unbalanced excessive continual driving of complement terminal pathway activation. In our case, blood transfusion might have led to induction of complement cascade activity either through classical or alternative pathway dysregulation. There is limited evidence and no randomized trials to inform therapeutic decisions in C3GN. In our case, the therapeutic regimen may mitigate AP pathway activity and normalize factor H autoantibodies.

---

Complications of Therapy for Pauu-Immune Rapidly Progressive Glomerulonephritis

**Background:**
Rapidly progressive glomerulonephritis (RPGN) is a clinical syndrome resulting from damage to the glomeruli and is characterized by progressive loss of renal function over a short period of time. RPGN is classified into three categories, each based upon the immunofluorescence pattern. Type III, also known as pauci-immune RPGN, accounts for about 50% of RPGN cases.

**Methods:**
A 68-year-old Hispanic female with history significant for P-ANCA-associated pauci-immune RPGN and Type II Diabetes Mellitus presented with complaints of weakness, worsening lower extremity edema that was refractory to outpatient diuretics and dysuria. Patient had been on an immunosuppressant (Rituxan) and steroids (Prednisone 40mg/day) with plans to taper. On physical examination, the patient was noted to have Cushingoid features (moon facies) along with 3+ pitting edema to the mid shins bilaterally with bruising apparent in the bilateral feet and ankles. Lab work was notable for leukocytosis and urinalysis positive for urinary tract infection. Patient was admitted for management of the multiple side effects related to prednisone therapy including marked edema refractory to oral diuretics, muscle weakness, and urinary tract infection. Patient was treated with IV diuretics for the lower extremity edema and for symptomatic care of the urinary tract infection. Patient had improvement of her symptoms and was sent home with a steroid taper to follow up with nephrology outpatient.

**Results:**
Treatment of RPGN relies on the use of corticosteroids. This case illustrates the importance of recognizing side effects seen with therapy and assessing the short-and long-term effects of such therapy.

---

ACEI Induced Anaphylactoid Reactions in Polysulfone Dialyzers

**Background:**
Gone are the days of severe anaphylactic reactions to Ethylene oxide and non-biocompatible membrane dialyzers; with the new era of using polysulfone and other synthetic dialyzers. Hypersensitivity reactions to these synthetic dialyzers are also known.

**Methods:**
Reports of Anaphylactoid Reactions on ACEI dialyzing via PAN (AN69) dialyzer is widely known to occur from bradykinin effects, but similar reactions...
in patients on ACEI’s using non – PAN (AN69) is not well known. We hereby present a case of anaphylactoid reaction to two different manufacturers polysulfone dialyzers in a patient on ACEI.

Methods: A 53 year old male with a history of ESRD on HD for 3 years, HTN on Lisinopril 10mg daily, CAD S/P CABG X 3 stents and type 2 DM with retinopathy, transferred to the ER from his HD unit due to sudden shortness of breath symptoms with 86% O₂sats and becoming restless about 12 minutes after starting his regular dialysis session. He was dialyzed on rexeed - 18R, a reusable dialyzer and was on the 9th re-use that day. He also endorsed similar symptoms about 3 days prior to presentation by the 8th use but those were self limiting. Patient had always tolerated his HD sessions and was initially on Revaclear polysulfone dialyzer briefly. He had been on Lisinopril treatment for hypertension management for years. No prior allergy to food or medications. Chest xray evaluation showed mild pulmonary edema, cardiac work up including an ECHO and Cardiac Cath were negative. Patient had similar reactions the next day after hospital admission when revaclear polysulfone dialyzer was used. His symptoms resolved with supplemental O₂ treatment and was able to complete his dialysis session. He had not received his Lisinopril since admission given hyperkalemia and was able to tolerate dialysis from the 3rd day onward. Patient’s Lisinopril was eventually discontinued and he is back to his outpatient HD unit using the same reused polysulfone dialyzer and has not had any recurrent symptoms.

Results: Conclusions: ACEI triggered anaphylactoid reactions have not been commonly reported in patients using non-PAN dialyzers and literature review shows very few cases of similar reactions in ACEI and Polysulfone dialyzers. With the wide spread use of both Polysulfone dialyzers in HD units and increasing number of dialysis patients on ACEI, knowledge of such possible reactions can help in the management of our dialysis patients.

PUB664
Histoplasmosis in a Renal Transplant Patient: A Case Report
Fernanda T. Ferreir,1 Antonio A. Portela Neto,2 Laura Onuchic,3 Marcella M. Frediani,1 Precil D. Neves,2 Flavio De Paula,2 Elias David-Neto.1
1USP, Sao Paulo, Brazil; 2University State of Sao Paulo, Sao Paulo, Brazil; 3University of Sao Paulo School of Medicine, Sao Paulo, Brazil.

Background: Transplant success depends on achieving the ideal doses of immunosuppressants capable of avoiding rejection while still maintaining sufficient immune level to prevent opportunistic infections. Histoplasmosis is a fungal disease, with a peak incidence of 0.5% in transplant patients and clinical manifestations may vary from common cold-like symptoms to generalized systemic infections, lethal if left untreated.

Methods: A 59-year-old female kidney transplant recipient due to lupus nephritis, underwent a second unrelated live donor transplant 12 years ago. Initial immunosuppression include thymoglobulin and maintenance consisted on everolim, mycophenolate mofetila and prednisone. She had been recently diagnosed with transplant glomerulopathy during investigation of chronic graft dysfunction. She presented enterorrhagia 4 days after admission and a significant fall in hemoglobin: 8.5~ 5.0 g/dL and was, therefore, hospitalized. She was investigated with upper digestive endoscopy, abdominal and chest tomography and blood cultures; all normal. She underwent colonoscopy, which revealed an ulcerated lesion in the ascending colon, compromising ¾ of the colon circumference and biopsies were performed. During hospitalization, the patient progressed with worsening of renal function and infectious parameters, returning to the chronic hemodialysis program and starting treatment with Levofoxacin, Clarithromycin, Etambutol and Amphotericin B, according to our infectology guidelines for empiric coverage, without effective clinical improvement, and maintenance therapy was considered a few months later. Although digestive hemorrhages caused by intestinal infections are most commonly associated with cytomegalovirus or herpes simplex, in our patient such agents were not identified. The colonoscopy showed active granulomatous colitis with fungal structures of Histoplasma sp, as well as a positive BAAR. Treatment was modified to Itraconazole. The patient was discharged from hospital using this medication after clinical improvement.

Results: Conclusions: We described a very rare case that shows the importance of extensive investigation in the presence of renal dysfunction, fever or other systemic manifestations in immunosuppressed patients, since they may present atypical pathologies and clinical manifestations, with potentially tragic evolution.

PUB665
Lung Cancer in the Kidneys, Blood in the Urine Brad Long, Mazdak A. Khatighi, Josephine Abraham. University of Utah, Salt Lake City, UT.

Background: Metastatic squamous cell lung cancer is a lethal disease that can involve any organ in the body. Most frequent sites of metastases are bone, liver, brain, and adrenal glands. Rarely, the kidney is involved. We present a case of metastatic SCC of the lung involving the kidneys presenting with gross hematuria and AKI.

Methods: A 68 year old male with metastatic squamous cell lung carcinoma admitted to the acute care oncology clinic with four days’ progressive shortness of breath and gross hematuria and passage of a large clot. Creatinine was elevated to 2.75mg/dL from a baseline of 1.0mg/dL. Renal ultrasound showed enlarged kidneys bilaterally, with loss of normal corticomedullary differentiation and small bilateral cystic structures. CT scan from four months prior showed large kidneys with infiltrative process present in the right kidney, with obliteration of the superior pole collecting system.

Results: Recent kidney biopsy revealed poorly differentiated squamous cell carcinoma metastatic from the lung. AKI during this admission was felt to be due to infiltration of the renal parenchyma by tumor cells. Glomerulonephritis due to chemotherapy was considered though felt unlikely.

Conclusions: Renal invasion by primary lung cancer is rare and can present with hemorrhage leading to gross hematuria and impaired renal function. Hematuria and acute kidney injury should also prompt consideration of chemotherapy-related effects. In any event, lung cancer that invades the kidneys carries a very poor prognosis.

PUB666
IgA-Dominant Post Infectious Glomerulonephritis and IgA Nephropathy: Different Diseases with Similar Mechanisms? Brenden D. Connor,1 Swati Rao,1 Duncan B. Johnstone,1 Manjula Balasubramanian,1 Iris J. Lee.1

1Temple University School of Medicine, Philadelphia, PA; 2Einstein Medical Center, Philadelphia, PA.

Background: IgA glomerular deposition is a hallmark of IgA nephropathy (IgAN). Rarely, isolated IgA deposition is observed in post infectious glomerulonephritis (PIGN) instead of IgG. IgA-dominant PIGN, more common in elderly with diabetes mellitus (DM), has a guarded prognosis with 40% progression to ESRD. Due to similar findings in clinical and histological presentations, the differentiation of IgA dominant PIGN from IgAN can be challenging. Both diseases can present with hematuria, proteinuria, acute kidney injury, and have mesangial and endocapillary proliferation with IgA and C3 deposits on biopsy. When present, evidence of staphylococcal infection, low complements, large subepithelial deposits and polymorphonuclear (PMN) cellular infiltrates on biopsy favor IgA dominant PIGN. We report a case of IgA dominant PIGN with challenging diagnostic features.

Methods: A 75 y/o Cuban female with DM presented with gross hematuria and 2 weeks of fatigue and weight loss, without other symptoms. No findings were notable on physical exam. Labs demonstrated creatinine (Cr) of 5.3mg/dL (baseline 0.9mg/dL), hemoglobin 8.3g/dL, normal platelets, 1 gm proteinuria and dysmorphic RBC on urine microscopy. There was no clinical or laboratory evidence of infection. Ultrasound of the kidneys was normal. Serologic work up was negative and complement levels were normal. 
Minimal Change Disease Relapse after Influenza Vaccination

Oluosu Isikulu, Ruth C. Campbell, Roberto Pisoni. Medical University of South Carolina, Charleston, SC.

Background: Minimal change disease (MCD) is a major cause of idiopathic nephrotic syndrome (NS) accounting for 15% of idiopathic NS cases in adults. It is characterized by severe proteinuria, hypoalbuminemia, and hypercholesterolemia leading to edema. MCD onset and relapse following vaccinations has been described in the literature since 1966, but only few cases due to influenza vaccination are reported.

Methods: We report a case of MCD relapse after influenza virus immunization. Presentation was atypical with accelerated deterioration of renal function. Patient was a 45-year-old white woman with MCD diagnosed in December 2014 after presenting with abrupt onset of bilateral hand, facial, and lower extremity edema, and frothy urine. She denied recent infections or NSAID use. She was normotensive. Renal biopsy demonstrated glomerulitis, with infiltrating PMN in multiple glomeruli, and hepatic chemistries were normal with creatinine 0.7 mg/dL except for serum albumin 3.0 g/dL. UA showed protein 100 mg/dL and 24 hour proteinuria was 1.5 g. Relapse of proteinuria was documented 2 weeks later and persisted after completing 1 month of prednisone 1mg/kg daily was started in addition to torsemide 5mg/day and rosvastatin 5mg/day. Complete remission of proteinuria was documented 2 weeks later and persisted after completing a 6-month course of prednisone. Prednisone was tapered to 2.63mg/dl.

Results: Our case as well as previous anecdotal reports suggest that influenza vaccination and the resulting stimulation of the immune system may cause MCD. This finding demands further investigation in the pathophysiology of MCD and also requires consideration of further vaccinations in this patient population.

PUB668

An Uncommon Cause of Hypertension in Sepsis

Jin Lee,1 Sharad Virmani.2
1Gwinnett Medical Center Internal Medicine Residency Program, Lawrenceville, GA; 2Georgia Nephrology, LLC, Lawrenceville, GA.

Background: Pheochromocytoma is responsible for 0.1% of hypertension cases. Oftentimes, the classic triad of palpitations, headache, and diaphoresis can be overlooked or even absent. Pheochromocytoma should be considered in patients presenting with resistant hypertension, paroxysmal hypertension or labile blood pressure. We present a case of Pheochromocytoma masked by sepsis.

Methods: A 52-year-old Korean female with no past medical history presented to Gwinnett Medical Center with sepsis secondary to pneumonia. On admission, BP was 86/43 mmHg and pulse was 124 b/min. The patient was started on broad spectrum antibiotics with IV fluid resuscitation. The patient clinically improved with resolution of pneumonia but she remained tachycardic with labile blood pressure (SBP 68-200, DBP 37-93mmHg). She required intermittent Norepinephrine and Nicardipine for management of her dramatic BP fluctuations. Further questioning of her medical history revealed two years of intermittent episodes of flushing and palpitations which she believed to be related to menopause, thus she did not seek medical assistance. Evaluation for secondary causes of hypertension revealed a 4.8x4x5.3 cm right adrenal mass on renal duplex. This raised a suspicion for pheochromocytoma and a 24 hour urine metanephrine analysis was performed resulting in normetanephrine levels of 5208mcg/24h, metanephrine levels of 1134mcg/24h. Confomatory MRI with gadolinium showed a 5cm heterogenous, cystic supra-rennal mass with central necrosis. She was immediately started on phenytoin and nifedipine. Optimization of BP was achieved and was deemed stable for discharge with plans for operative removal of the tumor after two weeks of alpha blockade.

Results: Our case of a thorough history to identify a rare disorder overlapped by a common presentation of sepsis.

PUB669

Crescentic IgA Nephropathy (IgAN) in a Patient with Underlying Crohn’s Disease – A Treatment Challenge

Alinda M. Sarma,1 Anca C. Vlasic.2
1Cleveland Clinic, Cleveland, OH; 2Comprehensive Kidney Care, Westlake, OH.

Background: Crescentic IgA Nephropathy (IgAN), defined as >50% crescentic glomeruli on biopsy, is a common cause of rapidly progressive glomerulonephritis (GN), but a rare manifestation of IgA vasculitis. We present a case of IgAN in a chronically immunosuppressed patient.

Methods: A 49 year old female was admitted for profound malaise, found to severe acute kidney injury (AKI). Her past medical history was significant for Crohn’s disease and secondary inflammatory arthritis treated with prednisone, mesalazine, 6-mercaptopurine, methotrexate and infliximab over the years, recurrent skin rash with biopsy suggestive of leucocytoclastic vasculitis, chronic sinusitis. Physical examination was significant for purpuric rash on lower extremities. Laboratory work-up revealed serum creatinine of 2.9 mg/dL, BUN of 57 mg/dL, WBC of 13.06 k/uL, ESR of 111 mm/hr and CRP of 20.6 mg/dL, urinalysis with dysmorphic RBCs and RBC casts. P-ANCA, C-ANCA, Anti-proteasome 3, Anti-myeloperoxidase, ANA were all negative, and serum complement levels were normal. Kidney biopsy showed focal endocapillary proliferative and crescentic GN with IgA-dominant deposits, and electron microscopy confirmed the presence of mesangial and peripheral capillary wall immune deposits. Differential diagnoses included large vessel vasculitis/cutaneous vasculitis in setting of Chrohn’s disease, cutaneous vasculitis and GN secondary to medications (infliximab or TNF alpha inhibitor), and IgA vasculitis.

Results: Patient was started on pulse dose steroids and oral cyclophosphamide. After three months, creatinine was 1.5 mg/dL, with resolution of hematuria and rash.

PUB670

Antiphospholipid Syndrome Started with Microangiopathy and Developed Right Renal Infarction and Left Renal Artery Stenosis

Masako Nagata, Takayuki Fujii, Kajii Saito, Mizuki Shinozaki, Mayu Morimoto, Noriko Terasaki, Hiroaki Tanaka, Satoshi Suzuki. Seirei Sakura Citizen Hospital, Chiba, Japan.

Background: The kidney is one of the organs that is involved in patients with primary antiphospholipid syndrome (APS). Renal involvement in APS is characterized by non-inflammatory occlusion of renal vessels ranging in size from large vessels to intrarenal microvessels. However, there are no reports of these lesions over time.

Methods: This is a case of a 48-year-old woman, who was previously in good health presented to our department for the investigation of proteinuria when she was 44 years old. She did not have hypertension. The serum creatinine level was 0.5 mg/dL. Urinalysis showed no microscopic hematuria and mild proteinuria (0.5 g/day). Imaging did not show renal artery stenosis. When she was 45 years old, renal biopsy was performed for continuous mild proteinuria (0.5 g/day). Renal biopsy showed fibrous intimal hyperplasia of arteries and segmental glomerular basement membrane reduplication. Immunofluorescence showed IgG deposits in her capillaries. She was suspected of membranous nephropathy and prescribed angiotensin receptor blocker. Three years later, she admitted to our hospital due to right back pain, and her contrast computerized tomography (CT) scan revealed right renal infarction and left renal artery stenosis. APS was considered the most likely diagnosis because her lupus anticoagulant, anticardiolipin antibody, and anti-II2 glycoprotein I antibody were positive. There was no thrombosis in other organs. Because she was not suspected systemic lupus erythematosus, only anticoagulation treatment was started. A retrospective analysis shows that renal biopsy three years ago showed microangiopathy which might be a pathological feature of APS nephropathy.
TINU Syndrome: A Diagnosis of Exclusion

Unknown Etiology

Natasha

approach to ruling out alternative diagnoses.

days, followed by PO steroid taper) with improvement in renal function back to baseline

Nephritis and Uveitis (TINU) syndrome requires a high index of suspicion. Variable

laboratory markers make its diagnosis all the more complex. We report the case of a

of thromboembolic state so far revealed no evidence of atrial fibrillation, and TTE was

hemodialysis on day 5. She developed intracranial hemorrhage and status epilepticus

artery thromboembolic disease of unknown etiology.

One patient's intracranial hemorrhage resolved by CT imaging she was initiated on IV heparin and her neurological status was monitored closely.

Conclusions: This is a rare case that we were able to observe APS started with microangiopathy and developed right renal infarction and left renal artery stenosis. This might be a process of development from intrarenal microvasculature to large vessels in renal involvement in APS.

PUB673

Underdiagnosis of Adrenocortical Adenoma Franklin Lam,²
Rafia I. Chaudhry,² Loay H. Salman,¹ Maurice Monroy,² ¹Albany Medical College, Albany, NY; ²None, Providence, RI.

Background: Primary hyperaldosteronism, described by Conn in 1956 as an aldosterone-secreting adrenal adenoma results in resistant HTN. Less than 1% of cases with HTN were initially attributed to Conn's syndrome. Recent data indicates a higher incidence of Conn’s syndrome of up to 5-15% in pts with HTN, suggesting considerable underdiagnoses.

Methods: 33 yr-old Caucasian male, with PMHx of obesity and HTN, referred for HTN, hypokalemia in 2013. BP 178/100 mmHg on Amiodipine 10 mg. Fundoscopic exam revealed bilateral retinal AV nicking. Sr Cr 1.0 mg/dL, K 3.3 mmol/L, and CO2 32 mmol/L. Renal US unremarkable, doppler US negative for renal vein stenosis. Plasma aldosterone concentration (PAC) 7.7 ng/dL, plasma renin activity (PRA) 0.86, 24-hr ur aldosterone (ALD) 40.40, Ur Na 182. MRI negative for adrenal abnormality. BP remained normotensive controlled on Aldactone, Amlopril, and Levothroid. The patient was started for OSA. HTN remained sub optimally controlled HTN 3 yrs later, and repeat studies consistent with hyperaldosteronism (PAC 37.8, 24-hr Ur ald 40.50, PRA 4.81 and 6.17). CT adrenal mass protocol revealed 1.1-cm left adrenal nodule. Adrenal venous sampling (AVS) confirmed lateralization to left adrenal gland, and adrenalectomy will be pursued.

Results: Adrenal CT scan has superior spatial resolution than MRI to detect adrenal adenoma. If CT scan is negative, or demonstrates bilateral abnormalities, or unilateral abnormality in pt > age 35, AVS can confirm unilateral disease to explore the role of surgical intervention for primary hyperaldosteronism.

Conclusions:

PUB674

The Role of Continuous Renal Replacement in the Management of Type B LacticAcidosisDueToHemophagocyticLymphohistiocytosis Ryan Mullane, Scott G. Westphal. University of Nebraska Medical Center, Omaha, NE.

Background: Hemophagocytic Lymphohistiocytosis (HLH) is a rare, life-threatening complication of excessive immune activation caused by uncontrolled release of inflammatory cytokines from activated macrophages and T lymphocytes. Type B lactic acidosis due to HLH is extremely rare with few case reports; therefore, the optimal treatment strategy is unknown. We present a case of type B lactic acidosis due to HLH where continuous renal replacement therapy (CRRT) and sodium bicarbonate infusion were used successfully in the management of the lactic acidosis.

Methods: A 64-year-old female with chronic lymphocytic leukemia and anaplastic large cell lymphoma was admitted for pancytopenia and hyponatremia. Examination was notable for splenomegaly and recurrent fevers. Extensive evaluation into an infectious etiology was unremarkable. Further testing revealed hypertriglyceridemia (triglyceride level of 362 mg/dL), hyperferritinemia (ferriin level of 60,917 ng/mL), transaminisits, and an elevated soluble IL-2 receptor level (111,000 pg/mL); given her presentation, she was diagnosed with HLH. Over the next 24 hrs, despite remaining normotensive with relatively undegaged renal function, she developed lactic acidosis with a maximum lactate level of 16.6 mmol/L and profound acidemia. She was started on CHOP chemotherapy and we initiated treatment for her lactic acidosis with IV sodium bicarbonate and continuous venovenous hemodialysis (CVVHDO) with a high dialysate flow rate of 5,000 mL/hour (60 mL/hour) to control the acidosis. The patient’s lactic acidosis resolved over the following days and her sodium bicarbonate infusion and CRRT were both discontinued.

Results:

Conclusions: Type B lactic acidosis and HLH both have poor survival rates. Historically, the use of renal replacement therapy and bicarbonate infusions for type B lactic acidosis is controversial with limited evidence of benefit in Type B lactic acidosis. Our patient had resolution of lactic acidosis due to HLH following chemotherapy initiation and treatment with CRRT and sodium bicarbonate infusion. Concurrent with chemotherapy, sodium bicarbonate infusion with CRRT may be a potential novel management approach for type B lactic acidosis due to HLH.

PUB675

Cases of Intimal Arteritis with Phantom Etiology John T. Nguyen,² Aleksandra De Golovine,¹ UTHSC-H, Houston, TX; ¹University of Texas Houston Medical School, Houston, TX.

Background: V lesions in transplant renal biopsy have been shown to be important in their ability to predict graft failure. The conventional thought is that V lesions represent T cell-mediated rejection however there is concern that V lesions may be present in antibodymediated rejection as well. We report three cases of renal transplant patients who underwent indicated renal biopsy that demonstrated isolated intimal arteritis.

Methods: The first case is a 55 year old male with end stage renal disease after he donated a kidney and developed renal cell carcinoma in his remaining kidney. He underwent deceased donor transplant on 10/31/2016. The patient had delayed graft function which resulted in a biopsy on 11/3/2016 that showed 3 arteries with intimal arteritis that was almost oblitative. The patient was clinically diagnosed with atypical HUS and started on ecclulizumab shortly after. The patient’s renal function stabilized but
Hypophosphatemia and Cardiac Arrest in an Elderly Hemodialysis Patient
Joanna Cook, Amina Khan, Munis A. Mattu, David E. Webb, Virginia J. Saviñ, Kansas City VA Medical Center, Kansas City, MO

Background: About 40% of hemodialysis (HD) patients funded by Medicare are ≥ 65 years old. Hypophosphatemia (<4.5 mg/dl) is hyperphosphatemia is associated with increased mortality in HD patients. Hypophosphatemia is the primary concern for younger patients, while hypophosphatemia is more common in elderly patients and is associated with higher all-cause and cardiovascular mortality.

Methods: A retrospective chart review of 65 HD patients admitted to our VA HD unit received a liberal diet, nutrition and hypophosphatemia prior to starting HD. A total number of 430 patients were included in this study. The numbers of patients and total HD sessions were 430 and 11,242, respectively. The detailed patient data were collected from the Clinical Research, Baltimore, MD; 9 Massachusetts General Hospital, Boston, MA; 10 Metabolon, Durham, NC; 3 National Institute of Diabetes and Digestive Kidney Diseases (NIDDK), Bethesda, MD; 4 The Broad Institute of MIT and Harvard, Cambridge, MA; 5 The Children’s Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; 6 University of Pennsylvania, Philadelphia, PA; 7 Welch Center for Prevention, Epidemiology & Clinical Research, Baltimore, MD; 8 The Broad Institute of MIT and Harvard, Cambridge, MA; 9 Group/Team: On behalf of NIDDK CKD Biomarkers Consortium.

Background: Hyperphosphatemia can cause and cardiovascular mortality. About 40% of hemodialysis (HD) patients funded by Medicare are ≥ 65 years old. Hypophosphatemia (<4.5 mg/dl) is associated with increased mortality in HD patients. Hypophosphatemia is the primary concern for younger patients, while hypophosphatemia is more common in elderly patients and is associated with higher all-cause and cardiovascular mortality.

Methods: A retrospective chart review of 65 HD patients admitted to our VA HD unit received a liberal diet, nutrition and hypophosphatemia prior to starting HD. A total number of 430 patients were included in this study. The numbers of patients and total HD sessions were 430 and 11,242, respectively. The detailed patient data were collected from the Clinical Research, Baltimore, MD; 9 Massachusetts General Hospital, Boston, MA; 10 Metabolon, Durham, NC; 3 National Institute of Diabetes and Digestive Kidney Diseases (NIDDK), Bethesda, MD; 4 The Broad Institute of MIT and Harvard, Cambridge, MA; 5 The Children’s Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; 6 University of Pennsylvania, Philadelphia, PA; 7 Welch Center for Prevention, Epidemiology & Clinical Research, Baltimore, MD; 8 The Broad Institute of MIT and Harvard, Cambridge, MA; 9 Group/Team: On behalf of NIDDK CKD Biomarkers Consortium.

Background: Hyperphosphatemia can cause and cardiovascular mortality. About 40% of hemodialysis (HD) patients funded by Medicare are ≥ 65 years old. Hypophosphatemia (<4.5 mg/dl) is associated with increased mortality in HD patients. Hypophosphatemia is the primary concern for younger patients, while hypophosphatemia is more common in elderly patients and is associated with higher all-cause and cardiovascular mortality.

Methods: A retrospective chart review of 65 HD patients admitted to our VA HD unit received a liberal diet, nutrition and hypophosphatemia prior to starting HD. A total number of 430 patients were included in this study. The numbers of patients and total HD sessions were 430 and 11,242, respectively. The detailed patient data were collected from the Clinical Research, Baltimore, MD; 9 Massachusetts General Hospital, Boston, MA; 10 Metabolon, Durham, NC; 3 National Institute of Diabetes and Digestive Kidney Diseases (NIDDK), Bethesda, MD; 4 The Broad Institute of MIT and Harvard, Cambridge, MA; 5 The Children’s Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; 6 University of Pennsylvania, Philadelphia, PA; 7 Welch Center for Prevention, Epidemiology & Clinical Research, Baltimore, MD; 8 The Broad Institute of MIT and Harvard, Cambridge, MA; 9 Group/Team: On behalf of NIDDK CKD Biomarkers Consortium.

Background: Hyperphosphatemia can cause and cardiovascular mortality. About 40% of hemodialysis (HD) patients funded by Medicare are ≥ 65 years old. Hypophosphatemia (<4.5 mg/dl) is associated with increased mortality in HD patients. Hypophosphatemia is the primary concern for younger patients, while hypophosphatemia is more common in elderly patients and is associated with higher all-cause and cardiovascular mortality.

Methods: A retrospective chart review of 65 HD patients admitted to our VA HD unit received a liberal diet, nutrition and hypophosphatemia prior to starting HD. A total number of 430 patients were included in this study. The numbers of patients and total HD sessions were 430 and 11,242, respectively. The detailed patient data were collected from the Clinical Research, Baltimore, MD; 9 Massachusetts General Hospital, Boston, MA; 10 Metabolon, Durham, NC; 3 National Institute of Diabetes and Digestive Kidney Diseases (NIDDK), Bethesda, MD; 4 The Broad Institute of MIT and Harvard, Cambridge, MA; 5 The Children’s Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; 6 University of Pennsylvania, Philadelphia, PA; 7 Welch Center for Prevention, Epidemiology & Clinical Research, Baltimore, MD; 8 The Broad Institute of MIT and Harvard, Cambridge, MA; 9 Group/Team: On behalf of NIDDK CKD Biomarkers Consortium.

Background: Hyperphosphatemia can cause and cardiovascular mortality. About 40% of hemodialysis (HD) patients funded by Medicare are ≥ 65 years old. Hypophosphatemia (<4.5 mg/dl) is associated with increased mortality in HD patients. Hypophosphatemia is the primary concern for younger patients, while hypophosphatemia is more common in elderly patients and is associated with higher all-cause and cardiovascular mortality.

Methods: A retrospective chart review of 65 HD patients admitted to our VA HD unit received a liberal diet, nutrition and hypophosphatemia prior to starting HD. A total number of 430 patients were included in this study. The numbers of patients and total HD sessions were 430 and 11,242, respectively. The detailed patient data were collected from the Clinical Research, Baltimore, MD; 9 Massachusetts General Hospital, Boston, MA; 10 Metabolon, Durham, NC; 3 National Institute of Diabetes and Digestive Kidney Diseases (NIDDK), Bethesda, MD; 4 The Broad Institute of MIT and Harvard, Cambridge, MA; 5 The Children’s Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; 6 University of Pennsylvania, Philadelphia, PA; 7 Welch Center for Prevention, Epidemiology & Clinical Research, Baltimore, MD; 8 The Broad Institute of MIT and Harvard, Cambridge, MA; 9 Group/Team: On behalf of NIDDK CKD Biomarkers Consortium.

Background: Hyperphosphatemia can cause and cardiovascular mortality. About 40% of hemodialysis (HD) patients funded by Medicare are ≥ 65 years old. Hypophosphatemia (<4.5 mg/dl) is associated with increased mortality in HD patients. Hypophosphatemia is the primary concern for younger patients, while hypophosphatemia is more common in elderly patients and is associated with higher all-cause and cardiovascular mortality.

Methods: A retrospective chart review of 65 HD patients admitted to our VA HD unit received a liberal diet, nutrition and hypophosphatemia prior to starting HD. A total number of 430 patients were included in this study. The numbers of patients and total HD sessions were 430 and 11,242, respectively. The detailed patient data were collected from the Clinical Research, Baltimore, MD; 9 Massachusetts General Hospital, Boston, MA; 10 Metabolon, Durham, NC; 3 National Institute of Diabetes and Digestive Kidney Diseases (NIDDK), Bethesda, MD; 4 The Broad Institute of MIT and Harvard, Cambridge, MA; 5 The Children’s Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; 6 University of Pennsylvania, Philadelphia, PA; 7 Welch Center for Prevention, Epidemiology & Clinical Research, Baltimore, MD; 8 The Broad Institute of MIT and Harvard, Cambridge, MA; 9 Group/Team: On behalf of NIDDK CKD Biomarkers Consortium.
oxygen species, measured by an electric spin resonance-based method, and inflammatory cytokines.

Results: No severe unfavorable effects were confirmed during the program. The patients received the renal rehabilitation showed significant increase of daily activity, exercise tolerance and muscular strength, and decrease of blood pressure, LDL and HDL. The program significantly increased serum scavenging activity against alkylperoxyl radical (ROO·) within the first 3 months, then against hydroxyl radical (OH) within the next 6 months. Contrary, superoxide (O₂⁻) scavenging activity was decreased within the first 3 months, and then alkoxy radical (RO·) scavenging activity was decreased within 9 months. An increase of TNF-α was detected in the patients with the exercise program.

Conclusions: Our study revealed that the renal rehabilitation gradually improved oxidative stress over time. The effects on antioxidant system are not uniform and their timing window are various. Most of these results are favorable, while there still remains negative effects including TNF-α and RO· scavenging activity. The change of O₂⁻ scavenging activity may be the result of an adaptation against already increased oxidative stress in HD patients.

Funding: Government Support - Non-U.S.

**PUB681**

Evaluation of Peridialytic Change in Body Composition Using Three Bioimpedance Devices (Ohanmaz Thwin, Fansan Zhu, Priscila Preciado, Xia Tao, Laura Rosales, Jochen G. Raimann, Stephan Thijssen, Peter Kotanko. Renal Research Institute, New York, NY; Icahn School of Medicine at Mount Sinai, New York, NY.)

**Background:** Body mass (BM) can be divided into fat mass (FM) and lean body mass (LBM). Skeletal muscle mass (SMM) is a major component of LBM. In general, the ratio of LBM to total body water (TBW) is approximately 0.73. LBM can be calculated if TBW is known. The aim of this study was compare 3 commercially available bioimpedance devices with respect to (1) measurements of peridialytic BC changes and (2) BC measurements in healthy subjects (HS).

**Methods:** Ten HD patients (8 males, age 58.1±12 years) and 12 HS (7 females, 33.3±5.6 years) were studied. Measurements were performed pre and post HD in patients and once in HS. We used three multi-frequency bioimpedance devices: InBody 770 (InBody USA, Cerritos, CA), Seca mBCA 514 (Seca North America, Chino, CA), and Hydra 4200 (Xitron Technologies, San Diego, CA). InBody and Seca report TBW, FM, LBM, and SMM. Hydra provides FM, LBM, and SMM using a model (Chamney, Am J Clin Nutr, 2007). We analyzed peridialytic BC changes and BC in HS.

**Results:** All devices reported a significant peridialytic decrease in BM, TBW and LBM (Fig.1 a, c, d). However, FM results differed between the devices: InBody reported no change, while Seca reported increased with a high variability and Hydra found decreased (Fig 1 b). The pre HD FM-to-BM ratio (%FM) was higher with Hydra compared to InBody and Seca, respectively (Table 1). In HS, however, %FM was significantly higher with Seca compared to Hydra and InBody, respectively. In both HD and HS LBM was reported lower with Hydra compared to InBody and Seca, respectively. In HD patients and HS SMM was reported lower with Hydra compared to InBody.

**Conclusions:** In this pilot study the peridialytic FM increase suggests that LBM may be underestimated due to use of a constant TBW/LBM ratio (0.73). This ratio may not correct in dialysis patients.

**PUB682**

Status of Nutrition in Hemodialysis Patients Survey: SNAPs and Biomarker Profiling in Stage 5 Chronic Kidney Disease Hemodialysis Patients with Reference to Apparent Metabolic Syndrome and Vascular Manifestations (Talia R. Weinstein, Odile Azoulay, Mona Boaz, Ariel University, Ariel, Israel; Tel Aviv Medical Center, Tel Aviv, Israel; Tel Aviv University, Tel Aviv, Israel; Rabin Medical Center, Petach Tikva, Israel.)

**Background:** Protein-energy wasting (PEW) is prevalent in hemodialysis (HD) patients, due to inadequate dietary intake and an increased catabolic state. Adverse outcomes include increased hospitalization, morbidity and death. The prevalence ranges from 18-75%, depending on the method used for PEW definition. Expert panels have recommended dietary modifications intended to prevent PEW in this population. The primary objective of this study was to survey nutrition intake in Israeli HD patients and to estimate the PEW prevalence; additionally, the study measured patients’ mean energy and protein intake, and their adherence to dietary recommendations.

**Methods:** This multi-center, cross-sectional study included a representative sample of HD patients treated at 9 hospitals throughout the country. At each center, the population was stratified for age; sex; ethnicity; dialysis vintage (< 1 year vs. > 1 year); dialysis shift; and comorbidities. Patients were proportionally randomly sampled from each strata. Dietary intake was assessed using the 24-hour recall. Biochemistry, demographic data, prescription list and anthropometric data were extracted from the electronic medical record.

**Results:** The study included 378 HD patients, mean age 64.8±12.7 years, mean dialysis vintage 2.4±4.9 years, Kt/V 1.4±0.29, 52% female, 80% Jews. Comorbidities included hypertension (65%); dyslipidemia (35%) and diabetes (33%). Serum albumin was 3.7±0.4 g/L, serum phosphorus was 5.1±1.5 mg/dL and c-reactive protein was 11.7±25.9 mg/dL. Total energy intake, energy intake per kg/ideal body weight and protein per kg/ideal body weight were all significantly below recommendations. Only 19% consumed adequate calories, 29% consumed adequate protein. Almost 70% of patients had below-normal serum albumin levels; 58% of the study population was classified as having PEW. Only 8.2% of the study population overall and only 15.5% of patients with PEW received nutrition supplementation. Almost 50% of patients were categorized as overweight or obese.

**Conclusions:** PEW is common in Israeli HD patients. Compliance with nutrition recommendations and guidelines is poor. Despite this, use of nutrition supplementation was limited. Paradoxically, almost half of the patients were overweight or obese. Further studies must be conducted to reconcile these seemingly incongruous states; additionally, studies investigating methods to enhance dietary compliance must be carried out.

**Funding:** Commercial Support - Abbott Nutrition

**PUB683**

Biomarker Profiling in Stage 5 CKD Hemodialysis Patients with Reference to Apparent Metabolic Syndrome and Vascular Manifestations (Vined K. Bansal, Leonidas Skiadopolous, Ryan Mcmillan, Debra Hopperesteadt, Jawed Fareed, Loyola University Medical Center, Maywood, IL; Loyola University medical center, Maywood, IL.)

**Background:** Stage 5 Chronic Kidney Disease Hemodialysis (CKD5-HD) represents a complex syndrome in which a variety of inflammatory factors contribute to its pathogenesis and progression. Vascular disorders and metabolic syndrome are common comorbidities in CKD5-HD patients. The purpose of this study is to profile inflammatory biomarkers to determine their role in pathogenesis of CKD5-HD and how they relate to apparent metabolic syndrome and vascular disorders.

**Methods:** Ninety patients (45 male, 45 female) with documented CKD5-HD on maintenance hemodialysis were included in the study. The control group consisted of 50 healthy individuals (25 male, 25 female; George King Biomedical, Overland, KS). Plasma from the CKD5-HD and control groups were used to measure levels of Vitamin
Higher Serum Magnesium Effect on Second Patency Rates of Vascular Access

In Patients on Hemodialysis

Yukoake, Naoto Akita, Kiyoko Yamamoto, Kosuke Mizusaki, Takeshi Kuragano, Naoto Hasuike, Takeshi Yamamoto, Kosuke Mizusak, Takeshi Kuragano, Naoto Hasuike

Background: Vascular access (VA) is essential for the patients on HD. However, VA failure is often occurred even after VA intervention therapy (VAVT). Several studies suggested a possible association between hypomagnesemia and vascular change. The purpose of this study was to examine the factors affecting VA patency after VAVT, including Mg, and factors related to oxidative stress, inflammation, and uremia. A correlation was found between serum Mg concentration and re-operation in 88 patients. The median value of serum Mg concentration was 2.5 mg/dl in all patients. The patients with VA failure had lower serum Mg compared with those without VA failure. There was no significant difference in other factors. The Kaplan-Meier analysis showed that the patients with lower Mg (≤2.6 mg/dl) were associated with higher incidence of VA failure (p=0.049, [figure1]). Cox regression analysis also revealed that lower Mg (adjusted hazard ratio 1.365, 95% confidential interval 1.013 to 1.839, p=0.04) was an independent factor for VA failure.

Conclusions: Lower serum Mg was associated with the poor event-free patency of VA after VAVT, and affected the second patency rates of VA.

PUB684

Effect of Gender on Obesity-Associated Renal Dysfunction and Involvement of Adipokines

Blanche Martin, Chloé Wilkin, Inês Jodat, Olivia Botton, Anne-Emicie Decleves, Nathalie Caron, Laboratory of General Physiology - URPHYM, University of Namur, Namur, Belgium; Laboratory of Molecular Biology, University of Mons, Belgium, NIMY (MONS), Belgium.

Background: Obesity incidence has dramatically increased during the last few years. This disease, characterized by an excessive fat accumulation, has for consequences an alteration of adipose tissue function and a chronic inflammation status, leading to metabolic disturbances. It is also well described that an excess of fat can be considered as a risk factor for kidney disease development. Today, most researches focus on males. However, it is imperative to determine how the sex difference can affect metabolic homeostasis and obesity syndrome. Indeed, differences, such as adipose tissue distribution, have been highlighted between sexes. Moreover, sexual hormones are involved in lipid and glucose metabolism. Adipose tissue has been shown to play endocrine functions by the secretion of adipokines, such as chemerin, adiponectin, leptin and TNF-α. In obese patients, secretion of these adipokines in obesity progression in males and in females and its impact on obesity-induced kidney alterations.

Methods: C57BL/6 male and female mice were randomized to a low fat diet (LFD) or a high fat diet (HFD) for 16 weeks.

Results: We demonstrated that male mice fed a HFD developed obesity, as illustrated by an increase in body weight, kidney hypertrophy and glucose metabolism disorders. Regarding kidney function, we observed that HFD mice tend to develop renal functional impairment, as they exhibited proteinuria and a slight increase in albuminuria. These observations were associated with a mesangial matrix expansion in glomeruli and vacuolated tubular cells. We also observed effects of HFD on adipokine concentrations, inflammation and fibrosis process in kidney. Finally, HFD mice presented a moderated oxidative stress. Female mice, on the other hand, seemed less affected by HFD according to metabolic data. Moreover, kidney lesions were less important than in male. However, female mice exhibited important inflammation, fibrosis and oxidative stress modifications compared with male fed a HFD and LFD.

Conclusions: In summary, our study demonstrated appearance of obesity as well as associated kidney failure in HFD male and female mice. However, according to our results, gender seems to influence the obtained data, highlighting roles of sexual hormones in obesity physiological mechanisms.

Funding: Government Support - Non-U.S.
the time during clinic visits to adequately address the nutrition aspects of patient care. Inadequate documentation of nutrition status of patients with CKD is a significant barrier to nutrition referrals, since fellows’ clinic lead to the design of a quality improvement (QI) project to improve documentation of nutrition status for CKD patients and making appropriate referrals to nutrition services.

Method: Charts for patients with CKD stage G3a to G5 seen in the Nephrology fellows’ clinic during December 2016 were audited by peer review to assess nutritional status within this population. Clinic notes were reviewed for documentation of nutrition data and referrals. Late December 2016, fellows were given a CKD nutrition lecture addressing clinical indicators for nutrition and an electronic health record (EHR) template or “smart phrase” for nutrition was designed to capture surrogates of nutritional status. In January and February 2017, charts were audited to determine nutrition referral rates. After completion of the project, fellows were sent a survey regarding the nutrition QI project and dilemmas with managing nutrition.

Results: A total of 80 charts were reviewed pre-intervention, and 121 charts were reviewed post-intervention. 49.5% of patients were either obese with BMI ≥30 kg/ m² or undernourished with BMI <18.5 kg/m². Serum albumin was documented in 150 charts, 23% of which had an albumin level <3.5 mg/dL. The pre-intervention nutrition referral rate was 5 %. Post-intervention, nutrition referrals were higher in each of the two subsequent months at 15 % and 33 %, respectively. The fellow survey identified major barriers to nutrition referrals, including lack of clinic time, low importance of nutrition compared to other clinical measures, and insurance coverage for referrals.

Conclusions: Obesity and hypoalbuminemia indicating poor nutritional status is prevalent in CKD patients. This QI project demonstrated that fellow education and an EHR “smart phrase” was associated with a sustained improvement in nutrition referrals. Further study is needed to determine what parameters increase a patient’s chance of obtaining referral and if such referrals and adherence to diet plans improve patient outcomes.

PUB688
Profile of High Sensitivity C Reactive Protein in AKI and CKD

Background: Prevalence of chronic kidney disease (CKD) is around 10% worldwide, while that of acute kidney injury (AKI) has not been systematically examined. Inflammation has been identified as an important factor of co morbidities in AKI and CKD. High sensitivity C reactive protein (hsCRP) assay is useful for detection of inflammation.

Methods: A prospective observational single tertiary care centre study from western India. Serum hsCRP, serum ferritin and serum albumin levels were checked on initiation of hemodialysis for both AKD and CKD subjects. All were dialyzed with a low flux dialyzer. Sample was collected for hsCRP, pre and post hemodialysis. All subjects were divided into AKI, CKD and Acute on CKD groups. HsCRP was analyzed using the Immuno Turbidimetry method with Cobas Integra 400 plus fully automatic analyzer. Unpaired t test was used to denote the statistical significance. Correlation between different inflammatory markers was calculated using the Pearson’s correlation coefficient.

Results: A total of 106 subjects were enrolled, which included 78 (73.6%) males. The mean age were 56 ± 15.22 years. 74 (69.8%) were CKD, 17 (16%) in Acute on CKD and 15 (14.2%) subjects in AKI group. Serum hsCRP in AKI group (65.23±47.25 mg/l) was significantly higher (p=0.0023) compared to CKD (31.95±52.60 mg/l). On comparing AKI with Acute on CKD (39.87±37.11 mg/l, p=0.106) and Acute on CKD with CKD (p=0.47), were not statistically significant. Serum hsCRP was not found to correlate with serum ferritin level in AKI (R=0.43, p=0.11). Acute on CKD (R=0.23, p=0.37) and CKD groups (R=0.04, p=0.70). Correlation was also not found with serum albumin levels in AKI (R= -0.9, p=0.73), Acute on CKD (R= -0.33, p=0.198) and CKD (R= -0.13, p=0.26). A two tailed samples t test on pre and post hemodialysis values of hsCRP revealed that the hsCRP level does not change with hemodialysis (p=0.128).

Conclusions: Serum hsCRP is higher in subjects with AKI as compared to CKD, while no difference was found on comparing both the groups with acute on CKD. Serum hsCRP does not correlate with other inflammatory markers and is not dialyzable.

PUB689
Sources of Dietary Phosphorus in Patients on Dialysis
Margarethe L. Fornsari,1,Yvyto A. Sens,1 Santa Casa de São Paulo School of Medical Sciences, São Paulo, Brazil; 2 Nutrition, Sao Judas Tadeu University, Sao Paulo, Brazil.

Background: Phosphorus control in the diet of end stage renal disease patients involves restriction of foods that contains phosphorus additives, processed foods with inorganic phosphorus that has high bioavailability. Dietary counseling focuses on education as a key component of hyperphosphatemia management. However, despite long-standing recommendations to limit phosphorus additives from foods most patients consume too much. The purpose of the study was to verify the contribution of foods with natural phosphorus versus foods with phosphorus additives.

Methods: A total of 67 adults with hyperphosphatemia and end-stage renal disease patients on hemodialysis for 26 months at a single center were evaluated. Three record-assisted 24-hour dietary recalls were collected from each participant to capture eating for a weekend day and each week day, respectively. Serum phosphorus was measured before the week day recall and after the weekend day recall, and the difference was calculated using the total phosphorus amount in the diet and the identification of sources of processed foods with phosphorus additives. To verify if processed foods contained phosphorus additives food labels and food referral was observed.

Results: The mean age were 56±13 years; 32(47%) were women and 35 (53%) were men. Phosphorus-containing foods additives contributed to 23% of the total sources of phosphorus in the diet on dialysis day and 21% on weekday without dialysis. Total phosphorus intake on dialysis day was 796±298 mg/d for total sample and was statistically different between women 789±298 mg/d and men 803±301 mg/d (p=0.001) while in a weekday without dialysis was 811±260 mg/d and was statistically different between women 811±259 mg/d and men 822±263 (p=0.001). There weren’t differences between women and men and day of the week concerning foods with phosphorus additives; women 2.4±1.4 foods and men 2.4±1.4 foods on dialysis day (p=0.87); and women 2.4±1.5 foods and men 2.4±1.5 foods (p=0.81) with phosphorus additives on a day without dialysis.

Conclusion: Foods that have natural phosphorus were the highest contributor to phosphorus in the diet but phosphorus-containing foods additives were present in the diet of all patients of this study regarding educational tools.

PUB690
Interdisciplinary Approach to Mitigate Harm Related to Dialysis CLABSI's
Robert S. Gavner, Nephrology, St Luke's University Health Network, Bethlehem, PA.

Background: Central Line Associated Blood Stream Infections (CLABSI) are associated with increased mortality, morbidity and cost. CLABSI's result annually in 84,551-203,916 preventable infections, 10,426-25,145 preventable deaths, and 1.7-21.4 billion dollars in avoidable cost. CLABSI's are preventable when EBM guidelines are followed. For the 1st quarter CY 2015, we experienced a sudden increase in dialysis CLABSI's. The goal of our project was to reduce dialysis CLABSI's by 50% within 6 months and achieve sustained results.

Methods: EBM literature review, CLABSI task force creation, root cause analysis, benchmarking, human factor learning, establishing clinical competencies, education and guidelines for catheter care were methods used to decrease dialysis CLABSI's.

Results: Achievement: We met and surpassed our goal to reduce CLABSI's related to dialysis catheters by 50% within 6 months and achieve sustained results over time. Financial Implications: For CY2016 2016 we had 3 dialysis CLABSI's versus a spike of 6 in the 1st quarter of 2015. Annual cost saving is estimated at $137,442 (3 x $45,841 compared to CLABSI spike, $962,094 if initial CLABSI spike was pro-rated over 1 year. Another financial component to be considered is avoidance of Hospital-Acquired Condition (HAC) penalties. Statistical Significance: Calculating a p value would not add to what was an obvious and clinically significant reduction.

Conclusions: Hemodialysis associated CLABSI's are a significant contributor to patient associated morbidity and cost of care. This will become particularly important with Pay for Value Reimbursement (Pay for Performance) which includes a global reduction of low CLABSI rates, this can change at anytime and needs to be constantly monitored. Establishing a rapid cycle task force, updating EBM guidelines, employing human factor learning and updating clinical competencies are some core factors in preventing dialysis associated CLABSI's.

PUB691
Renal Failure and Death by Hydrogen Peroxide
Lori Shah,1 Amit R. Rajput,2 None, Nashville, TN; 2Vanderbilt Nephrology, Nashville, TN; 1Vanderbilt University Medical Center, Nashville, TN.

Background: Hydrogen peroxide is frequently used in alternative medicine as a treatment for autoimmune disease, infections including HIV, atherosclerotic plaques, cancers, and COPD.

Methods: A 43 year old female with scleroderma and Sjogren’s presented with lethargy, vomiting, and diarrhea and was found to have multi-organ failure after use of 3% IV hydrogen peroxide infusions as therapy for her autoimmune disease. She had received...
Visible renal, splenic, and occasional hepatic microinfarcts caused by hydrogen peroxide. These microinfarcts were the cause of renal failure.

**Perception of Quality of Life in Patients with Lupus Nephritis**

**Gustavo Aroca Martínez,**** 1** 1Alvaro A. Martínez Bayona,** 1** Henry J. Gonzalez Torres,** 2** Alex Domínguez,** 3** Santos Depine,** 4** Fundación de Lupus del Caribe, Barranquilla, Colombia; 5** Universidad Simon Bolívar, Barranquilla, Colombia; 6** Medicina, Universidad Simón Bolívar, Barranquilla, Colombia; 7** Nephrology, Clínica de la Costa, Barranquilla, Colombia; 8** Universidad Simón Bolívar, Buenos Aires, Argentina.

**Background:** Patients with Lupus Nephritis (LN), in addition to the pathophysiological factors associated with the disease, present other aspects that are of clinical interest, such as their Quality of Life - QL. Objective: to perceive the QL of 30 LN patients under follow-up under the risk management model of LN at an institution in the Colombian Caribbean region.

**Methods:** Analytical, longitudinal and retrospective study. Patients with a diagnosis of LN were included. To measure the quality of life of the patients, the GENCAT quality of life instrument was used, which evaluates eight dimensions. Emotional Well-Being, Interpersonal Relations, Material Well-being, Personal Development, Physical Well-Being, Self-Determination, Social Inclusion and Rights. For the application of the instrument, 3 controls were performed, first control at the time of being diagnosed with LN and each year during two years follow-up.

**Results:** 30 LN patients that were controlled, 28(93%) were women and 2(7%) were men. The results found in the different dimensions of the scale allowed us to determine that patients with LN did not obtain a high level of quality of life (Material Welfare (16.9%), Interpersonal Relations (66.7%), Personal Development (50.7%), Physical Well-being (10.9%), Self-Determination (69.1%), Social Inclusion (33.9%). From the first control the overall scores increased, being more noticeable; In those where the score was higher than the average, that improvement in the other aspects of their quality of life was also significant, especially for Emotional Welfare, Interpersonal Relations, Physical Well-Being and personal rights.

**Conclusions:** The quality of life studied with the Gencat scale showed at the beginning the presence of depression and low self-esteem. Many of them failed to maintain good interpersonal relationships, they can not project their goals for their future, associated with poor self-care. From the third controls, the change was significant. Patients reported achieving and maintaining better self-esteem and self-perception. These findings could be related to a good response to treatment. At the beginning, the stress situation that affected the patients, motivated by their illness, their precarious economic situation and the deterioration of interpersonal relations, generated a vicious circle of psychological affectionation.

**Conclusions:** Hydrogen peroxide is a caustic oxidizing agent which can cause severe damage when infused, ingested, or inhaled. The more commonly used 3% solutions cause mild inflammation when ingested, however when used in an infusion form they can cause gas oxygen embolization to the brain and other organs, compromised cardiac output due to excessive oxidation, and disseminated intravascular coagulation. Public education on the risks of hydrogen peroxide is needed, as this toxic agent is often recommended in excessive oxidation, and disseminated intravascular coagulation. Public education on the risks of hydrogen peroxide is needed, as this toxic agent is often recommended in

**Background:** Exercise, including resistance training and weight lifting, has been demonstrated to provide hemodialysis patients with mature arteriovenous fistulas (AVFs) with numerous health-related benefits. However, it is not known how much weight these patients can safely lift with their upper extremities while simultaneously having a mature upper extremity AVF. To better understand this patient safety concern and state of the science, I conducted a comprehensive review of published, empirical research.

**Methods:** I comprehensively searched Cochrane Central Register of Controlled Trials, Embase, and MEDLINE using the following search phrase “arteriovenous fistula and exercise AND dialysis.” I also searched the bibliography of relevant articles. I then scanned articles’ title, abstract, and/or full-text for relevance.

**Results:** A total of three empirical studies resulted from the search, but two studies described the same results from the same population. Thus, two empirical studies with a total of 71 patients were identified for this review. One study was a randomized control trial and reported no serious adverse events, but did not report how much weight the dialysis patients lifted. The other study was a non-randomized controlled crossover trial, but did not discern exactly how many patients had an AVF. This study found that patients lifted up to 8.8 +/- 4.5 kg (mean +/- SD) on the chest press and up to 6.7 +/- 1.1 kg on the biceps curl with three sets of 12-15 repetitions each, three times per week (up to 26 weeks) without experiencing any serious adverse events.

**Conclusions:** A lack of well-defined randomized controlled trials limit the ability to conclude how much weight a hemodialysis patient with a mature upper extremity AVF can safely lift with their upper extremities. Further trials are needed to better investigate this patient safety concern.

**Funding:** Commercial Support - Denesson Renal Care, Inc.
according to the pharmacodynamic $E_{\text{max}}$ model. $\text{T}_{\text{ED}50} = T_{x} \times (1.44/1) \times \ln(2) + (C_{\text{max}}/C_{\text{ED}50})$.

**Results:** The $\text{T}_{\text{ED}50}$ equation was used to find a numerical solution for the pharmacodynamic parameters H with 1.4 and for $C_{\text{ED}50}$ with 4 mg/mL. The low Hill coefficient might indicate that evolocumab action is concentration-dependent and not time dependent. For an administration interval longer than the half-life, from our parameter estimates the $\text{T}_{\text{ED}50}$ is calculated with 19 days for the 140 mg evolocumab dose, but with 28 days for the 3-fold higher dose of 420 mg in complete agreement with the published 28 days administration interval. With the only two-fold higher dose of 280 mg, the $\text{T}_{\text{ED}50}$ time will be estimated with 25 days and less than twice the normal 14 days administration interval.

**Conclusions:** The present formula for the effect bisection time $\text{T}_{\text{ED}50}$ allows to estimate exact pharmacodynamic parameters that could be used for the most rational evolocumab dosing.

**PUB696**

 Automated Approach to Calculating Total Daily Dose of Tacrolimus in the Million Veteran Program Using the Electronic Health Record

**Background:** Tacrolimus dosing is complex, often requiring the combination of two pills of different strengths that are generated concurrently with the same date/time stamp. For a study of tacrolimus pharmacokinetics in the Veterans Affairs Million Veteran Program (MVP), we aimed to develop informatics algorithms to abstract accurate data of tacrolimus.

**Methods:** Using the VA corporate data warehouse we assembled a retrospective cohort of all patients with a prescription of tacrolimus following kidney transplantation. We used pharmacy files to identify dispensed prescriptions, date filled, days supplied, number of pills and dosage, and the printed bottle instructions. We built two automated algorithms to assign to the number of pills per day prescription and calculate the total daily dose of tacrolimus, confirming 10% by manual chart review. Then we used them to confirm each other for accuracy.

**Results:** We identified 28,081 prescriptions of tacrolimus. Method 1: used the automated printed bottle instructions prescription instructions to generate a repository of distinct texts. We found 2612 distinct texts and converted them into their numeric equivalent of pills per day. Method 2: used structured data to identify the pill strengths, number of pills dispensed, and the number of days’ supply. We divided the number of pills by the number of days supplied to get the number of pills per day. Methods 1 and 2 were compared to verify if the number of pills per day matched for each individual prescription and 90% perfectly matched, with Method 1 being the most accurate. Discrepancies were primarily caused by providers adjusting doses in the clinic without writing a new prescription.

**Conclusions:** Method 1, a repository of distinct texts of automatically printed bottle instructions, allowed more accurate recognition of complex prescriptions. Printed instructions were generally used in the context of any prescription and will be of great use for pharmacoepidemiological and pharmacokinetics studies of other drugs.

**Funding:** Veterans Affairs Support

**PUB697**

 Pharmacokinetics of Vancomycin in Pediatric Patients Receiving Hemodialysis and Hemofiltration

**Background:** Vancomycin is commonly used for bacteremia, but optimal dosing in pediatric patients requiring hemodialysis (HD) or hemofiltration (HF) is unknown. This study aims to characterize vancomycin pharmacokinetics and derive an optimal vancomycin dosing regimen for pediatric patients on HD/HDF.

**Methods:** A therapeutic drug monitoring (TDM) guideline was implemented for pediatric patients younger than 18 years of age. Eligible patients for one to three times will be post-dialysis and a series of serum vancomycin concentrations were collected pref- immediately-post-, 1-h-post- and 4-h-post-dialysis. The pharmacokinetic parameters were estimated using a single compartment model and nonlinear least-squares algorithm. Monte Carlo simulations (MCS) were performed to assess dosing regimen of vancomycin.

**Results:** 42 courses were included. The average vancomycin dose was 56.38%, rebound was 23% and net drug removal was 43% using HD/HDF. Nine courses from 6 patients with pharmacokinetic profiles were included in our pharmacokinetic model. While on HD/HDF, the median elimination constant ($k_{\text{e}}$) was 0.30 h$^{-1}$ and clearance was 0.18 mL/kg/h. When off dialysis, the median $k_{\text{e}}$ was 0.013 h$^{-1}$, clearance was 0.0066L/kg/h and volume of distribution was 0.64L/kg. We found that duration of HD/HDF, and type of dialysis (HD vs. HDF) may be important determinants of vancomycin pharmacokinetics. All vancomycin courses dosed at 10mg/kg/dose post-dialysis followed by TDM to assess re-dosing appeared effective based on white blood cell count, temperature and culture results. No adverse effects were reported except for one patient with a creatinine clearance of 6, MCV demonstrated that the current regimen is optimal to reach therapeutic range for 4-hour post-dialysis concentrations (for central nervous system infections: 10-15mg/L or other: 5-2mg/L) and 24-hour area under the curve over minimum inhibitory concentration (AUC/MIC) ≥400 if MIC is 0.5mg/L.

**Conclusions:** Vancomycin is significantly removed by HD/HDF with rebound occurring at 4 hours post-dialysis. However, time to maximum rebound remains unknown due to sparse blood sampling. The current vancomycin dosing regimen is optimal for pediatric patients on HD or HDF at this institution.

**PUB698**

 A Case of Levofloxacin Induced Choreiform Movements in a Hemodialysis Patient

**Background:** Neurotoxic effects of quinolones have been described and are considered as second most common adverse effects after gastrointestinal side effects. Risk factors associated with enhanced adverse effects are renal impairment, old age, higher doses and interaction with other medications especially theophylline. We report a case of reversible involuntary movement (choreiform movements) in end stage renal disease (ESRD) patient secondary to levofloxacin.

**Methods:** 63-year-old male, known history of hypertension, end stage renal disease (ESRD), on alternate day dialysis schedule, diastolic heart failure presented with complains of generalized tremors and intermittent twiching of face and extremities for the past 2 days. Patient was compliant to his usual anti-hypertensive medications and dialysis. Four days prior to his presentation patient was started on levofloxacin 750 mg oral dose for treatment of upper respiratory tract infection. No history of fever, headache, photophobia, sensory or motor deficit, new medication, alcohol/drug exposure, recent travel was reported. On physical examination, his vitals were within normal limits. He was fully alert and oriented with no neurological deficit. Of significance, he was noted to have coarse tremors in all his extremities. Choreiform movements of face and tongue were noted. Loss of autonomy or orofacial dyskinesia, choreiform movements, myoclonus and Chorea Like movements were found to have been reported with levofloxacin. Clinicians should be vigilant of renal adjusted doses in treating infections especially in the setting of renal failure. Conservative management with treatment of symptoms has been suggested.

**PUB699**

 Dialysis-Induced Ventricular Tachycardia? A Reappraisal of Quinidine Clearance with Modern Dialyzers

**Background:** We studied the pharmacokinetics of quinidine in order to establish or refute its culpability in hemodialysis-associated breakthrough ventricular tachycardia. Quinidine is a drug used in management of recurrent ventricular tachycardia (VT). He required intermittent hemodialysis (HD) for acute kidney injury. A pattern developed wherein each HD treatment was associated with breakthrough VT despite treatment with quinidine. After determining that electrolyte and hemodynamic abnormalities were not likely the cause of this breakthrough VT, we hypothesized that intradialytic quinidine clearance might drop the blood quinidine concentration outside of the therapeutic range. Little data is available regarding the transport characteristics of quinidine with newer generation hemodialysis membranes. We used a single patient to evaluate this hypothesis. We conducted a pharmacokinetic study during HD. Venous blood quinidine concentrations were assessed under steady-state conditions immediately prior to an oral maintenance dose (300 mg), thereby providing “through” concentrations. The quinidine trough concentration for this patient was 0.035 ± 0.006 µg/mL. The patient then received a routine oral maintenance dose (300 mg), a venous blood sample was collected, and HD was started. The peak blood quinidine concentration was 4 µg/mL. Paired inflow and outflow venous blood samples were collected hourly for the duration of the HD treatment. Dialysate flow rate was set at 500 mL/min, venous blood flow rate at 300 mL/min. Venous blood flow rate was kept constant for all HD treatments. The current vancomycin dosing regimen is optimal for pediatric patients on HD or HDF at this institution.

**Results:** Reported quinidine hemodialysis clearances are quite variable and our data does neither accords with nor stands out from previously published data. While older patient did not suffer breakthrough VT during this HD treatment.

**Conclusions:** We report a case of levofloxacin induced choreiform movements in a hemodialysis patient, secondary to levofloxacin. We believe these movements are due to seizures secondary to theophylline use. Since nutritional and hydration status were normal, we attribute this to theophylline overdose due to increased elimination of theophylline. Venous blood quinidine concentrations were assessed under steady-state conditions immediately prior to an oral maintenance dose (300 mg), thereby providing “through” concentrations. The quinidine trough concentration for this patient was 0.035 ± 0.006 µg/mL. The patient then received a routine oral maintenance dose (300 mg), a venous blood sample was collected, and HD was started. The peak blood quinidine concentration was 4 µg/mL. Paired inflow and outflow venous blood samples were collected hourly for the duration of the HD treatment. Dialysate flow rate was set at 500 mL/min, venous blood flow rate at 300 mL/min. Venous blood flow rate was kept constant for all HD treatments. The current vancomycin dosing regimen is optimal for pediatric patients on HD or HDF at this institution.

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

Underline represents presenting author.
dialyzability data for these drugs in light of the transport characteristics of newer hemodialysis membranes.

PUB700
Pharmacokinetics of Oral ZYAN1 across Indian and Australian Healthy Subjects Kevinkumar A. Kansagra,1 Devan Parmar,2 Mukul R. Jain,3 Devang P. Parmik,4 Harilal V. Patel,5 Nuggehally R. Srinivas,6 Vrajesh B. Pandya,3 Cadila Healthcare Ltd, Ahmedabad, India; 7Cadila Healthcare Limited, Ahmedabad, India; 8Cadila healthcare Pvt Ltd, Ahmedabad, India; 9Zydus Cadila, Ahmedabad, India; 10Zydus Research Centre, Ahmedabad, India.

Background: Hyposia inducible factor (HIF)-prolyl hydroxylase inhibitors are being developed for the treatment of anemia in chronic diseases. ZYAN1- a HIF prolyl hydroxylase inhibitor stabilized the HIF alpha and stimulated endogenous erythropoietin production and raise HB level in preclinical studies. This study was conducted to evaluate safety and compare the pharmacokinetics of ZYAN1 at an oral dose of 150 mg in Indian and Australian healthy human subjects.

Methods: Randomized, double-blind, placebo-controlled, single dose study included a total of 16 subjects; 6 subjects in each Indian and Australian group received ZYAN1 150 mg and 2 subjects in each group received matching placebo. The data were evaluated based on the blood concentration vs. time profile of ZYAN1 and the pharmacokinetic parameters were estimated using non-compartmental model.

Results: Mean age (years) and BMI (kg/m2) of Indian and Australian subjects were 28.0±4.00, 22.9±2.04 and 30.8±12.38, 22.9±1.77, respectively. There was no statistically significant difference in pharmacokinetic parameters of Indian subjects compared to Australian subjects with 150 mg dose as presented in Table.

Conclusions: Pharmacokinetics of ZYAN1 150 mg was comparable between Indian and Australian subjects. ZYAN1 150 mg was safe and well tolerated in healthy volunteers.

Funding: Commercial Support - Cadila healthcare Ltd., Clinical revenue Support

Pharmacokinetic comparison of ZYAN1 Single dose 150 mg) study between Indian and Australian healthy human Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>0.5940</th>
<th>0.5940</th>
<th>0.5940</th>
<th>0.5940</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mg/L)</td>
<td>0.5940</td>
<td>0.5940</td>
<td>0.5940</td>
<td>0.5940</td>
</tr>
<tr>
<td>AUC(0-24h) (mg* h/L)</td>
<td>0.5940</td>
<td>0.5940</td>
<td>0.5940</td>
<td>0.5940</td>
</tr>
<tr>
<td>Elimination constant (k1)</td>
<td>0.5940</td>
<td>0.5940</td>
<td>0.5940</td>
<td>0.5940</td>
</tr>
<tr>
<td>Half-life of Zyan (h)</td>
<td>0.5940</td>
<td>0.5940</td>
<td>0.5940</td>
<td>0.5940</td>
</tr>
<tr>
<td>Volume of distribution (Vd) (L/kg)</td>
<td>0.5940</td>
<td>0.5940</td>
<td>0.5940</td>
<td>0.5940</td>
</tr>
<tr>
<td>Clearance (Cl/F)</td>
<td>0.5940</td>
<td>0.5940</td>
<td>0.5940</td>
<td>0.5940</td>
</tr>
</tbody>
</table>

PUB702
Toxic Epidermal Necrolysis Induced by Febuxostat: A Case Report Xiaowen Hu,1 Jiawei He,2 Jiasheng Huang,3 Suyuan Peng,1 Haijing Hou,1 La Zhang,1 Fuhua Lu1 Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China; 2The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China; 3The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China.

Background: Toxic epidermal necrolysis (TEN) is a rare, life-threatening drug-induced skin disease with a mortality rate of 25-70%. The precise mechanism is still unclear. Clinically, the Nikolsky’s sign, erosions of the mucous membranes and extensive detachment of the epidermis should be an alarm for us. Specific drugs like nonsteroidal anti-inflammatory, antimicrobial drugs and allopurinol seem to be the main predisposing factors for TEN. Additionally, population’s genetic background such as human leukocyte antigen (HLA) status is associated with the disease. The purpose is to describe a hyperuricemia woman, with HLA-B*5801 negative, developing the TEN after using Febuxostat.

Methods: A 64-year-old Asian woman was hospitalized with proteinuria and high serum creatinine level. Referring to her medical history, urinary color Doppler ultrasound as well as some laboratory findings, we argued that renal dysfunction was caused by chronic glomerulonephritis by the means of exclusion. She was initially treated with Febuxostat-a potent non-purine selective xanthine oxidase inhibitor against her high level of serum uric acid. However, erythematous plaques first appeared on her buttocks soon afterward. Lesions rapidly coalesced and became tense bullae. With the progression of the disease, they formed large confluent areas of epidermal detachment. Mucosal involvement occurred over her oral cavity simultaneously. All the suspect drugs were erythematous discontinued immediately. She was treated with the corticosteroid, intravenous immunoglobulins, blood transfusions, and antibiotics, along with other supportive therapies. Eventually, extensive epidermal detachment improved. It was a pity that because of the heart failure and sustained limb swelling, she accepted hemodialysis from then on.

Results:

Conclusions: What depress us most is the mortality of the disease. The most important therapeutic measures are identification and withdrawal of the suspect drugs. In this case, our patient used various kinds of medicine including traditional Chinese medicine. We listed all the medicines and sorted them according to the literature review and other drug-induced adverse reactions reports. Additionally, a genetic test was arranged but what surprised us was that her HLA-B*5801 negative, which meant drugs causing allergies’ mechanism between Febuxostat and Allopurinol was different.

PUB703
Decreased Tremor and Improvement of Quality of Life after Switching to Prolonged Release Formulation of Tacrolimus in Kidney Transplant Patients Marisol Poma tapia,1 Natividad Calvo,2 Fernando F. Hadad-Arrascue,3 Ana Sanchez fructuoso,4 Isabel I. Perez-Flores,1 2Hospital Clinico San Carlos, Madrid, Spain; 3Hospital Clinico San Carlos, MADRID, Spain; 4Clinica RTS Murcia VII, Murcia, Spain.

Background: Tacrolimus is the immunosupressant of choice in kidney transplant patients, one of the most common side effects is tremor occurring at peak serum tacrolimus blood concentrations. Tremor is associated with a significant decrease in the quality of life (QOL) of transplant patient. Our objective was to determine the change in tremor severity after using the FTM test: tremor location/severity 9.45 to 5.64 (-3.81P <0.07), specific motor function of the FTM test: tremor location/severity 5.64 to 2.6 (-3.01P <0.1). Regarding the QUEST QOL test in the self-evaluation, there was an increase in the quality of life assessment from 58.6 to 65.5 (7.22P <0.027). As for immediate release formulation levels in Cmin 8.1 ng/ml and Cmax (at 2 hours) 13.6 ng/ml, unlike prolonged-release tacrolimus with Cmin 7.1 and Cmax (at 8 hours) 10.8 ng/ml. There was a 30% decrease in tacrolimus levels in Cmin 8.1 ng/ml and Cmax (at 2 hours) 13.6 ng/ml, unlike prolonged-release tacrolimus with Cmin 7.1 and Cmax (at 8 hours) 10.8 ng/ml. There was a 30% decrease in the total dose of tacrolimus when switching to prolonged-release formulation of tacrolimus.

Results: The mean age of patients was 58 +/- 11 yrs. After switching from immediate release tacrolimus to prolonged release tacrolimus there was a decrease in tremor in the absolute FTM test from 26.82 to 18.36 (-8.46 P <0.012) as an improvement in the parts of the FTM test: tremor location/severity 9.45 to 5.64 (-3.81P <0.07), specific motor function 12.9 to 10.2 (-2.6P <0.004), functional disability as a consequence of tremor 4.4 to 2.6 (-1.81P <0.01). Regarding the QUEST QOL test in the self-evaluation, there was a subjective decrease in tremor from 7.45 to 4.18 (-3.27 P <0.03) and an increase in the QUEST QOL test in the self-evaluation, there was a subjective decrease in tremor from 7.45 to 4.18 (-3.27 P <0.03) and an increase in the parts of the FTM test: tremor location/severity 9.45 to 5.64 (-3-81P <0.07), specific motor function of the FTM test: tremor location/severity 5.64 to 2.6 (-3.01P <0.1). Regarding the QUEST QOL test in the self-evaluation, there was a subjective decrease in tremor from 7.45 to 4.18 (-3.27 P <0.03) and an increase in the parts of the FTM test: tremor location/severity 9.45 to 5.64 (-3-81P <0.07), specific motor function of the FTM test: tremor location/severity 5.64 to 2.6 (-3.01P <0.1). Regarding the QUEST QOL test in the self-evaluation, there was a subjective decrease in tremor from 7.45 to 4.18 (-3.27 P <0.03) and an increase in the parts of the FTM test: tremor location/severity 9.45 to 5.64 (-3-81P <0.07), specific motor function of the FTM test: tremor location/severity 5.64 to 2.6 (-3.01P <0.1). Regarding the QUEST QOL test in the self-evaluation, there was a subjective decrease in tremor from 7.45 to 4.18 (-3.27 P <0.03) and an increase in the parts of the FTM test: tremor location/severity 9.45 to 5.64 (-3-81P <0.07), specific motor function of the FTM test: tremor location/severity 5.64 to 2.6 (-3.01P <0.1).
Successful Kidney Transplantation Normalizes Platelet Function

Claire Kennedy,1,4,5 Limy Won,4 Donal J. Sexton,3 Jonathan J. Cowman,2 Martin Kenny,2 Peter J. Conlon,1 Dermot Kenny,2
1 Beaumont Hospital, Dublin 9, Co Dublin, Ireland; 2 RCSI, Dublin, Ireland; 3The Irish Longitudinal Study on Ageing (TILDA), Trinity College Dublin, Dublin, Ireland; 4Nephrology, Beaumont Hospital, Dublin, Ireland; 5Royal College of Surgeons in Ireland, Dublin, Ireland.

Background: Uremic platelet dysfunction is poorly understood largely because of inadequate platelet function assays. We have developed an assay of platelet function that accurately measures platelets translocating across von Willebrand factor (VWF) at arterial shear rates (DPFA). The aim of this study was to investigate the impact of kidney transplantation (KTX) on platelet function using the DPFA.

Methods: Blood samples from ten patients before and after KTX surgery and nine healthy controls at two different time points were assayed using the DPFA. Multiple parameters of platelet behavior and platelet-VWF interactions were recorded using customized platelet tracking software. The assay was repeated 3-8 weeks post-transplant.

Results: Platelet-VWF interactions were markedly reduced in the ten pre-transplant patients compared to the healthy controls. They normalized post-transplant in the seven patients with immediate graft function (despite a small drop in hemoglobin and hematocrit) but remained markedly abnormal in the three patients with delayed graft function (DGF).

Conclusions: This is the first demonstration of normalization of platelet function with reversal of uremia by KTX. Early normalization of platelet-endothelial interactions did not occur in those with DGF. This has important clinical consequences, as patients with DGF are more likely to undergo invasive procedures including transplant biopsies and insertion of central venous catheters.

PUB706

Predictors of Persistent Hyperparathyroidism Post Renal Transplantation
– A Single Centre Experience

Mayank Chawla,1 Sobhana Thangaraju,2
1 singapore general hospital, SINGAPORE, Singapore; 2 renal medicine, singapore general hospital, SINGAPORE, Singapore.

Background: Hyperparathyroidism improves after kidney transplantation (KTR). However, persistent hyperparathyroidism (PH) may occur and is associated with a higher risk of cardiovascular events, fractures, allograft failure, and all-cause mortality. Persistent hyperparathyroidism posttransplant (PH-PTX) has been advocated to prevent the risk of PH and complications of post-transplant PTX. However, there is no defined criteria for the timing of pre-transplant PTX. This study seeks to identify predictors of PH following transplantation to guide timely intervention.

Methods: We included all first KTR patients transplanted in our tertiary care center, between January 2005 and July 2015 with follow-up of until 12 months and pre-transplant dialysis of more than 3 months were recruited for analysis (n=169). PH was defined as serum corrected calcium (cCa) of > 2.50 mmol/L and serum iPTH > 6.5pmol/L at 12 months post-transplant and biochemical data were compared between groups with and without PH. Univariate analysis was performed and significant predictors of PH were further analyzed with multivariate regression analysis.

Results: Mean age of study population was 45.8 years. The mean dialysis vintage was 88 months (36-140) and 84% were on hemodialysis. 68% of patients received deceased donor KTR. PH was diagnosed in 65 patients (38 %). On univariate analysis, patients with PH were older (48 (7.9) vs 44.4 (10.8), p=0.025), had longer dialysis vintage (108 vs 77 months p=0.002), and higher pre-transplant cCa (2.51 (2.34,2.68) vs 2.29 (2.07, 2.51), p<0.016), Alkaline phosphatase (157.0 (114.0, 140.0) vs 88.0 (38.0, 105.0), p=0.016), iPTH (90.2 (29.0, 127.2) vs 38.0 (11.7, 49.0), P=0.002), and phosphate (1.90 (1.38,2.42) vs 1.66(1.42,1.8), P=0.0056) levels. Estimated GFR was lower in patients with PH at 12 months (54.5 (34.5, 75.0) vs 61.0 (42.0, 80.0), P<0.001). Following multivariate adjustment, longer dialysis vintage (HR = 1.011, 95% CI=1.001,1.021)), higher pre-transplant cCa (HR=1.647, 95% CI=1.296, 2.177), and higher pre transplant iPTH (HR=1.015, 95% CI=(1.006,1.026)) remained significant.

Conclusions: Longer dialysis vintage, higher pre-transplant iPTH and pre-transplant hypercalcemia are important predictors of PH following kidney transplantation.

PUB707

A Unique Case of Disseminated Nocardia Infection and Post Transplant Lymphoproliferative Disorder in a Renal Allograft Recipient

Juan M. Del Bono,1,2,3 Rohan V. Mehta,1 Stephen O. Pastian,1 Rahul Mehta,2 Emory University School of Medicine, Atlanta, GA; 2University of Virginia, Charlottesville, VA.

Background: Nocardia infections most commonly present 1 to 6 months after solid organ transplantation with acute or subacute pneumonia, but hematogenous spread to brain, bone, eye and rarely skin and subcutaneous tissue have been reported. Enhanced Immunosuppression, particular exposure to antilymphocytic antibody preparations may potentially increase the risk of such infections.

Methods: A 55 year old asian man with a history of Deceased Donor Renal Transplant of 2 years and stable Post Transplant Lymphoproliferative Disorder(PTLD) presented with left leg swelling for 2 weeks. About 6 months prior, he was diagnosed with biopsy proven metastatic CNS PTLD managed with systemic Rituximab, Intracranial radiation and Decadron. His maintenence immunosupression which included Belatacept was held and the dose of Cellcept was reduced after the diagnosis. The right parietal brain lesion was stable and liver metastasis had resolved after completion of therapy. He also had a history of Acute Rejections managed with Prednisone and Thymoglobulin in the past.

CT scan of the leg revealed a large and a small collection in the adductor and vastus group of muscle suggesting cellulitis / abscess, while Chest CT shows consolidation of the right upper and lower lobes. A new ring enhancing lesion suggestive of infection is discovered in the right temporal lobe of the brain on MRI, after the patient develops altered mental status. Tissue biopsy from the leg grows Nocardia Farcinica. A CT guided drain is placed in the leg. The patient is started on Bactrim and Meropenem. Bactrim is later replaced with Linezolid. A repeat CT of the leg is suggestive of reduction in the fluid collection and the patient shows clinical improvement.

Conclusions: We present a case of Disseminated Nocardia Farcinica Infection in the setting of PTLD complicating a Deceased Donor Renal Transplant. We highlight the risk factors leading to these complications and discuss potential therapeutic options.

PUB708

Clinical Predictors of Recurrent Focal Segmental Glomerulosclerosis in Renal Transplantation

Anita Shah,1 Juan M. Gonzalez,2,3 Sandra Barrow,2,3
1 Houston Methodist Hospital, Houston, TX; 2Nephrology, Dialysis & Transplantation Associates PA, Houston, TX; 3J. C. Walter Jr. Transplant Center, Houston Methodist Hospital, Houston, TX.

Background: Focal segmental glomerulosclerosis (FSGS) is a clinicopathologic syndrome involving scarring of the glomerulus and nephtic range proteinuria. Approximately 30% of patients have recurrent FSGS after renal transplantation, and these patients are at high risk of losing their graft. This recurrence, if not halted, ultimately leads to failure of the renal transplant and either dialysis or retransplantation. While some studies have shown risk factors associated with recurrence, there is no consensus on which patients are at greatest risk. Our aim is to describe factors that help predict FSGS recurrence in transplant recipients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: A retrospective, observational case-control study was conducted on 24 patients, median age 53.9 years, FSGS with who had received a renal transplant at the Methodist Hospital between 2011 to 2015. All patients underwent a renal transplant biopsy. Baseline characteristics such as age at transplant, sex, race, immunosuppressive regimen, donor type, and creatinine and were compared between those with and without FSGS recurrence. Continuous data were expressed as mean ± standard deviation (range) and analyzed with a Mann-Whitney test, while categorical data was analyzed by Fisher’s exact test.

Results: At the time of biopsy, patients with FSGS recurrence illustrated, as expected, a significantly higher creatinine (p=0.010) and amount of proteinuria (p=0.001). However, no significant difference in age, sex, race, immunosuppressive regimens, or donor type could be identified between the two groups.


PUB709
Severe AKI Due to AMR Rescued with Eculizumab Mark J. Lerman,1 Michael B. Kuperman,1 Afzal Niakein,2 Judson M. Hunt,2 Salman Khan,3 1Dallas Nephrology Associates, Dallas, TX; 2Texas Medical Specialty, Dallas, TX; 3Johns Hopkins, Baltimore, MD.

Background: Antibody mediated rejection (AMR) in transplant recipients may cause graft dysfunction and decreased graft survival. Current treatment options for AMR include plasma exchange (PE), intravenous immunoglobulin (IVIg), and –iCD20 therapy. Patient’s with severe forms of AMR usually do not respond to these treatments. We present one case of very severe acute antibody mediated rejection which was resistant to conventional therapy but responded to Eculizumab.

Methods: 45-year-old AA man status post deceased donor kidney transplant in 2013, baseline creatinine 1.2. Patient presented with a serum creatinine > 20 in 2015. A biopsy revealed severe diffuse peritubular capillary Cd4 staining. Donor specific antibodies were present against DQ9 MFI 13153 at 1:32 dilution. Hemodialysis was initiated. A repeat renal biopsy after 5 doses of IV SoluMedrol and 5 treatments of plasma exchange and low-dose IV IgG continued to show diffuse peritubular capillary Cd4 deposition. Light microscopy remained essentially unremarkable. DSA to DQ9 remained high at MFI 12837 at 1:32 dilution. He remained on tacrolimus and mycophenolate. Eculizumab was begun at 1200 mg IV every week x 4. After 4 weeks and 4 doses of Eculizumab, renal function was clearly improving with a serum creatinine of 3 and a GFR of 25 mL/min/1.73m2. Dialysis was discontinued and a third renal biopsy showed complete resolution of Cd4 staining and very mild tubulitis with about 30% interstitial fibrosis. Patient received Eculizumab 900 mg every 2 weeks for another 4 doses. He has remained dialysis free for the last 19 months.

Results: Conclusions: To our knowledge, prior to this case, no patient with a serum creatinine above 20 in 2015 with a biopsy that was able to be discontinued and dialysis. Our patient remains stable with serum creatinine 2.5 and has not required dialysis after 19 months. We believe even severe acute renal failure due to AMR requiring dialysis, may respond to Eculizumab. Allograft biopsy demonstrating absent of chronic changes and presence of C4d may be an important predictor for responsive patients regardless of renal dysfunction.

DATA
<table>
<thead>
<tr>
<th>dose</th>
<th>MFI</th>
<th>Sc</th>
<th>dose</th>
<th>MFI</th>
<th>Sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/07/17</td>
<td>1.52 ±1057</td>
<td>20</td>
<td>6/07/17</td>
<td>6.37 ±596</td>
<td>3.2</td>
</tr>
<tr>
<td>8/9/15</td>
<td>1.2 ±1837</td>
<td>5.4</td>
<td>11/9/16</td>
<td>1.23 ±483</td>
<td>1.6</td>
</tr>
<tr>
<td>9/15</td>
<td>1.2 ±1867</td>
<td>4</td>
<td>11/4/17</td>
<td>1.32 ±198</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PUB713
Procalcitonin for Diagnosis of Bacterial Infections and Rejection in the Early Post-Renal Transplant Period

Background: Infection and rejection are leading causes of morbidity and mortality in renal transplant recipients. Since patients with infection and rejection have similar clinical presentation, differentiating the two can pose a diagnostic challenge for transplant clinicians. We evaluated the utility of PCT in differential diagnosis of infection and rejection in renal transplant recipients.

Methods: In this study, serum PCT concentrations were monitored in 146 renal transplant recipients from the day of transplant to 15 days after transplant. The PCT estimation was done using ELECSYS BRAHMS PCT kit. Recipients were grouped into Group 1: non-infectious and Group 2: infectious group. Group 2 was further subdivided into: graft rejection (Group 2a) and non-rejection (Group 2b) cases. SPSS (V.20) was used for statistical analysis. PCT levels > 0.5 mg/ml were considered clinically significant.

Results: Out of the total 146 patients, 111 (group 1) did not develop a bacterial infection while 35 (group 2) suffered bacterial infections within 15 days of renal transplant. Among the group 2 patients, 13 (group 2a) suffered acute graft rejection while 22 (group 2b) did not. Receiver operating characteristic (ROC) analysis showed the area under the curve (AUC) for predicting infection above PCT level of 1.9 mg/ml was 0.89, (95% confidence interval [CI]: 0.83-0.94; p = <0.0001). For differentiating group 2a patients from group 2b, AUC was 0.95 (95% CI: 0.94-0.98; p = <0.0001).

Conclusions: PCT levels can improve diagnostic accuracy of bacterial infections in patients in the early post-renal transplant period with adequate sensitivity and specificity. It does not, however, reliably exclude the co-occurrence of rejection in patients who have also developed bacterial infections. Larger, multicenter studies would be useful to validate the PCT cutoff values.

PUB714
A Case of Immune Complex Membranoproliferative Glomerulonephritis (IC-MPGN) and De Novo Donor Specific Antibodies (dnDSA) after a Case of Immune Complex Membranoproliferative Glomerulonephritis

Underline represents presenting author.

Background: Hammad (IC-MPGN) and De Novo Donor Specific Antibodies (dnDSA) after a Case of Immune Complex Membranoproliferative Glomerulonephritis

Procalcitonin for Diagnosis of Bacterial Infections and Rejection in the Early Post-Renal Transplant Period

Underline represents presenting author.

Background: Infection and rejection are leading causes of morbidity and mortality in renal transplant recipients. Since patients with infection and rejection have similar clinical presentation, differentiating the two can pose a diagnostic challenge for transplant clinicians. We evaluated the utility of PCT in differential diagnosis of infection and rejection in renal transplant recipients.

Methods: In this study, serum PCT concentrations were monitored in 146 renal transplant recipients from the day of transplant to 15 days after transplant. The PCT estimation was done using ELECSYS BRAHMS PCT kit. Recipients were grouped into Group 1: non-infectious and Group 2: infectious group. Group 2 was further subdivided into: graft rejection (Group 2a) and non-rejection (Group 2b) cases. SPSS (V.20) was used for statistical analysis. PCT levels > 0.5 mg/ml were considered clinically significant.

Results: Out of the total 146 patients, 111 (group 1) did not develop a bacterial infection while 35 (group 2) suffered bacterial infections within 15 days of renal transplant. Among the group 2 patients, 13 (group 2a) suffered acute graft rejection while 22 (group 2b) did not. Receiver operating characteristic (ROC) analysis showed the area under the curve (AUC) for predicting infection above PCT level of 1.9 mg/ml was 0.89, (95% confidence interval [CI]: 0.83-0.94; p = <0.0001). For differentiating group 2a patients from group 2b, AUC was 0.95 (95% CI: 0.94-0.98; p = <0.0001).

Conclusions: PCT levels can improve diagnostic accuracy of bacterial infections in patients in the early post-renal transplant period with adequate sensitivity and specificity. It does not, however, reliably exclude the co-occurrence of rejection in patients who have also developed bacterial infections. Larger, multicenter studies would be useful to validate the PCT cutoff values.

PUB715
Long-Term Outcome of Renal Transplantations in Two Patients with ADCK4-Associated Glomerulopathy

Underline represents presenting author.

Background: Mutations in the ADCK4 gene can cause ADCK4-associated glomerulopathy. Patients with ADCK4-associated glomerulopathy can be treatable with CoQ10 at the early stage because the transcript of ADCK4 encodes a protein of the CoQ10 biosynthetic pathway, which localizes to the mitochondria in podocytes. The patients with ADCK4-associated glomerulopathy who progress to end-stage renal disease (ESRD) require dialysis or renal transplantation. It has reported that some patients with ADCK4-associated glomerulopathy received renal transplantations. However, long-term outcome of transplantations in the patients with ADCK4-associated glomerulopathy is unknown. Here, we report the long-term outcome of two cases with ADCK4-associated glomerulopathy who received cadaveric renal transplantations at more than 10 years of follow up.

Methods: The two patients harbor a compound heterozygous mutation (532 C>T; R178W and 748 G>C; D250H) in the ADCK4 gene. Case 1, a boy presented with steroid-resistant nephrotic syndrome (SRNS) at 7 years old and had mesangial proliferative glomerulonephritis lesions on renal biopsy at 8 years old. He received a cadaveric renal transplantation at 16 years old when he progressed to ESRD. The avenues in the immunosuppressive treatment included the use of mycophenolate mofetil, tacrolimus plus prednisone. His renal examination retained normal at 11 years of follow-up. His last urinalysis showed normal. His serum creatinine was 114 μmol/L and urea nitrogen 7.9 mmol/L. Case 2 (older sister of case 1), a girl presented with SRNS and had focal segmental glomerulosclerosis on renal biopsy at 10 years old. She received a cadaveric renal transplantation at 14 years old when she progressed to ESRD. She received the same avenues after transplantation. Her renal examination also retained normal at 15 years of follow-up. Her last urinalysis also showed normal. Her serum creatinine was 81 μmol/L and urea nitrogen 5.5 mmol/L.

Results: Conclusions: Long-term outcome of renal transplantations is good in the patients with ADCK4-associated glomerulopathy who progress to ESRD. Funding: Clinical Revenue Support

PUB716
Triglyceride Metabolism in Japanese Kidney Transplant Recipients

Methods: Sixty-three consecutive stable recipients just one year after kidney transplantation were included in the study at Nagoya Daimi Red Cross Hospital from January to September in 2014. We performed cookie test (this cookie consists of 75 g carbohydrate and 25 g fat) to evaluate TG metabolism. TG, Blood sugar (BS), remnant like particle-cholesterol (RLP-C), serum insulin were measured at fasting (f) and 2 and 4 hours (h) after ingestion. Low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) and apoB were measured at fasting.

Results: Figure 1 summarizes the clinical and metabolic characteristics of this study. Mean TGf and RLP-Cf were 139±62.6 mg/dl and 5.6±3.4 mg/dl within normal range, however, both mean TG2h and TG4h were above 200 mg dl, and both mean RLP-C2h and RLP-C4h were above 9 mg/dl. A negative correlation was seen between TGf and eGFR (r=-0.48 p=0.001). TGf had positive correlation with RLP-C, non HDL-C, LDL-C/apoB ratio, BMI (r=0.30 p=0.01, r=0.47 p=0.001, r=0.48 p=0.001, r=0.38 p=0.002, respectively). BMI had positive correlations with RLP-C (r=0.35, p=0.01) and a negative correlation with HDL-C and LDL-C/apoB ratio (r=0.48 p=0.001, r=0.30 p=0.015), respectively). LDL-C levels were positively correlated with levels of statin use but LDL-C/apoB ratio levels in 50% of recipients were below 1.2, meaning the rate of small dense LDL-C in LDL-C increased. TG metabolism in non DM group was similar with that in DM group. In Etworimus (EVER) group, TGf levels were higher than that in non EFR group (p=0.04).

Conclusions: Prevalence of postprandial hypertriglyceridemia among kidney transplant recipients was high, however, whether it should be treated remained unknown.
The Relationship Between Intra-Patient Tacrolimus Variability and Immunosuppression Regimens in Kidney Transplant Patients: A Comparative Multi-Centre Retrospective Study

**Background:**
It is increasingly recognised that high tacrolimus trough level intra-patient variability (IPV) is a predictor for poor long-term outcome after renal transplant. This study aimed to evaluate the relationship between IPV and the use of induction and maintenance immunosuppressive agents has not been previously evaluated.

**Methods:**
Database records of all kidney transplant recipients on standard-release Tacrolimus were interrogated across 5 UK transplant centres (Oxford, Manchester, Liverpool, Glasgow and King’s College London) between 2009 and 2014. Each centre compared trough level IPV in patients on different immunosuppression during the 6-12 month post-transplant (T1) and the last 12 months of follow-up (T2) using Kruskal-Wallis analysis. Patients were excluded if they received dual-organ transplants or modified release tacrolimus and if death or graft loss occurred within two years of transplantation.

**Results:**
1066 patients were included from 5 UK centres (Table 1). There was no significant difference in tacrolimus IPV between patients receiving induction with basiliximab or alemtuzumab and those on maintenance mycophenolate and Azathioprine during T1 and T2 (p=0.05 for all comparisons). In Oxford and King’s College London, patients receiving steroids had significantly higher IPV in T2 (p=0.001 and p=0.013 respectively) compared to those on steroid-free regimen. A similar trend was seen in other centres but the difference in IPV did not reach significance.

**Conclusions:**
This study represents the first multicentre comparative evaluation of tacrolimus IPV in kidney transplant patients on different immunosuppression across the UK. Our results demonstrate an association between the use of steroids and higher tacrolimus IPV in 2 out of 5 centres. Further study of pooled data is awaiting ethical approval.

**Funding:**
Commercial Support - Educational grant from Astellas Pharma Ltd

---

### Table 1. Comparison of Median (IQR) Tacrolimus IPV in Patients on Different Immunosuppression Agents across 5 UK Renal Transplant Centres.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Oxford (n=284)</th>
<th>King’s College (n=248)</th>
<th>Manchester (n=112)</th>
<th>Glasgow (n=107)</th>
<th>London (n=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>(µg/L)</td>
<td>(µg/L)</td>
<td>(µg/L)</td>
<td>(µg/L)</td>
<td>(µg/L)</td>
</tr>
<tr>
<td>Tacrolimus IPV</td>
<td>(µg/L)</td>
<td>(µg/L)</td>
<td>(µg/L)</td>
<td>(µg/L)</td>
<td>(µg/L)</td>
</tr>
<tr>
<td>Steroid-free</td>
<td>2.1 (1.6-2.7)</td>
<td>1.7 (1.2-2.4)</td>
<td>2.0 (1.6-2.5)</td>
<td>1.6 (1.2-2.2)</td>
<td>1.9 (1.4-2.3)</td>
</tr>
<tr>
<td>Steroid-free</td>
<td>2.1 (1.6-2.7)</td>
<td>1.7 (1.2-2.4)</td>
<td>2.0 (1.6-2.5)</td>
<td>1.6 (1.2-2.2)</td>
<td>1.9 (1.4-2.3)</td>
</tr>
</tbody>
</table>

*p<0.05, (,) insufficient data

---

**Table 1: Baseline characteristics of renal transplant patients who received a renal transplant in the US 2017**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53 ± 12</td>
</tr>
<tr>
<td>Gender</td>
<td>Male 55%</td>
</tr>
<tr>
<td>Race</td>
<td>White 70%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes 30%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes 40%</td>
</tr>
<tr>
<td>Obesity</td>
<td>Yes 20%</td>
</tr>
<tr>
<td>Smoking</td>
<td>Yes 10%</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>Yes 15%</td>
</tr>
<tr>
<td>History of CHD</td>
<td>Yes 5%</td>
</tr>
<tr>
<td>History of CVA</td>
<td>Yes 10%</td>
</tr>
<tr>
<td>History of TIA</td>
<td>Yes 5%</td>
</tr>
<tr>
<td>History of MI</td>
<td>Yes 5%</td>
</tr>
<tr>
<td>History of Stroke</td>
<td>Yes 10%</td>
</tr>
<tr>
<td>History of PCOS</td>
<td>Yes 5%</td>
</tr>
<tr>
<td>History of DM2</td>
<td>Yes 10%</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>40 ± 10</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>120 ± 20</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>150 ± 50</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>40 ± 10</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>120 ± 20</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>150 ± 50</td>
</tr>
</tbody>
</table>

---

**Methods:**
This study is the first multicentre comparative evaluation of tacrolimus IPV in kidney transplant patients on different immunosuppression across the UK. Our results demonstrate an association between the use of steroids and higher tacrolimus IPV in 2 out of 5 centres. Further study of pooled data is awaiting ethical approval.

**Funding:**
Commercial Support – Educational grant from Astellas Pharma Ltd

---

**Access to Kidney Transplant: Limitations from the Patient’s Perspective in Jalisco, Mexico**

**Background:**
CKD is a major public health problem in Mexico, the incidence is 421 per million inhabitants according to the latest 2016 USRDS report. Renal replacement therapy is expensive and in the majority of low and middle-income countries is prohibitive. Renal transplantation is the treatment of choice for patients with ESRD. Objective is to evaluate the main obstacles encountered by prevalent hemodialysis patients to undergo a kidney transplant.

**Methods:**
A cross-sectional study of 200 prevalent hemodialysis patients in Jalisco. Insured and uninsured patients were included. Demographic variables, time on hemodialysis, social security status and main reasons to undergo or refuse the kidney transplant protocol, The data are shown in numbers, percentages, mean and standard deviation.

**Results:**
Only 72 (36%) patients were under a kidney transplant protocol, 78% of these patients belonged to the Social Security. 32 (44.5%) had completed the protocol, with an average time of 8.8 months for completion, and an average waiting time for surgery of 12.4 months. 128 (64%) patients were not on the transplant protocol; 103 (80.5%) of patients are insured. Main reasons were 46 (36%) were medically unsuitable candidates, 21 (16.5%) did not have a compatible living-related donor, 20 (15.6%) were afraid of being transplanted, 20 (15.6%) were not offered transplant, 18 (14.1%) lacked financial resources.

**Conclusions:**
Being medically unsuitable candidate, lack of a compatible living-related donor, fear of transplantation, not offered the option of transplantation, lack of financial resources, and lack of relatives not willing to donate were the most commonly identified obstacles to kidney transplantation. The findings were similar among the insured and non-insured populations.

---

**Five Year Outcomes of Adult and Pediatric Kidney Transplantation: A Single Center Experience from Guatemala**

**Background:**
The Latin American Dialysis and Transplant Registry, indicates that the overall kidney transplant rate increased from 3.7 per million population (pmp) in 1987 to 19.4 pmp in 2013, nevertheless Guatemala is a country with very low birth rate (5.6 pmp), and this rate has not changed during the last ten years. This study presents the experience of kidney transplants from foundation Amor, this is a nongovernmental and nonprofit institution that provides renal transplants in adults and childrens without social security. This is the first report of long term follow up kidney transplants to our country. The objective is determine 5 years graft and patient survival rates associated to graft lost.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Tuberculous Constrictive Pericarditis after Renal Transplantation: Case Report

Larissa G. Andrade, Alexandre D. Pinto, Diogo B. Cabral, Giselle Vaijel, Guilherme G. Danzi, Joaquim O. Borba, Marcelbio M. Dourado, Maria Carolina R. Colelho, Zaira R. Menezes, Filipe C. Aguiar.

1. Federal University Of Pernambuco, Recife, Brazil; 2. Hospital Universitario 12 de Octubre, Madrid, Spain; 3. University of Mississippi Medical Center, Jackson, MS; 4. Nephrology Department, Hospital Universitario 12 de Octubre, Madrid, Spain.

Background: Constrictive pericarditis (CP) results from chronic scarring caused by inflammation of pericardium. The main causes of CP are idiopathic, viral, or after cardiac surgery, acute pericarditis or radiation therapy. Tuberculosis (TB) is still an important cause of pericarditis in developing countries and immunosuppressed patients.

Case Report: A 35-year-old male patient with end-stage renal failure of unknown etiology received a live donor renal transplant (Tx) in 2001 after 3 years undergoing hemodialysis. His tuberculosis skin test was negative before Tx. He received cyclosporine, prednisone and azathioprine as maintenance medications and no induction. Baseline serum creatinine was 1.4mg/dL. In 2012 changed to sirolimus and prednisone due to pelvic chondrosarcoma. In 2016 the patient was admitted to Hospital with dyspnea. Physical examination revealed hepatomegaly and distended jugular veins. Chest X-ray revealed pericardial calcification (figure 1). Echocardiogram showed increased thickness of the pericardium and biaural dilatation. Polymerase Chain Reaction (PCR) to TB were positive in blood and urine. He started rifampicin, isoniazid, pyrazinamide and ethambutol. Despite initial treatment, symptoms worsened and he underwent anterior pericardiectomy. Histopathological examination showed diffuse fibrosis, but PCR to TB was negative. Patient improved symptoms and was discharged under antituberculous drugs.

Results: The incidence of CP following kidney Tx is unknown, and there are only a few case reports in literature. CP is a serious sequel of TB pericarditis. CP has progressive symptoms worsened and he underwent anterior pericardiectomy. Histopathological examination showed diffuse fibrosis, but PCR to TB was negative. Patient improved symptoms and was discharged under antituberculous drugs.

Conclusions: TB has a high incidence in Brazil and is 14 times more common in Tx patients. The incidence of CP following kidney Tx is unknown, and there are only a few case reports in literature. CP is a serious sequel of TB pericarditis. CP has progressive symptoms worsened and he underwent anterior pericardiectomy. Histopathological examination showed diffuse fibrosis, but PCR to TB was negative. Patient improved symptoms and was discharged under antituberculous drugs.
PUB724

Hypophosphatemia Post Kidney Transplant – A Single Centre Experience

Background: Intrapatient Tacrolimus Level Variability (IPV) is a common complication after kidney transplantation (Tx). It requires correction by either oral or intravenous phosphate (PO4). We aim to identify predisposing factors for developing HP post-Tx.

Methods: We identified 57 kidney Tx recipients from Nov/14 to Dec/15. We collected demographics, causes of ESRD, prevalent RRT, Tx type, duration of admission, serum phosphate (SPO4) levels 3 days post-Tx and at discharge, requirement of PO4 supplementation and Tx function for the period of 6 months. We defined HP as SPO4 levels <0.8 mmol/L and delayed graft function (DGF) as requiring RRT 7 days post-Tx.

Results: Mean age was 47.2 years. Causes for ESRD were GN (31.6%), unknown aetiology (22.8%), hereditary (19.3%), interstitial nephritis (14%), renovascular (7%) and DM nephropathy (5.3%). Prior to Tx, 47.4% and 29.8% were on HD or PD respectively. 10 patients received a living donor Tx (LD) (17.5%), 32 deceased brain-death Tx (DBD) (56.1%) and 14 deceased cardiac-death Tx (DCD) (24.6%). Mean duration of admission was 9.4 days (SD 9.3). 29 presented with drop in SPO4 levels of >0.3 mmol/L 3 days post-Tx. Mean SPO4 at discharge was 0.94 mmol/L (SD 0.3), 10 (17.5%) had normal graft function, 45 (78.9%) had DGF and 2 (3.5%) had primary graft dysfunction. Mean SCR at Day 1, 1.3 and 6 months post-Tx were 561.7 mmol/L (SD 248.2), 150.3 mmol/L (SD 102.4), 159.1 mmol/L (SD 100) and 147.5 mmol/L (SD 71.7) respectively. At the end of follow-up, 37 patients presented HP 27 (47.3%) required oral PO4, 3 (5.2%) needed IV PO4 while 7 (12.2%) required both. Mean PO4 dose of supplementation was 44.34 mmol/day (SD 44.74) for oral and 130 mmol (SD 48.3) for IV. There is a correlation between HP and type of Tx (p < 0.018); (LD 70%, DBD 78%, DCD 35.7%); SPO4 mmol/day (SD 44.74) for oral and 130 mmol (SD 48.3) for IV. There is a correlation between HP and type of Tx (p < 0.018); (LD 70%, DBD 78%, DCD 35.7%); SPO4 level at discharge <0.01). Tx function on the 1st, 3rd and 7th day post-Tx (p values 0.203, 0.021, 0.05). We found no correlation between HP and cause of ESRD, prevalent RRT, Tx function 1 day post-Tx, initial drop of PO4 levels 3 days post-Tx and presence of DGF.

Conclusions: 1. Probably, DBD and LD Tx are more likely to develop HypoP in comparison with DCD Tx. Ongoing Tx function is associated with higher incidence of HypoP, close monitoring of these patients is advisable to prevent complications. 3. The presence of DGF and initial monitoring of renal function are not reliable factors to predict the onset of HypoP.

PUB727

The Coefficient of Variation (CV) and the Mean Absolute Deviation (MAD) Are Both Acceptable Measures of Intrapatient Variability (IPV) in Tacrolimus Trough Levels

Background: Tacrolimus is the preferred first line immunosuppressant following renal transplant in the UK. It has a narrow therapeutic index which is measured by serum trough levels. Studies have shown that a high IPV (the variability observed in a patient’s trough level over time) is associated with poorer outcomes post-transplant. In previous studies IPV has been inconsistently calculated using CV or MAD. CV is calculated using the square value of differences from the mean whereas MAD is calculated using the absolute difference of each measurement from the mean. In this unique national retrospective study demonstrates that at 3 centres there was no significant difference between the tacrolimus IPV during T1 and T2. We have previously shown that high IPV is associated with increased rates of rejection, hospitalisations and other complications. The majority of hospitals use the CV method, whereas, the MAD method is calculated using the square root of the mean of the squares of differences from the mean.

Methods: Patients transplanted in 5 UK centres between 2009-2014 and who were taking standard release Tacrolimus preparations were included in the study. IPV data was captured for each patient from 2 predetermined time points – 6-12months post-transplant and the most recent 12 months, with a minimum of four separate trough levels for each time point. MAD and CV were calculated for both time points and a rank correlation performed using Spearman’s Rho Test.

Results: The results are shown in table 1: Although the values calculated for IPV by the CV method were overestimates IPV when compared with MAD. IPV data was calculated using the square value of differences from the mean whereas MAD is calculated using the absolute difference of each measurement from the mean.

Conclusions: This unique national retrospective study demonstrates that at 3 centres there was no significant difference between the tacrolimus IPV during T1 and T2. We have previously shown that high IPV is associated with increased rates of rejection, hospitalisations and other complications. The majority of hospitals use the CV method, whereas, the MAD method is calculated using the square root of the mean of the squares of differences from the mean. This study is the first to prove that both methods are equally useful to track IPV.

PUB726

Intrapatient Tacrolimus Level Variability Can Vary Significantly During Separate Time Periods, Depending on Transplant Centre: A Multicentre UK Retrospective Study

Background: Tacrolimus is the first choice primary immunosuppressant used after kidney transplantation in the UK. It has a narrow therapeutic range, and its successful use requires regular monitoring of serum trough levels. There is emerging evidence that low levels of intra-patient variability (IPV) in tacrolimus levels during the first year after kidney transplantation are associated with improved outcomes in the short term. Longer term data examining IPV and its association with outcomes is limited. It is also not known whether transplant recipients tend to maintain a consistent IPV over longer time periods or not.

Methods: Five UK Transplant Centres calculated IPV from trough tacrolimus levels during two separate time periods; months 6-12 after transplantation (T1) and the most recent 12 months of follow up (T2). Hospital databases were interrogated to provide demographic details and laboratory results for all recipients of kidney transplants between 1 January 2009 and 31 December 2014. Patients were excluded if they received dual-organ transplants, if they died or lost graft function within two years of transplantation, if their immunosuppression regimens were not based on tacrolimus or if they were given modified release tacrolimus preparations. Each centre examined the correlation of IPV during the first two time periods and results between centres were compared. The means from each time period were compared using a paired t test.

Results: Data from 1063 eligible transplant recipients were included. Follow up periods ranged from two to five years. Results are summarised in table 1.

Conclusions: This unique national retrospective study demonstrates that at 3 centres there was no significant difference between the tacrolimus IPV during T1 and T2. However, recipients from Glasgow and Oxford had statistically significant differences in IPV between the two time periods. These results are inconsistent across centres, and this prompts further study. Relatively small sample sizes limit the power of the individual analyses. We propose to combine the data after gaining ethical approval, which we hope will expand upon these findings.

Funding: Commercial Support - Educational grant from Astellas Pharma Ltd

Table 1

<table>
<thead>
<tr>
<th>Centre</th>
<th>Time Period</th>
<th>Mean (SD) T1 Tacrolimus IPV</th>
<th>Mean (SD) T2 Tacrolimus IPV</th>
<th>T-test P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital</td>
<td>CV</td>
<td>MAD</td>
<td>CV</td>
<td>MAD</td>
</tr>
<tr>
<td>Oxford</td>
<td>0.06 (0.02)</td>
<td>0.02 (0.01)</td>
<td>0.06 (0.02)</td>
<td>0.01 (0.00)</td>
</tr>
<tr>
<td>King’s College (London)</td>
<td>0.03 (0.01)</td>
<td>0.01 (0.00)</td>
<td>0.04 (0.02)</td>
<td>0.01 (0.00)</td>
</tr>
<tr>
<td>Manchester</td>
<td>0.02 (0.01)</td>
<td>0.01 (0.00)</td>
<td>0.03 (0.01)</td>
<td>0.01 (0.00)</td>
</tr>
</tbody>
</table>

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

Underline represents presenting author.

1148
Belatacept Conversion and Improved eGFR in Transplant Recipients

Background: CNI and BK viruses are polyomaviruses that commonly infect humans but become latent in immunocompetent individuals. In immunocompromised patients such as transplant recipients, JC and BK viruses can reactivate and result in re-infection of the renal parenchyma with associated allograft dysfunction. Polyomavirus nephropathy (PVAN) is primarily associated with BK virus while JC nephropathy is a very rare complication in transplant patients. Here we report two transplant patients with evidence of JC nephropathy.

Methods: Of review transplant biopsy reports from our institution between 07/2016 and 05/2017 showed three cases with biopsy-proven PVAN but without significant plasma BK viral loads. Subsequent plasma JC viral load was quantified and two of the cases exhibited substantial JC DNA levels.

Results: The two renal transplant patients were noted to have rises in serum creatinine from baseline several years post-transplant. Both underwent allograft biopsies, which revealed evidence of PVAN with positive SV40 immunohistochemical (IHC) staining in tubular epithelial cells. One showed viral cytopathic changes involving viral inclusions. The other case did not show definitive viral cytopathic changes. Moderate to severe chronicity and severe chronic vascular disease were noted in the biopsies as well. No evidence of rejection was identified. Serologically, neither patient had BK viremia but CNI intolerance was found to be resolved. Subsequent JC virus in situ hybridization (ISH) on the biopsy material was positive. Each patient underwent reduction in immunosuppression regimen with decreased JC viral loads.

Conclusions: JC nephropathy may be missed both clinically and on biopsy if one is not aware of this entity. In some cases, no viral cytopathic changes are identified on biopsy although SV40 IHC may reveal allograft infection. Although BK nephropathy typically occurs early in the post-transplant period, our cases of JC nephropathy were detected late in the transplant course. JC virus screening should be considered in patients with PVAN and negative BK serologies.

R E S U L T S

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.5 years</td>
<td>6.5 years</td>
</tr>
<tr>
<td>Tacrolimus, Mycophenolate mofetil, Prednisone</td>
<td>Tacrolimus, Mycophenolate mofetil, Prednisone</td>
</tr>
<tr>
<td>&lt;0.05 eGFR decline, Positive</td>
<td>&lt;0.05 eGFR decline, Positive</td>
</tr>
<tr>
<td>Post-transplant immunosuppression</td>
<td>Post-transplant immunosuppression</td>
</tr>
</tbody>
</table>

| Initial Immunosuppression | Tacrolimus, Mycophenolate mofetil, Prednisone |

<table>
<thead>
<tr>
<th>Transplant</th>
<th>Plasma BK viral load</th>
<th>SV40 IHC</th>
<th>JC DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>5000 copies/ml</td>
<td>Positive</td>
<td>75.68 copies/ml</td>
</tr>
<tr>
<td>Case 2</td>
<td>1500 copies/ml</td>
<td>Positive</td>
<td>48.37 copies/ml</td>
</tr>
</tbody>
</table>

Belatacept Conversion and Improved eGFR in Transplant Recipients with Calcineurin Inhibitor Intolerance

Background: Calcineurin inhibitors (CNIs) are the mainstay of immunosuppressive therapy after renal transplant, but nephrotoxicity has been thought to limit long term allograft survival. Belatacept, a chimeric CTLA4-IgF fusion protein which blocks T cell costimulation has been shown to afford superior composite patient and graft survival rates compared to CNI in patients treated for renal transplant when used de novo after kidney transplant. We report our experience with 19 patients converted from CNI-based maintenance immunosuppression to belatacept for CNI intolerance.

Methods: Nineteen transplant patients from 2009 to 2016 underwent conversion from tacrolimus or cyclosporine to belatacept. The overall reasons for switching to belatacept, the mainstay of immunosuppressive therapy after renal transplant, was due to CNI-related adverse effects. The majority of patients (68%, n=13) were switched to belatacept due to biopsy-proven or suspected CNI renal toxicity. Excluding patients with eGFR of >60 mL/min/1.73 m² before and after conversion, eGFR increased after the switch (30.9 ± 11.1 vs 36.1 ± 13.8, p=0.031) at a median of 43 months from initial transplantation.

Conclusions: In patients with CNI intolerance or renal toxicity, our series suggests an improvement in short- and long-term eGFR for most patients converted to belatacept. This warrants a randomized trial comparing late conversion to belatacept to continued maintenance of CNI in recipients with evidence of chronic allograft injury.

GFR and Biomarkers of CKD in Diabetic and Prediabetic Rhesus Monkeys

Background: In view of the known similar renal physiology and fundamental mechanisms of diabetic kidney disease between humans and nonhuman primates, rhesus monkeys with chronic kidney disease (CKD) have been proven to provide an excellent large animal model to validate the efficacy of drugs targeting nephropathy. Research on biomarkers is providing improved experimental methods to assess early stage CKD status before the disease becomes irreversible.

Methods: Forty one adult male rhesus monkeys were studied for the purpose of examining the relationships between glomerular filtration rate (GFR) determined by the iohexol clearance with five-plate plasma method) and plasma biomarkers that may detect early CKD. Creatinine (Cr), receptor for advanced glycation end products (RAGE), kallikrein B1 (KLKB1), vascular endothelial growth factor (VEGF), homocysteine (HCYS), Cystatin-C (CYS), high sensitivity C reactive protein (hsCRP) were measured. Pearson’s correlation was performed.

Results: GFR was significantly negatively correlated with Cr (r=-0.599, p<0.01), HCYS (r=-0.319, p<0.05) and CYSC (r=-0.478, p<0.01). Cr was moderately correlated with CYSC (r=0.312, p=0.05). RAGE, KLKB1 and VEGF were highly correlated between each pair (RAGE vs KLKB1, r=0.998, p<0.01; RAGE vs VEGF, r=0.995, p<0.01; and KLKB1 vs VEGF, r=0.996, p<0.01).

Conclusions: Cr and CYSC were broadly used in both the MDRD and CKD EPI equations to calculate the estimated GFR in patients. Cr, HCYS and CYSC were all significantly negatively related to GFR. These biomarkers will help to diagnose early stage CKD in monkeys.

Correlation between GFR and biomarkers of CKD (n=41)

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Correlation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cr</td>
<td>-0.599</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CYSC</td>
<td>-0.319</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CYSC</td>
<td>-0.478</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RAGE</td>
<td>0.998</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>KLKB1</td>
<td>0.995</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>VEGF</td>
<td>0.996</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* p-value<0.05, ** p-value<0.01
**Impact of Prostate Cancer (PCa) on Waiting Time for Transplant and Mortality in ESRD**

**Background:** Prostate cancer is a very slow growing cancer with a low mortality. It is unclear if kidney transplant should be delayed after a diagnosis of prostate cancer and how it affects mortality post-transplant.

**Methods:** This study included incident cases of end-stage renal disease for males 40-79 years old from the 1999-2012 United States Renal Data System, linked with Medicare claims data. Our main study variable of interest was prostate cancer as indicated through an ICD-9-CM diagnosis code. Primary outcomes of interest were time to kidney transplant and mortality. We used propensity score matching to control for selection bias, and Cox proportional hazards models and Kaplan Meier curves to compare the risk between men with prostate cancer and those without.

**Results:** Figure 1 shows that the baseline characteristics are all well matched between prostate cancer group, and the control group except that the prostate cancer has slightly more patients in the older age groups. Prostate cancer was associated with prostate cancer and those without.

**Conclusions:** Kidney transplant improves survival in prostate cancer patients and should not be delayed.

**Funding:** Commercial Support - University Hospitals Cleveland Medical Center

---

**Acute Brucellosis in Renal Transplant Patient**

**Background:** Brucellosis is common in developing countries and is usually transmitted by the consumption of unpasteurized milk or direct exposure with the infected animals. Very few cases have been reported regarding the incidence of Brucellosis in the renal transplant patients. We are reporting a case of Brucellosis in the renal transplant patient presenting to Prince Sultan Military Medical City, Riyadh.

**Methods:** We report a case of 61-year-old male, known case of living related transplant 7 years ago with co-morbid conditions including Diabetes (DM), Hypertension (HTN) and Coronary Artery Disease (CAD). Presented to emergency department transplant 7 years ago with co-morbid conditions including Diabetes (DM), Hypertension (HTN) and Coronary Artery Disease (CAD). Presented to emergency department transplant 7 years ago with co-morbid conditions including Diabetes (DM), Hypertension (HTN) and Coronary Artery Disease (CAD). Presented to emergency department transplant 7 years ago with co-morbid conditions including Diabetes (DM), Hypertension (HTN) and Coronary Artery Disease (CAD). Presented to emergency department transplant 7 years ago with co-morbid conditions including Diabetes (DM), Hypertension (HTN) and Coronary Artery Disease (CAD). Presented to emergency department transplant 7 years ago with co-morbid conditions including Diabetes (DM), Hypertension (HTN) and Coronary Artery Disease (CAD). Presented to emergency department transplant 7 years ago with co-morbid conditions including Diabetes (DM), Hypertension (HTN) and Coronary Artery Disease (CAD). Presented to emergency department transplant 7 years ago with co-morbid conditions including Diabetes (DM), Hypertension (HTN) and Coronary Artery Disease (CAD). Presented to emergency department.

**Results:** There were 47 TxPed with deceased donors and 1 with living donor, and their main results are shown in table 1. There was significant increase of the mean z score with 1 month of Tx (Z = -3.3) and after 12 months of Tx (Z = -2.3) (Figure 1).

**Conclusions:** Brucellosis is a rare zoonotic disease in renal transplant recipients especially in endemic areas however timely diagnosis and appropriate treatment results in complete recovery.

---

**Results of a Pediatric Kidney Transplantation Cohort in Brazil**

**Background:** Pediatric kidney transplantation (TxPed) is the renal replacement therapy (RRT) of choice in pediatrics. The aim of this study was to outline the results of the pediatric kidney transplantation in a single center in Brazil.

**Methods:** Analysis of a retrospective cohort of 48 TxPed conducted between 2011 and 2017.

**Results:** There were 47 TxPed with deceased donors and 1 with living donor, and their main results are shown in table 1. There was significant increase of the mean z score for height with 1 month of Tx (Z ~ -3.3) and after 12 months of Tx (Z ~ -2.3) (Figure 1).

**Conclusions:** The graft survival rate of pediatric TxPed at the analyzed center is similar to other centers. KDPI was not a valuable index to predict graft loss in children. There was significant improvement in stature with 1 year of TxPed.
BK Virus in Renal Transplantation Patients Using Alemtuzumab for Induction Immunosuppression

Katie L. Korneffel, Bradley B. Gehring. University of Toledo College of Medicine, Toledo, OH.

Background: Alemtuzumab (Ale) is a monoclonal antibody that targets CD52+ lymphocytes, causing profound B- and T-cell depletion. The use of potent immunosuppressive agents poses an increased threat of BK virus infection in organ transplants. We sought to determine the impact of Ale immunodepletion, with steroid freedom for low risk patients, on the incidence of BK virus viremia and associated patient outcomes.

Methods: An IRB-approved retrospective analysis was performed on 676 patients at the University of Toledo Medical Center who underwent renal transplantation between 3/06 and 11/15. All patients were induced with Ale. BK Viremia was defined as clinically positive BK was not associated with increased rejection. BK was not associated with death-censored graft failure or two consecutive eGFRs less than 45 mL/min/1.73m2 occurring within 3 years was evaluated.

Results: Delayed graft function (DFG) was more common in DCD kidney transplantation (14.20% vs. 0.35%, P<0.001). 3-year graft survival (94.3% vs. 96.6%, P=0.172) and death-censored graft survival (97.1% vs. 97.3%, P=0.757) were similar between DCD and DCD living donor kidney transplantation. The recipient survival was similar between two groups once DCD kidney transplantation recipients survived over 2 months (98.8% vs. 99.3%; P=0.671). The graft function assessed by eGFR at 3 years after transplantation for DCD kidney transplantation was better than living donor kidney transplantation (mean, 71.08 vs. 62.72 ml/min/1.73m2; P<0.001). DCD kidney transplantation was an independent risk factor of poor kidney function in multiple-variables analysis of Cox proportional hazards regression models, although it had similar 3-year graft survival and superior 3-year graft function compared with living donor kidney transplantation.

Conclusions: In spite of higher DGF rate, 3-year kidney survival of DCD is comparable with that of living kidney transplantations. And 3-year graft function for DCD is superior to living donor kidney transplantation. DCD kidney transplantation remained to be an independent risk factor of poor kidney function.

Comparison between DCD and living donor kidney transplantation

Page Kidney after Kidney Transplant Biopsy: A Case Series

Camilo Cortesi, Mai Seeki, Giselle Guerra, Adela D. Mattiauzzi. University of Miami/Jackson Memorial Hospital, Miami, FL.

Background: Kidney (PK) is a rare but serious complication that is seen in kidney transplant (KT) recipients after renal allograft biopsy. PK results from a large perinephric collection compressing the allograft parenchyma, characterized by a triad of hypertension (HTN), perinephric collection, and creatinine (Cr) elevation. This condition has been poorly described in KT recipients with a few cases reported in the literature. This is a case series of 3 patients that developed PK after KT biopsy (KTb). We provide a full demographic description of each patient in Table1.

Methods: Case 1: 66-year-old (yo) woman with deceased donor kidney transplant (DDKT) due to ESRT from HTRN and diabetes mellitus (DM) was admitted with elevated Cr. Ultrasound (US)-guided KTb was done, the next day she developed HTN up to 205/95 mmHg, lower abdominal pain and anuria. US of the KT revealed a large hematoma measuring 7x4cm. Patient was taken to the OR for exploratory surgery with drainage of 500ml of blood. After the procedure, Cr was 6.08mg/dL resolving 2 weeks later at 1.6mg/dL. Case 2: 45 yo man with DDKT due to ESRD from FSGS underwent US-KTb given high donor specific antibodies. Three days after biopsy he presented with diffuse abdominal pain, HTN up to 192/83 mmHg, and Cr elevation from 2.54 to 11.41mg/dL. CT scan showed a subcapsular hematoma of the KT measuring 6.7x2.6x10cm and 17.5x10.9x16cm retroperitoneal collection. Patient underwent exploratory surgery with removal of 3L; one month later Cr was 3.4mg/dL. Case 3: 56 yo man with DDKT due to ESRT from HTRN and DM had an elevated Cr, he underwent US-KTb to rule out allograft rejection. Immediately after, he had pain at the site of KT and HTN up to 202/82 mmHg. Subsequently patient became anuric and Cr rose from 2.1 to 13.2mg/dL. CT scan unveiled be an independent risk factor of poor kidney function.
a perinephric hematoma measuring 8.7x4.5x10.9cm which was then percutaneously drained. Patient required dialysis indefinitely after this event.

**Results:**

**Conclusions:** PK diagnosis relies on clinical suspicion and the use of appropriate imaging. Once PK is diagnosed, aggressive management is often necessary to ensure optimal viability of the allograft. This highlights the importance of identifying risk factors associated with this complication. Large cohort studies are needed to adequately assess the risk.

**PUB738**

Characterization of H2-Blocker and Proton Pump Inhibitor Prescribing Practices in Maintenance Care of Kidney Transplant Recipients

**Vicki K. Sands, Amy Hudson, Catherine M. Brown, Sean F. Leavy. Nephrology, University Hospital Waterford, Waterford, Ireland.**

**Background:** Antacids, either histamine type 2 receptor-blockers (H2Bs) or proton pump inhibitors (PPIs) are routinely prescribed post-transplant. Interactions with immunosuppressants occur in the case of PPIs, through the inhibition of cytochrome P-450 and alteration of the gastric milieu. Of concern, evidence linking PPIs to acute interstitial nephritis now shows an association with progressive chronic kidney disease.

**Methods:** Active prescriptions for patients attending transplant clinic at UHW on Jan 15th 2017, were extracted from the electronic health record (EMedrenal), with demographic, clinical and laboratory covariates. A variable describing the sum of all non-immunosuppressant medications per patient (excluding antacids) was created as an indicator for polypharmacy. Descriptive and both univariate and multivariate inferential analysis was undertaken using SPSS (version 23).

**Results:** 1540 prescriptions identified in 168 patients. 75% of patients were on antacids (41.7% (70) on H2B, 33.3% (56) on PPI). Significant positive associations with any antacid use (p<0.05) were found in univariate analysis for older age, male gender, immunosuppressant type, anticoagulant, statin and polypharmacy. Lower eGFR indicated preference for PPI over H2B (p<0.05). In multivariate modelling, the prescription of prednisone, MMF and each additional non-immunosuppressant independently increased the Odds of antacid prescribing by 4.7, 3.8 and 1.4 fold.

**Conclusions:** There is a high prevalence of antacid use. Polypharmacy and immunosuppressant use independently influence prescribing. The use of PPIs long-term, post-transplant may have clinical implications for graft survival. The factors influencing the indication for and choice of antacid post-transplant merits further study.

**PUB739**

Association between Vascular Access Type in Hemodialysis Patients and Subsequent Kidney Transplant Outcomes

**Medha Airy, Colin L. Lenihan, Monnie Wasse, Wolfgang C. Winkelmayer. 1Baylor College of Medicine, Houston, TX; 2Rush University Medical Center, Chicago, IL; 3Stanford University School of Medicine, Palo Alto, CA.**

**Background:** Type of vascular access is associated with outcomes in patients with end-stage kidney disease undergoing hemodialysis. Whether associations exist with outcomes after kidney transplantation are unknown. Potential mechanisms towards worse outcomes include patency of residual peripheral accesses potentially contributing to heart failure as well as retained vascular grafts that may cause chronic inflammation.

**Methods:** A retrospective cohort study of hemodialysis patients receiving a first kidney transplant between 2006-2011. We chose using medical data from US Renal Data System and a large dialysis organization. We ascertained the access used for the last hemodialysis prior to transplantation: arteriovenous fistula (AVF); arteriovenous graft (AVG); central venous catheter (CVC). Patients were followed from kidney transplant for all-cause mortality, kidney allograft loss from any cause, and allograft loss not due to death.

**Results:** Among 9291 patients who underwent kidney transplantation between 2006-2011, 65.3% had an AVF and 20.4% had an AVG and 14.3% used a CVC. Cox proportional hazards regression models adjusted for demographic, comorbidity, and transplant characteristics, as well as laboratory parameters indicated no associations between vascular access type and all-cause mortality or all-cause allograft loss (Table). Central venous catheter use was associated with a 30% higher risk of allograft loss from causes other than death compared to use of an arteriovenous fistula (HR=1.30; 95% CI, 1.01-1.57).

**Conclusions:** No clear associations between vascular access use for dialysis and subsequent transplant outcomes were identified. The association of central venous catheter use with allograft loss from causes other than death lacks a plausible explanation and requires confirmation.

**PUB740**

Twelve-Year Experience in ABO Incompatible Kidney Transplantation:

**Differences in Infection Rate and Short-Term Outcomes between Hemodialysis and Peritoneal Dialysis Patients**

**Georgios Spanos, Christina Melexopoulou, Chrysanthi Skalioti, Smaragdi Marinaki, John Bokos, Georgios Zavos, John N. Boletis. 1Nephrology Department & Renal Transplantation Unit, Laiko General Hospital, National & Kapodistrian University of Athens, Medical School, Athens, Greece; 2Renal Transplantation Unit, Laiko General Hospital, National & Kapodistrian University of Athens, Medical School, Athens, Greece.**

**Background:** The use of intensified desensitization protocols in ABO-incompatible kidney transplantation (ABOi KTxs) seems to increase postoperative infection rates. Currently, no clear consensus has emerged regarding whether the peritoneal dialysis (PD) catheter should be removed at the time of transplant surgery or not, in the event dialysis is required in the immediate post-transplant period. The purpose of this study was to audit infection complications and outcomes in ABOi KTxs in PD patients and compare them with heamodialysis (HD) patients.

**Methods:** A single centre prospective cohort of ABOi KTxs patients from June 2005 till May 2017 with a desensitization protocol including the use of rituximab 30 days pre-KTxs, immunoadsorptions, intravenous immunoglobulin and double oral immunosuppression administered 15 days pre-KTxs was followed up for one year post KTxs.

**Results:** The cohort included 42 patients (14% PD patients, 76% HD patients and two preemptive) with a mean age of 37.4 ± 10.8 years, 26% female. No significant difference was observed in baseline characteristics between two groups. One episode of peritonitis during desensitization period was successfully treated causing rescheduling the KTxs date, while one episode of central venous catheter related septicaemia was observed during follow up. The incidence of post-KTxs bacterial infections leading to hospitalization, viral infections (cytomegalovirus and polyoma virus) and surgical complications were similar between the two groups. There was no significant difference in serum creatinine at the end of follow up (1.73±0.95 vs 1.51±0.35, p=ns), and patient and graft survival was 100% vs 99% and 100% vs 97.6% in the PD vs HD group, respectively (p=ns). Furthermore, the rate of biopsy-proven acute rejection was comparable. Two patients in the PD group and 3 in the HD group had acute cellular rejection, treated successfully. Only one HD patient developed acute antibody-mediated rejection and graft loss in the immediate post KTxs period.

**Conclusions:** Peritoneal dialysis and hemodialysis patients undergoing ABO incompatible kidney transplantation have comparable infectious complication rate and short term outcomes.

**PUB741**

Kidney Autotransplantation as an Effective Alternative to Percutaneous Transluminal Renal Angioplasty for Renal Artery Stenosis: A Case Report

**Hirofumi Sumi, Atsuko Uehara, Tsutomu Sakurada, Yugo Shibagaki. St. Marianna University School of Medicine, Kawasaki, Japan.**

**Background:** Acute kidney injury (AKI) caused by renal artery stenosis is common. The most common treatment is percutaneous transluminal renal angioplasty (PTRA); however, this procedure is technically difficult in some cases. In these cases, the indications and effectiveness of kidney autotransplantation (AutoTx) remain unclear. We describe the case of a patient with renal artery in-stent restenosis successfully treated with kidney AutoTx.

**Methods:** The patient was a 76-year-old woman with a right solitary kidney attributable to left renal thromboembolism. Two years prior to admission, she underwent an endovascular aortic aneurysm repair with a stent graft for infrarenal aortic aneurysm, which led to ostial occlusion of the right renal artery. She underwent PTRA and stenting. Two days prior to admission, she developed leg edema and hypertension, and thus visited our emergency room. An endovascular aortic aneurysm repair with a stent graft for infrarenal aortic aneurysm was performed. Two years prior to admission, she underwent an endovascular aortic aneurysm repair with a stent graft for infrarenal aortic aneurysm, which led to ostial occlusion of the right renal artery. She underwent PTRA and stenting. Two days prior to admission, she developed leg edema and hypertension, and thus visited our emergency room. An endovascular aortic aneurysm repair with a stent graft for infrarenal aortic aneurysm was performed.

**Conclusions:** Peritoneal dialysis and hemodialysis patients undergoing ABO incompatible kidney transplantation have comparable infectious complication rate and short term outcomes.
Acute Tacrolimus Toxicity Successfully Treated with Phenyo

Background: Tacrolimus is an integral part of immunosuppression following solid organ transplantation. We present a case of acute tacrolimus toxicity in a renal transplant recipient successfully treated with phenytoin.

Methods: A 55-year-old male with history of end-stage renal disease due to tuberous sclerosis and polycystic kidney disease who had undergone a living related renal transplant 17 years ago was transferred to our facility for evaluation of acute kidney injury (AKI). The patient was admitted to a psychiatric facility for suicidal ideations and had been recently initiated on multiple psychotropic drugs including haloperidol, quetiapine, benzotropine, hydroxyzine, citalopram and fluoxetine. Anti-psychothic therapy was held due to AKI. Upon arrival, the patient had progressive worsening of generalized body tremors. Vital signs were normal and physical examination was unremarkable. Laboratory results revealed a serum chloride concentration of 113 mEq/L, bicarbonate 11 mEq/L, blood urea nitrogen 98 mg/dL, creatinine 3.42 mg/dL (increased from baseline of 1.7 mg/dL). Serum trough tacrolimus level was >30 ng/mL. Within a few hours, the patient had worsening mental status and was intubated for airway protection. Tacrolimus was held and he was started on phenytoin 100 mg every 8 hours. On hospital day 3, tacrolimus levels dropped to 7.5 ng/mL and creatinine was 1.7 mg/dL. The patient became more alert, his tremors resolved and he tolerated extubation. Phenytoin was stopped and tacrolimus was restarted at a dose of 2 mg twice daily.

Results: Conclusions: Calcineurin inhibitors form the backbone of immunosuppression in solid organ transplant recipients. Tacrolimus is metabolized by the Cytochrome P450 (CYP) 3A4 enzyme and levels ranging from 5-15 ng/mL are recommended post-transplant. Clinical features of tacrolimus toxicity can vary from complete absence of symptoms to renal failure and neurotoxicity. Our patient developed tacrolimus toxicity likely due to drug interactions with multiple psychotropic drugs given without checking tacrolimus levels. This in turn led to the AKI and worsening body tremors. Very few cases of tacrolimus toxicity treated with phenytoin have been reported in the literature. Phenytoin is an inducer of the CYP system. It increases the metabolism of tacrolimus, and can be considered in cases where rapid decrease in tacrolimus levels is desired.

Hyperammonemia after Lung Transplant, an Often Fatal Complication

Background: Hypermamonemia is a common complication after lung transplantation that is a complication of chronic lung disease and post-transplant lymphoproliferative disorders. It can be a result of amino acid metabolism, bowel decontamination, or drug interactions. Hypermamonemia can be a serious complication and is associated with increased mortality.

Methods: A 69-year-old man with a history of alpha-1 antitrypsin deficiency underwent lung transplantation with an initial uneventful post operative course and discharge on day 14. He was induced with basiliximab and maintained on mycophenolate, tacrolimus, and prednisone. On postoperative day 9, he was noted to have pancytopenia, renal failure, and an ammonia level of 250. He was started on phenytoin and tacrolimus levels were decreased. Despite the use of dialysis and treatment with phenytoin, the patient continued to deteriorate and died on day 31.

Results: Conclusions: Early identification and treatment of recurrent TMA after transplantation require a high clinical suspicion but result in improved graft function and patient outcome. IgG4/2-kappa deposits are rare pathological findings seen following eculizumab therapy. In this case, the deposits were seen in the renal allograft and are thought to be caused by eculizumab therapy.

Cytomegalovirus Infection and Hemophagocytic Lymphohistiocytosis in a Renal Transplant Recipient

Background: Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening hyper-inflammatory syndrome characterized by hypercytokinemia, histiocytic proliferation and hemophagocytosis. Renal transplant recipients (RTRs) are at increased risk of developing HLH due to chronic immunosuppression and high prevalence of viral infections including cytomegalovirus (CMV) infection. We present a unique case of HLH due to CMV infection in a renal transplant recipient.

Methods: A 75-year-old female with a history of polycystic kidney disease status post renal transplantation 12 years prior to presentation, maintained on tacrolimus, mycophenolate mofetil, and prednisone presented with watery diarrhea and generalized weakness. Initial work-up revealed thrombocytopenia, acute kidney injury and tacrolimus toxicity with a serum level of 29 ng/mL. Tacrolimus was held and levels returned to therapeutic range after administration of rifampin. After 7 days of hospitalization, the patient became lethargic, febrile and hypotensive. Mycophenolate was held, empiric antibiotics were started, and the patient was resuscitated with intravenous fluids. Laboratory work-up at that time showed worsening pancytopenia, rising transaminases, elevated ferritin and coagulopathy with hypofibrinogenemia. Despite multiple blood cultures and other tests, the patient remained febrile and hypotensive. A bone marrow biopsy was performed revealing thrombocytopenia, dyserythropoiesis and dysgranulopoiesis. CMV polymerase chain reaction returned showing over 33 million viral copies/mL. The patient was diagnosed with HLH secondary to disseminated CMV infection and was started on intravenous ganciclovir with resolution of viremia and improvement in clinical condition.

Results: Conclusions: RTRs are at high risk for CMV infection, a known precipitant of HLH. CMV infections are most commonly seen during the first post-transplantation period, particularly in the early post-transplantation period. Unlike HLH in non-transplant patients, etosopide is not a mainstay of therapy and treatment remains controversial with little consensus on the role of immunosuppression. Intensive supportive care and organ-directed antimicrobials are essential in patient survival. Prognosis remains poor despite therapy making early diagnosis and prompt initiation of directed therapy crucial in this population.

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

1153
Is There an Association between Frailty and Relative Telomere Length in Pre-Renal Transplant Recipients? Vasanthaa Muthuppanishanapan,2 Kieran Mccafferty,1 Muhammad M. Yaqoob.2 NHS, LONDON, United Kingdom; 2William Harvey Research Institute, London, United Kingdom.

Background: Both telomere length (TL) and frailty is associated with aging. Frailty is emerging as an important risk factor for adverse renal transplant (RT) outcomes and increasingly recognized as potential tools in risk stratifying RT candidates. Strong associations between frailty and relative TL (rTL) have been reported but sparse data is found in renal transplantation. The aim of the study was to assess the association of frailty in RT recipients with rTL and outcome in this cohort.

Methods: This was a single centre prospective study from October 2016 - April 2017. Frailty was measured as defined and validated by Fried based on 5 components at admission for RT. Non-frail was defined as a score of 0 or 1; intermediate frailty as a score of 2 and frail if the score was ≥3. TL was measured from peripheral white blood cell pre-transplant using quantitative PCR (T/S ratio) using a modified Cawthon protocol. Data on co-morbidities, complications, and length of stay in hospital and readmissions were recorded.

Results: 33 recipients (14 male, 19 female) were recruited prior to RT. Ages ranged from 26-77 year with a median age of 47.97 ± 12.84. Cadaveric transplantation was performed in 66.7% of patients and 33.3% had living donor transplant. 66.7% of patients were non-frail (68.2% cadaveric, 63.6% living donor); 24.2% were intermittently frail (18.2% cadaveric, 36.4% living donor) and 9.1% were frail (13.6% cadaveric) at the time of RT. There was no correlation between age and length of stay (R² = 0.03). A higher Charlson co-morbidity index was strongly associated with longer length of stay post RT (p = 0.001). Length of stay post RT was increased with shorter rTL but this was subsequently found not to be significant (p = 0.392). There was no significant association with raised frailty scores and increased hospital admissions (p = 0.35). There was no association between frailty score and rTL was found in this study. Dialysis vintage was inversely proportional to rTL (p = 0.046). rTL was also significantly shorter in RT recipients on haemodialysis in comparison to peritoneal dialysis (p = 0.001).

Conclusions: Despite literature suggesting a correlation between frailty and shorter rTL, our study failed to replicate these findings. There was no significant association between frailty index and rTL, however a small sample size may be the limiting factor.

Clinical Features, Treatment, and Outcomes of Kidney Transplant-Associated Thrombotic Microangiopathy: A Single-Center Experience Kohei Unagami,2 Masayoshi Okumi,2 Hideki Ishida,1 Kosaku Nitta,2 Kazunari Tanabe.2 1Tokyo Women’s Medical University, Tokyo, Japan; 2Tokyo Women’s Medical University, Tokyo, Japan.

Background: Thrombotic microangiopathy (TMA) is a dangerous disorder characterized by fragmented red blood cells, decreased platelet count, and organ failure due to thrombosis. In recent years, atypical HUS has been reported to present such a state. Furthermore, TMA was also considered to present the same state, so strict differentiation between the two conditions is difficult. Kidney transplant-associated TMA (TA-TMA) presents a severe state; thus, rapid differential diagnosis is required.

Methods: We conducted a retrospective study of kidney transplantations performed between January 1999 and December 2015 at our institution, and investigated and evaluated diagnoses, treatment, and graft survival.

Results: 1,109 renal transplantations were performed, and 24 recipients were diagnosed as having TA-TMA (Table1). The prevalence of ABO incompatible cases with TA-TMA was higher than that of ABO compatible cases (odds ratio, 2.39; p = 0.03). We confirmed pathological findings of TMA in 23 cases, including rejection in 11 cases. Using our proposed TA-TMA diagnostic scoring system (Table2), 23 cases were diagnosed as TMA (95.8%). By contrast, the positivity rate without TMA was 0%. As evaluated diagnoses, treatment, and graft survival.

Conclusions: Despite literature suggesting a correlation between frailty and shorter rTL, our study failed to replicate these findings. There was no significant association between frailty index and rTL, however a small sample size may be the limiting factor.
Acute Antibody Mediated Rejection Associated With the Use of the New Anti-HCV Medications—A Case Report

Khaled Karkouti, Saleema Sharief, Qutaiba Hussain, Youssef Boobeis, Tawam Hospital, Al Ain, United Arab Emirates; Tawam Hospital, Al Ain, United Arab Emirates.

Background: Hepatitis C virus (HCV) infection is prevalent in renal allograft recipient and associated with increased morbidity and mortality. The new direct acting antiviral agents (DAAs) are highly effective in clearing the virus and considered safe for use in kidney transplant patients, no acute graft rejection has been reported so far after their use. Here we are reporting for the first time a case of biopsy-proven acute graft rejection after the use of DAAs.

Methods: We report a case of a 47-year-old, type 1 diabetic male who had a living unrelated kidney transplant in 2006. Prior to his transplant, he acquired HCV infection. In 2009, he was found to have 12 million copies of HCV, with a deranged liver function test. In 2015, the patient showed F3 fibrosis on fibro-scan. However, due to the risk of graft rejection he wasn’t started on INF therapy, he was kept on low immunosuppressive treatment consists of cyclosporine (Cyc) 75-50 mg daily, mycophenolic acid 180 mg twice daily and prednisolone 5 mg daily. Recently, DAAs became available and he was started on Daclatasvir 60 mg daily with Sofosbuvir 400 mg daily. Creatinine level (Cr) was maintained mostly around 1.4-1.5 mg/dL. About 3 months after initiating anti-HCV treatment, his Cr raised to 2.4 mg/dL, and kept rising steadily reaching 4.78 mg/dL. During the course DAAs treatment Cyc trough level was kept always therapeutic (140-180 ng/mL), a renal biopsy was done almost three month after starting DAAs, and revealed the presence of acute anti-body mediated rejection (AMR) as well as features of advanced diabetic nephropathy and severe interstitial fibrosis and tubular atrophy. He received methylprednisolone IV pulses and Cyc was replaced by tacrolimus together with increase of the dose of mycophenolic acid. The AMR responded with gradual improvement of his serum Cr

Results: In our patient, the use of DAAs was associated with biopsy proven acute AMR raising the need to be more cautious when using these medications in kidney transplant patients. More studies are needed to establish the link between this treatment and graft rejection.

Drug Resistant CMV Infection in Post Kidney Transplant Recipients – High Dose Gancyclovir as a Safe Treatment Option

Swotha Rani Kanduri, Desiere Garcia Antón, Pradeep Vaitha. University of Mississippi Medical Center, Jackson, MS; Nephrology, University of Mississippi Medical Center; Jackson, MS.

Background: CMV virus load. There are multiple reports of poor graft survival and increased mortality associated with CMV reactivation in kidney transplant patients with an incidence of 0.54%–1%. The factors that promote the emergence of resistance include CMV donor-positive recipient-negative status, (D+/R_), receipt of potent immunosuppression, prolonged exposure to anti-CMV agents and high CMV virus load. There are multiple reports of poor graft survival and increased mortality with resistant CMV infections noted in literature. Here we present a case of gancyclovir (GCV) resistant CMV infection and its successful treatment.

Methods: A 28-year-old African American female, with end stage renal disease underwent disease donor renal transplant secondary to hypertensive nephrosclerosis. She received thymoglobulin induction along with Mycophenolate mofetil, Tacrolimus and Prednisone. She is low risk for CMV with both donor and recipient being positive for CMV IgG. 3 months post-transplant, patient was diagnosed with CMV colitis after she completed valgancyclovir prophylaxis. Received treatment with high dose oral valgancyclovir. CMV PCR levels initially decreased however trended back up and had persistent leukopenia. Genetic testing noted to have GCV resistant CMV viremia. Resistance testing showed mixed CMV population with resistance at UL97 gene target. Available treatment options were induction with Foscarnet vs Cidofovir vs high dose Gancyclovir. Foscarnet and Cidofovir have adverse nephrotoxic profiles along with electrolyte abnormalities and Fanconi picture. They also cause significant disease burden with need for IV fluids and close monitoring of labs. Option of high dose GCV induction was chosen for two weeks followed by high dose oral valgancyclovir. Colitis and leukopenia improved along with significant decrease in CMV PCR levels.

Results: Resistance to GCV can be explained by mutations in two CMV genes: UL97, encoding a kinase responsible for the initial phosphorylation and activation of GCV; and UL54, encoding the viral DNA polymerase. Therapeutic options for GCV-resistant CMV are limited and with some therapeutic options being extremely toxic. So far, we have no controlled trial data to support the best alternative therapy. The use of
higher doses of IV GCV 10 mg/kg twice daily has been one of the successful options considering side effect patterns of other options.

PUB753
Utility of Day 0 Urine Screening Protocol in Predicting Early Onset Urinary Tract Infection after Renal Transplantation Anil Mishra, Olanrewaju Aboderin, Bradley B. Gehring, Katie L. Korneffel, Graham Mitro. University of Toledo College of Medicine, Toledo, OH.

Background: Urinary tract infection (UTI) limits allograft survival and is the most common form of bacterial infection in patients who undergo renal transplantation. Many hospitals including the University of Toledo Medical Center routinely screen patients via urinalysis (UA) and/or urine culture (UC) for nitrites or bacteria prior to operation (Day 0) in order to address this issue. Our study investigates the utility of this protocol in predicting the onset of UTI within two weeks of transplantation (early onset UTI).

Methods: An IRB-approved retrospective cohort study was conducted on 675 patients who received renal transplantation between 03/2006 and 11/2015 at the University of Toledo Medical Center. Day 0 through Day 14 UA and UC data were collected and analyzed. A positive UA was defined as a UA containing nitrites and positive UC as a UC containing greater than or equal to 10^2 colony forming units per milliliter (CFU/mL). All patients were induced with Alemtuzumab.

Results: Of the 675 patients, 227 (33.3%) received screening on Day 0. Eleven of these patients (1.6% of total) had a positive UA and/or positive UC within two weeks of transplantation. Only one patient (0.15% of total) was positive on Day 0, and this patient did not have another positive result within two weeks of transplant. 448 patients (66.4%) did not receive Day 0 screening, and this group was used as a control. Twelve of these patients (1.3% of total) had a positive UA and/or positive UC within two weeks of transplantation. Day 0 urine screening was not a significant predictor of early onset UTI in patients (p=0.143).

Conclusions: Based on our single-center study at UTMC, the practice of Day 0 Urine screening is not a significant predictor of UTI within two weeks of renal transplantation. Hospitals should re-evaluate this protocol and further investigate its utility at their local site before permanently implementing.

Day 0 Urine Screen and the Development of UTI (14 days after Transplant)

<table>
<thead>
<tr>
<th>With Day 0 Urine Screen</th>
<th>Without Day 0 Urine Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>No UTI</td>
<td>451 (64.6%)</td>
</tr>
<tr>
<td>UTI</td>
<td>12 (1.7%)</td>
</tr>
<tr>
<td>Total</td>
<td>463 (66.4%)</td>
</tr>
</tbody>
</table>

PUB754
Abstract Withdrawn

PUB755
Early Acute Antibody Mediated Rejection in a Simultaneous Liver Kidney Transplant Patient Requiring Bortezomib Therapy Winston A. Alley, Gayle M. Vrancic, Karen M. Warburton, Angie G. Nishio-Lucar, Peter I. Lobo, Alden M. Doyle. 1University of Virginia, Charlottesville, VA; 2University of Virginia Health System, Charlottesville, VA.

Background: In simultaneous liver kidney transplantation, the liver is traditionally thought to be protective of the kidney. Herein, we present the case of early acute antibody mediated rejection in a simultaneous liver kidney transplant patient.

Methods: A 61 year old female with a history of hepatitis C cirrhosis and type 2 hepatorenal syndrome on hemodialysis was admitted for deceased donor simultaneous liver kidney transplantation. This was a donation after brain death donor with a positive low level donor specific antibodies (DSA) at the time of transplant (MF1: A68=1487, A24=343, A61=260, B35=269, DR4=3044, DR11=1360, DR52=1243). The patient received induction immunosuppression with 1.5 mg/kg rabbit anti-thymocyte globulin, methylprednisolone 500 mg IV and 1.5 mg/kg IVIG (2g/kg in OR and 0.5 g/kg on POD 1 and 4). Maintenance immunosuppression included steroid taper and mycophenolate with tacrolimus initiated on POD5. The patient had delayed graft function of the kidney requiring renal replacement therapy (RRT). On POD 11, the kidney allograft biopsy revealed marked peritubular capillaritis and robust C4d staining associated with elevated DSAs (DQ7=9977 on POD 11 vs. 150 on POD 4) consistent with antibody mediated rejection. Therapy was initiated including 9 sessions of plasmapheresis followed by IVIG 0.5 g/kg. Although the patient no longer required RRT by POD 35, kidney function remained poor with serum creatinine ranging from 3.1 to 3.9 mg/dl.

Repeat biopsy on POD 47 was significant for ongoing antibody mediated rejection, DSAs remained elevated (DQ7=14011 on POD 47 vs. 11500 on POD 40). Due to the lack of response, treatment with four sessions of plasmapheresis and bortezomib therapy (4 doses of 1.3 mg/m²) was initiated on POD48 with continued improvement in renal allograft function.

Results:
Conclusions: This represents a case of early antibody mediated rejection in a simultaneous liver kidney transplant patient non-responsive to extended IVIG/ plasmapheresis therapy, now requiring treatment with bortezomib, a proteasome inhibitor targeting plasma cells. Although the liver is thought to be protective in simultaneous liver kidney transplantation, close monitoring and careful consideration of induction therapy as warranted, as this is not always the case.

PUB756
Hemophagocytic Syndrome Associated with Acute Renal Allograft Dysfunction Mialagros M. Flores fonseca,1 Claudia A. Mendoza cerpa,2 Sandra F. Velasco,2 Benjamin Gomez-Navarro,1 Viridiana Rodriguez,3 Jorge Andrade-Sierra,1 1Nefrologia y Trasplantes, Centro Medico Nacional de Occidente. Instituto Mexicano de Seguridad Social,1 Guadalajara, Mexico; 2Quimica, Universidad de Guadalajara, Guadalajara, Mexico.

Background: Although there are few reports of hemophagocytic syndrome (HPS) and histoplasmosis infection, we present two cases of renal allografts that developed acute allograft dysfunction.

Methods: Case 1. A 31-year-old male with chronic kidney disease (CKD) of unknown etiology, kidney transplant recipient, kidney biopsy with an acute cellular rejection (ACR) 1A receiving IV methylprednisolone, hospitalized with fever and diarrhea, paraclinical exams with pancytopenia, serum creatinine (Scr) 3.7mg/dl, hyperferritinaemia, hypertriglyceridemia, lymphopenia and abdomen tomography showed hepatosplenomegaly. Bone marrow reports sporadic hemophagocytosis (Figure 1). Discontinuing immunosuppressive therapy, followed by amphotericin and itraconazole. He clinically improves, discharged Scr 2.3mg/dl, and restarting immunosuppressive therapy. Case 2. A 25-year-old male with CKD of unknown etiology, kidney transplant recipient, kidney biopsy with an ACR 1A receiving IV methylprednisolone, hospitalized complaining of fever and productive sputum, bicytopenia, Scr 2.2 mg/dl, hyperferritinaemia, hypertriglyceridemia, chest tomography with areas of consolidation, and abdominal ultrasound with hepatosplenomegaly. Positive culture for Histoplasma capsulatum. Peripheral blood smear revealed megaloblastic changes and hemophagocytosis. Immunosuppressive therapy was suspended, administer amphotericin and itraconazole. Clinically improving and discharged Scr 1.7 mg/dl.

Results:
Conclusions: We report two cases of HPS with acute allograft dysfunction, followed by a ramped up immunosuppressive treatment after ACR episodes, initially unfavorable evolution, discharged patients with a partially recovered renal function. These findings suggests a reasonable management strategy might be discontinued immunosuppressive drugs and considering additional treatment with antifungals, IVIg or high-dose steroids.
Long-Term Outcome after Multimodal Treatment of Kidney Transplant Rejection with Microvascular Injury

Background: Microvascular injury (MVI) (peritubular capillaritis (ptc) and/or glomerulitis (g)) with DSA is a common histopathological feature of acute and chronic active AMR, but MVI was not independently associated with graft loss. The aim of the study was to analyze patient (pt) survival, death-censored graft survival, and overall graft survival after treatment of kidney rejection with MVI.

Methods: Retrospective analysis included all pts who had kidney tx (KT) or simultaneous pancreas and kidney tx (SPKT) at Merkur hospital between 2007 and 2016. We found 75 pts (68 KT and 7 SPKT) who had a rejection episode with MVI. 87% KT were from deceased donors. In induction, 75% pts received anti IL-2 receptor antibody, with TAC, MMF ± steroid maintenance.

Results: The mean time from tx to index bx was 1.1±4.1 mos (median 0.3 mos). 64% pts experienced early graft rejection (within 90 d from tx). Index biopsies were classified as: TCR (49%), borderline (28%), and AMR (23%). Cumulative treatment included steroids (79%), plasmapheresis (27%), anti-thymocyte globulin (23%), IVIG (15%), bortezomib (13%), and rituximab (6%). Last follow-up bx after the treatment revealed persisting rejection in 42% pts (borderline 32%, TCR 4%, and AMR 6%). Average number of bx per pt was three. Time from index to last bx was 6.2±9.6 mos (median 3.9 mos). During follow up period of 33.3±27.4 mos pt survival was 93.3%, death-censored graft survival was 78.4%, and overall graft survival was 74.3%. In univariate analysis v-score in the index bx, ptc in the last bx, i-score in the last bx, steroids, and rituximab were associated with death censored graft survival, but none of these factors was found to be significant in multivariate analysis (Tbl).

Conclusions: Neither MVI, nor Banff classification of rejection was independently associated with long-term death-censored graft loss regardless of the onset and the type of the rejection, possibly reflecting effect of a multimodal cumulative rejection treatment pts have received based on follow up bx.

Univariate and multivariate Cox proportional-hazards regression analysis for death-censored graft survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>v-score</td>
<td>2.1 (1.3-3.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>ptc</td>
<td>1.9 (1.3-2.8)</td>
<td>0.05</td>
</tr>
<tr>
<td>i-score</td>
<td>3.2 (1.3-7.7)</td>
<td>0.005</td>
</tr>
<tr>
<td>steroids</td>
<td>3.1 (1.5-6.4)</td>
<td>0.022</td>
</tr>
<tr>
<td>rituximab treatment</td>
<td>0.1 (0.05-0.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HR = hazard ratio; CI = confidence interval
KEYWORD INDEX

The number refers to the location of the body of the abstract in the publication section.
albuminuria

APKD

AIDS

anemia

angiotensin

anemia

angiotensin

arteriovenous fistula

arteries

arteriosclerosis

arteriovenous access

arteriovenous fistula

AIDS

Alport syndrome

aldosterone

antibody

anaphylaxis

anemia

anemia

angiotensin

anemia

angiotensin

artery

arteriovenous fistula

arteries

arteriovenous fistula

arteries

artery

antigens

antigen

antigens

antigens

antigens

antigens

antigens

antibodies

antibody

anaphylaxis

anaphylaxis

anaphylaxis

anaphylaxis

antibodies

anaphylaxis

antibodies

anaphylaxis

antibodies

anaphylaxis

antibodies

anaphylaxis

antibodies

anaphylaxis

antibodies

anaphylaxis

antibodies

anaphylaxis

antibodies

anaphylaxis

antibodies

anaphylaxis

antibodies

chronic kidney disease
(continued)................ SA-PO889, SA-PO890,
SA-PO891, SA-PO892, SA-PO894,
SA-PO899, SA-PO901, SA-PO902,
SA-PO904, SA-PO906, SA-PO907,
SA-PO911, SA-PO912, SA-PO917,
SA-PO919, SA-PO925, SA-PO927,
SA-PO1021, SA-PO1033, SA-PO1036,
SA-PO1085, SA-PO1089, SA-PO1109,
PUB001, PUB003, PUB064, PUB067,
PUB087, PUB092, PUB096, PUB097,
PUB109, PUB110, PUB112, PUB115,
PUB116, PUB119, PUB120, PUB121,
PUB122, PUB123, PUB126, PUB127,
PUB130, PUB131, PUB134, PUB135,
PUB136, PUB138, PUB140, PUB141,
PUB142, PUB144, PUB145, PUB148,
PUB149, PUB150, PUB151, PUB152,
PUB155, PUB156, PUB158, PUB159,
PUB160, PUB163, PUB165, PUB166,
PUB170, PUB171, PUB172, PUB173,
PUB175, PUB182, PUB185, PUB187,
PUB188, PUB189, PUB192, PUB195,
PUB201, PUB202, PUB207, PUB208,
PUB213, PUB214, PUB217, PUB241,
PUB246, PUB299, PUB331, PUB404,
PUB411, PUB414, PUB427, PUB487,
PUB523, PUB538, PUB542, PUB546,
PUB566, PUB568, PUB573, PUB581,
PUB592, PUB596, PUB599, PUB603,
PUB604, PUB606, PUB677, PUB687,
PUB688, PUB695, PUB730, PUB733
chronic kidney failure.... TH-PO285, TH-PO436,
TH-PO541, TH-PO549, TH-PO551,
TH-PO601, TH-PO1069, FR-OR027,
FR-PO105, FR-PO272, FR-PO432,
FR-PO442, FR-PO497, FR-PO535,
FR-PO552, FR-PO591, FR-PO651,
FR-PO660, FR-PO784, FR-PO822,
SA-OR053, SA-PO080, SA-PO183,
SA-PO321, SA-PO342, SA-PO350,
SA-PO359, SA-PO430, SA-PO672,
SA-PO866, SA-PO910, PUB405, PUB564
chronic metabolic acidosis.................TH-PO516,
FR-PO270, FR-PO429, SA-OR070,
SA-PO165
chronic nephropathy.......... SA-PO352, PUB125,
PUB670
chronic rejection........... TH-PO984, FR-PO1007,
SA-PO468
chronic renal disease......TH-OR110, TH-PO125,
TH-PO352, TH-PO456, TH-PO485,
TH-PO526, TH-PO616, TH-PO659,
TH-PO675, TH-PO676, TH-PO810,
FR-OR111, FR-PO183, FR-PO257,
FR-PO303, FR-PO348, FR-PO349,
FR-PO363, FR-PO366, FR-PO388,
FR-PO431, FR-PO677, FR-PO1047,
SA-OR021, SA-PO084, SA-PO110,
SA-PO179, SA-PO328, SA-PO343,
SA-PO386, SA-PO392, SA-PO398,
SA-PO441, SA-PO447, SA-PO609,
SA-PO621, SA-PO699, SA-PO871,
SA-PO875, SA-PO878, SA-PO898, PUB153,
PUB180, PUB197, PUB211, PUB221,
PUB409, PUB412, PUB685
chronic renal failure....... TH-PO425, SA-PO059,
SA-PO367, SA-PO373, SA-PO810, PUB209

chronic renal insufficiency.................TH-PO479,
TH-PO513, TH-PO541, SA-OR067,
SA-PO366, SA-PO632, SA-PO711, PUB542
cisplatin.......TH-OR016, TH-PO236, TH-PO252,
TH-PO292, TH-PO305, TH-PO313,
TH-PO336, TH-PO1128, FR-PO124,
FR-PO958, SA-OR108
cisplatin nephrotoxicity.................... TH-OR020,
TH-PO246, TH-PO247, TH-PO252,
TH-PO261, TH-PO264, TH-PO291,
TH-PO298, TH-PO300, TH-PO304,
TH-PO305, TH-PO306, TH-PO307,
TH-PO308, TH-PO337, FR-PO249,
FR-PO251, SA-PO024, PUB207
clinical epidemiology..... TH-OR004, TH-OR105,
TH-PO466, TH-PO512, TH-PO532,
TH-PO556, TH-PO719, TH-PO753,
TH-PO799, TH-PO812, TH-PO816,
TH-PO896, TH-PO1081, FR-OR029,
FR-PO051, FR-PO084, FR-PO096,
FR-PO098, FR-PO113, FR-PO381,
FR-PO435, FR-PO473, FR-PO478,
FR-PO777, FR-PO794, FR-PO795,
FR-PO811, FR-PO858, FR-PO888,
FR-PO895, FR-PO910, FR-PO913,
FR-PO923, SA-OR018, SA-OR059,
SA-OR072, SA-OR109, SA-PO002,
SA-PO005, SA-PO011, SA-PO015,
SA-PO018, SA-PO029, SA-PO166,
SA-PO352, SA-PO438, SA-PO441,
SA-PO452, SA-PO633, SA-PO752,
SA-PO826, SA-PO847, SA-PO893,
SA-PO905, SA-PO1002, PUB018, PUB154,
PUB239, PUB390, PUB518, PUB659
clinical hypertension.......FR-PO026, FR-PO540,
FR-PO541, FR-PO557, FR-PO585,
SA-PO473, PUB220, PUB428
clinical immunology.......TH-OR023, TH-PO039,
TH-PO112, TH-PO620, TH-PO907,
FR-OR028, FR-PO025, PUB478, PUB488
clinical nephrology.........TH-OR024, TH-PO106,
TH-PO140, TH-PO143, TH-PO157,
TH-PO171, TH-PO499, TH-PO508,
TH-PO546, TH-PO647, TH-PO840,
TH-PO849, TH-PO946, TH-PO1078,
TH-PO1108, TH-PO1124, TH-PO1127,
FR-OR009, FR-OR021, FR-PO015,
FR-PO057, FR-PO059, FR-PO098,
FR-PO126, FR-PO127, FR-PO144,
FR-PO384, FR-PO734, FR-PO748,
FR-PO907, SA-PO011, SA-PO026,
SA-PO031, SA-PO034, SA-PO041,
SA-PO051, SA-PO071, SA-PO073,
SA-PO114, SA-PO287, SA-PO358,
SA-PO425, SA-PO673, SA-PO928,
SA-PO996, PUB016, PUB179, PUB224,
PUB332, PUB376, PUB483, PUB633,
PUB645, PUB738
clinical trial.................... TH-OR034, TH-OR037,
TH-OR099, TH-PO141, TH-PO160,
TH-PO171, TH-PO462, TH-PO494,
TH-PO495, TH-PO500, TH-PO506,
TH-PO509, TH-PO717, TH-PO727,
TH-PO788, TH-PO910, TH-PO1073,
TH-PO1115, TH-PO1117, FR-OR045,
FR-OR093, FR-PO064, FR-PO200,
FR-PO304, FR-PO538, FR-PO585,
FR-PO750, FR-PO767, FR-PO825,
FR-PO875, FR-PO876, SA-OR032,
SA-OR070, SA-OR115, SA-PO112,

1216

clinical trial (continued).................... SA-PO164,
SA-PO186, SA-PO278, SA-PO434,
SA-PO452, SA-PO485, SA-PO496,
SA-PO503, SA-PO504, SA-PO725,
SA-PO730, SA-PO747, SA-PO760,
SA-PO827, PUB187, PUB188, PUB236,
PUB346, PUB388, PUB515, PUB585,
PUB587, PUB700
collapsing FSGS............. TH-PO169, TH-PO183,
TH-PO207, FR-OR027, FR-PO741,
SA-PO534, PUB468, PUB494, PUB499,
PUB641
collecting ducts.............. TH-OR071, TH-OR077,
TH-PO245, TH-PO276, TH-PO318,
TH-PO366, TH-PO561, TH-PO593,
TH-PO1018, TH-PO1024, TH-PO1025,
TH-PO1028, FR-OR126, FR-OR128,
FR-OR129, FR-OR130, FR-OR132,
FR-OR133, FR-PO254, SA-PO550,
SA-PO553, SA-PO1034, SA-PO1050,
PUB194, PUB584
complement..................... TH-PO001, TH-PO002,
TH-PO004, TH-PO005, TH-PO006,
TH-PO007, TH-PO008, TH-PO010,
TH-PO011, TH-PO012, TH-PO013,
TH-PO014, TH-PO015, TH-PO018,
TH-PO019, TH-PO020, TH-PO022,
TH-PO023, TH-PO091, TH-PO097,
TH-PO108, TH-PO109, TH-PO113,
TH-PO126, TH-PO176, TH-PO191,
TH-PO192, TH-PO209, TH-PO279,
TH-PO439, FR-OR063, FR-OR064,
FR-PO136, FR-PO678, FR-PO700,
FR-PO723, FR-PO724, FR-PO725,
FR-PO726, FR-PO745, SA-PO038,
SA-PO191, SA-PO247, SA-PO263,
SA-PO264, SA-PO265, SA-PO278,
SA-PO421, SA-PO592, SA-PO626,
SA-PO646, PUB028, PUB051, PUB114,
PUB434, PUB472, PUB478, PUB651,
PUB661, PUB744
complications..................TH-OR005, TH-PO188,
TH-PO212, TH-PO435, TH-PO493,
TH-PO613, TH-PO633, TH-PO634,
TH-PO718, TH-PO823, TH-PO828,
TH-PO842, TH-PO853, TH-PO866,
TH-PO867, TH-PO869, TH-PO886,
TH-PO927, TH-PO963, TH-PO987,
FR-PO325, FR-PO565, FR-PO758,
FR-PO818, FR-PO873, FR-PO876,
FR-PO877, FR-PO878, FR-PO885,
FR-PO929, FR-PO946, SA-PO069,
SA-PO163, SA-PO422, SA-PO455,
SA-PO476, SA-PO649, SA-PO731,
SA-PO745, SA-PO890, SA-PO963,
SA-PO965, SA-PO967, PUB085, PUB160,
PUB171, PUB184, PUB268, PUB278,
PUB279, PUB288, PUB355, PUB365,
PUB367, PUB370, PUB527, PUB561,
PUB587, PUB664, PUB698, PUB737
congestive heart failure......................TH-PO490,
FR-OR017, FR-PO213, FR-PO455,
SA-PO076, SA-PO687, SA-PO968, PUB156
coronary artery disease.................... TH-OR002,
TH-OR006, TH-OR039, TH-PO489,
FR-PO050, FR-PO116, FR-PO800,
SA-PO001, SA-PO002, SA-PO061,
SA-PO072, SA-PO828, SA-PO845


diuretics

dialysis withholding

dialysis access

dialysis volume

dialysis withholding

distal tubule

diuretics

drug excretion

drug interactions

drug nephrotoxicity

drug transporter

dyslipidemia

echocardiography

electrolytes

endocytosis

epithelial transport

epidemiology and outcomes

eosinophilia

epidemiology and outcomes (continued)............ SA-PO519, SA-PO587, SA-PO609, SA-PO681, SA-PO764, SA-PO772, SA-PO774, SA-PO790, SA-PO799, SA-PO820, PUB049, PUB077, PUB087, PUB083, PUB123, PUB125, PUB296, PUB299, PUB322, PUB323, PUB338, PUB357, PUB366, PUB398, PUB418
epidermal growth factor............. TH-OR108, FR-PO351, FR-PO436, FR-PO439, FR-PO453, FR-PO730, FR-PO747, SA-PO324, SA-PO338
epithelial........ TH-OR046, TH-OR077, TH-OR065, FR-OR132, SA-OR047, SA-PO537, SA-PO1053, PUB114
epithelial sodium channel........... TH-OR072, FR-PO195, SA-PO1057
epithelial sodium transport........... TH-OR059, TH-OR072, SA-PO1092
epoetin.................................. SA-PO803, SA-PO811
erythropoetin............. TH-PO407, TH-PO666, TH-PO944, FR-OR069, FR-PO212, FR-PO259, FR-PO336, FR-PO524, FR-PO549, FR-PO693, FR-PO984, SA-PO233, SA-PO390, SA-PO565, SA-PO750, SA-PO794, SA-PO798, SA-PO801, SA-PO802, SA-PO804, SA-PO805, SA-PO809, SA-PO811, SA-PO812, SA-PO815, SA-PO1023, SA-PO1027, PUB216, PUB429
ESRD (end-stage renal disease)...... TH-OR040, TH-OR090, TH-OR106, TH-PO169, TH-PO459, TH-PO552, TH-PO557, TH-PO558, TH-PO628, TH-PO675, TH-PO730, TH-PO771, TH-PO777, TH-PO779, TH-PO787, TH-PO795, TH-PO805, TH-PO813, TH-PO814, TH-PO815, TH-PO818, TH-PO826, TH-PO828, TH-PO853, TH-PO857, TH-PO867, TH-PO868, TH-PO880, TH-PO883, TH-PO884, TH-PO885, TH-PO890, TH-PO897, TH-PO910, TH-PO915, TH-PO933, TH-PO968, TH-PO973, TH-PO977, TH-PO981, TH-PO982, TH-PO1041, TH-PO1082, TH-PO1107, TH-PO1130, FR-OR005, FR-OR119, FR-PO202, FR-PO444, FR-PO558, FR-PO588, FR-PO593, FR-PO598, FR-PO707, FR-PO708, FR-PO711, FR-PO712, FR-PO713, FR-PO718, FR-PO719, FR-PO994, SA-OR094, SA-PO310, SA-PO562, SA-PO595, PUB031, PUB198, PUB199
Fabry disease............ SA-PO619, SA-PO626, SA-PO629, SA-PO630, PUB342, PUB412, PUB414, PUB418, PUB423, PUB493
factor .................. SA-PO721, PUB177, PUB201
failure ............ TH-OR091, TH-PO763, FR-PO1021, FR-PO1048, SA-PO670, SA-PO721
familial nephropathy............ TH-PO619, SA-PO561, SA-PO566, SA-PO577, SA-PO599, SA-PO604
family history.................. FR-PO135, SA-PO167, PUB409, PUB419
fibronectin............ FR-PO712, SA-PO306
gastrointestinal complications......... TH-OR127, TH-PO777, TH-PO830, TH-PO984, FR-PO535, SA-PO507, SA-PO736, SA-PO942, SA-PO991, SA-PO1001, PUB171, PUB330, PUB399, PUB463
gastrointestinal medications............... TH-PO420
gender difference............ TH-PO254, TH-PO301, FR-PO411, TH-PO532, TH-PO688, TH-PO694, TH-PO774, TH-PO808, TH-PO881, TH-PO1083, FR-PO178, FR-PO394, FR-PO915, FR-PO937, SA-PO160, SA-PO659, SA-PO693, SA-PO793, SA-PO1048, SA-PO1110
gene expression................ TH-OR136, TH-PO065, TH-PO254, TH-PO270, TH-PO275, TH-PO297, TH-PO411, TH-PO660, TH-PO669, TH-PO679, TH-PO706, TH-PO749, TH-PO918, TH-PO1005, TH-PO1065, FR-OR023, FR-OR083, FR-OR086, FR-OR102, FR-OR104, FR-OR130, FR-PO215, FR-PO227, FR-PO234, FR-PO281, FR-PO282, FR-PO661, FR-PO713, FR-PO969, FR-PO995, FR-PO997, SA-OR002, SA-PO192, SA-PO322, SA-PO394, SA-PO425, SA-PO543, SA-PO557, SA-PO618, SA-PO621, SA-PO1027, SA-PO1032, SA-PO1061, SA-PO1106, PUB206, PUB218, PUB496, PUB544, PUB686
gene therapy ................ TH-PO286, TH-PO777, FR-PO996, SA-PO301, PUB394
gene transcription......... TH-PO365, FR-OR109, FR-PO438, FR-PO611, SA-PO202, SA-PO463, SA-PO537
glomerular disease (continued).........TH-PO156, TH-PO160, TH-PO171, TH-PO173, TH-PO174, TH-PO175, TH-PO179, TH-PO181, TH-PO182, TH-PO185, TH-PO198, TH-PO204, TH-PO205, TH-PO217, TH-PO218, TH-PO386, TH-PO620, TH-PO631, TH-PO647, TH-PO648, TH-PO649, TH-PO650, TH-PO654, TH-PO656, TH-PO691, TH-PO699, TH-PO702, TH-PO707, TH-PO710, TH-PO714, TH-PO728, TH-PO740, TH-PO742, FR-PO743, FR-PO754, FR-PO756, FR-PO992, SA-OR03, SA-OR09, SA-OR09, SA-OR101, SA-PO119, SA-PO119, SA-PO193, SA-PO204, SA-PO205, SA-PO216, SA-PO271, SA-PO275, SA-PO284, SA-PO286, SA-PO358, SA-PO390, SA-PO394, SA-PO354, SA-PO567, SA-PO581, SA-PO585, SA-PO586, SA-PO587, SA-PO588, SA-PO590, SA-PO593, SA-PO595, SA-PO596, SA-PO599, SA-PO600, SA-PO601, SA-PO603, SA-PO605, SA-PO606, SA-PO607, SA-PO608, SA-PO610, SA-PO613, SA-PO615, SA-PO617, SA-PO623, SA-PO624, SA-PO630, SA-PO632, SA-PO943, SA-PO998, PUB389, PUB392, PUB406, PUB407, PUB408, PUB412, PUB414, PUB420, PUB421, PUB715
genetics and development.........TH-OR008, TH-OR008, TH-OR013, TH-PO598, FR-OR037, FR-OR083, FR-OR096, FR-OR097, FR-PO392, FR-PO561, FR-PO562, SA-OR048, SA-OR049, SA-PO478, SA-PO539, SA-PO543, SA-PO546, SA-PO549, SA-PO552, SA-PO555, SA-PO574, SA-PO576, SA-PO593, SA-PO631, SA-PO1031, SA-PO1071, SA-PO1100, PUB124, PUB224, PUB413
gentamicin...........................................TH-PO909
geriatric nephropathy.........TH-OR100, TH-PO551, TH-PO804, FR-PO759, FR-PO911, FR-PO916, FR-PO919, FR-PO920, FR-PO922, FR-PO925, FR-PO926, FR-PO928, FR-PO929, FR-PO931, FR-PO934, FR-PO937, FR-PO938, FR-PO939, FR-PO942, FR-PO943, FR-PO944, FR-PO1033, SA-OR068, SA-PO597, PUB294, PUB427, PUB432, PUB676
gitelman syndrome.........TH-PO1120, SA-PO999, SA-PO1001, SA-PO1042, PUB416
glomerular disease.........TH-OR022, TH-OR023, TH-OR026, TH-OR061, TH-OR129, TH-PO402, TH-PO405, TH-PO406, TH-PO606, TH-PO607, TH-PO688, TH-PO808, TH-PO808, TH-PO808, TH-PO808, TH-PO808, TH-PO808, TH-PO808, TH-PO808, TH-PO903, TH-PO111, TH-PO114, TH-PO122, TH-PO127, TH-PO132, TH-PO134, TH-PO135, TH-PO140, TH-PO147, TH-PO148, TH-PO151, TH-PO152, TH-PO153,
hyperparathyroidism (continued) ... FR-PO297, FR-PO298, FR-PO301, FR-PO305, SA-PO836, SA-PO837, SA-PO838, SA-PO839, SA-PO840, PUB527, PUB530
hypokalemia.................. TH-OR096, TH-PO265, TH-PO285, TH-PO1015, TH-PO1017, TH-PO1110, TH-PO1116, TH-PO1132, FR-OR125, SA-PO895, SA-PO897, SA-PO991, SA-PO993, SA-PO994, SA-PO999, SA-PO1001, SA-PO1002, SA-PO1005, SA-PO1041, PUB261, PUB382, PUB386, PUB400
hypotenremia.................. TH-PO895, TH-PO1097, TH-PO1114, TH-PO1116, TH-PO1123, TH-PO1128, TH-PO1133, TH-PO1137, TH-PO1141, FR-PO964, SA-PO066, SA-PO445, SA-PO1003, SA-PO1004, SA-PO1005, SA-PO1006, SA-PO1007, SA-PO1030, SA-PO1031, SA-PO1066, PUB381, PUB382, PUB384, PUB610, PUB618, PUB632, PUB636
hypotension.................. TH-OR088, TH-PO781, TH-PO1099, FR-PO196, FR-PO580, FR-PO841, FR-PO846, FR-PO890, FR-PO982, FR-PO1000, SA-PO743, SA-PO776, PUB262, PUB295, PUB307
hypoxia.................. TH-OR019, TH-OR131, TH-PO232, TH-PO238, TH-PO256, TH-PO294, TH-PO404, TH-PO666, FR-PO891, FR-PO990, SA-PO099, SA-PO305, SA-PO235, SA-PO308, SA-PO310, SA-PO311, SA-PO313, SA-PO389, SA-PO523, SA-PO542, SA-PO556, SA-PO597, SA-PO900, SA-PO1075, SA-PO1082, PUB006, PUB256, PUB700
ICD-9-CM codes........... TH-PO530, TH-PO537, TH-PO889, TH-PO906, FR-PO491, SA-PO149, SA-PO806
idiopathic nephritic syndrome............ TH-OR029, TH-PO141, TH-PO167, TH-PO356, FR-OR028, FR-PO746, FR-PO971
IgA.................. TH-PO203, TH-PO404, TH-PO405, TH-PO406, TH-PO407, TH-PO408, TH-PO571, TH-PO573, TH-PO575, FR-PO578, FR-PO579, FR-PO580, FR-PO627, FR-PO628, FR-PO885, FR-PO890, SA-OR025, SA-OR027, SA-OR044, SA-OR050, SA-PO235, SA-PO289, SA-PO323, SA-PO350, SA-PO355, SA-PO374, SA-PO389, SA-PO396, SA-PO405, SA-PO445, SA-PO564, SA-PO620, SA-PO625, SA-PO639, SA-PO837, SA-PO950, SA-PO960, SA-PO967, SA-PO1038, SA-PO139, SA-PO1043, SA-PO1047, SA-PO1063, SA-PO1064, SA-PO1068, SA-PO1070, SA-PO1071, SA-PO1072, SA-PO1073, SA-PO1074, SA-PO1075, SA-PO1077, SA-PO1079, SA-PO1080, SA-PO1086, SA-PO1088, SA-PO1098, SA-PO1106, SA-PO1107, SA-PO1108, SA-PO1109, PUB030, PUB059, PUB133, PUB134, PUB139, PUB140, PUB217, PUB222, PUB247, PUB300, PUB326, PUB357, PUB540, PUB547, PUB548, PUB553, PUB554, PUB574, PUB595, PUB607, PUB623, PUB624, PUB647, PUB668, PUB673, PUB737
hypertrophy.................. TH-OR130, TH-PO089, TH-PO424, TH-PO450, TH-PO612, TH-PO677, FR-OR112, SA-OR085, SA-PO949, PUB458
hyperalbuminemia........... FR-PO405, SA-PO409, PUB257, PUB307
immune complexes............. TH-PO288, TH-PO294, TH-PO124, TH-PO175, TH-PO189, FR-PO402, FR-PO770, SA-PO258, SA-PO257, SA-PO262, PUB482, PUB497, PUB656
immune deficiency............. TH-PO271, TH-PO879, FR-PO406, PUB461, PUB664, PUB720
immunohistochemistry........ TH-PO503, FR-PO994, FR-PO743, FR-PO1007, PUB442, PUB449, PUB472, PUB653
immunology.................. TH-OR015, TH-OR057, TH-OR064, TH-OR065, TH-OR122, TH-PO007, TH-PO024, TH-PO026, TH-PO040, TH-PO041, TH-PO049, TH-PO050, TH-PO093, TH-PO108, TH-PO259, TH-PO260, TH-PO265, TH-PO270, TH-PO273, TH-PO280, TH-PO362, TH-PO373, TH-PO377, TH-PO407, TH-PO412, TH-PO440, TH-PO684, TH-PO854, TH-PO1072, TH-PO1090, FR-OR082, FR-PO78, FR-PO112, FR-PO183, FR-PO239, FR-PO359, FR-PO379, FR-PO456, FR-PO598, FR-PO693, FR-PO737, FR-PO879, FR-PO1005, FR-PO1013, SA-PO996, SA-PO105, SA-PO239, SA-PO245, SA-PO466, SA-PO695, SA-PO840, SA-PO845, SA-PO1076, SA-PO1077, PUB203, PUB215, PUB438, PUB441, PUB495, PUB702, PUB754
immunology and pathology............ TH-OR021, TH-OR027, TH-OR028, TH-OR066, TH-OR123, TH-PO004, TH-PO005, TH-PO205, TH-PO208, TH-PO209, TH-PO300, TH-PO301, TH-PO304, TH-PO527, TH-PO262, TH-PO268, TH-PO277, TH-PO281, TH-PO284, TH-PO412, TH-PO571, TH-PO698, TH-PO1003, FR-PO777, FR-PO990, FR-PO997, FR-PO667, FR-PO680, FR-PO692, FR-PO696, FR-PO746, SA-PO100, SA-PO237, SA-PO241, SA-PO265, SA-PO397, SA-PO458, SA-PO465, SA-PO878, SA-PO10195, PUB440, PUB441, PUB477, PUB497, PUB505, PUB538, PUB592
immunosuppression............. TH-OR022, TH-OR065, TH-OR120, TH-OR121, TH-PO129, TH-PO132, TH-PO136, TH-PO143, TH-PO152, TH-PO158, TH-PO167, TH-PO940, FR-OR078, FR-PO335, FR-PO1001, FR-PO1006, FR-PO1011, FR-PO1029, SA-PO127, SA-PO252, SA-PO257, SA-PO260, SA-PO261, SA-PO470, SA-PO474, SA-PO484, SA-PO494, SA-PO503, SA-PO505, SA-PO506, SA-PO507, SA-PO509, SA-PO510, SA-PO511, SA-PO512, SA-PO514, SA-PO517, SA-PO641, SA-PO643, SA-PO940, SA-PO951, PUB007, PUB108, PUB167, PUB480, PUB522, PUB573, PUB705, PUB707, PUB710, PUB717, PUB725, PUB729, PUB735, PUB738, PUB745, PUB751, PUB752, PUB753, PUB755
lean body mass

left ventricular hypertrophy

lupus nephritis

liver cysts

liver failure

lupus nephritis

mesangial cells

metabolism

lymphocytes

macrophages

maligning proteins

malnutrition

mCP-1 (monocyte chemoattractant protein 1)

membranous nephropathy

mitochondria

molecular biology

molecular genetics

mortality

microalbuminuria

mineral metabolism

molecular genetics

molecular biology

maligning proteins

malnutrition

mCP-1 (monocyte chemoattractant protein 1)

membranous nephropathy

mitochondria

molecular biology

molecular genetics

mortality

microalbuminuria

mineral metabolism

maligning proteins

malnutrition

mCP-1 (monocyte chemoattractant protein 1)

membranous nephropathy

mitochondria

molecular biology

molecular genetics

mortality

microalbuminuria

mineral metabolism

maligning proteins

malnutrition

mCP-1 (monocyte chemoattractant protein 1)

membranous nephropathy

mitochondria

molecular biology

molecular genetics

mortality

microalbuminuria

mineral metabolism

maligning proteins

malnutrition

mCP-1 (monocyte chemoattractant protein 1)

membranous nephropathy

mitochondria

molecular biology

molecular genetics

mortality

microalbuminuria

mineral metabolism

maligning proteins

malnutrition

mCP-1 (monocyte chemoattractant protein 1)

membranous nephropathy

mitochondria

molecular biology

molecular genetics

mortality

microalbuminuria

mineral metabolism

maligning proteins

malnutrition

mCP-1 (monocyte chemoattractant protein 1)

membranous nephropathy

mitochondria

molecular biology

molecular genetics

mortality

microalbuminuria

mineral metabolism

maligning proteins

malnutrition

mCP-1 (monocyte chemoattractant protein 1)

membranous nephropathy

mitochondria

molecular biology

molecular genetics

mortality

microalbuminuria

mineral metabolism

maligning proteins

malnutrition

mCP-1 (monocyte chemoattractant protein 1)

membranous nephropathy

mitochondria

molecular biology

molecular genetics

mortality

microalbuminuria

mineral metabolism

maligning proteins

malnutrition

mCP-1 (monocyte chemoattractant protein 1)

membranous nephropathy

mitochondria

molecular biology

molecular genetics

mortality

microalbuminuria

mineral metabolism

maligning proteins

malnutrition

mCP-1 (monocyte chemoattractant protein 1)

membranous nephropathy

mitochondria

molecular biology

molecular genetics

mortality

microalbuminuria

mineral metabolism

maligning proteins

malnutrition

mCP-1 (monocyte chemoattractant protein 1)

membranous nephropathy

mitochondria

molecular biology

molecular genetics

mortality

microalbuminuria

mineral metabolism

maligning proteins

malnutrition

mCP-1 (monocyte chemoattractant protein 1)

membranous nephropathy

mitochondria

outcomes (continued)......................... FR-PO903,
FR-PO905, FR-PO913, FR-PO923,
FR-PO934, FR-PO940, FR-PO943,
FR-PO944, FR-PO964, FR-PO983,
FR-PO1022, FR-PO1027, FR-PO1030,
FR-PO1036, FR-PO1038, SA-OR035,
SA-OR057, SA-OR071, SA-OR075,
SA-PO010, SA-PO014, SA-PO042,
SA-PO059, SA-PO074, SA-PO089,
SA-PO098, SA-PO109, SA-PO131,
SA-PO240, SA-PO242, SA-PO243,
SA-PO262, SA-PO441, SA-PO466,
SA-PO476, SA-PO530, SA-PO691,
SA-PO719, SA-PO731, SA-PO819,
SA-PO919, SA-PO923, PUB052, PUB119,
PUB167, PUB237, PUB251, PUB281,
PUB314, PUB331, PUB334, PUB346,
PUB352, PUB357, PUB397, PUB465,
PUB587, PUB746
oxidative stress.............. TH-OR003, TH-OR117,
TH-PO224, TH-PO234, TH-PO245,
TH-PO251, TH-PO261, TH-PO286,
TH-PO288, TH-PO295, TH-PO305,
TH-PO307, TH-PO309, TH-PO313,
TH-PO361, TH-PO364, TH-PO368,
TH-PO376, TH-PO401, TH-PO406,
TH-PO408, TH-PO409, TH-PO486,
TH-PO498, TH-PO552, TH-PO586,
TH-PO673, TH-PO687, TH-PO697,
TH-PO733, TH-PO739, FR-OR113,
FR-OR114, FR-PO149, FR-PO151,
FR-PO163, FR-PO178, FR-PO216,
FR-PO356, FR-PO365, FR-PO367,
FR-PO405, FR-PO602, FR-PO613,
FR-PO618, FR-PO659, FR-PO664,
FR-PO856, FR-PO942, FR-PO1004,
SA-OR120, SA-PO185, SA-PO308,
SA-PO330, SA-PO368, SA-PO387,
SA-PO810, SA-PO859, SA-PO1091,
SA-PO1102, PUB005, PUB036,
PUB097, PUB103, PUB111, PUB204,
PUB226, PUB679
pancreas transplantation................... FR-PO269,
SA-PO507, SA-PO733
parathyroid hormone..... TH-PO766, TH-PO789,
TH-PO922, TH-PO925, TH-PO1035,
TH-PO1052, FR-OR074, FR-OR076,
FR-PO261, FR-PO275, FR-PO278,
FR-PO280, FR-PO283, FR-PO285,
FR-PO287, FR-PO288, FR-PO291,
FR-PO292, FR-PO293, FR-PO294,
FR-PO295, FR-PO296, FR-PO297,
FR-PO539, FR-PO815, FR-PO887,
SA-PO655, SA-PO753, SA-PO782,
SA-PO884, SA-PO896, SA-PO937,
SA-PO938, SA-PO996, PUB159, PUB240,
PUB250, PUB265, PUB327, PUB380,
PUB567, PUB570, PUB578, PUB598
pathology.... TH-OR093, TH-OR126, TH-PO076,
TH-PO086, TH-PO088, TH-PO098,
TH-PO102, TH-PO120, TH-PO123,
TH-PO149, TH-PO210, TH-PO617,
TH-PO643, TH-PO745, TH-PO840,
TH-PO846, FR-OR009, FR-OR058,
FR-PO283, FR-PO383, FR-PO579,
FR-PO644, FR-PO653, FR-PO699,
FR-PO700, FR-PO731, FR-PO974,
FR-PO1015, SA-OR007, SA-PO063,
SA-PO119, SA-PO250, SA-PO267,
SA-PO459, SA-PO589, PUB192, PUB414,
PUB419, PUB513, PUB528

patient satisfaction......... TH-PO812, TH-PO835,
TH-PO838, TH-PO997, FR-PO804,
FR-PO960, SA-OR072, SA-PO422,
SA-PO450, SA-PO676, SA-PO678,
SA-PO779, SA-PO785, PUB186, PUB190,
PUB191, PUB255, PUB284, PUB286,
PUB315, PUB431
patient self-assessment.......................TH-PO166,
TH-PO555, TH-PO802, TH-PO833,
TH-PO835, TH-PO957, FR-PO321,
FR-PO791, FR-PO804, FR-PO806,
FR-PO906, FR-PO950, FR-PO960,
SA-OR011, SA-OR015, SA-OR020,
SA-PO449, SA-PO453, SA-PO627,
SA-PO673, SA-PO777, SA-PO779,
SA-PO780, SA-PO926, SA-PO931, PUB315,
PUB335, PUB547
pediatric intensive care medicine..... FR-PO072,
FR-PO114, SA-PO018, SA-PO043,
SA-PO065
pediatric kidney transplantation......TH-PO144,
TH-PO947, TH-PO949, TH-PO950,
TH-PO951, TH-PO955, TH-PO956,
TH-PO957, TH-PO958, TH-PO959,
TH-PO961, FR-PO544, SA-PO504, PUB718,
PUB722, PUB734
pediatric nephrology...... TH-PO103, TH-PO117,
TH-PO144, TH-PO432, TH-PO504,
TH-PO585, TH-PO623, TH-PO650,
TH-PO651, TH-PO652, TH-PO655,
TH-PO658, TH-PO659, TH-PO660,
TH-PO662, TH-PO663, TH-PO664,
TH-PO666, TH-PO893, TH-PO916,
TH-PO948, TH-PO960, TH-PO963,
TH-PO1061, FR-OR024, FR-OR030,
FR-PO030, FR-PO072, FR-PO106,
FR-PO114, FR-PO133, FR-PO293,
FR-PO308, FR-PO322, FR-PO452,
FR-PO464, FR-PO492, FR-PO542,
FR-PO543, FR-PO545, FR-PO548,
SA-OR020, SA-OR042, SA-OR043,
SA-OR045, SA-OR046, SA-OR049,
SA-OR107, SA-PO083, SA-PO244,
SA-PO266, SA-PO268, SA-PO281,
SA-PO453, SA-PO533, SA-PO574,
SA-PO584, SA-PO601, SA-PO603,
SA-PO609, SA-PO614, SA-PO616,
SA-PO617, SA-PO695, SA-PO729,
SA-PO754, SA-PO809, SA-PO813,
SA-PO901, SA-PO915, PUB121, PUB220,
PUB222, PUB377, PUB424, PUB425,
PUB551, PUB553, PUB600, PUB630
pediatrics..... TH-PO146, TH-PO147, TH-PO431,
TH-PO442, TH-PO535, TH-PO658,
TH-PO685, TH-PO858, TH-PO893,
TH-PO954, FR-OR029, FR-OR120,
FR-PO063, FR-PO065, FR-PO106,
FR-PO474, FR-PO546, FR-PO547,
FR-PO551, FR-PO617, FR-PO794,
SA-OR107, SA-PO043, SA-PO075,
SA-PO576, SA-PO908, PUB135, PUB161,
PUB552, PUB553, PUB600, PUB697,
PUB722
peritoneal dialysis......... TH-OR001, TH-OR089,
TH-OR090, TH-OR091, TH-OR092,
TH-OR093, TH-OR094, TH-OR095,
TH-OR096, TH-OR097, TH-PO796,
TH-PO820, TH-PO827, TH-PO828,
TH-PO830, TH-PO832, TH-PO833,
TH-PO834, TH-PO835, TH-PO837,
TH-PO838, TH-PO839, TH-PO841,

1226

peritoneal dialysis (continued)..........TH-PO842,
TH-PO843, TH-PO846, TH-PO847,
TH-PO849, TH-PO850, TH-PO851,
TH-PO852, TH-PO853, TH-PO856,
TH-PO857, TH-PO858, TH-PO859,
TH-PO861, TH-PO863, TH-PO864,
TH-PO865, TH-PO866, TH-PO867,
TH-PO868, TH-PO869, TH-PO870,
TH-PO871, TH-PO873, TH-PO874,
TH-PO875, TH-PO876, TH-PO877,
TH-PO878, TH-PO912, TH-PO913,
TH-PO914, TH-PO915, TH-PO916,
TH-PO982, FR-OR053, FR-OR057,
FR-PO322, FR-PO812, FR-PO837,
FR-PO859, FR-PO866, FR-PO880,
FR-PO904, FR-PO943, FR-PO944,
SA-PO169, SA-PO171, SA-PO173,
SA-PO324, SA-PO654, SA-PO671,
SA-PO675, SA-PO676, SA-PO678,
SA-PO691, SA-PO692, SA-PO693,
SA-PO695, SA-PO696, SA-PO697,
SA-PO698, SA-PO699, SA-PO700,
SA-PO701, SA-PO702, SA-PO703,
SA-PO704, SA-PO705, SA-PO706,
SA-PO707, SA-PO708, SA-PO709,
SA-PO710, SA-PO711, SA-PO712,
SA-PO713, SA-PO716, SA-PO717,
SA-PO718, SA-PO719, SA-PO720,
SA-PO721, SA-PO722, SA-PO723,
SA-PO724, SA-PO725, SA-PO726,
SA-PO727, SA-PO728, SA-PO729,
SA-PO730, SA-PO731, SA-PO732,
SA-PO733, SA-PO734, SA-PO735,
SA-PO737, SA-PO739, SA-PO740,
SA-PO741, SA-PO783, SA-PO802,
SA-PO822, SA-PO864, SA-PO922,
SA-PO929, SA-PO933, SA-PO962,
SA-PO964, SA-PO965, SA-PO966,
SA-PO968, SA-PO969, SA-PO970,
SA-PO999, PUB156, PUB283,
PUB336, PUB337, PUB339, PUB342,
PUB343, PUB344, PUB345, PUB346,
PUB348, PUB349, PUB350, PUB351,
PUB352, PUB353, PUB354, PUB355,
PUB356, PUB357, PUB358, PUB359,
PUB361, PUB362, PUB363, PUB369,
PUB370, PUB469, PUB551, PUB578,
PUB631, PUB740
peritoneal membrane........................ TH-OR095,
TH-PO839, TH-PO846, TH-PO848,
TH-PO851, TH-PO855, TH-PO856,
TH-PO858, TH-PO871, TH-PO872,
TH-PO878, FR-PO015, SA-PO692,
SA-PO700, SA-PO712, SA-PO713,
SA-PO714, SA-PO716, SA-PO717,
SA-PO720, SA-PO722, SA-PO729,
SA-PO733, SA-PO735, SA-PO737,
PUB356, PUB359
pharmacokinetics...........TH-OR066, TH-PO668,
FR-OR076, FR-PO472, FR-PO750,
FR-PO991, SA-PO504, SA-PO512,
SA-PO635, SA-PO636, SA-PO638,
SA-PO641, SA-PO642, SA-PO644,
SA-PO654, SA-PO655, SA-PO656,
SA-PO813, PUB695, PUB696, PUB700,
PUB701, PUB702
phosphate binders..........TH-OR038, TH-PO514,
TH-PO785, TH-PO1030, TH-PO1031,
TH-PO1032, TH-PO1033, TH-PO1039,
TH-PO1043, TH-PO1044, TH-PO1048,
FR-PO802, FR-PO882, FR-PO886,


transgenic mouse  
transplant nephrectomy  
transplant outcomes  
transplant pathology  
transplantation  
tubular epithelium  
tubule cells  
uninephrectomy  
uirema  
uiretic bud  
USDRS (United States Renal Data System)  
vascular  
vascular access (continued)  
vascular calcification  
vascular disease  
vasculitis  
vitamin C  
vitamin B1  
vesico-ureteral reflux  
vitamins  
vitamins B1 and B12  
VGEF  
virology  
vitamin B1  
vitamin C  
vitamin D  
urea  
ureteric bud  
urea modeling  
urethra  
vascular access
vitamin D (continued) .......................... TH-PO1064, FR-PO131, FR-PO261, FR-PO274, FR-PO275, FR-PO276, FR-PO277, FR-PO278, FR-PO279, FR-PO280, FR-PO284, FR-PO288, FR-PO294, FR-PO524, FR-PO623, FR-PO674, FR-PO685, SA-OR027, SA-PO125, SA-PO154, SA-PO362, SA-PO371, SA-PO855, SA-PO885, SA-PO889, PUB008, PUB175, PUB264, PUB565, PUB568, PUB569, PUB575, PUB583, PUB596, PUB598, PUB757

water channels .................. FR-OR129, FR-OR131, FR-PO590, SA-PO767, SA-PO1032, SA-PO1034, PUB219, PUB378

water transport ................. TH-OR095, TH-PO1136, FR-OR129, FR-PO989, SA-PO1026, SA-PO1088, PUB091, PUB359, PUB378

water-electrolyte balance ............ TH-PO1120, TH-PO1123, TH-PO1124, TH-PO1130, FR-OR051, FR-OR114, FR-OR127, FR-PO505, SA-OR065, SA-OR066, SA-PO811, SA-PO850, SA-PO921, water-electrolyte balance (continued) .............. SA-PO1002, SA-PO1003, SA-PO1006, SA-PO1025, SA-PO1031, SA-PO1037, SA-PO1040, SA-PO1050, PUB120, PUB268, PUB376, PUB379, PUB400, PUB416, PUB610, PUB635
Tolvaptan Slows GFR Decline in Late-Stage ADPKD Vicente E. Torres,1 Arlene B. Chapman,2 Olivier Devusyt,3 Ron T. Ganevoort,4 Ronald D. Perrone,5 Gary G. Koch,5 John Ouyang,6 Robert D. Mccuevo,7 Jaime Blais,8 Frank S. Czerwiec,9 Olga Sergeyeva,10 Mayo Clinic, Rochester, MN; Otsuka Pharm. Dev. & Comm., Rockville, MD; Otsuka Pharma. Devel. & Commercialization, Inc., Rockville, MD; Otsuka Pharmaceutical Development and Commercialization, Princeton, NJ; Otsuka Pharmaceuticals, Princeton, NJ; Tufts Medical Center, Boston, MA; UMC Groningen, Groningen, Netherlands; 1University of Chicago, Chicago, IL; 2University of North Carolina at Chapel Hill, Chapel Hill, NC; 3University of Zurich, Zurich, Switzerland; 4Otsuka Pharmaceutical Development and Commercialization Inc., Rockville, MD. Group/Team: REPRISE Trial Investigators.

Background: In subjects with autosomal dominant polycystic kidney disease (ADPKD) and relatively early disease (estimated creatinine clearance ≥60 mL/min) the vasopressin V2 receptor antagonist tolvaptan slowed kidney growth and estimated glomerular filtration rate (eGFR) decline, but also caused more frequently transaminase and bilirubin elevations. Tolvaptan efficacy and safety in later-stage ADPKD are unknown.

Methods: REPRISE is a 3 phase, multi-center, randomized withdrawal, placebo controlled, double-blind trial. After an 8-week pre-randomization period including sequential placebo and tolvaptan treatments, 1,370 ADPKD subjects, 18-55 years with eGFR 25-65 mL/min/1.73 m2 or 56-65 years with eGFR 25-44 mL/min/1.73 m2, were randomized 1:1 to placebo or treated for 12 months. Safety assessments were conducted monthly.

Results: The primary endpoint, annualized eGFR change from pre-treatment baseline to post-treatment follow-up, was -2.34 mL/min/1.73 m2 with tolvaptan versus -3.61 mL/min/1.73 m2 with placebo, indicating a 35% reduction in rate of eGFR decline (P<0.001). The secondary endpoint, annualized eGFR slope was -3.16 mL/min/1.73 m2 for patients treated with tolvaptan and -4.17 mL/min/1.73 m2 for placebo treated for 12 months. Transaminase elevations were reversible and no subjects showed bilirubin elevations ≥2×ULN.

Conclusions: Compared with placebo, tolvaptan slowed eGFR decline by 35% over 1-year in subjects with late-stage ADPKD. While transaminase elevations occurred more frequently with tolvaptan treatment, these were reversible after withdrawal of tolvaptan, without concurrent bilirubin elevation, and none met Hy’s laboratory criteria, likely due to more frequent transaminase monitoring and earlier discontinuation.

Funding: Commercial Support - Otsuka Pharmaceuticals

Bardoxolone Methyl Improved GFR Measured by Standard Inulin Clearance to more frequent transaminase monitoring and earlier discontinuation. The secondary endpoint, annualized eGFR slope was -3.16 mL/min/1.73 m2 for patients treated with tolvaptan and -4.17 mL/min/1.73 m2 for placebo treated for 12 months. Transaminase elevations were reversible and no subjects showed bilirubin elevations ≥2×ULN.

Conclusions: Compared with placebo, tolvaptan slowed eGFR decline by 35% over 1-year in subjects with late-stage ADPKD. While transaminase elevations occurred more frequently with tolvaptan treatment, these were reversible after withdrawal of tolvaptan, without concurrent bilirubin elevation, and none met Hy’s laboratory criteria, likely due to more frequent transaminase monitoring and earlier discontinuation.

Funding: Commercial Support - Otsuka Pharmaceuticals

Kidney Injury After Intravenous or Intracoronary Contrast Agents for Noninvasive or Invasive Coronary Angiography: An Industry-Independent, Phase 3, Randomized Controlled Trial Marc Dewey,1 Peter Martus,2 Maria Bossert,3 Elke Zimmermann,4 Michael Laule,5 Eva Schönberger,6 Christoph Dötsch,7 Charité, Berlin, Germany; 2UKT Tübingen, Tübingen, Germany. Group/Team: CAD-Man Study Group.

Background: X-ray contrast agents can have nephrotoxic effects, while it is unknown whether acute kidney injury is more likely after intravenous or intracoronary administration of these agents and whether contrast-induced acute kidney injury is associated with impaired chronic kidney function.

Methods: In this randomized controlled trial, patients with suspected coronary artery disease were recruited. Patients with known coronary artery disease and a clinical indication for invasive coronary angiography (ICA) based on atypical chest pain were eligible. Patients were randomly assigned (1:1) to ICA with intracoronary contrast or coronary computed tomography angiography (CTA) with intravenous contrast. The same low osmolality ionic contrast agent was used for ICA (CHI). The primary outcome of this analysis was contrast-induced acute kidney injury within 3 days following contrast agent administration defined as an increase in serum creatinine of ≥0.5 mg/dL or ≥25% after 18-24 hours. Laboratory investigators were masked to randomization group.

Results: Between February 18, 2009, and August 2, 2015, 162 and 165 patients were randomly assigned and underwent ICA and CTA. Follow-up creatinine after 18-24 hours or 46-50 hours was available for 159 patients (98%) in the ICA group and 161 (98%) in the CTA group. Baseline estimated glomerular filtration rates were not significantly different between patients in the CTA (84.3±17.2 mL/min/1.73 m2) and the ICA group (87.1±16.7 mL/min/1.73 m2; p=0.14). There were 30 cases of contrast-induced acute kidney injury overall: 9 in the CTA group (6%, 95% CI 3-10%) and 21 in the ICA group (13%, 95% CI 8-19%; p=0.036). The 3-day creatinine rise beyond baseline serum creatinine follow-up was available in 97% of patients (311 of 320) after a median duration of 1.9 years, and a greater proportion of patients with acute kidney injury still had increased creatinine compared to CTA (84%) compared to ICA (57%) without acute kidney injury (AKI).

Conclusions: In patients with suspected coronary artery disease, acute kidney injury seems to be less likely after intravenous than after intracoronary contrast agent administration and contrast-induced acute kidney injury was associated with impaired chronic kidney function.

Funding: Government Support - Non-U.S.
SA-OR125
The Pivotal Multicenter Trial of Ultrasound Guided Percutaneous Arteriovenous Fistulae for Hemodialysis Access
Jeffrey E. Hull,1 William C. Jennings,2 Randy L. Cooper,3 Umar Waheed,4 Matthew E. Schaefer,5 Rajeev Narayan,6 Richmond Vascular Center, North Chesterfield, VA; 7Univ OK Med Col, Tulsa OK, Tulsa, OK; 8Southwest Kidney Institute, PLC, Tempe, AZ; 9San Antonio Kidney Disease Center, San Antonio, TX.

Background: Arteriovenous fistulae for hemodialysis are usually created by a surgical procedure. Percutaneous creation of an arteriovenous fistulae with a thermal resistance anastomosis device (TRAD) in an office based vascular center is emerging as an alternative to surgery.

Methods: One hundred seven patients were enrolled in a prospective, non-inferiority trial at 5 sites. Patients underwent ultrasound guided anastomosis creation between the proximal radial artery and perforating vein with the Ellipsys® Vascular Access System followed by separate maturation procedures. All procedures were performed in outpatient vascular centers. The primary endpoints were brachial artery flow volume ≥500 mL/min and vein diameter ≥4 mm in >49% of patients, and absence of device related complications at 90 days.

Results: Arteriovenous fistulae with fused anastomoses were created in 95% (102/107) patients. Maturation procedures included anastomotic balloon dilation in 72% (77/107), brachial vein embolization in 32% (34/107), cubital vein ligation in 27% (29/107), and surgical transposition in 26% (28/107). The primary flow and diameter endpoints were achieved in 86.0% (92/107) of the patients exceeding the performance goal of 49% (p < 0.0001). There were no major adverse events attributed to the device. Cumulative patency was 96.1%, 93.7%, 91.0% at 90, 180, and 360 days, respectively. The target dialysis vein was the cephalic, basilic, and brachial veins in 74% (73/99), 4% (4/99), 24% (24/99), 2% (2/99), respectively. 2-needle dialysis was achieved in 88% (71/81) of patients on hemodialysis at a mean 113.1 ± 72.0 days. Functional patency was 98.4%, 98.4%, and 92.3% at 90, 180, and 360 days, respectively.

Conclusions: The Ellipsys® Vascular Access System met the primary safety, and efficacy endpoint goals in the United States pivotal trial.

Funding: Commercial Support - Avenu Medical Inc.

SA-OR126
Primary Results of the Time to Reduce Mortality in End-Stage Renal Disease (TIME) Trial: A Pragmatic Trial Demonstration Project of the NIH Health Care Systems Research Collaboratory
Laura M. Dember,1 Eduardo K. Lacson,1 Steven M. Brunelli,2 Jesse Y. Hsu,3 Alfred K. Cheung,4 John T. Daugirdas,5 Tom Greene,6 Csaba P. Kovacs,7 Dana Miskulin,8 Ravi I. Thadhani,9 Frank W. Maddux,10 Michael F. Flessner, Kevin C. Abbott, J. R. Landis,11 Baylor College of Medicine, Houston, TX; 2DaVita Clinical Research, Needham, MA; 3DaVita Healthcare Partners Inc., El Segundo, CA; 4Fresenius Medical Care, Waltham, MA; 5Massachusetts General Hospital, Boston, MA; 6NIDDK, NIH, Bethesda, MD; 7The National Institutes of Health, NIDDK, Bethesda, MD; 8Tufts Medical Center, Somerville, MA; 9Tufts University School of Medicine, Boston, MA; 10University of Illinois College of Medicine, Burr Ridge, IL; 11University of Pennsylvania, Philadelphia, PA; 12University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; 13University of Tennessee Health Science Center, Memphis, TN; 14University of Utah, Salt Lake City, UT; 15Group/Team: TiME Trial Study Group.

Background: Observational studies of patients receiving maintenance hemodialysis suggest that mortality is lower with dialysis sessions longer than 4 hours but this hypothesis has not been evaluated in a randomized trial, and broad acceptability of longer treatments has not been established.

Methods: Cluster-randomized trial fully embedded in clinical care delivery with no online research staff or primary data collection. 266 dialysis units operated by two US dialysis providers were randomized to Intervention or Usual Care. Intervention units were to adopt a default hemodialysis session duration of at least 4.5 hours (255 minutes) for incident patients. Usual Care units had no trial-driven approach to duration. The primary outcome was mortality. The major secondary outcome was hospitalization rate.

Results: 7035 incident patients highly representative of the US dialysis population were enrolled between 12/18/13 and 9/30/16. The trial was discontinued at a median follow-up of 1.1 years after an interim analysis showed a smaller than targeted group difference in session duration and no difference in outcomes. For the primary analysis, patients with Watson V ≤4.5 L, per-patient mean session durations were 219 and 210 minutes for Intervention and Usual Care, respectively, and there was no difference in mortality (HR 0.97, 95% CI 0.84, 1.12; p=0.69) or hospitalization rate (204 vs 213 per 100 patient-yrs, p=0.44). Findings were similar for the full analysis population (all patients). The TiME trial results demonstrate feasibility of several aspects of large-scale pragmatic trials in dialysis. However, effective strategies for engaging clinicians and patients are required to evaluate interventions fully incorporated into routine care delivery. NCT02019225

Funding: NIDDK Support, Other NIH Support - NIH Common Fund

SA-OR127
A Multi-Center Randomized Controlled Trial of Rituximab versus Cyclosporine in the Treatment of Idiopathic Membranous Nephropathy (MENTOR)
Fernando C. Fervenza,4 Pietro A. Canetta,5 Sean Barbour,1 Richard A. Lafayette,6 Brad H. Rovin,7 Nabeel Aslam,8 Michelle A. Hladunewich,9 Heather N. Reich,10 Paul E. Brenchley,11 Debbie S. Gips,12 Matthias Kretzler,13 Jai Radhakrishnan,14 Lee A. Hebert,15 Patrick E. Gips,16 Leslie F. Thomas,15 Ellen T. McCarthy16

Background: Membranous nephropathy (MN) remains the leading cause of nephrotic syndrome in Caucasian adults. Cyclosporine (CSA) is successful in reducing proteinuria, but its use is associated with a high relapse rate. Rituximab (RTX) is effective in reducing proteinuria but whether RTX is as effective as CSA in inducing and maintaining complete (C) or partial remission (PR) of proteinuria in MN is unknown. The MENTOR trial hypothesized that B-cell targeting with RTX is non-inferior to CSA in inducing long-term remission of proteinuria.

Methods: Patients with proteinuria ≥ 4g/24h, estimated GFR ≥ 40 mL/min/1.73m2 and ≥3 months of All blockade were randomized into a 12-month treatment period with IV RTX, 1000 mg (2 infusions, 14 days apart; repeated at 6 months if proteinuria reduction ≥25% at 6-months or oral cyclosporine 3.5-5mg/kg/day for 6-months (continued for another 6 months if a substantial reduction in proteinuria (equal to or >25%) was seen at 6-months). Treatment efficacy was assessed by an intention-to-treat analysis of remission status (C or PR) at 24-months follow-up. At the 6-month post-randomization, patients who did not have proteinuria reduction ≥25% were considered treatment failures and exit the study. Follow up was at 3, 6, 9, 12, 18 and 24 months, and included quantification of creatinine clearance, serum albumin, 24h proteinuria, anti-PLA2R antibodies levels as well as quality of life assessment.

Results: One hundred and eighty one were screened and 130 patients (mean age 52 ± 12.4 SD, 76.9% male) were randomized. Mean BP 125/76 ± 14 mmHg, Median SCR 1.2 mg/dL (range 0.5-2.5), serum albumin 2.6 g/dL (range 1.6-4.1), proteinuria 10.3 g/24h (range 8.9-27.5).

Conclusions: Last patient randomized was September 2015 and follow-up will be completed on 9/11/2017. We guarantee that will be able to present preliminary results by the time of the ASN.

Funding: Commercial Support - Genentech Inc, South San Francisco, CA, Private Foundation Support
A Phase 1 Trial of ALN-GO1: An Investigational RNAi Therapeutic for Primary Hyperoxaluria Type 1

**Background:** In previous studies that enrolled over 2,600 patients, primarily including patients with CKD caused by type 2 diabetes, barboxaline methyl (BARD) improved mean estimated GFR (eGFR) and inulin clearance. A Phase 2/3 trial (CARDINAL, NCT03019185) was initiated to test the hypothesis that BARD will improve eGFR in patients with Alport syndrome (AS).

**Methods:** The Phase 2 open-label portion of the study was designed to enroll 30 patients on stable RAAS blockade, ages 12 to 60 years, with confirmed diagnosis of AS, eGFR values from 30 to 90 mL/min/1.73 m², treatment with BARD produced mean improvements of 6.9 mL/min/1.73 m² [1]. The primary efficacy endpoint was change from baseline in eGFR after 12 weeks of treatment. interim results are described here.

**Results:** 30 patients were enrolled (mean age 44 years, 60% female, 73% X-linked AS). Data were extracted after the first 8 patients had received 12 weeks of treatment. From a mean baseline eGFR of 54.7 mL/min/1.73 m², eGFR improved at least 2.7 mL/min/1.73 m² at Week 4 (n=19; p<0.0005), which further improved to 12.7 mL/min/1.73 m² at Week 12 (n=8; p<0.0005), as of July 24th, 2017. Over 80% of patients demonstrated clinically meaningful improvement in eGFR of at least 25% per MDRD. eGFR improvements were associated with decreases in BUN, uric acid, and phosphorous. Median UACR increased, however, for Primary Hyperoxaluria Type 1.

**Conclusions:** BARD was generally well tolerated and improved kidney function in patients with AS. The Phase 2 double-blind, randomized, placebo-controlled portion of the trial that will enroll up to 150 patients has been initiated.

**Funding:** Commercial Support - Reata Pharmaceuticals

---

**FR-PO1056**

**IV Cyclophosphamide vs Tacrolimus and Azathioprine as Induction in Proliferative Lupus Nephritis: A Randomized Controlled Trial**

**Background:** Therapy for proliferative lupus nephritis is limited to cyclophosphamide or mycophenolate as induction regimens. We present a randomized controlled trial of a regimen comprising intravenous azathioprine and steroids compared to IV cyclophosphamide and steroids for induction of lupus nephritis.

**Methods:** Patients of lupus nephritis (classes III, IV, V/II or V/I), age 15-60 years were included. Exclusion criteria included patients with biopsy proven class IIIC IV lupus nephritis, an estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m², severe infections or contraindications to any drugs. All patients received 3 pulses of methylprednisolone (500 mg). Subsequently, prednisolone was given at doses of 0.5 mg/kg/day and tapered. The Triple Drug regimen group received tacrolimus (0.075 mg/kg, trough 5-10 mg/ml) and azathioprine (2mg/kg). The control group received IV cyclophosphamide, 500 mg/m² monthly. All patients received hydroxychloroquine.

**Conclusions:** The primary end point was achievement of complete renal remission. Secondary end points included decrease of proteinuria, decrease in disease activity scoring (SLDAI Score) and incidence of severe adverse events.

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

---

**FR-PO1057**

**Rituximab (RTX) Treatment of Fibrillary Glomerulonephritis (FGN): A Pilot Study**

**Methods:** We recruited 11 patients with biopsy proven idiopathic FGNs into an open-label study testing the efficacy of RTX in reduction of proteinuria and preservation of renal function. All patients completed 12 mos of the study. There was no significant change in CrCl values at each time point prior to comparing the values using a paired t-test. No serious adverse events were reported.

**Results:** All patients completed 12 mos of the study. There was no significant change in CrCl: 47.73 (SD 24.02) at baseline, 43.73 (SD 23.08) ml/min/SA at 12 mos, p=0.21 Following 4 doses of RTX, patients had stable renal function. There was a tendency for proteinuria to decrease although it did not quite meet statistical significance (p= 0.068). A subgroup of 3 (27%) patients had a dramatic response[Fig 2]. CD-19 B cells, the RTX target, dropped from an avg of 158.9 cells/mL at pre-RTX to nearly 0 at day 28 post-RTX. With the exception of patients 1 and 6 who had nephrotic to non-nephrotic p=0.068. A subgroup of 3 (27%) patients had a dramatic reduction in proteinuria.

**Funding:** Commercial Support - Study funded by Alnylam Pharmaceuticals
FR-PO1058

Canagliflozin and Renal Outcomes in Type 2 Diabetes: Data from the CANVAS Program

Vladko Perkovic,1,2 Dick de Zeeuw,3 Kenneth W. Mahaffey,4 Greg Fulcher,4 Ngozi Erondu,5 Wayne Shaw,5 Terrance D. Barrett,6 Michele Weidner-Wells,3 Hisaeoii Deng,7 Norm Rosenthal,8 Mehul Desai,9 David R. Matthews,10 Bruce Neal.11 The George Institute for Global Health, University of Sydney, Sydney, NSW, Australia; 2The Royal Northern Shore Hospital and University of Sydney, Sydney, NSW, Australia; 3University of Groningen, University Medical Center Groningen, Groningen, Netherlands; 4Stanford Center for Clinical Research (SCCR), Stanford University, Department of Medicine, Stanford, CA; 5Janssen Research & Development, LLC, Raritan, NJ; 6University of Oxford, Oxford, United Kingdom; 7University of Groningen, University Medical Center Groningen, Groningen, Netherlands; 8Janssen Research & Development, LLC, Raritan, NJ; 9University of Oxford, Oxford, United Kingdom.

Background: Canagliflozin (CANA) is an SGLT2 inhibitor that may have beneficial effects on the kidney in people with diabetes. The effects of CANA on prespecified renal outcomes in people with type 2 diabetes (T2D) and an elevated risk of cardiovascular (CV) disease were assessed in the CANagliflozin cardioVascular Assessment Study (CANVAS) Program.

Methods: The CANVAS Program consists of 2 double-blind, randomized trials conducted in 10,142 people with T2D and elevated CV risk (defined by the presence of documented CV disease or ≥2 risk factors), who received CANA (pooled analysis of 100 and 300 mg doses) or matching placebo (PBO). The prespecified exploratory renal outcomes were changes in urinary albumin:creatinine ratio (UACR), estimated glomerular filtration rate (eGFR), and composite clinical outcomes.

Results: At baseline, median UACR was 12.3 mg/g and mean eGFR was 76.5 mL/min 1.73 m². Urinary albumin excretion was 18% lower in participants treated with CANA versus PBO overall (95% CI 16%-20%), and 34% (95% CI 29%-38%) and 36% (95% CI 28%-43%) lower in participants with micro- and macroalbuminuria, respectively. Annual rate of eGFR decline was also reduced (difference 0.13 mL/min/1.73 m²/year, 95% CI 1.15-1.48). The composite outcome of end-stage kidney disease, doubled serum creatinine, or renal death occurred less frequently in the CANA group (hazard ratio 0.53, 95% CI 0.33-0.84). Rates of renal adverse events were similar with CANA and PBO.

Conclusions: CANA reduced urinary albumin excretion, slowed eGFR decline, and reduced the risk of substantial loss of kidney function.

Funding: Commercial Support - Astellas Pharma Inc

FR-PO1059

Vascular Adhesion Protein-1 Inhibitor (VAP-1i) Reduces Albuminuria in Diabetic Kidney Disease (DKD) patients treated with Angiotensin Converting Enzyme inhibitors (ACEi) or Angiotensin Receptor Blockers (ARB) have residual albuminuria and high risk for disease progression. We investigated the efficacy of a novel and specific VAP-1i, ASP8232, for reducing albuminuria on top of ACEi or ARB treatment in DKD. VAP-1i is an amine-oxidase with pro-inflammatory and pro-oxidative stress actions that is elevated and predicts cardiovascular risk in diabetes.

Methods: ALBUM was a randomized, double-blind, placebo-controlled, Phase 2 study in 46 European centers, enrolling 125 patients with type 2 diabetes with DKD. Inclusion criteria included Urinary Albumin Creatinine Ratio (UACR) ≥200 mg/g, eGFR 25-75 mL/min/1.73 m², and stable ACEi or ARB and anti-diabetic treatment for ≥3 months. After a 5-week screening/run-in, patients were randomized to ASP8232 40 mg or placebo once daily for 12 weeks. Primary endpoints were changes from baseline to end of treatment in first morning void (FMV) UACR. Secondary endpoint was change in 24-h albuminuria. A sample size of 110 was sufficient to detect 30% UACR reduction vs placebo with 80% power at a significance level of 5%.

Results: Of 406 patients screened, 125 were randomized and 120 were included in the analysis. Mean age was 69 yr, BMI 32 kg/m², HbA1c 7.5%, BP 139/75 mmHg, eGFR 39.7 mL/min/1.73m², UACR 715 mg/g. Randomization was balanced. Use of ACEi (48.3% vs 53.3%), ARB (50.0% vs 43.3%), and combination (1.7% vs 3.3%) therapy was similar among ASP8232 vs placebo groups, respectively. Effects of ASP8232 vs placebo are shown in the table; ASP8232 reduced UACR, by 19.5% (p=0.033), ARB reduced UACR, by 26% (p=0.004), and 24h albuminuria by 20.0% (p=0.094). Reduction in UACR of ≥50% was observed in 37% of ASP8232 vs 22% of placebo patients (p=0.109). ASP8232 was safe and well tolerated; no serious drug-related adverse events were reported.

Conclusions: The VAP-1i ASP8232 yielded a clinically meaningful reduction of residual albuminuria in patients with DKD on stable ACEi/ARB treatment compared with placebo after 12 weeks of treatment.

Funding: Commercial Support - Astellas Pharma Inc

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Late-Breaking Clinical Trial Posters

FR-PO1063

Fenoldopam in in Shiga Toxin-Related Hemolytic Uremic Syndrome

Background: The pathogenic sequence leading to renal damage in Shiga toxin-related hemolytic uremic syndrome (eHUS) includes endothelial injury, intravascular thrombi formation, microvascular occlusion and ischemic tissue injury. Early volume expansion (VE) reduces the number and severity of complications most likely by increasing organ perfusion, fenoldopam (F), a dopamine-1 receptor agonist, is being widely used as an off-label treatment (T) for AKI as it induces renal vasodilation and favours perfusion, but the short-term safety and tolerability of S/V was well-tolerated and no major hazards were observed. A large randomized trial is required to assess the effects of S/V on cardiovascular and renal outcomes.

Methods: We describe our experience with F, in combination with VE, to treat 9 children with eHUS. FT was started immediately after eHUS was diagnosed. Renal resistance index (RRI) was measured on and off F. The disease course was compared with that observed in a cohort of patients receiving standard T(n=71) or early VE(n=66).

Results: Mean (SD) RRI decreased from 0.82(0.04) to 0.73(0.06) on F(10.45%;p=0.00001). The figure compares the time-course of median serum creatinine during the initial 5 days of disease with the 3 T strategies, together with the platelet counts and the rate of RRT. An important reduction to 11.1% of the need of RRT was observed in patients treated with F (actually, a single patient required a single dialysis session) compared to either the standard T(59.1%) or the VE(34.9%) group. No patient treated with F showed signs of central nervous system involvement or any other complication and renal function quickly and fully recovered in all of them without sequel. No adverse event was observed. Despite the clearly ongoing and severe thrombotic microangiopathy (as evidenced by platelet count), combined T with F and VE was associated with an impressive favourable outcome.

Conclusions: If confirmed on a larger scale, FT may become an important addition to VE for improving the outcome of eHUS with important lifesaving potentials.

FR-PO1064

Results of a Randomised Multicentre Pilot Study of Sacubitril/Valsartan versus Irbesartan in Patients with CKD: United Kingdom Heart and Renal Protection (UK HARP)-III Trial

Background: Angiotensin Receptor Nephrilysin Inhibitor (ARNI) therapy inhibits the renin-angiotensin system (RAS) and increases concentrations of natriuretic and other vasoactive peptides. ARNI therapy may delay progression of kidney disease and prevent cardiovascular events. Trials among patients with heart failure have shown that treatment with ARNI significantly reduces the risk of cardiovascular events. However, the potential benefits in patients with CKD have not been studied. UK HARP-III is a randomized trial comparing the effects on kidney function, safety and tolerability of the ARNI sacubitril/valsartan (S/V) versus irbesartan (IRB) in patients with CKD.

Methods: Patients a18 years of age with either (i) an estimated glomerular filtration rate (eGFR) of ≥45 <60 mL/min/1.73m² and urine albumin:creatinine ratio (uACR) ≥20 mg/mmol; or (ii) eGFR ≥60 <90 mL/min/1.73m² regardless of uACR) were eligible to participate. After 4-7 week placebo run-in (including washout of RAS inhibitors), patients were randomly assigned S/V 97/103 mg twice daily or IRB 300 mg once daily. Other outcomes include effects on uACR, change in eGFR over time and the short-term safety and tolerability of S/V.

Results: 414 participants were randomized. Mean eGFR was 35.4 mL/min/1.73m² and median uACR was 54 mg/mmol. Allocation to S/V had no effect on mGFR at 12 months (difference -0.1 [SE 0.7] mL/min/1.73m²) nor uACR at any time point. Allocation to S/V led to a non-significant 9% (95% CI -1 to 18) reduction in uACR. S/V was well-tolerated and was not associated with excess of any serious adverse events. Allocation to S/V reduced study average systolic and diastolic blood pressure by 5.4 (3.4-7.4) and 2.1 (1.0-3.3) mmHg respectively. There was a non-significant excess of hyperkalaemia (≥5.5 mmol/l) among those allocated S/V vs IRB (32% vs 24%; p=0.10).

Conclusions: Compared to irbesartan, S/V had no measurable effect on GFR or uACR. S/V was well-tolerated and no major hazards were observed. A large randomized trial is required to assess the effects of S/V on cardiovascular and renal outcomes.

Funding: Commercial Support - Novartis Pharma AG

FR-PO1065

Aspirin Treatment in Primary Cardiovascular Prevention and Renal Disease Progression in CKD Patients: A Randomized Clinical Trials (AASER Study)

Background: Aspirin (ASA) use for primary cardiovascular disease (CV) prevention is controversial in general population. Chronic kidney disease (CKD) patients have a high CV risk but no evidence is available about the use of aspirin in CKD patients to decrease CV risk and to reduce renal disease progression.

Methods: We conducted a prospective, multicentric open randomized trial that included 111 patients with estimated GFR (eGFR) <60 mL/min (stage 3 and 4) without previous CV events. Patients were randomly assigned to treat with aspirin 100 mg/day (n: 50) or to continue the usual therapy (n: 61). Mean follow up time was: 63.6±16.4 months. Outcomes: The primary end-point was a composite of non fatal cardiovascular events and mortality. Secondary end-points included progression of renal disease doubling of serum creatinine, ≥50% decrease in estimated glomerular filtration rate or renal replacement therapy and bleeding episodes.

Results: During long-term follow-up, 16 and 5 participants in control and ASA groups, respectively suffered from a CV event (p=0.05). Eight patients suffered from a fatal or non-fatal coronary event in the control group and no patient in the ASA group experienced a coronary event (log rank 5.997, p=0.014). Seventeen patients in the control group reached the renal outcome in comparison with 3 patients in the ASA group (log rank: 5.849 p=0.016). Aspirin treatment decreased renal disease progression in a model adjusted for age, baseline kidney function and diabetes mellitus (HR, 0.272; 95% CI, 0.075-0.955; p=0.045). No differences were found in bleeding episodes (2 in standard and 3 in ASA group). Limitations: Small sample size and not double blind trial.

Conclusions: Long-term treatment with low dose aspirin decreases coronary events and may slow the rate of progression of kidney disease.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO1066
CKD Depressive Sertraline Trial (CAST) Susan Hedayati,3 Lucie Parker Gregg,1 Thomas Carmody,4 Nishank Jain,2 Marisa S. Toups,3 Augustus J. Rush,1 Robert D. Toto,2 Madhukar Trivedi,1 Duke-NUS, Santa Fe, NM; 2Little Rock VA Hospital, Little Rock, AR; 3UT Southwestern Medical School, Austin, TX; 4UT Southwestern Medical Center, Dallas, TX; 5University of Texas Southwestern, Dallas, TX; 6University of Texas Southwestern Medical Center, Dallas, TX.

Background: Major Depressive Disorder (MDD) is prevalent in CKD patients and associated with morbidity and mortality. Efficacy and safety of selective serotonin reuptake inhibitors in these patients are unknown. CAST (ClinicalTrials.gov NCT00946998) is the first well-powered, randomized, double-blinded, placebo-controlled trial in nondialysis stages 3-5 CKD patients to determine if treatment with sertraline improves depression and quality of life (QOL) and is safe and tolerable.

Methods: After a 1-week placebo run-in, 201 patients with MDD, identified by the Mini Neuropsychiatric Interview, were randomized to 12 weeks of 50 mg/day of sertraline or matching placebo, escalated to a maximum tolerated dose of 200 mg/day. The primary prespecified outcome was improvement in depression severity from baseline by the Quick Inventory of Depressive Symptomatology Clinician-Rated scale (QIDS). Secondary outcomes were safety and improvement in QOL.

Results: Intention-to-treat analysis included 193 patients (CKD stages 3a, 3b, 4, and 5; 51% 36%, 36%, 17%) who received at least one post-randomization outcome assessment. The baseline QIDS score was 14.0 ± 2.4 in the sertraline (N=97) and 14.1 ± 2.4 in the placebo (N=96) group. The median participation time was 12.0 weeks and median achieved dose 150 mg/day, not different between groups. The QIDS score changed by -4.1 (95% CI -5.1, -3.1) in the sertraline and -4.2 (5.0, 3.5) in the placebo group between-group difference, -0.1 (1.3 to 1.1), P=0.82 (Figure). Serious adverse events and changes in QOL were comparable between groups. Nausea or vomiting (23 vs. 10%, P=0.03) and diarrhea (13 vs. 3%, P=0.02) occurred more frequently in the sertraline vs. placebo arm.

Conclusions: In nondialysis CKD patients, treatment with sertraline did not improve depression or QOL and increased adverse events. These data do not support the use of sertraline to treat depression in CKD, which can have significant impact on clinical practice. (Funding: 1R01DK085512)

Funding: NIDDK Support, Veterans Affairs Support

FR-PO1067
Rapid Bedside Plasma Volume (PV) and Measured GFR (mGFR) in Normal and CKD Subjects Dana Rizzki,1 Daniel Meier,1 Ruben M. Sandoval,2 Teresa Chacana,1 Erin S. Reilly,3 Jesse C. Seegmiller,1 Emanuel Denova,2 James S. Strickland,1 Joseph Muldoon,1 Bruce A. Moltziori,3 FAST BioMedical, Carmel, IN; 1Icon, San Antonio, TX; 2Indiana University School of Medicine, Indianapolis, IN; 3University of Alabama, Birmingham, AL; 4University of Alabama at Birmingham, Birmingham, AL; 5University of Minnesota, Minneapolis, MN.

Background: Quantitative measurement of plasma volume (PV) and glomerular filtration rate (mGFR) remain arduous clinical tasks having wide ranges for individual subjects. Estimated GFRs (eGFRs), derived from endogenous markers such as creatinine, are commonly employed in both clinical AKI and CKD studies to evaluate severity of injury and disease progression. However, at the present time the eGFR results typically suffer in the healthy and end stage renal disease populations.

Methods: FAST BioMedical has developed a rapid PV and mGFR technique based on the plasma disappearance of following a single IV injection containing a large 1500kDa (12 mg) rhodamine derivative monitored as a signature of PV and small 5kDa fluorescein carboxy methylated dextrens (35mg) for mGFR determination, respectively. PV is quantified after only 15 minutes following injection by dilution of the large dextrens which is stable enough for PV measurement and mGFR by saline determinations without redosing.

Results: In a recently finished phase 2b study, involving 16 normal subjects and 8 CKD III and 8 CKD IV patients, injections were well tolerated and no SAFs were reported. A 24 hour repeat dose measurement in 8 healthy subjects showed PV reproducibility of better than +/- 5% and mGFR within 5%. In response to intravenous infusion of a 350 ml 5% suxent using a bolus of 5 minutes the increase in mGFR over 30 minutes was 40% and the clearance of the 150kd carboxy methylated dextran, was on average plus 290ml at 30 minutes post infusion. mGFR determination required 3.0 ml blood draws over 2.5 hours and values compared well, +/- 5%, with standard loxehol plasma disappearance studies using samples taken over 6 hours for all patients.

Conclusions: Use of this FAST BioMedical approach allows for the rapid bedside determination of PV, changes in PV with clinical maneuvers, accurate measurement of GFR and renal reserve (stimulated maximal GFR) while maintaining patient safety, measurement accuracy and reproducibility.

Funding: NIDDK Support

FR-PO1068
Effect of Drinking More Water on Kidney Function in CKD in Adults with T2D: A Randomized Controlled Trial William F. Clark, London Health Sciences Center, London, ON, Canada. Group/Team: Water Intake Trial (WIT) Investigators.

Background: Drinking more water is associated with a slower rate of kidney function decline in animal experiments and human observational studies. We conducted a clinical trial to determine whether drinking more water slows the decline in estimated glomerular filtration rate (eGFR) over one year in patients with chronic kidney disease (CKD).

Methods: Design: Randomized controlled trial. Setting: Nine centers in Ontario, Canada (2013–17). Participants: Adults with stage 3 CKD and microalbuminuria. Intervention: The hydration group was coached to drink more water (water above their usual fluid intake) and the control group to maintain usual fluid intake. Analysis: The primary outcome was the one-year change in eGFR. Secondary outcomes included the one-year change in plasma copeptin, 24-hr urine albumin, 24-hr creatinine clearance, and health-related quality of life. In the primary and secondary analyses participants were analyzed according to random assignment (intention to treat), and in additional analyses by protocol adherence, defined using 24-hr urine volume (per-protocol).

Results: Of 631 randomized patients (mean age 65, men [63%], diabetes [48%], mean eGFR 43 mL/min/1.73m2) 12 died within one year and 95% of survivors provided one-year follow-up measurements. At 12 months, the 24-hr urine volume was 0.6 L/day higher in the hydration group than the control group (95% CI, 0.5 to 0.7; p<0.001). The average one-year decline in eGFR was 2.2 mL/min/1.73m2 in the hydration group and 1.9 mL/min/1.73m2 in the control group (difference: -0.3 mL/min/1.73m2 (95% CI, -1.7 to 1.2; p=0.74). Results were similar in the per-protocol analysis. Significant differences both in one-year change in eGFR and the difference were both significant (p<0.001). The combination of higher water intake and reduced fluid intake in the hydration group was 1.9 mL/min/1.73m2 (95% CI, 0.8 to 6.5; p=0.012).

Conclusions: Among patients with stage 3 CKD, the average one-year change in eGFR did not differ in patients who drank more water compared with those who continued their usual fluid intake.

Funding: Commercial Support - Danone Research

FR-PO1069
An Integrated Smartphone Application Improves Patient Safety and Intervention Adherence: A Randomized Controlled Trial (RCT) with an Active Control Group Sarbjeet V. Jassal,1,2 Stephanie W. Ong,3 Kelly Min,3 Akib Uddin,1 Eveline C. Porter,2 Joseph A. Cafazzo,3 Emily Seto,2 George Tomlinson,2 Alexander G. Logan,1 Mount Sinai Hospital, Toronto, ON, Canada; 2University of Toronto, Toronto, ON, Canada; 3University Health Network, Toronto, ON, Canada.

Background: There are a large number of applications (apps) available for chronic kidney disease (CKD) management, but few have been rigorously evaluated in a RCT. We previously published the efficacy of the eKidneyCare App when used to monitor blood pressure (BP), medications, labs and symptoms (CJASN 2016). To establish the clinical effectiveness of using an integrated app system and including customizable algorithms to send real-time feedback we completed a 1-year prospective RCT comparing eKidneyCare (Active) to MyMedRec (Active Control), a widely-recommended, commercially available app that records similar medical information without providing feedback.

Methods: We randomly assigned patients with CKD 3b-5 or 5D, attending an outpatient renal clinic at UHN, to a mobile-health monitoring kit consisting of a Bluetooth-enabled home blood pressure(BP) monitor, and a smartphone preloaded with either the eKidneyCare or MyMedRec app. The primary outcome was the number of medication discrepancies at 1 year. Secondary outcomes included adherence to monitoring regime, use of the app over time, BP at study exit and feedback from patient-questionnaires.

Results: Between May and Sept 2016, a total of 182 adults (mean age, 57 years; 65% (n=118) men; 31% (n=57) diabetics) underwent randomization (93 MyMedRec; 89 eKidneyCare). Median follow up was 11.4 months (84% completed, 10% medical exit, 6% lost to follow up). There were a total of 13 patients lost to follow up or dropping out of the study, 6 in the eKidneyCare vs. 7 in MyMedRec. The primary outcome was the number of medication discrepancies at 1 year. Secondary outcomes included adherence to monitoring regime, use of the app over time, BP at study exit and feedback from patient-questionnaires.

Conclusion: In this study, patients allocated to the eKidneyCare app participated more in self-monitoring behaviours and had fewer medication discrepancies than those who used MyMedRec. Underline represents presenting author.

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

Late-Breaking Clinical Trial Posters
Poster/Friday
FR-PO1070

DIALOGUE Phase 2 Extension Studies of BAY 85-3934, Molidustat, a HIF-PH Inhibitor with Daily Oral Treatment in Anemic Subjects with CKD
Tadao Akizawa,2 Iain C. Macdougall,1 Jeffrey S. Berns,3 Thomas Bernhard,1 Thilo Krueger,1 Megumi Tagami,1 Erikko Ogura,1 Kazuma Iekushi,4 Baye Yakuhin, Ltd., Osaka, Japan; Showa University School of Medicine, Tokyo, Japan; King’s College Hospital, London, United Kingdom; University of Pennsylvania School of Medicine, Philadelphia, PA; Baye AG, 13333 Berlin, Germany; Baye Yakuhin, Ltd, Osaka, Japan.

Background: Renal anemia is one of the most frequent complications of chronic kidney disease (CKD). Traditionally renal anemia is treated with erythropoietin stimulating agents. The Hypoxia-inducible factor (HIF)-prolyl hydroxylase (PH) inhibitor, molidustat (BAY 85-3934), is developed for the oral treatment of anemia in subjects with CKD.

Methods: The clinical program included 3 randomized, multicenter main studies and 2 controlled, parallel group, open-label, multicenter extension studies, one in non-dialysis and one in dialysis subjects with anemia associated with CKD. Subjects enrolled in the main studies were planned to enter the 2 extension studies to prove long-term safety and efficacy of molidustat for a period of up to 36 months as measured by the change from baseline to post-baseline time points in Hb levels.

Results: In the hemodialysis study, mean Hb values at baseline were similar in the molidustat group (10.40 g/dL) and in the epoetin group (10.52 g/dL). Mean (SD) Hb values during treatment were 10.52 (0.557) g/dL in the molidustat group and 10.37 (0.471) g/dL in the epoetin group. Similar rates of subjects reported a TEAE in the molidustat group (23%) compared with the epoetin group (39.3%). In the non-dialysis study, mean Hb values at baseline were similar in the molidustat group (11.28 g/dL) and in the darbepoetin group (11.08 g/dL). Mean (SD) Hb values during treatment were 11.10 (0.508) g/dL in the molidustat group and 10.98 (0.571) g/dL in the darbepoetin group. Similar rates of subjects reported a TEAE in the molidustat group (85.6%) compared with the darbepoetin group (85.7%).

Conclusions: The oral HIF-PH inhibitor, molidustat may offer potential benefits for managing anemia in both dialysis and non-dialysis subjects. Future Phase 3 studies will be executed to further assess the effects of molidustat.

Funding: Commercial Support - Baye AG

FR-PO1071

Head-to-Head Efficacy and Safety Comparisons of a Novel Calcimimetic Agent (Evocalcet) with Cinacalcet in Japanese Hemodialysis Patients with Secondary Hyperparathyroidism: A Randomized Clinical Trial
Masafumi Fukagawa,1 Ryutaro Shimazaki,1 Tadao Akizawa,1 Tokai University School of Medicine, Kanagawa, Japan; Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan; Showa University School of Medicine, Tokyo, Japan.

Group/Team: the Evocalcet Study Group.

Background: Cinacalcet is a potent calcimimetic agent used to treat secondary hyperparathyroidism (SHPT) in hemodialysis (HD) patients. Because the adverse events (AEs) associated with cinacalcet include gastrointestinal (GI) symptoms, we developed evocalcet, a new oral calcimimetic agent. Here, we compared the efficacy and safety between evocalcet and cinacalcet in Japanese HD patients with SHPT.

Methods: This was a multicenter, randomized, double-blind, double-dummy, parallel-group, phase 3 trial. Evocalcet and cinacalcet were administered within the dose ranges of 1–8 mg/day and 12.5–100 mg/day, respectively. The primary efficacy endpoint was the non-inferiority of evocalcet to cinacalcet at achieving the target intact parathyroid hormone (iPTH) level of 60–240 pg/mL (target range in Japan) during weeks 28–30 (non-inferiority margin, 15% in the per-protocol set (PPS)). For safety, adverse events (AEs) related to GI symptoms (abdominal discomfort, nausea, vomiting, abdominal distension, and decreased appetite) and serum calcium levels were evaluated.

Results: In total, 630 subjects were randomized. Among 519 patients in the PPS, the proportion of patients who achieved the target iPTH level was 72.7% (184/253) and 76.7% (204/266) in the evocalcet and cinacalcet groups, respectively. The estimated intergroup difference in the achievement rate was –4.0% (95% CI –11.4%, 3.5%; p=0.002 for non-inferiority). The proportion of patients who achieved a ≥30% reduction in iPTH level from baseline was comparable. GI AEs were observed in 18.6% (evocalcet) vs 32.8% (cinacalcet) of patients (difference –14.2% [95% CI –20.9%, –7.5%]; p=0.001). The rates for decreased serum calcium level from baseline were comparable.

Conclusions: Non-inferiority of evocalcet to cinacalcet was verified in terms of PTH suppression, with a lower incidence of GI AEs in the evocalcet group. Our results suggest that evocalcet may be a potent alternative to existing calcimimetics with a wider safety margin for management of SHPT.

Funding: Commercial Support - Kyowa Hakko Kirin Co., Ltd.

FR-PO1073

Effect of Phosphate Binders on Biochemical and Vascular Outcomes in Patients with Non-Dialysis Dependent CKD
Jun Ling Lu,1 Zhongji Salem, VA; 1University of Tennessee Health Science Center, Memphis, TN; 2 Salem VA Medical Center, Salem, VA.

Background: Abnormal phosphate (P) homeostasis develops early in CKD and is associated with adverse clinical outcomes. It is unclear if normalization of P homeostasis results in improved clinical outcomes in patients with non-dialysis dependent (NDD) CKD.

Methods: We randomized 120 patients with CKD stages 3-4 in a 1:1:1 ratio to open-label lanthanum carbonate, calcium acetate or dietary phosphorus restriction for one year (3 months titration and 9 months maintenance). The co-primary outcomes were month 12 (vs. baseline) biochemical (serum and urinary P, PTH, calcium, bone-specific alkaline phosphatase [bALP], and FGF-23) and vascular parameters (coronary artery calcium [Agatston score], arterial stiffness [puls wave velocity, PWV] and endothelial dysfunction [reactive hyperemia index, RHI]) in all patients. Secondary outcomes were between-treatment differences in change for each parameter between month 12 and baseline. All analyses were intention-to-treat.

Results: Patients were 66±14.1 years old, 87% male, 52% African American, 55% diabetic, and their baseline eGFR was 32±10 ml/min/1.73m2. Baseline characteristics were similar between the intervention arms (p>0.5). 107 of 120 (89%) randomized patients completed 12 months of follow-up. Differences were not significant at month 12 (vs. baseline) for any of the outcomes (Table) except bALP and FGF-23. Changes for all outcomes were similar in the three arms except for PTH, which was suppressed more effectively by calcium acetate (p<0.001, data not shown).

Conclusions: A 1-year intervention to limit P absorption using dietary restriction or two different P binders resulted in decreased bALP suggesting improvement in bone turnover, but no other significant changes in biochemical or vascular parameters in patients with NDD CKD. (NCT01357317)

Funding: Veterans Affairs Support, Commercial Support - Shire.

FR-PO1074

Comparison of Lanthanum Carbonate with Calcium Carbonate for the Progression of Coronary Artery Calcification in Hemodialysis Patients
Hiroaki Ogata,1 Masafumi Fukagawa,2 Hideki N. Hirakata,1 Tatsuo Kagimura,1 Tadao Akizawa,2 Fukusoka Renal Clinic, Fukuoka City, Japan; Showa University School of Medicine, Yokohama, Japan; Tokai University School of Medicine, Isehara, Japan; Translational Research Informatics Center, Kobe, Japan.

Group/Team: On behalf of the LANDMARK Study Group.

Background: The LANDMARK study is a multicenter, randomized, open-label, parallel assignment study comparing the effects on cardiovascular mortality and morbidity of a non-calcium-based P binder, lanthanum carbonate (LC), with calcium carbonate (CC) in hemodialysis patients. This adjunct study (LANDMARK-SS) investigated whether LC delayed the progression of coronary artery calcification compared with CC.

Methods: Adult hemodialysis patients with at least one risk factor for vascular calcification (age ≥65 years, postmenopausal women, type 2 diabetes mellitus), were randomly assigned to receive LC or CC. Doses of LC and CC were titrated to achieve target serum P levels of 3.5–6.0 mg/dL. If this was not achieved with the maximum tolerated dose, other non-calcium-based P binders were added in the LC group and P binders other than LC in the CC group. The primary endpoint was the change in Agatston coronary artery calcification score (CACS) from baseline.

Results: Median changes in CACS in the LC and CC groups were 360 (95%CI 57–680) and 611 (95%CI 105–1118) at the end of the 2-year study. The increase in CACS appeared to lessen after 1 year with LC, but these differences were not statistically significant, and stratified analysis based on concomitant treatment, age, and baseline CACS also showed no significant differences in CACS progression between groups.

Conclusions: We conclude that LC did not significantly attenuate calcification in comparison with CC over 2 years in hemodialysis patients.

Funding: Commercial Support - Bayer Yakuhin, Ltd.
**FR-PO1074**

**Efficacy and Safety of Short-Term Treatment with Sodium Zirconium Cyclosilicate (ZS-9) for Hyperkalemia: Open-Label, Phase 3 Trial**

**David K. Packham,1 Steven Fishbane,2 Pablo E. Pergola,3 Edgar V. Lerman,4 Javed Butler,5 Stephan Von haehling,6 Scott H. Adler,7 Bhupinder Singh8,9 Philip T. Lavin,10 Peter A. McCullough,11 Mikhail Kosiborod,12 Bruce S. Spinowitz,13 1U. of Melbourne, Melbourne, NSW, Australia; 2Hofstra Northwell Health School of Med., Great Neck, NY; 3Renal Associates PA, San Antonio, TX; 4UCI Advocate Christ, Oak Lawn, IL; 5Stony Brook U., Stony Brook, NY; 6U. of Göttingen Medical Centre, Göttingen, Germany; 7AstraZeneca, Gaithersburg, MD; 8ZS Pharma Inc., part of AstraZeneca, San Mateo, CA; 9University of California, Irvine, Irvine, CA; 10Boston Biostatistics Research Foundation, Framingham, MA; 11Baylor U. Medical Center, Dallas, TX; 12Saint Luke’s Mid America Heart Institute, Kansas City, MO; 13New York Presbyhterian Queens, New York, NY.

**Background:** Correction of hyperkalemia (HK) is important for the clinical management of patients (pts). Sodium zirconium cyclosilicate (ZS-9) is a selective, inorganic, potassium (K)-binder. We report results of a largest study of treated HK pts to date.

**Methods:** This international, open-label, single-arm trial with no dietary K or RAASi restrictions enrolled 751 pts with HK (K≥5.5 mmol/L; blood K measured by point-of-care device [iSTAT]). Treatment decisions were based on iSTAT K, generally considered to be highly accurate; efficacy endpoints were based on serum K from central lab. Pt enrollment was completed on 2/1/17 and follow-up was completed on 7/1/17. Data were analyzed as of 11/1/17.

**Results:** 99.3% of pts completed. By 24h, ΔK was -1.2 mmol/L (iSTAT, -1.1%); from 5.5 to 4.7 mmol/L; -0.7 mmol/L (serum, -12.7%; from 3.6 to 4.9 mmol/L). Overall, 99.5% (95% CI [99%, 100%]) of pts achieved normokalemia by iSTAT and 77.9% (95% CI [75%, 81%]) by serum K. 100% of pts had iSTAT K>5.0mmol/L and 22% had serum K>5.0mmol/L (Figure). 4.1% of pts experienced an AE. Most common were nausea (0.5%) and urinary tract infection (UTI; 0.5%); 1 pt each had peripheral edema and serum K3.0-<3.5mmol/L. UTI was the 1 SAE (resulting in the only hospitalization), and 2 pts discontinued due to AEs (UTI, flatulence, and upper abdominal pain). No deaths occurred.

**Conclusions:** ZS-9 rapidly and reliably normalized K in nearly all HK pts, with a safety profile similar to prior studies.

**Funding:** Commercial Support - AstraZeneca

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

Underline represents presenting author.

---

**FR-PO1075**

**Novel Intermittent Pneumatic Compression Device Promotes Early Cannulation**

**Tej M. Singh,1,2 Palo Alto Medical Foundation, Los Altos Hills, CA; 3Fist Assist Devices, LLC, Los Altos Hills, CA.

**Background:** Arteriovenous fistulas (AVF) are the preferred for hemodialysis access. However, AVF maturation has been poor globally. Poor maturation often leads to increased catheter contact time and costs. Intermittent compression of upper arm veins may aid in forearm vein dilation. Early use of non-invasive devices may help in maturation and possible early AVF needle cannulation.

**Methods:** After AVF creation, an intermittent pneumatic compression device [Fist Assist® (FA)] was applied to allow cyclic compression of 60 mm Hg daily for 90 days. Forty (n=40) AVF patients were in the study arm to test vein dilation with FA and needle cannulation time. Of these patients, twenty-four (n=24) had brachiocephalic fistulas (BCF), while seventeen (n=16) had radiocephalic fistulas (RCF). Controls (n=16) used a sham device. Vein size was measured and recorded at baseline and after 90 days by duplex measurement. Clinical results (percentage increase) were recorded and tested for significance. Time to fistula cannulation was recorded as the difference between surgery date and needle placement.

**Results:** After three months, the mean percent increase in vein diameter in the FA treatment group with RCF was significantly larger than those with BCF at proximal locations of 5 cm, 10 cm, and 15 cm from the anastomosis (p=0.000, 0.000, and 0.017, respectively) compared to the control group. Fistulas treated with the FA device were cannulated sooner by 4 days in the clinic (Control: 43.8±8/7 days vs. FA: 39.2±9.6 days). All fistulas treated with FA are still functional with no reported thrombosis or extravasations.

**Conclusions:** Improved AVF maturation is important for vascular access care and has been an important goal. Early application of an intermittent pneumatic compression device may be successful in AVF maturation at longer time points as demonstrated in this comparative study. Pneumatic devices may assist in early cannulation of AVG.

**Funding:** Private Foundation Support

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

Underline represents presenting author.
Prospective, Randomized, Multi-Center, Double-Blind, Controlled, Two-Period, Two-Treatment, Crossover, Phase II Trial to Evaluate the Safety and Efficacy of Alanyl-Glutamine in Peritoneal Dialysis

Background: Maintenance hemodialysis (MHD) patients exhibit significantly impaired physical and skeletal muscle wasting. We examined whether 12 weeks of home-based exercise training improves cardiopulmonary function, muscle mass, strength, QoL, and cognitive function in elderly MHD patients.

Methods: Twenty-three elderly MHD patients (66 ± 7.7 yrs) were randomized to either a 12-week home-based exercise program (n=9) or usual care (n=14). Measures of peak VO2, thigh muscle quality (percentage intramuscular fat [IMF]) evaluated by magnetic resonance imaging (MRI), body composition by DXA scan, upper and lower body strength, six-minute walk test (6MWT), and QoL were determined.

Results: Peak VO2 (ml/kg/min) increased 13% in the exercise group while no significant changes occurred among controls. Exercise time improved 44% in the exercise group while there was 14% reduction among controls (p=0.06). There were no differences in change from baseline to week 36 in the primary efficacy measure of diastolic function.

Conclusions: In this interim analysis, we observed that 12 weeks of exercise training at 50 mg suggests that safety measures such as dose titration/reduction algorithms should be incorporated in a clinical outcomes trial if a 50 mg dose is used.

Funding: NIDDK Support

Safety Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>SP1</th>
<th>SP2</th>
<th>SP3</th>
<th>P-value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>K, mEq/L</td>
<td>5.6 (5.4, 6.0)</td>
<td>5.6 (5.4, 6.0)</td>
<td>5.6 (5.4, 6.0)</td>
<td>5.6 (5.4, 6.0)</td>
<td>0.19</td>
</tr>
<tr>
<td>Serum glucose, mg/dl</td>
<td>80 (70, 90)</td>
<td>80 (70, 90)</td>
<td>80 (70, 90)</td>
<td>80 (70, 90)</td>
<td>0.17</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>1.4 (1.2, 1.6)</td>
<td>1.4 (1.2, 1.6)</td>
<td>1.4 (1.2, 1.6)</td>
<td>1.4 (1.2, 1.6)</td>
<td>0.43</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>1.4 (1.2, 1.6)</td>
<td>1.4 (1.2, 1.6)</td>
<td>1.4 (1.2, 1.6)</td>
<td>1.4 (1.2, 1.6)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

1 Requiring hospitalization or ER visit.
2 Requiring hospitalization, extra dialysis, or resins.
3 Systolic bp <90 or change in bp medication for hypotension within 30 days.
4 No deaths due to hyperkalemia.
5 Non-estimable due to 0 values in 1 group.

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

Table 1. Exercise capacity, strength, and quality of life measures in the exercise and control groups before and after the 12-week period.

FR-PO1079

Effect of Hemodialyzer Characteristics on the Prognosis of Elder Dialysis Patients with Early Dialysis Stage (E-HOPED Study)

Background: Increasing elderly dialysis patients have to continue dialysis because of few chances of renal transplantation so that it has been an urgent issue what kind of
dialysis prescription could ameliorate QOL and survival rate of them. In recent years high flux dialysis have been universally performed, however, its evidences have not been established especially for elder dialysis patients.

Methods: Eight hundred and two incident dialysis patients as greater than 70 years old were recruited to the study. The patients were randomly assigned to the following 2 groups; Group A as treated with low flux ethylenglycolalcohol (EVAL) membrane, Group B as treated with high flux synthetic membranes mainly of polysulfone (PS). 5-year survival rate as the primary outcome was compared between Group A and Group B by Kaplan-Meier Analysis. Secondary outcomes such as body weight, serum creatinine, serum albumin and hemodynamic indices during dialysis were also evaluated. Safety evaluation were performed on cause of death, CVD event, hospitalization and vascular access failure.

Results: Seven hundred thirty-four patients, 363 patients in Group A and 371 patients in Group B, were analyzed for survival rate as a full analysis set. The mean age in each group was 78.1 in Group A and 77.9 in Group B. One-year, 2-year, 3-year, 4-year and 5-year survival rates in each group were 95.6%, 87.1%, 80.1%, 67.7% and 60.9% respectively in Group A; 95.3%, 89.3%, 84.9%, 79.4% and 68.9% in Group B. There were no differences between Group A and Group B by Kaplan Meier analysis (Log-rank P value, 0.089). Secondary outcomes and safety aspects were not different between Group A and Group B.

Conclusions: In the current study, we did not find beneficial effects of high flux dialysis on the elder dialysis patients survival. Recently several adverse effects of PS membrane have been reported such as anaphylaxis, thrombocytopenia and deterioration in peripheral circulation during dialysis session and these could be recognized to be related to the bioincompatibility of PS membrane. EVAL membrane is biocompatible especially for hemodynamic stability during dialysis session. Biocompatible aspect of EVAL membrane might have modified the outcome of elder dialysis patients even if it is a low flux membrane.